Not So Fast: Research on Infectious Links to MS Questioned

Brian Vastag

WASHINGTON—Amid scattered reports of physicians prescribing antiviral and antibiotic medicines for patients with multiple sclerosis (MS)—both unproven against the disease—research into infectious triggers for MS is generating controversy over two pathogenic suspects, one a virus, the other a bacterium.

In 1998, separate teams of researchers announced that they had found higher-than-expected amounts of human herpesvirus 6 (HHV-6) and *Chlamydia pneumoniae* in the central nervous systems of MS patients, findings that have been roundly debated. And while the two organisms appear in different chapters of the microbiological textbook, their paths through the scientific wringer have been similar.

The advocates present compelling cases and confirmatory data; the skeptics find flaws and fail to replicate findings. Like a boxing match, each round of journal reports and letters tilts the balance, only to be knocked back by the next month's offerings. The instigating scientists—a team at Vanderbilt University seeking *C pneumoniae* and a group in Wisconsin chasing HHV-6—stand behind their discoveries, and both are hard on the trail of buttressing evidence from clinical trials.While the dizzying debate leaves observers puzzled, it all sounds very familiar to veteran MS researchers, who have sought an infectious origin of the disease for more than a century. Rabies, rubella, measles, influenza, and "almost the full gamut of viruses associated with neurological diseases" have been implicated in MS, writes Richard T. Johnson, MD, the Johns Hopkins University researcher who helped found the field of neurovirology. Dismissed like stooges in a police station lineup, no suspect remains standing after the withering scrutiny of science. And while trendier pathogens have supplanted the old-time bad guys, the story may well repeat itself.

A SPINAL TAP AND QUESTIONS

Vanderbilt University neurologist Subramianiam Sriram, MD, is eager to talk about his research. Three years ago he published the case study of a 24-year-old man newly diagnosed with MS (*Neurology*. 1998;50:571-573). After 6 months of worsening symptoms, a spinal fluid sample offered something unexpected: positive cultures for *C pneumoniae*. Polymerase chain reaction (PCR) tests confirmed the presence of the bacteria's DNA in cerebrospinal fluid and blood. A cause of respiratory infections, *C pneumoniae* had received extra attention for newly reported possible links to heart disease. But until Sriram's finding, no one was seriously pursuing the pathogen in MS.

Following up with a series of patients, a 1999 article from Sriram and colleagues (*Ann Neurol*. 1999;46:6-14) reported positive cerebrospinal fluid cultures in 64% of patients with MS but in only 11% of control patients. Genetic profiling via PCR picked up even more *C pneumoniae*, in 97% of patients with MS vs 18% in controls.

An editorial accompanying the report, from Donald Gilden, MD, at the University of Colorado Health Sciences Center, Denver, said that "if Sriram and colleagues are correct, other laboratories with access to MS material should have no trouble amplifying *C pneumoniae* DNA" from brain tissue and spinal fluid.

But there's been nothing but trouble. An onslaught of work from investigators studying *Chlamydia* has failed to reproduce the Vanderbilt team's results, engendering a debate over methods and qualifications.

Chief among the critics, Margaret Hammerschlag, PhD, a microbiologist at the State University of New York at Brooklyn who has worked with *Chlamydia* organisms for 25 years, says that the Vanderbilt work "has serious problems." In a recent report, her laboratory and that of Jens Boman, PhD, at Umeå University, Sweden, did not find any *C pneumoniae* in blinded samples of brain tissue from 12 MS patients and seven controls.

Sriram responded by saying, "The fact that they can't find it in the brain is not surprising at all" because of difficulties his group had finding *C pneumoniae* after injecting it into the brains of mice. "We know we put the bug there," he said. "But we're having difficulty finding out exactly what the conditions are to extract it from brain tissue. I don't know why."

To help settle the dispute, Sriram agreed to participate in a blinded study with three other teams. All received spinal fluid from patients with MS and controls, sent by Michael Kaufman, MD, of the MS Center of the Carolinas Medical Center in Charlotte, NC. The results, presented at the 2000 meeting of the American Neurology Association, further isolate the Vanderbilt team, who found *C pneumoniae* DNA in 22 (73%) of 30 MS cases and in 5 (23%) of 22 controls. The other teams, at Johns Hopkins, the Centers for Disease Control and

Prevention, and Umeå University, detected no traces of the organism.

Hammerschlag said the mass of evidence points to contamination or a lack of experience with delicate screening tests on the part of Sriram and his colleagues. "All of his work is being published in neurology journals, and they just kind of accept the methods. None of it would get published in microbiology journals," she said.

