

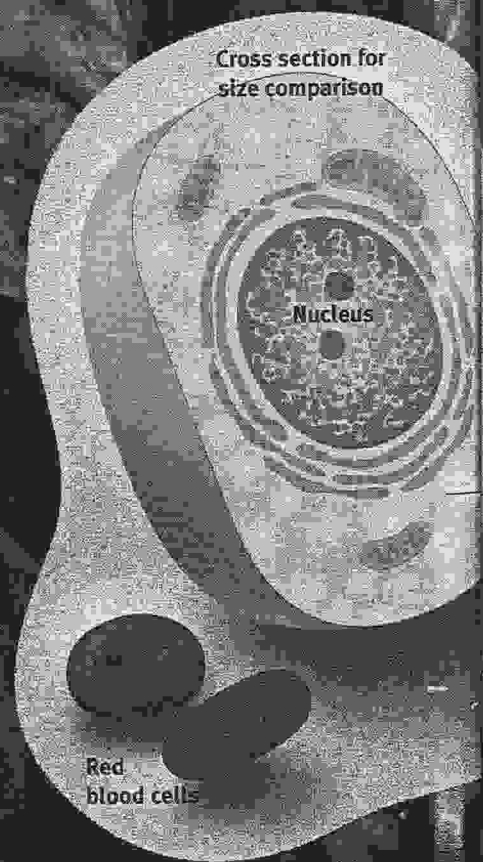


# What's Really Causing One man's dogged research points to an Gulf War Illness?

By Gunjan Sinha

INFOGRAPHICS BY SEWARD HUNG

**Popular  
Science**





WHILE THE WORLD WAS watching cruise missiles descend on Iraq like giant blurry sparklers in the night sky, Blackhawk helicopter pilot Sharon Nicolson was ferrying special forces and Navy SEALs. It was February 1991, Operation Desert Storm.

Her chopper flew near Patriot missiles that were obliterating Iraqi Scuds and was involved in several air raids. While Nicolson was airborne, the wind whipped up sandstorms so severe that she rarely ever saw anything clearly, including the ground. But something else that Nicholson couldn't see would soon turn one of the shortest wars in history into the longest nightmare of her life.

That April, after the war ended, Nicolson returned to Fort Campbell, Kentucky, to continue Army pilot training. But she slowly began to experience disturbing symptoms. She found herself sweating in her sleep, and her joints ached. Dragging herself out of bed each morning, she sometimes couldn't see straight. One by one, she failed every one of the Army's routine physical strength tests, and eventually she dropped out of flight training.

