

diseases doctors often miss

Jan Pankey, M.D., 50, a pediatric anesthesiologist well trained in figuring out what ails her young patients, was clueless about what was wrong with her. So was her physician husband.

An admitted “fanatic” cyclist, Jan was feeling short of breath just riding in the car. It was the summer of 2003, the start of a bike tour on the steep switch-back roads of Glacier National Park in Montana. All of a sudden she felt pain grip her lower right chest.

“I assumed it was my asthma kicking up,” she says. She and her husband stopped at an emergency room in Missoula to get her checked out. Doctors there found nothing seriously wrong with her chest scan. They said she was suffering spasms in her esophagus, gave her pills to combat pain, and sent her on her way to the mountains.

Once on her bike, the first time she had to pedal—on level ground—“I almost fainted,” she says. She was

forced to dismount. “I would walk my bike a few yards, then set it down,” she says. “Sit down and pant. Get up and try again. It took me half an hour to travel the 50 yards to a place where a van could pick me up.”

As she went home in pain to Peralta, New Mexico, her symptoms worsened. A stop at another hospital ER confirmed that arteries leading to her lungs had been clogged. “Parts of my lung tissue had died,” she says.

Medications and other treatment lessened the threat to her life. She was

able to go back to work taking care of young patients. But the most fearful complication of the clotting was yet to come: “brain fog.”

It began after the bike trip, when she realized that she had trouble spelling words and became forgetful. “Sometimes I couldn’t think what I was supposed to be doing,” she says. “I would get to the middle of a word and not know how to finish it. It was like being in a steel box.”

In all, seven doctors examined Jan without deter-

mined.

By Gurney Williams III

Gurney Williams III is a writer in Rye, New York.



After her mysterious and debilitating disease was diagnosed, Dr. Pankey got active again.



Be wary when morning stiffness of the hands lasts more than an hour.

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mining what was wrong. But she was comparatively lucky. Within two months of the ill-fated bike trip, she met a physician at a medical conference who soon diagnosed her problem. She had antiphospholipid syndrome (APS), he said, an autoimmune disease. Her own disease-fighting immune system had turned against her. Antibodies generated in the system that normally would have fought infections instead made her highly vulnerable to dangerous clotting. He prescribed an even stronger dosage of anticoagulating drugs.

They worked. Last summer, carrying enough syringes and alcohol pads to give herself injections of the medication twice a day, she biked, hiked and kayaked for a week in British Columbia. Her "brain fog" has lifted. Her passion for biking—and life—is back. "I feel so much better," she says.

Autoimmune diseases like APS affect about 50 million Americans, the majority of them women. Because their symptoms often mimic those of other diseases, or seem vague, doctors have often misdiagnosed or ignored these mysterious disorders. On average, it takes an autoimmune-disease patient nearly five years (and visits to many doctors) to get a firm diagnosis. In that time the uncontrolled conditions can take a heavy toll in miscarriages, stroke, crippling fatigue, joint aches and other consequences, some of them fatal. Even though a total of about 80 autoimmune diseases afflict some

35 million U.S. women (and 15 million men), fewer than six percent of Americans can name even one of the disorders. Patients often feel as though they suffer diseases at the fringes of medical research and attention.

Here's a wake-up call about five of the most common autoimmune diseases that millions suffer, many without ever receiving a diagnosis, plus symptoms to watch for. Our sobering report about these incurable disorders is leavened with good news: The latest, often very aggressive treatments may hold them at bay, particularly if patients and doctors respond quickly enough to end the suffering they cause.

The "Sticky Blood" Syndrome

What it is: Antiphospholipid syndrome. The immune system in APS patients like Jan interferes with other protective systems that help prevent excessive clotting. The result is "sticky blood," rendering patients more prone to blockages. In some APS patients the clots clump up

in arteries, increasing the risk of heart attacks and strokes.

About one to four percent of the U.S. population—up to almost 11 million people—carry one of the three measurable antibodies associated with APS. "No one is certain how many of these people suffer symptoms of the syndrome, like Jan's, that enable doctors to diagnose it," says Michelle Petri, M.D., M.P.H., professor of rheumatology at Johns Hopkins Medical Center in Baltimore, Maryland.

