Does a Retrovirus Explain Fatigue Syndrome Puzzle?

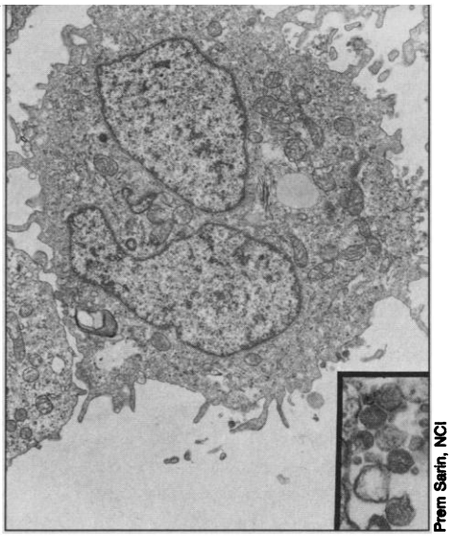
Provocative findings about a retroviral association with chronic fatigue syndrome made headlines, but scientists are skeptical

TEN DAYS AGO when Elaine DeFreitas of the Wistar Institute in Philadelphia presented some preliminary findings at a relatively obscure meeting in Kyoto, Japan, the news media pounced. Headlines appeared in almost every major newspaper in the United States. The reason? Her findings offered a possible cause for the still unexplained chronic fatigue syndrome (CFS). And the putative agent was HTLV-II, a human retrovirus—the same general category that includes the AIDS virus.

It now seems clear that the media's enthusiasm was, at the very least, premature. Even DeFreitas doesn't claim to have pinned down HTLV-II as the cause of the puzzling syndrome. And among other virologists, her team's findings are meeting a markedly cool reception, both because they are so sketchy and because several other viruses have been proposed as the cause of CFS only to fall by the wayside under closer scrutiny.

DeFreitas collaborated with two private clinicians who have dealt extensively with patients suffering from the syndrome: Paul Cheney of Charlotte, North Carolina, and David Bell of Lyndonville, New York. Cheney was one of the first to identify CFS in a 1984 outbreak around Lake Tahoe (see *Science*, 31 October 1986, p. 541). Bell recently identified a cluster of CFS in pediatric patients in a single town in New York.

According to a definition developed by the Centers for Disease Control (CDC), CFS is characterized by at least 6 months of debilitating fatigue that reduces normal activities more than 50%. In addition, a patient must be shown to be free of any preexisting organic or psychiatric disease and exhibit most of the following symptoms: headache, fever, sore throat, muscle aches, joint pain, generalized muscle weakness, lymph node pain, prolonged fatigue following exercise, and sleep alterations. All of the patients in the study (12 adults and 19 children) met the CDC criteria.



Prem Sarin, NCI

Viral invader. *Electron micrograph of HTLV-II, a human retrovirus.*

Using the polymerase chain reaction (PCR), which amplifies rare stretches of DNA, DeFreitas examined blood from both adult and pediatric cases. In 10 of 12 adult and 14 of 19 pediatric patients she found DNA sequences extremely similar to some in HTLV-II, a human retrovirus discovered by Robert C. Gallo of the National Cancer Institute. DeFreitas also used in situ hybridization to find DNA sequences complementary to viral messenger RNA probes in lymphocytes, the white blood cells infected

Chronic Fatigue as Chameleon

London—As scientists from the Wistar Institute were announcing that HTLV-II might be linked to chronic fatigue syndrome (CFS), the Royal Society was holding a meeting to discuss the attitudes of British doctors toward that puzzling syndrome. The meeting made clear how little consensus there is about CFS: whether it is psychological or physical, indeed whether it exists.

Most of the scientists agreed that, in today's world, fatigue is a problem. Survey evidence suggests that one in five men and one in three women "always feel tired," said Anthony Mann, an epidemiologist at the Institute of Psychiatry in South London. And among the rest of us there's continuum of symptoms: On a 10-point fatigue scale, Mann said, most people score 1 or 2, while a few go all the way to 10. But Mann argues that "there is no evidence of a discrete syndrome. Like 'high blood pressure,' CFS is just one end of a continuous distribution of fatigue."

Furthermore, in the vast majority of CFS cases there is a psychological component. About 75% of CFS sufferers are clinically depressed, according to Peter White, senior lecturer in the department of psychiatric medicine at St. Bartholomew's Hospital in London. White said he believes depression is often a cause, rather than a consequence, of CFS and in preliminary studies he has seen marked improvement in CFS patients treated with an anti-depressant. Yet the presence of psychological factors does not rule out a role for infectious agents. Many viruses, including Epstein-Barr virus (EBV), have been associated with the syndrome. "But stopping EBV doesn't stop CFS," said Les Borysiewicz, a clinical virologist at Addenbrookes Hospital in Cambridge. "Whatever causes CFS, it isn't the virus itself."

The failure to find a conclusive link between CFS and a particular virus leads some researchers here to think there is no one cause. As Linda Parsons, senior research fellow in neurovirology at St. Thomas's Hospital Medical School in London, put it: "EBV and cytomegalovirus can do it. Coxsackie can do it. Maybe there is a single final common pathway in the brain for all these viruses. If so, we should be able to treat CFS whatever the cause."

Until there is a final understanding of what CFS is, there will be tension between doctors and the self-help groups for CFS patients. For example, Richard Edwards, a physiologist and clinician at the Royal Hospital in Liverpool, prescribes for CFS patients a graded exercise program—and says he gets good results. The toughest part, Edwards says, is persuading patients to start: self-help organizations say they should avoid exercise.