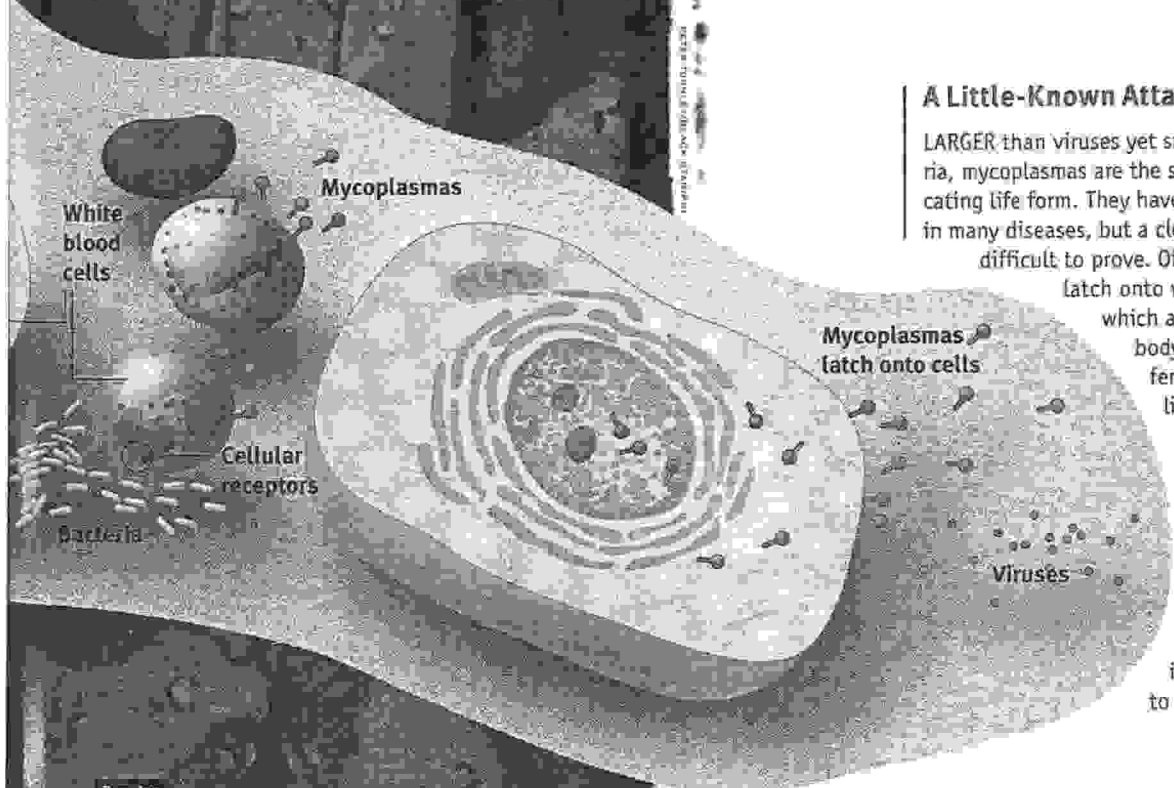
Enter Garth Nicolson, chairman of tumor biology at the University of Texas M.D. Anderson Cancer Center in Houston—and also Sharon's stepfather. With Sharon's doctors offering nothing more than a prescription for rest and relaxation, Nicolson began experimenting on his own to find a cure. He searched the medical literature for similar illnesses and scrutinized their treatments. Some of Sharon's symptoms resembled those caused by certain bacterial infections. So Nicolson tried a series of antibiotics until he found one that seemed to work, a drug called doxycycline. After taking it for almost a year, Sharon finally recovered.

unusual—and likely—suspect.

### A Little-Known Attacker

LARGER than viruses yet smaller than bacteria, mycoplasmas are the smallest self-replicating life form. They have been implicated in many diseases, but a clear link has been difficult to prove. Often, mycoplasmas

latch onto white blood cells, which are part of the body's disease defenses, with a hook-like tip; then they transmit chemical signals that force blood cells to behave abnormally. Mycoplasmas can burrow deep inside cells, making them difficult to detect.



But that wasn't the end of the mystery malady. Other vets from Sharon's division, and even their family members, were falling ill and turning to Nicolson for advice. "Even without a diagnosis, we saw that the antibiotics were helping people recover. We decided right then that we were going to have to prove this [had a biological cause]," says Nicolson, a feisty middle-aged man with a mop of dense silver hair and mottled eyebrows as thick as hedges. He'd ruled out the placebo effect because certain antibiotics like penicillin didn't work. And since family members were also falling ill, he assumed it was something that was being transmitted.

Nicolson didn't realize it at the time, but his quest to find what ailed his stepdaughter would consume him for the next four years. He began by compiling a list of possible culprits based on organisms that were known to cause similar symptoms. These included brucella, coxiella, anthrax, and a group of poorly characterized microorganisms called mycoplasmas—amorphous microscopic organisms larger than viruses and related to bacteria—which he had only learned about in 1991 after reading a newspaper article about symptoms they cause in AIDS patients.

When Nicolson tested veterans' blood, one microorganism kept popping up over and over again: *Mycoplasma fermentans*—the most poorly studied bug on the list and the one he now contends is associated with the ailment known as Gulf War Illness (GWI). In studies with almost 200 Gulf War veterans who suffer from aching joints, unrelenting fatigue, headaches, and numerous other maladies estimated to affect as many as 100,000 Americans who served during the Gulf War, Nicolson has found *M. fermentans* nestled inside the cells of almost half

all cases. Even more compelling, most patients recovered and then tested negative for the microbe after taking the antibiotic doxycycline.