Symptoms: Clots, for example deep vein thromboses—vessel blockages that affect mainly the veins in the lower leg and thigh and cause swelling, redness and pain. Up to half of patients endure blockages in the blood vessels of their lungs, as Jan did. Common with APS are recurrent pregnancy problems—"usually several first-trimester miscarriages," Dr. Petri says, or one or more miscarriages late in pregnancies. "Brain fog" results from blockages in small vessels in the brain that cloud memory and slow

a swollen joint disorder

What it is: Rheumatoid arthritis. RA affects the synovium, which is tissue lining the capsule surrounding the joints. Genes and other factors, like smoking, contribute to the risk of RA.

Symptoms: They may be subtle, with stiffness, swelling or tenderness in the hands, wrists, shoulders, elbows, knees, ankles or the joint where the big toe meets the foot. The discomfort of RA haunts the same joints each time it returns, often spreading to new sites as the disease progresses. Morning stiffness lasting more

than an hour can signal RA. So can severe fatigue for four to six hours after awakening.

Diagnosis: Doctors take into account a medical history and a physical exam, X-ray images and a blood test for an antibody called rheumatoid factor, found in most people with RA.

Treatment: Some of the newer medications interfere with the biological processes leading to RA, according to James F. Fries, M.D., professor of medicine at Stanford University School of Medicine in California. They include Enbrel

(etanercept), requiring injections twice a week; Remicade (infliximab), given intravenously; and Humira (adalimumab), injected every two weeks. Another recent "biological" medication, Kineret (anakinra), blocks the activity of a protein in the body that causes joint damage. Kineret is injected daily. "With the help of these drugs and others in the research pipeline, our goal in most cases is to treat until symptoms diminish," Dr. Fries says. "That doesn't mean curing RA, but it does mean enabling most patients to lead a normal life."

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simple tasks like adding or spelling. Many patients—up to about 60 percent—suffer abnormalities in their heart valves.

Diagnosis: Doctors look for a combination of blood vessel blockages or pregnancy complications as well as blood-test results that show the presence of at least one of the three APS-related antibodies. But some patients like Jan are diagnosed with scant help from lab results. “Antibodies wax and wane,” says Jan.

Treatment: Clot-fighting drugs like aspirin, or stronger medications like warfarin (Coumadin) or heparin, make blood less sticky. Jan takes daily shots of a type of heparin called Lovenox. “Heparin is the first-line treatment of choice” in pregnant women

with APS, says Robert M. Silver, M.D., associate professor of obstetrics and gynecology at the Utah School of Medicine in Salt Lake City and an expert on APS and lupus.

A Rash Reaction

What it is: Lupus. The immune system in lupus patients most often targets the joints, skin, kidneys, lungs and nervous system. Lupus appears in three basic forms. The most common is systemic lupus erythematosus (SLE), one of the most frequently encountered autoimmune diseases in pregnancy. Discoid lupus produces a skin rash, but doesn't usually extend to internal organs. Drug-induced lupus results from taking certain medications like procainamide (for abnormal heart rhythms) or methyl dopa (for high blood

pressure). Symptoms are more likely to occur after taking a drug for at least three to six months.

About one out of 10 SLE patients are related to someone with SLE, suggesting that gene mutations play a part in lupus development.