NO BIAS

But Sriram countered that if contamination were the issue, *C pneumoniae* would appear in a higher proportion of his laboratory's control samples. He points to the multilaboratory study as vindication of his group's ability to amplify small amounts of DNA from *C pneumoniae*. "All of us were blinded, there was no bias," he said, adding that his "simplistic explanation" for the discrepancy is "technical differences," specifically in sample preparation.

Kaufman said that the Vanderbilt team does use a different PCR method than the other labs. In fact, no standard test for *C pneumoniae* exists, a situation Hammerschlag calls "infuriating." But she hopes that a forthcoming standard, developed by a panel of *Chlamydia* experts and set for publication later this year, will provide the right tools to settle the matter.

In the meantime, heavyweights in MS research are lining up against *C pneumoniae*. Hopkins' Johnson, editor of the *Annals of Neurology*, called the association between the bacterium and MS "weak." Stephen Reingold, PhD, vice president for research at the National Multiple Sclerosis Society (NMSS), said, "The bulk of the papers are against *C pneumoniae* right now. And Sriram is kind of sitting there with a fortress mentality, which is not helpful." Reingold added that the NMSS, in the interest of finding an answer, funds research at Vanderbilt as well as at facilities that have not found *C pneumoniae*. "This will all work itself out in the scientific process," he said.

The scientific process has already worked out a great deal about MS. Because the disease is directly caused by the immune system attacking the nerves and brain tissue, a ream of circumstantial evidence points to an infectious connection. A famous incident in the Faroe Islands, where the rate of MS skyrocketed after British troops disembarked during World War II, is one of some 300 epidemiological and family linkage studies that suggest an infectious agent at work. Genetic predisposition plays a role, as confirmed by twin studies, and geneticists speculate that a few dozen genes are involved. But they note that environmental factors must weigh just as heavily.

Over his long career, Johnson has seen enough to say, "There's an environmental exposure that occurs early in life, but it's unknown." Several studies show that miscellaneous viral respiratory infections can exacerbate symptoms, and the immune systems of people with MS tend to overreact to all infections. But exactly how a virus or bacterium may trigger the disease is a mystery.

Molecular mimicry, one theory gaining momentum, holds that the immune system develops its appetite for the nervous system after fighting off an infection. Under this hypothesis, the part of the infectious agent recognized by immune cells is nearly the same shape as key proteins coating cells of the nervous system. Immune cells targeted to that shape proliferate to fight the infection. After the organism is defeated—perhaps even years later—the immune system attacks the nerve cells in a case of mistaken identity.

At a recent meeting of the NMSS in Washington, DC, Roland Martin, PhD, a researcher at the National Institute of Neurologic Disorders and Stroke (NINDS) and a leading proponent of molecular mimicry, said, "There is strong evidence that viruses can trigger the disease." He added, "But I'm convinced that in different patients it could be different viruses; there is no single virus responsible."

THE LATEST VIRUS

If true, Martin's assertion would not bode well for the work of Donald Carrigan, PhD, and Konstance Knox, PhD, who 4 years ago created the Institute for Viral Pathogenesis (IVP) in Milwaukee. Carrigan and Knox are working to prove that HHV-6 is not only associated with MS, but causes it. "I think that HHV-6 is necessary, but not sufficient, for multiple sclerosis," said Carrigan. According to this thinking, eliminating the virus would halt the disease.

The model Carrigan and Knox prefer holds that MS begins as an acute viral encephalitis caused directly by HHV-6. After a time, perhaps years, the body's immune system learns—through molecular mimicry—to attack the myelin sheath that coats nerves and other parts of the nervous system. Carrigan said that the hunt for a mechanism is turning up proteins from HHV-6 that resemble proteins on the myelin sheath.

Much of their work focuses on detecting HHV-6 in the blood and brains of patients with MS. Most recently, they found signs of "active infection" in the blood of 22 (54%) of 41 MS patients but none in 61 controls. They also reported finding HHV-6 in the nervous systems of 8 (73%) of 11 MS patients and in 2 (7%) of 28 controls (*Clin Infect Dis*. 2000;31:894-903). Other groups, most notably that of Hugh McFarland, PhD, at NINDS, have published work that at least partially supports IVP's findings (*J Infect Dis*. 2000;185:1321-1325).

But Knox and Carrigan have been the loudest proponents. They created a media buzz at the 1998 American Neurological Association meeting after presenting a study that found HHV-6 in the brain lesions of MS patients, and they continue to be regularly quoted in the lay press.

This outspokenness has some researchers on edge. "They are overinterpreting their data," said Reingold. "This is all association. It's interesting to know, but cause and effect is what matters."