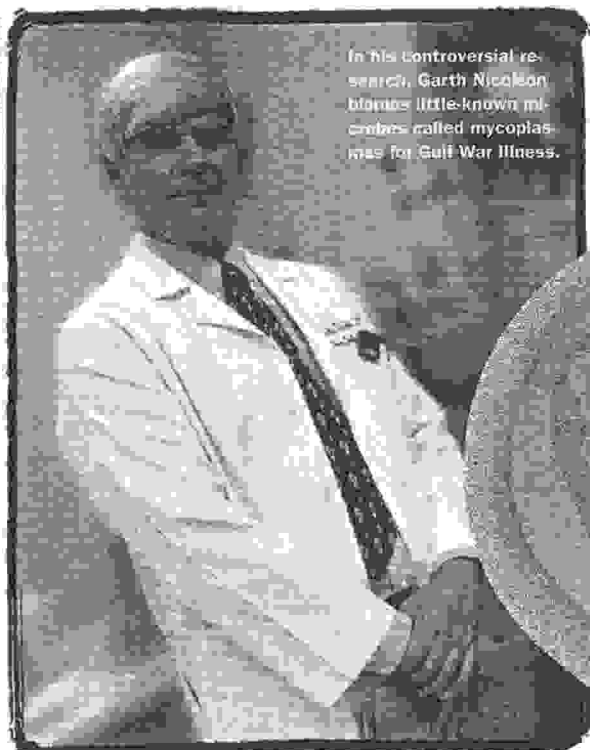
A major breakthrough, one would think, since there is no other treatment for GWI. But Nicolson's work has been mired in controversy. When Nicolson went to a veterans' hospital in Houston, Texas, in 1994 to share his idea that mycoplasmas may be causing GWI and to suggest that doxycycline might help, he was lambasted.

At the time, mycoplasmas' association with disease was spotty at best, and most doctors had never even heard of them. And the situation was politically loaded. Admitting the illness existed would mean conceding that something had gone awry during the Gulf War, opening a Pandora's box of scrutiny. Money also was an issue. If vets were sick because of their service, the military would have to dole out millions of dollars in compensation and benefits. "Back then, we had this naive belief that people were interested in the truth," recalls Nicolson. "But as we found out, some people were more interested in hiding the truth."

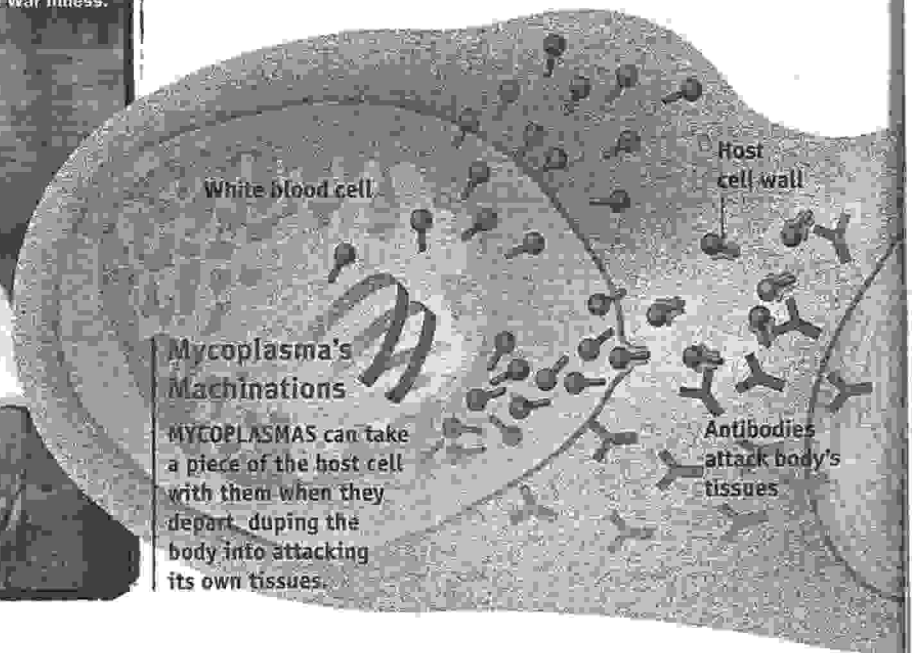
Nicolson's scientific peers also criticized his data. His patient and control groups are too small, they argued, and more than 5 million American civilians with Chronic Fatigue Syndrome, Fibromyalgia Syndrome, rheumatoid arthritis, and several other chronic, long-lasting diseases experience symptoms similar to Gulf War Illness. How could mycoplasmas be the cause of GWI when so many civilians experience the same symptoms? What's more, government-appointed investigators found no statistical evidence indicating that Gulf War vets were any sicker than civilians in the general population. And so the vets' maladies were deemed a psychological disorder that manifested itself in physical symptoms—posttraumatic stress disorder, Veterans Affairs doctors called it.

