

## *Making Lyme Disease Testing and Treatment Less Controversial*

**Rheumatologist Arthur Weinstein, M.D., has two NIH grants to research why some patients continue to suffer even after treatment with antibiotics.**

While some doctors attribute the discontent to depression, Arthur Weinstein, M.D., takes his patients seriously when they complain about aches and pains, fatigue and difficulty in concentrating after a bout with Lyme disease--even if they were initially treated with antibiotics. Apparently, so does the National Institutes of Health (NIH), which has awarded Dr. Weinstein, professor of medicine and chief of the Division of Rheumatic Diseases and Immunology, two major grants to study *why* people continue to suffer and *how* they can finally be cured of the tick-borne infection. The research may go a long way toward assuaging Lyme disease support groups, which continue to press for a longer course of drug therapy, earlier accurate testing and further research into treating what has become a significant health problem for residents of Westchester and Fairfield (Conn.) counties and Long Island communities.



**Arthur Weinstein, M.D.**, checks out Andra Sramek, who volunteered for a research study in the Division of Rheumatic Diseases and Immunology. Taking notes is Sara Guardino, research assistant.

### **From lupus to Lyme**

This year, Dr. Weinstein is working with more than half a million dollars in grants from the NIH, pharmaceutical companies and private foundations on research that includes systemic lupus, rheumatoid arthritis and scleroderma. But the bulk of the funds belong to chronic Lyme disease, which was not his interest when he joined New York Medical College from the University of Connecticut School of Medicine in 1985; lupus was. Still, Dr. Weinstein became intimately involved in the evolution of Lyme here as his experience with the disease went from nothing to plenty, and fast.

"The College has recognized that Lyme disease is a major clinical and research interest on this campus. The main players in the development of the program were Fish, Wormser and Connolly, Dr. Weinstein advises. The entrepreneurial trio are Durland Fish, Ph.D., former director of the College's Lyme Disease Center and now a research scientist at Yale; Gary P. Wormser, M.D., still professor of medicine and

pharmacology and chief of the Division of Infectious Diseases at the College; and John J. Connolly, Ed. D., former College president and current chairman of the board of the American Lyme Disease Foundation, Inc., which had its genesis on the Valhalla campus in 1990.

### **A golden opportunity**

"When I came here, Lyme tests were being sent to Albany and it took four to six weeks to get results," Dr. Weinstein recalls. "I set up a lab to do testing because I saw the need--to have testing done reliably on this campus. There was an educational need, too, for rheumatology residents to see how the tests were performed and interpreted. And it was also important for my clinical research to have serums frozen away...For 10 years, our lab did all the Lyme testing for faculty practice. Now Lyme tests are also being done by other labs on campus."

(Besides Lyme testing, the lab in Munger Pavilion--co-designated the Lyme Disease Research Laboratory and the Diagnostic Immunology Laboratory and owned by the Department of Medicine--also screens for lupus and connective tissue disorders such as scleroderma and vasculitis.)

Over the years, testing for Lyme has become controversial, which disturbs Dr. Weinstein. Since he was a member of the committee that developed the standards for Lyme testing--now referred to as the Dearborn criteria and used throughout the nation--he is especially perturbed when the tests are maligned as unreliable. "What is unreliable is the interpretation of results by doctors and patients," he claims. "A patient can have nine negative tests and then one positive one and the diagnosis is mistakenly confirmed...The best test would be to culture the bug, like you do for a urinary infection. But the Lyme bug is slow growing and you have to decide whether to treat or not before the culture is finished. Besides, the lab test to grow the bug is not very sensitive and too many patients have negative cultures of the skin or blood for it to be a routine test."

### **Perfection denied**

It is true that in early acute Lyme disease, an antibody test may be of little value because it will read negative for the first several weeks and, in fact, may never be positive. But overall, 70 to 80 percent will have a positive test one to two months after being infected, says Dr. Weinstein, and in late Lyme arthritis, the test is virtually always positive months after the infection.

"A test usually isn't all or nothing. It is just a statistical probability of something," he insists. "A test is always evaluated as a range of normal, which includes 95 percent of people in that range. So at anytime, 5 percent can be outside the range, but not far outside, and still be normal."