Establishing cause and effect will be difficult. For one, HHV-6 is ubiquitous; that is, almost everyone is exposed to it as a child. (The virus sometimes causes roseola infantum, a condition with rashes and high fevers.) The virus then turns off, becoming la-

tent, leaving behind clues like antibodies and DNA. So finding HHV-6, by either blood studies or PCR, does not mean a person harbors an active infection. On top of that, people with MS tend to overreact to all pathogens, rendering the finding of higher-than-normal antibody levels in the blood dubious.

To get around the problem, Carrigan says the test he and Knox developed detects active infections in the blood and central nervous system. Several groups have published work that does not support IVP's theories—by finding DNA from HHV-6 in controls at the same rate as in MS patients, for example. Carrigan says those experiments fail to distinguish between active and latent infection.

But there are other critics. Johnson, for one, said that no one has proven HHV-6 is more than an innocent bystander, perhaps ferried to the damaged areas of the brain by immune system cells during or after the disease process.

TOWARD CLINICAL TRIALS

With a host of complicated immune reactions muddying the picture, many researchers say that proving any infectious connection with MS will be difficult, if not impossible. At a 1999 meeting on the origins of MS, held in Brighton, England, discussion turned to Koch's postulates—time-honored rules for establishing an infectious etiology. Much of the talk focused on whether the postulates apply to MS. "With respect to HHV-6 and *C pneumoniae*, there was a general sense that we would probably never be able to develop a causation," said Reingold.

Nevertheless, both IVP and Vanderbilt are plowing ahead with clinical trials. The Institute for Viral Pathogenesis had planned a trial with ganciclovir (Cytovene, Roche), a drug originally developed to treat cytomegalovirus, a close cousin to HHV-6. But the clinicians recruited for the study balked at ganciclovir's means of delivery—twice a day through a central line. Carrigan said the manufacturer had pledged enough drug for the study but that he and his colleagues are anticipating an oral version, currently wending its way through the FDA approval process.

While waiting, Carrigan says he gets several calls a week from neurologists wondering if they should prescribe antiviral drugs for their patients with MS. "If the patients really want to try an antiviral," Carrigan says, he suggests acyclovir (Zovirax, Glaxo Wellcome). One of Carrigan's collaborators, Joseph Brewer, MD, at St Luke's Hospital in Kansas City, said he has treated 10 patients with acyclovir, despite data questioning its effectiveness against HHV-6, a problem that Carrigan admits.

The practice is drawing fire. In an open letter to patients, John Fleming, MD, director of the MS clinic at the University of Wisconsin, wrote, "I think that it is premature to be taking antiviral drugs; at current doses, these may not go to the brain effectively, and long-term use may cause significant side effects." David Irani, MD, a Johns Hopkins researcher who develops viral models of MS, said he regularly encounters patients taking antivirals. "It's not being done in a rigorous manner, it's sort of off the cuff. And that makes it hard to know; it doesn't allow you to understand why or what's going on."

Reingold sees another problem. "Some people would like to think that a specific virus is responsible for the disease. But the more general view is that there is an immune reactivity problem. It's how a person's genetically predisposed immune system responded to infection a long time ago that triggers the disease. And if that's the case, then treating an adult with an antiviral medication won't do much good."

Meanwhile, the Vanderbilt team has begun a phase 2 trial of 40 patients, using the antibiotics rifampin and erythromycin. Supported by the NMSS, the study will use magnetic resonance imaging scans to image the size and location of brain lesions, tracking how they respond to the drugs. But because MS tends to progress and regress spontaneously, the brain lesions waxing and waning on their own, sorting out the drug's effects from background noise may be tricky. In addition, critics like Hammerschlag say that the two drugs under study may not kill *C pneumoniae* or effectively cross the blood-brain barrier.

But until scientists' understanding of autoimmunity deepens, clinical research trials of drug treatments may be the best approach. Johnson summarizes the situation this way: "With such a complex web of cause and effect, you almost get down to the point where you say, if I give patients antibiotics and they get well, that's pretty good evidence. That's a throwback, a primitive way we used to do things." For the moment, though, it may be the only way. □

Some Radiologists Want More Money Up Front

Mike Mitka

CHICAGO—Radiologists warn of a growing paradox that potentially threatens women's health.

These physicians claim they are not being reimbursed adequately for mammography. The paradox is that record numbers of women are being screened for breast cancer, so the more patients that are tested, the more money clinicians lose. This predicament could wind up driving physicians away from the subspecialty, meaning women may one day find that they can't get mammograms locally or may face intolerably long waiting lists. Both of these scenarios could make it easier for them to skip the examination and possibly miss detection of breast cancer at an early, treatable stage. About 180 000 US women died from breast cancer in 2000.