But within the past two years, as scientists have gained a better understanding of mycoplasmas, most doctors who

MICHAEL ROSE



In his controversial research, Garth Nicolson blames little-known microbes called mycoplasmas for Gulf War Illness.



treat GWI have come to admit that the illness isn't purely psychological. All of Nicolson's results have been published in peer-reviewed journals, so the work has been scrutinized by other researchers and found to be sound. And two commercial laboratories, Immunosciences in Beverly Hills, California, and Medical Diagnostic Laboratories in Mt. Laurel, New Jersey, have also found similar, though as-of-yet unpublished, results in GWI patients. And with mounting anecdotal evidence of GWI victims recovering with antibiotic therapy, Nicolson's theory that mycoplasmas may be involved in at least some cases of GWI is gaining momentum. As a result, the Veterans Affairs Administration has agreed to fund a large-scale clinical trial, involving between 500 and 1,000 veterans across several institutions, that will finally pit Nicolson's theories against rigorous scientific principles. Patient recruitment began this spring and should take about six months; trial results will be available a minimum of one year afterward.

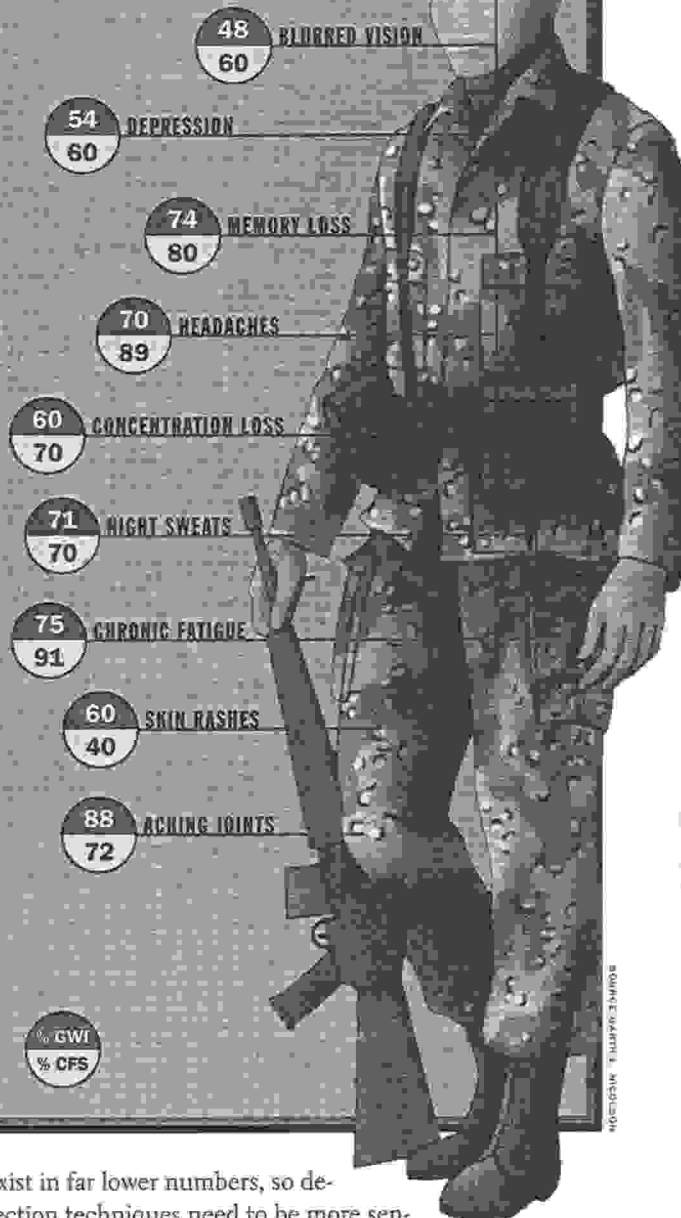
"The issue here is that many aspects of [Nicolson's] studies need to be confirmed," says Joel Baseman, chairman of microbiology at the University of Texas Health Science Center in San Antonio. Baseman has been studying the role of mycoplasmas in disease for almost 30 years. Mycoplasmas exist naturally in the serum—a component of blood—of horses and cows, and even in various parts of the human body. But scientists think most strains are innocuous. The *M. fermentans* strain also exists naturally in the mouth, for example. In fact, says Baseman, one of the fundamental flaws in Nicolson's research is that he hasn't done large-scale studies examining how much of the civilian population might be carrying *M. fermentans*. "We need some major number crunching that says the strain exists in X percent of the healthy civilian population, and in Gulf War veterans it is X percent higher. That way, we could definitively say whether these people's symptoms are likely caused by the infection," Baseman adds.