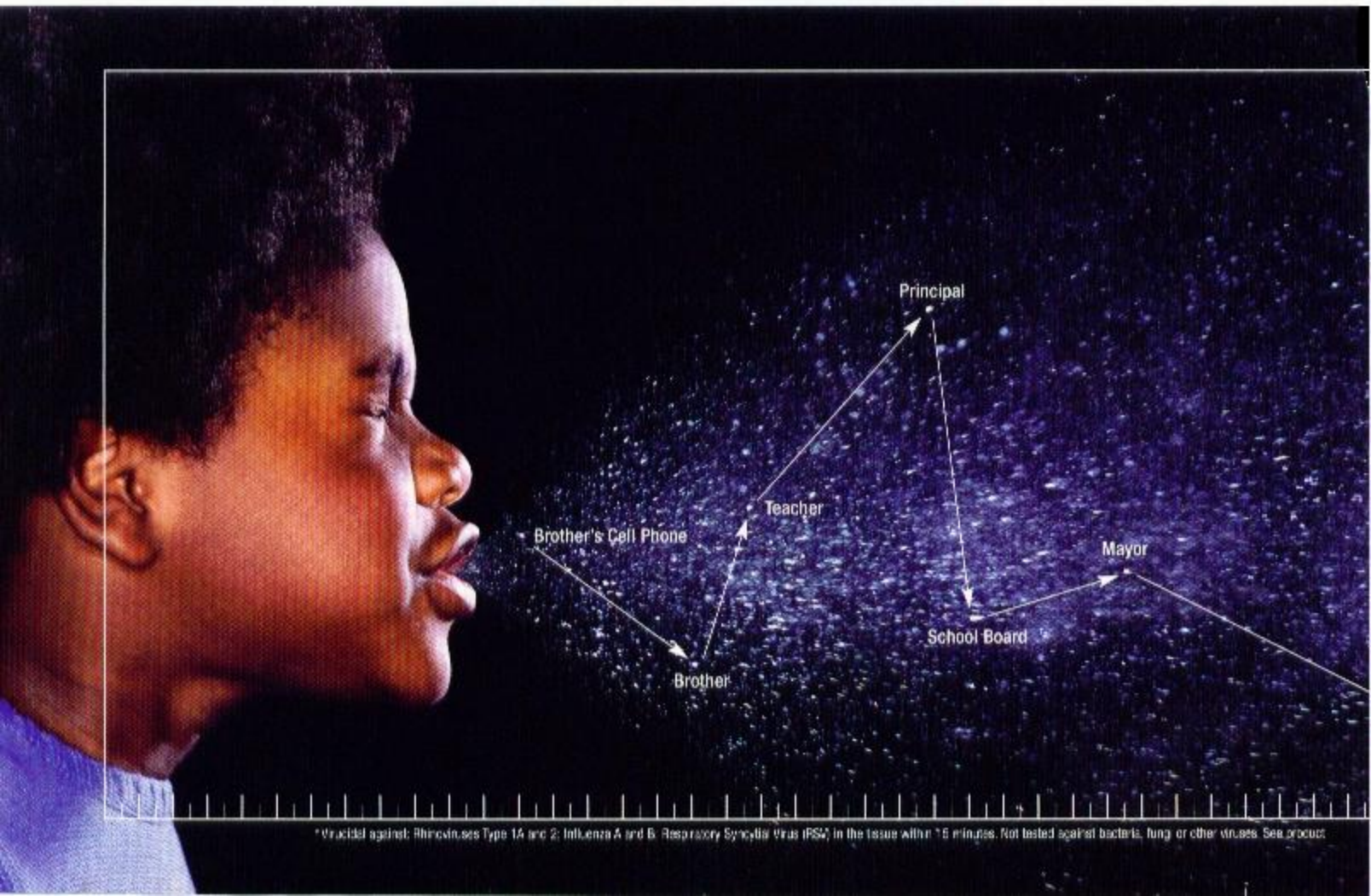
Symptoms: These include arthritis pains, fatigue, fever, muscle ache, weight loss and sensitivity to light. SLE patients usually develop a distinctive red facial rash in the shape of a butterfly; some drug-induced-lupus patients also have this. Symptoms of drug-induced lupus usually fade a few days to a few weeks after stopping the medication.

Diagnosis: Doctors consider about a dozen factors, including symptoms and lab tests, before diagnosing lupus. Some patients who don't entirely meet accepted criteria are identified as hav-

ing “lupuslike” disease. Some of these will ultimately develop full-fledged lupus.

Treatment: Medications used to lessen inflammation and relieve pain in arthritis, like naproxen (Aleve, Naprosyn), can counter the fever and joint aches of lupus. Doctors can use steroids, some delivered by intravenous injection, when lupus attacks major organs or causes neurological disease. And some patients take drugs to suppress immune system activity; these include Rheumatrex (methotrexate) and Cytosan (cyclophosphamide).

Greater confidence in using medications during pregnancy has led to better outcomes for mothers with lupus and their babies, says Dr. Silver. “It used to be that doctors counseled these patients not to get pregnant,” he says. No



longer, but there are some warning flags on some drugs. For example, during pregnancy women with lupus should avoid aspirin and NSAIDs like ibuprofen. They're linked with significant fetal illness, including kidney or lung problems. Rheumatrex and Cytoxan can be harmful to embryos and can cause birth defects.

Steroids, such as prednisone, are generally safe. Antimalarial drugs, like Plaquenil, carry some risks, but stopping them during pregnancy can lead to lupus flare-ups and less-favorable pregnancy outcomes. Such drugs are "rapidly gaining favor as a first-line therapy for SLE," Dr. Silver says, "even during pregnancy."