The warning was issued by an expert panel convened here during the an-

nual meeting of the Radiological Society of North America (RSNA). Ellen Mendelson, MD, director of the Breast Diagnostic Imaging Center at Western Pennsylvania Hospital in Pittsburgh, said the situation "is not a crisis yet, but it's becoming one."

"Ironically, success in educating the patient and physician may compromise the procedure," said Mendelson, who was joined by four colleagues on the panel who agreed with her. "Higher volume accentuates the problem. The more you use, the more you lose. Ultimately we can't offer services that don't pay for themselves."

NEGATIVE EFFECTS GROWING

Stephen Feig, MD, another panel member, director of breast imaging at Mount Sinai Medical Center in New York City and president of the Society of Breast Imaging, noted that the number of mammographies, the performance of which can reduce breast cancer deaths by up to 40%, has doubled in the past 10 years. Today more than 60% of US women over age 40 have had a mammogram in the past 2 years.

However, the low reimbursement rates are affecting the recruitment of radiologists who specialize in mammography. Panel members recounted anecdotes about positions not being filled or fellowship applications for breast imaging plummeting.

In an interview after the RSNA meeting, Harvey L. Neiman, MD, chair of the Board of Chancellors of the American College of Radiology (ACR), said the economics surrounding the issue are having an effect and are creating longer waiting times for women to be screened.

"Centers are tending to decrease the slots available for screening mammography, or not increasing the number of slots for the increasing demand," Neiman said. "ACR is worried that a significant access problem may be looming."

The Medicare reimbursement in 2000 for screening mammograms was $67.81. Congress approved increasing the rate, beginning January 1, 2001, to $69.23, with 32% apportioned to the professional component and 68% to the technical. This rate serves as the benchmark for most insurers when reimbursing for mammograms performed on women not using Medicare. In a letter written by the California Radiological Society early last year, private insurance reimbursement rates published ranged from $62.10 to $86.18 (available at http://www.calrad.org/bdgltr.html).

Neiman said the small increase by Congress doesn't cover the growing additional costs—especially those mandated by the government through the Mammography Quality Standards Act—affecting screening. For example, the fee a facility must pay the US Food and Drug Administration for an annual inspection is $1549 for the first mammography unit and $204 for each additional machine. Follow-up inspections, if needed to ensure that problems found on a first inspection are fixed, are $878.

"These quality assurance requirements are estimated to run about $8 a case, and these costs are escalating because of increased mandated requirements," Neiman said. "Assuring quality is fine, but when the government mandates a layer of quality to the program, it adds a cost, and we're not getting reimbursed for this."

Robert Smith, PhD, director of cancer screening for the American Cancer Society (ACS) in Atlanta, said in an interview that these factors are turning physicians away from mammography screening.

"This environment is leading to a decline in the number of recent graduates who want to specialize in mammography," Smith said. "Residents applying for positions now ask if they have to read mammograms, and if so, how many." Smith said many radiology residents are drawn to other areas of the specialty that use more cutting-edge technology or pay much better.

IS THE "CRISIS" REAL?

A skeptic regarding the laments of the radiologists is Charles M. Cutler, MD, chief medical officer of the American Association of Health Plans, the health maintenance organization trade group.

"The only looming crisis in mammography that I've read about is in the press," Cutler said. "When I talk with health plans about access to mammograms, none have reported problems for their members. And the statistics show, if anything, the number of women having timely mammograms is increasing."

Cutler said he is confident that if reimbursement rates are wrong, the marketplace will correct them.

"Health plans want to provide easy access to high-quality services, and health plans negotiate with physicians for that," Cutler said. "Changes in the health care market drive health care costs."

HOW MUCH IS ENOUGH?

So if the RSNA's expert panel believes a crisis looms, what is the correct price for mammography that will draw radiologists to the field? No one on the panel could offer a firm figure or percentage increase.

Josh Cooper, the ACR's director of congressional relations, said the group is surveying members to find that number and present it to Congress in the next few months in hopes of getting a higher Medicare reimbursement rate for mammography.

The ACS's Smith said payers and physicians both need to play a part in creating a high-quality, reasonably priced breast cancer screening program.

"It is fair and reasonable for payers to expect that screening will be organized efficiently because the costs are immense," Smith said. "But the reimbursement level needs to be an amount that makes mammography attractive as a specialty. It is unreasonable to hold mammography to a different standard of reimbursement, and that doesn't draw professionals to do it."

Smith is frustrated that a powerful tool to fight breast cancer could be compromised just at a time when its acceptance is growing.