One big obstacle to acceptance of Nicolson's theory has been the findings of Shyh-Ching Lo, of the Armed Forces Institute of Pathology in Washington, D.C. Lo, sometimes called "the father of *fermentans*," first isolated the strain from AIDS patients in the late '80s and argued that mycoplasma infection might be the final blow that kills them. As far back as 1994, when Nicolson first went public with his theory, the Army asked Lo to confirm Nicolson's results by testing veterans' blood for *M. fermentans*. Lo's findings were all negative.

Nicolson has countered that his technique is more sensitive than Lo's. Lo tests for mycoplasma by looking for antibodies in blood serum. But Nicolson has reasoned that since mycoplasmas can hide inside cells, an accurate test must look for mycoplasma DNA inside a patient's white blood cells—something he says his technique does. Nicolson also argues that the immune systems of AIDS patients are so weakened that infectious organisms can readily proliferate, making them easier to detect. In other patients who are otherwise healthy, mycoplasmas might

## What Ails Them?

AS MANY AS 100,000 veterans experience ailments that range from minor headaches to debilitating joint pain, called Gulf War Illness (GWI). Many symptoms match Chronic Fatigue Syndrome (CFS). Scientists are investigating if they're variations of the same illness.—G.S.



exist in far lower numbers, so detection techniques need to be more sensitive. And blood samples need to be handled very carefully.

"Perhaps Lo's lab handled the samples wrong," Nicolson speculates. "We know that mycoplasma-infected cells degrade rapidly, leaving nothing to detect if blood samples sit at room temperature for too long." Even Lo admits that in any scientific study, "a negative result doesn't really mean anything. The organism might still be there; the scientist

## HIV's Partner in Crime

LIKE MANY PERPETRATORS, HIV, the AIDS virus, is more successful when paired with a partner, research suggests. In a study of HIV-positive couples, Shyh-Ching Lo of the Armed Forces Institute of Pathology in Washington, D.C., and Donald Louria at St. Michael's Medical Center in Newark, New Jersey, found evidence indicating that HIV is more readily transmitted to people who are also infected with an obscure microorganism called *Mycoplasma genitalium*. The study examined the behaviors of heterosexual couples, in which one partner was HIV positive and the other HIV negative. Tracking the participants over the course of seven years, scientists compared the experiences of couples in which the second partner became positive with those of couples whose HIV status remained the same. The researchers concluded that an important factor determining whether a partner became HIV positive was co-infection with *M. genitalium*.