A Gut Gripper

What it is: Crohn's disease. In patients with Crohn's, inflammation—the

body's response to infection or injury—becomes a chronic problem in the digestive tract, usually in the lower part of the small intestine. The painful, inflamed swelling extends deep into the lining of the intestinal wall. Crohn's is a medical cousin of several diseases, known collectively as inflammatory bowel disease, with similar symptoms. The cause is unknown, but researchers believe that genetic mutations play a role. In 2001 researchers discovered one faulty gene linked to about 40 percent of Crohn's cases. But the discovery may not lead to a useful gene test, because many people with the mutation don't get the disease. Crohn's probably strikes when a genetic susceptibility to Crohn's collides with other factors, like smoking.

"People who smoke are



A rash shaped like a butterfly is a symptom of an autoimmune disease known as lupus.

twice as likely to get Crohn's disease as people who don't," says William Sandborn, M.D., an expert on inflammatory bowel disease at the Mayo Clinic in Rochester, Minnesota. The use of nonsteroidal painkillers like naproxen can sometimes trigger the inflammation in genetically susceptible people. "It can also start with a bacterial infection like traveler's diarrhea," he says. Stress doesn't cause Crohn's but

may make flare-ups worse.

Symptoms: Diarrhea, abdominal pain, cramping, nausea, weight loss and rectal bleeding are signs of Crohn's. Patients can make up to 20 trips to the bathroom per day. Sensitivities to foods vary. Culprits can include corn, popcorn, coffee (with caffeine), beans and carbonated drinks. But each patient is different, "so we can't really make good recommendations for what to avoid," says Dr.

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Sandborn. In some cases the inflammation becomes so severe that patients need surgery to remove scar tissue on the intestinal wall.

Diagnosis: Symptoms alone can lead doctors to an initial diagnosis. A small-bowel X-ray can reveal inflammation in the bowel. And a colonoscopy, a visual inspection of the full length of the lower intestine, can help doctors spot abnormal tissue characteristic of Crohn's. Antibodies associated with Crohn's aren't present in all patients, so blood tests for the disease aren't entirely accurate.

Treatment: Anti-inflammatory drugs like Asacol (mesalamine) are a major frontline therapy. Medications like Imuran (azathioprine) and Remicade (influx-

imab, also used to fight rheumatoid arthritis) rein in an overactive immune system. Remicade has been underused in the past, Dr. Sandborn says, but doctors are more likely to prescribe it now, as they've come to know how well it works.

"If physicians are comfortable giving the full range of drugs that are available and doing surgery when it's necessary," says Dr. Sandborn, "the majority of patients can feel well most of the time."

The Nerve Destroyer

What it is: Multiple sclerosis. In people with MS the body's defenses turn against the brain and spinal cord—the central nervous system. "The immune system attacks the nerves, then leaves them alone, then at-

tacks again, causing pockets of damage at multiple sites here, there and everywhere," says Robert J. Fox, M.D., medical director at the Mellen Center for Multiple Sclerosis at the Cleveland Clinic Foundation in Ohio. The assault appears to zero in on myelin, a sheath surrounding nerves like insulation around a pipe. Damage to the sheath slows down the traffic of messages through the nervous system, leading to MS's many symptoms. The aftermath of the attacks on the myelin sheath cause scar tissue (sclerosis) in the brain and spinal cord, which can impair nerve function. Research published in 1998 shows that the attacks also damage nerve cells by slicing through the nerve fibers, a process called transection. "It's like snipping

telephone wires out on the street," says Dr. Fox. "At first the telephone company can find ways to reroute the signals, but eventually the phone service starts failing. That's what we think happens in the later stages of MS, when the brain can no longer compensate for the loss of nerve pathways."

The exact cause is unknown, but genes hold some sway. If a mother has MS, there is a 2 percent chance that a son of hers will have it and a 3 percent chance that a daughter will.

Symptoms: Common signs include fatigue, weakness, numbness, pain, difficulty with balance and coordination, depression and memory problems, although many of these may be signs of other disorders like chronic fatigue syndrome or fibromyalgia.

Symptoms tend to encroach gradually over a period of days to weeks, then gradually fade away over several weeks to a few months, then return again.

Diagnosis: A physical exam can detect abnormal responses of pupils in the eye, subtle changes in speech patterns or altered reflex responses, among other clues that suggest MS. Magnetic resonance imaging (MRI) can help spot areas of damage in the nervous system. Testing of the colorless liquid circulating through the brain and spinal cord (the cerebrospinal fluid) can turn up abnormalities, like high white-blood-cell levels, linked with MS. A slowdown in the speed of signals from the optic nerve to the brain is another possible sign of the disease. It's detected with a test that in-

volves attaching electrodes to the scalp to measure brain activity as patients view flashes of light or patterns. A computer records the brain's response and helps doctors pinpoint any areas of nerve damage. A firm diagnosis also requires ruling out other possible causes, such as lupus, diabetes, stroke, even neurological problems associated with Lyme disease.