"Mammography has accomplished so much, and it's difficult to do—it's not rocket science, but it's not for amateurs, either," he said. "It needs to be shown more respect." □

UN Touts World Health Success Stories

Brian Vastag

WASHINGTON—In an effort to combat the perception that developing world health problems are incurable, the United Nations (UN) in December released a report detailing 20 infectious disease and reproductive health success stories from around the globe.

The stories are "evidence that this vicious cycle of poverty and ill-health can be broken, even in some of the world's poorest countries," writes Carol Bellamy, JD, executive director of the United Nations Childrens Fund (UNICEF), in her introduction to *Health, A Key to Prosperity*. UNICEF is one of six UN agencies, including the World Health Organization (WHO), the World Bank, the Joint United Nations Programme on HIV/AIDS, the United Nations Educational, Scientific, and Cultural Organization, and the UN Population Fund, that coauthored the report.

With a focus on making available simple tools to fight disease—such as bednets to prevent malaria, antibiotics for pneumonia, and oral rehydration therapy for diarrhea—the report calls for increased political commitment and more international cooperation from the pharmaceutical industry and nonprofit organizations.

The report also notes that improving world health is in everybody's best interest. "Our nation's peace and prosperity is firmly linked to that of the rest of the world," said Jordan Kassalow, a senior fellow at the Council on Foreign Relations, one of three partner organizations invited to a press conference where the report was introduced. Speakers from the Pharmaceutical Research and Manufacturers of America, an industry lobbying group, and Results, a nonprofit antipoverty organization, also took the podium.

Many of the success stories document the potency of political commitment. In 1990, a new Peruvian government recognized tuberculosis (TB) as a major health problem, with only half of infected people in the country receiving treatment. With help from the UN, the government upped its TB budget from $660 000 per year to $5 million per year. By 1998, Peru had reached its goal by detecting 94% of new cases and curing 90%. Consequently, the incidence rate for the disease has dropped by nearly half, from 220 cases per 100 000 in 1992 to less than 120 cases per 100 000 in 1999.

The world's two most populous countries, China and India, also report progress against TB. In China, the WHO-recommended treatment, called DOTS (for directly observed therapy–short-course), has cured a half million cases over the past 8 years. Driven by a $58-million World Bank loan, the country established a program of free TB care in 1992 that now covers 700 million Chinese. In India, which accounts for 30% of the world's TB burden, some 250 million people are covered by DOTS.

Other successes include local production of insecticide-treated bednets and antimalarial drugs in Vietnam that slashed the death toll from the disease by 97%; a 60% reduction in childhood deaths from diarrhea in Mexico; and a measles immunization campaign in Malawi that reduced new cases and deaths to almost zero.

While obviously proud of successes like these, the UN representatives warned that the biggest challenge is in scaling them up to reach other blighted corners of the world. "These success stories are not magical, they are practical," said Chris Lovelace, director of the World Bank's health, nutrition, and population group. That means more funds will be needed: the UN estimates an additional $5 billion is needed over the next several years to reach worldwide health goals.

The United States lags behind the rest of the world in foreign aid, donating just 0.1% of its gross domestic product (GDP), as opposed to Denmark's world-leading aid rate of 1.0% of GDP.

The report is available online at http://www.who.int/inf-new/. □

MISCELLANEA MEDICA

• **Larry J. Goodman,** MD, has been appointed dean of Rush Medical College at Rush-Presbyterian-St Luke's Medical Center, Chicago, Ill. He succeeds Erich Brueschke, MD, now Rush's vice president for university affairs.

• **Randi Hagerman,** MD, has become the first director of the M.I.N.D. (Medical Investigation of Neurodevelopmental Disorders) Institute at the University of California, Davis, School of Medicine. She has been at the University of Colorado School of Medicine, where the focus of her research was fragile X syndrome. Also at UC Davis, **Reginald Low,** MD, has joined the faculty as chief of the Division of Cardiovascular Medicine.

• **Marcel E. Salive,** MD, MPH, a preventive medicine researcher in the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Md, has received the Surgeon General's Exemplary Service Medal for 10 years of outstanding leadership and representation as the US Public Health Service delegate to the American Medical Association's Young Physician Section.

• **Ronald R. Blanck,** DO, president of the University of North Texas Health Science Center at Fort Worth, has been appointed to the board of regents of the Potomac Institute for Policy Studies.

Editor's Note: Miscellanea Medica appears in the Medical News & Perspectives section occasionally. Items submitted for consideration should be directed to the attention of Marsha F. Goldsmith, Editor, Medical News & Perspectives.