The idea that mycoplasmas might act as cofactors in AIDS patients goes back to the early 1980s, when Luc Montagnier—the French co-finder of the HIV virus—and Lo isolated mycoplasmas from HIV-positive patients. They argued that since some women are infected after only one sexual encounter, yet only 15 percent of women who are steady partners of HIV-infected men acquire the virus, cofactors must exist that increase viral transmission.

"We don't know the exact mechanism," says Lo, "but we know that mycoplasmas act as modulators of immune cells—they force them to divide. HIV more readily infects dividing cells, so mycoplasmas might be facilitating cellular infection."—G.S.

just wasn't able to find it." As for large-scale studies comparing the incidence of mycoplasmas in veterans with that of civilians, Nicolson scoffs: "I never had the funding."

The criticisms went back and forth for almost two years until Rep. Norm Dicks of Washington state, who learned about Nicolson in the press, organized a meeting with Nicolson, Baseman, Lo, and others in December 1996 to discuss the controversy. After this meeting, the Department of Defense eventually agreed to pay for Baseman, Lo, and several other scientists to spend three days in January 1998 at Nicolson's lab, learning his technique.

Now, as part of the clinical trial, Baseman, possibly Lo, and a few other scientists will use Nicolson's technique to look for mycoplasma infections in vets' blood and also retest their blood after one year of doxycycline treatment to measure the antibiotic's effectiveness. The trial is designed to prove whether or not *M. fermentans* is a cause of GWI, and if doxycycline is a viable treatment.



Magnified image of the hook-like organ that allows mycoplasma to latch onto cells.

## Most doctors who treat that the illness isn't

A tall order, says Baseman, considering the complex nature of mycoplasmas themselves. The more than 100 mycoplasma species are further broken down into strains. Pathogenic, or disease-causing, mycoplasmas often latch onto cells, then send signals ordering them to behave abnormally, distorting their shape or proliferating wildly, for example. Certain mycoplasma species can suppress the body's immune system while others act as cellular invaders and eventually kill their host cells.

In addition, *M. fermentans* has had a checkered history. That the species causes disease was first hinted in the '70s, when doctors found it in the joints of patients with rheumatoid arthritis. But subsequent studies were unable to reproduce the same results. Recently, however, Nicolson published a small study in which he detected various species of mycoplasma in 50 percent of rheumatoid-arthritis patients, as compared with only 10 percent of people who do not have the ailment.

Scientists have also found evidence of mycoplasma infections in patients with Chronic Fatigue Syndrome and Fibromyalgia Syndrome—diseases whose symptoms overlap with those of GWI. And Daryl See, while studying chronic fatigue at the University of California in Irvine, found various mycoplasma infections including *M. fermentans* in almost 60 percent of his patients. His results are not yet published.

Making things even more difficult, mycoplasmas don't grow very well in the lab. Only in the past 10 years, with the advent of sophisticated technology that enables scientists to examine the organisms' DNA, have researchers been able to look at them more closely. They've found that certain antibiotics, like penicillin, don't work because they either can't penetrate the organisms' cells or don't do so at high enough concentrations. But doxycycline, minocycline, and a few other types of antibiotics can. And when those drugs get inside, they are only able to weaken mycoplasma metabolism, leaving it up to the body's immune system to eventually kill the infection. So if the immune system is deficient, a person can relapse when he stops taking antibiotics; to maintain immune strength, Nicolson advises doctors to tell their GWI patients to follow an immune-boosting dietary and vitamin regimen.