Essentially a two-tier system, the Lyme tests comprise a screening analysis called ELISA, followed by the Western blot which is considered more reliable. In the ELISA test, an "alphabet soup" of proteins of the Lyme disease bug, *Borrelia burgdorferi*, is placed on a plastic plate with wells and a patient's serum is added. If the patient has antibodies to Lyme they will stick to the bug's proteins.

## Just say Lyme

But there are more than 100 proteins in the mixture, so the test can be positive even when Lyme is not present. So diagnosis is confirmed by Western blot, where the proteins are separated out by electric current so that you can determine if the antibodies react with proteins specific to *Borrelia*. They can be read visually or interpreted by computer through a program that Dr. Weinstein developed with the help of a graduate student. Dr. Weinstein mentions that Western blot is not used right off the bat because, among other reasons, it is too labor intensive and expensive, as opposed to the ELISA, which is automated.

After he established the Lyme Disease Research Laboratory, Dr. Weinstein found himself increasingly drawn to Lyme despite its status as an infectious disease. As a rheumatologist, he found the complaints of lingering aches and pains too seductive to disregard. "Rheumatology is the subspecialty of internal medicine that deals with the diagnosis and treatment of joints, muscle and bone disorders," he imparts. "If your family physician can't figure out the cause of your pain, you need to go to a rheumatologist."

## Other specialties involved

As the Lyme disease program expanded to encompass other clinicians and basic scientists on campus, Dr. Weinstein found the time right in 1994 to apply to the NIH for a grant to study the "Pathogenesis of Lyme Induced Fibromyalgia." The first major funded study of Lyme's chronic rheumatic symptoms, the research utilized SPECT brain scans and other neurologic tests to detect abnormal blood flow. Psychiatrists performed psychological and neurocognitive examinations while biochemistry and molecular biologists used DNA probes to study whether there were active infections. And his own rheumatology department examined samples of blood and spinal fluid to measure for quantities of specific Lyme antibodies that came from the patients enrolled in the study. Analysis of the data began last spring.

In an effort to spread credit around among his collaborators, Dr. Weinstein says, "These years have been a very academically productive time for me, and I'm appreciative of my colleagues in the clinical and basic sciences and those in the school administration who have helped me. Working in Munger Pavilion, which geographically is midway between the Basic Sciences Building and Westchester County Medical Center, is also a symbolic link between basic science and clinical activities."



**Arthur Weinstein, M.D.**, director of the Diagnostic Immunology Laboratory, began testing for Lyme disease in 1985. He is evaluating an ELISA test, which is confirmed by Western blot analysis, with, from left, **DeLona Norton**, laboratory supervisor, and **Lois Zentmaier**, laboratory technician.

## Second post-Lyme study

While his fibromyalgia study was proceeding, Dr. Weinstein was awarded another NIH grant in conjunction with New England Medical Center/Tufts University School of Medicine in Boston. The new five-year study into the cause and treatment of post-Lyme disease syndrome, awarded in 1996, has been delayed in getting started because of "legal complications from a competing institution that wanted to wrest the grant from us," Dr. Weinstein advises. Now back on track, he started screening in June for volunteers similar to those in the fibromyalgia study. Subjects must be able to document having had Lyme disease and submit to a current spinal tap to ensure they do not have active infection in the brain. "Some people in the study will get a placebo, but if they actually have proven active Lyme, they should be treated," Dr. Weinstein explains.

"This is a double-blind, placebo-controlled study. Treatment will be for three months," he continues, "which is longer than usual. During the first month subjects will be prescribed intravenous ceftriaxone, followed by two months of oral doxycycline...So these patients will get both drugs or nothing."

## Lots of questions

The purpose of the research is to determine whether this treatment regimen results in long-lasting improvement in patients with these chronic symptoms. "Lyme patients claim to feel better on antibiotics and relapse when they stop," says Dr. Weinstein, "but this is not typical in treating other infections. Does it mean we are not really treating an infection in post-Lyme disease syndrome, and that they are getting better from a placebo effect? Or is there really an infection, but the bugs are hiding and not reached by antibiotics, only to start growing again when the antibiotics are stopped? Or, are the antibiotics working by some different mechanism unrelated to killing bugs--say, are they just having some chemical effect on the brain?..."

"I think this study will help to clarify which, if any, patients with chronic Lyme disease symptoms really have Lyme and should be treated with antibiotics long term. This result is a very important answer."

Considering his familiarity with the subject, is there a gut feeling about what he will find? In his best impartial viewpoint of a principal investigator, he replies, "I have no idea."