Treatment: A shift in strategies in recent years means that most doctors are more aggressive in treating MS if symptoms flare and an MRI reveals damaged sites in the brain. "We'll start treatment today even before we've confirmed the 'multiple' part of multiple sclerosis," says Dr. Fox. Four drugs form the backbone of defenses against the disease: Avonex, Betaseron and

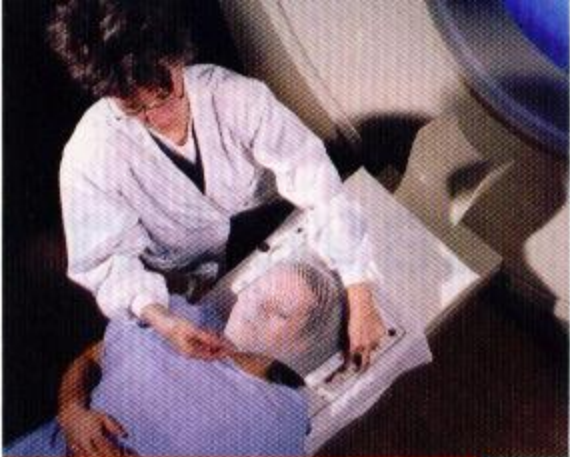
Rebif (the generic name for all three is interferon beta-1) and Copaxone (glatiramer acetate). All help prevent MS relapses and brain degeneration, and slow the progression toward disability. Researchers believe that each of the medications may help protect against nerve fiber slicing. Current drugs, though, are only partially effective, reducing relapses by about a third.

One new drug called Antegren (natalizumab) has shown promise in cutting relapse rates by about 66 percent. At press time Food and Drug Administration approval of the medication was still pending.

"Antegren is a sort of traffic cop," Dr. Fox says. "It blocks white cells from

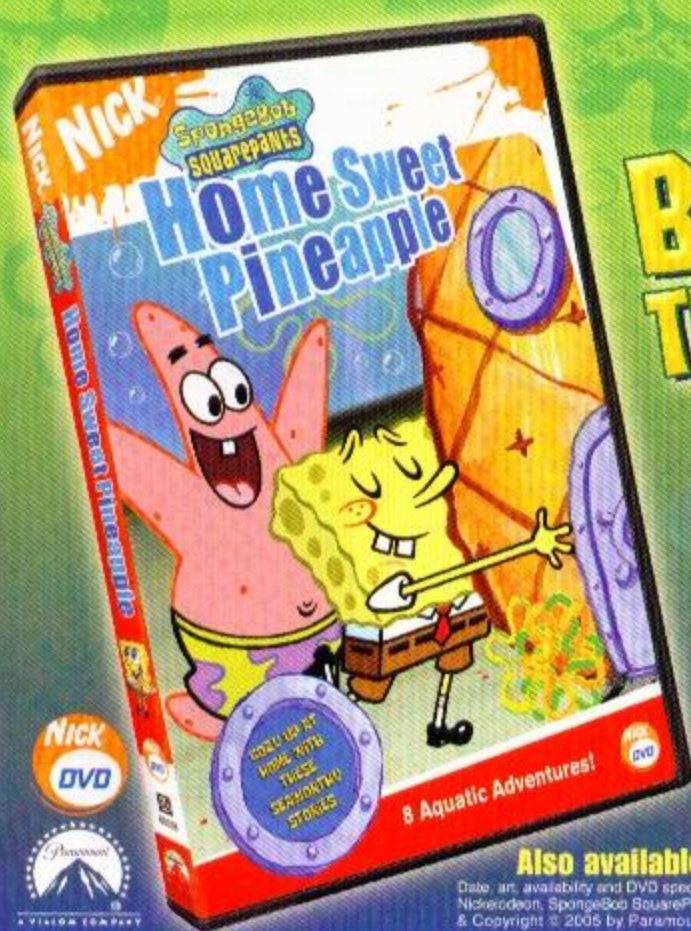
entering and bulking up the plaque within brain tissue." Other clinical trials are under way to determine whether the drug might also benefit rheumatoid arthritis and Crohn's disease patients.

For further information, go to the American Autoimmune Related Diseases Association Web site at www.aarda.org. **FC**



An MRI can help detect MS by pinpointing damaged brain tissue.

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