While scientists now have a clearer picture of how mycoplasmas behave, they still don't really understand how they make people sick. "You and I could carry *fermentans* and be healthy, but your sibling could carry it and be sick

# GWI have come to admit purely psychological.

from it," explains Baseman. "Why? A lot of reasons, nutritional, immunologic, genetic." Scientists haven't pinned down an exact mechanism; right now, they merely have hypotheses. They agree that most mycoplasma species cause disease by working in concert with other factors. In GWI, for example, Nicolson proposes that veterans might have come into contact with some environmental factor—say chemical weapons, stress, radiation, or another illness—that knocked out their immune systems and allowed mycoplasmas to take hold. Or conversely, mycoplasma infection might have rendered veterans more sensitive to environmental factors that themselves may ultimately be causing their ailments. And since genetics plays a role in dictating how a person responds to an infection, some people can fight off mycoplasma infections easily, while others are easy prey. Scientists give a similar explanation for how mycoplasmas might cause illness in civilians diagnosed with such illnesses as chronic fatigue.

Another theory posits that mycoplasmas might be working in concert with another undetected organism. In fact, this

is the explanation Nicolson gives for sick veterans who test negative for mycoplasma: They might be infected with something that no one has yet looked for or has never been identified. Co-infections with mycoplasma then might make a patient's condition worse. "It's not totally out there that mycoplasmas are in some way causing these types of illnesses, but it's [an idea that's] still looking for credibility," says Baseman. "People working on this have split into camps. Garth Nicolson and Daryl See are on one side, Lo is over somewhere else, and I'd like to think that I'm just floating in no-man's land waiting to do the science that will allow me to say, 'Yeah, Garth, you're right' or 'This is a red herring,'" Baseman adds. "But if Garth's right, it would be a breakthrough for millions of people suffering from chronic, persistent illness."

While scientists work on the clinical trial that will provide the necessary answers to Baseman's questions, the government has seemed to favor a wait-and-see approach. Even though officials have since released more information about the vets' experience in the Gulf, the issue of whether their symptoms constitute a real physical syndrome is still highly controversial. In 1996, for example, the Department of Defense (DOD) admitted that as many as 100,000 troops might have been exposed to chemical weapons when Iraqi chemical weapons bunkers were blown up. But DOD still contends that, based on its studies, no statistical evidence suggests that Gulf War vets experience unique symptoms that might be related to these exposures, nor are they sicker than the general population. Stoking the fire, a recent study published in the *American Journal of Epidemiology* found flaws in the government studies.

Based on similar statistical data, the DOD also still denies that veterans' family members have contracted GWI. This is despite a 1994 U.S. Senate Committee Survey on 1,200 veterans that found 77 percent of spouses and 65 percent of their children born after the war experience symptoms of GWI.

"What I would like most," Nicolson says, "is for the U.S. government to finally acknowledge the sacrifices that Gulf War illness families have made. I have seen too many families broken and destroyed because it was not acknowledged that they were suffering and that they need help. We've never had a support system to handle this."

So what's next for Nicolson? Today, he heads the Institute for Molecular Medicine, housed in an austere two-story building in Huntington Beach, California. With a small staff, he develops and administers diagnostic tests for chronic illnesses. He still conducts cancer research using leftover grant money, and hopes that the Veterans Affairs-funded clinical trial will finally bring vindication for him and others who have supported his research on mycoplasmas. Sharon, now completely recovered and a third-year medical student, hopes that as a doctor, she can help people overcome their own illnesses. ♦



## Gulf War Illness: Psychological?

IT'S WELL-KNOWN that stress causes physical illness; but how about Gulf War Illness (GWI)? To find out, the Veterans Administration and the Department of Defense have earmarked almost \$10 million to investigate the effectiveness of exercise and psychotherapy in alleviating symptoms.

"We try to help patients understand that their symptoms drive a certain course that can make their condition worse," says Charles Engel, who heads the Gulf War Health Center in Washington, D.C., and will help conduct part of the trial. Many sick vets come to the health center after having been given the wrong advice from a physician, says Engel. "To alleviate back pain a doctor might say, 'Don't lift, lay down, take muscle relaxants.' But that results in muscle and bone loss. What's more, for many vets, the very idea of Gulf War Illness causes stress that can lead to physical symptoms." Non-pharmacologic treatment has helped in some cases, and part of the trial will attempt to quantify the treatment's success.—G.S.