What angers the self-help groups most is the notion that CFS is not a specific disease with a specific cause. Anthony Clare, psychiatrist and medical director of St. Patrick's Hospital in Dublin, pointed out that in medical history there have been many fatigue "diseases" with shifting causes: "Neurasthenia, focal sepsis . . . food allergies, now viruses. Some people would always rather have a disease that might kill them than a syndrome they have to live with." ■ JEREMY CHERFAS

by HTLV-II. By this technique, half the adult CFS patients appeared to have been infected by HTLV-II.

But DeFreitas faces an uphill battle to get others to accept the idea that HTLV-II in fact causes CFS. For one thing, the sequences she sees need not imply that CFS patients are infected with HTLV-II. The DNA she found might be cellular DNA homologous to a small portion of the HTLV-II genome. Even DeFreitas acknowledges that possibility, saying they could be part of a "viral-like cellular gene associated with this disease."

Other virologists have looked for retroviruses in CFS patients and failed to find them. Gallo looked at about a dozen CFS patients: "We didn't find anything relevant to HTLV in those patients." Garth Ehrlich, a virologist at the University of Pittsburgh used PCR to look for sequences from five retroviruses (HTLV-I, HTLV-II, HIV-1 , HIV-2, and bovine leukemia virus, a close relative of HTLV-1) in the blood of 20 patients. "We found absolutely no evidence of homologous sequences for these five viruses," says Ehrlich.

Compounding the skepticism is lingering doubt about some previous work from Wistar. Five years ago, Wistar scientists, including DeFreitas and institute director Hilary Koprowski, stirred the world of virology by proposing that HTLV-I, a virus closely related to HTLV-II, was associated with multiple sclerosis. At first, others seemed to confirm this result, but several recent studies have been negative. In a paper soon to appear in *Neurology*, a team led by Ehrlich reports that a carefully controlled study of more than 1000 patients did not support a role for HTLVs in multiple sclerosis. This follows other studies in *Science* (10 November 1989, p. 821) and more recently the *Journal of General Virology* [**71**, 1103 (1990)] that failed to find an association.

Perhaps the HTLVs are fated to join the ranks of the other (failed) viral candidates for the cause of CFS. Both Epstein-Barr virus (EBV) and human herpes virus–6 (HHV-6) have been proposed, and rejected, as possible causes of CFS. But some researchers say it isn't out of the question that all three viruses—HTLV-II, EBV, and HHV-6—could actually interact to produce CFS. Walter J. Gunn, principal investigator on a multicenter surveillance project on the syndrome led by the CDC, says there is some evidence that reactivation of latent infection with EBV, HHV-6, or cytomegalovirus could bring on CFS-type symptoms. Other preliminary evidence has shown there is immune suppression in the syndrome (in fact, some go so far as to insist it be called chronic fatigue immune dysfunction syndrome). And those clues could point to HTLV-II. "A retrovirus can have effects on the immune system, and possibly the immune system could be allowing the reactivation of these latent herpes viruses," says Gunn. "None of it's proven, but it is one model that we're thinking of."

Finding patients to test these hypotheses shouldn't pose a problem. According to Gunn, in the year the four CDC surveillance centers have been in operation nearly 400 patients have been referred to CDC by their physicians, and a significant number have met the CDC criteria. Gunn says CDC gets between 1000 and 2000 calls per month from people who think they have CFS.

Somewhere in that patient population lies the answer to what really causes CFS. The answer could even be HTLV-II. But the consensus in the community of virologists and epidemiologists is that we're not there yet. Says Gunn: "We're at the ground floor of this in many ways, and there's a lot to be learned." ■ **JOSEPH PALCA**

Laskers Back for 1991

Six months ago, to everyone's surprise, the Albert and Mary Lasker Foundation suspended its famous Lasker Awards in medicine and basic science. At the time, Mary Lasker's sister, Alice Fordyce, director of the awards program, simply said that the awards were taking a "sabbatical" while the foundation took stock of its activities and its limited resources (*Science*, 2 March 1990, p. 1026).

Now, Fordyce says, the Laskers are back by popular demand. "The unsolicited reaction of the international scientific community" was what made Mary Lasker and her board decide to reinstate the awards, which the foundation has long promoted as the American equivalent of the Nobel Prize. The next batch of Lasker Awards will be bestowed in 1991.

The golden Lasker. *Winged goddess Samothrace symbolizes victory over disease and death.*

The $15,000 Lasker prizes are presented at a glittering luncheon in New York at which celebrated heart surgeon Michael DeBakey takes the part played by the King of Sweden at the Nobel ceremonies. DeBakey has been chairman of the awards jury for more than a decade. In the 44 years that the Laskers have been handed out, 49 winners have subsequently received the Nobel.

Although the Lasker foundation is generally associated with wealth and high-society glamour, its assets, initially derived from Albert Lasker's succes in the advertising business, have shrunk to an estimated $2.4 million. For such a small foundation, the awards program is expensive, coming in at about $750,000 a year. However, in a world where publicity is often equated with influence, the press attention accorded the Lasker prizes is central to the foundation's mission which, Fordyce says, is a "unique contribution in encouraging public support of medical research."

Over the years, Mary Lasker herself—a friend of congressmen, presidents, and first ladies—has had a remarkable influence on the direction of research in this country. Lasker has been skilled at getting her friends on Capitol Hill to hold hearings and introduce legislation on issues she deems vital to health. And through her connections, numerous Lasker winners have testified at congressional hearings to back her causes.

Her personal conviction that cancer can be conquered drove the political machine that established the "War on Cancer" in 1971. A year later, that conviction was reflected in a Lasker Award that went to 14 pioneers in chemotherapy. And Lasker has been a political power behind the nation's crusade against hypertension, so impressed was she by the work that won cardiologist Edward D. Freis the 1971 prize for studies of drugs that lower blood pressure.

During the 1980s, the Laskers that have won most public attention were those in the basic sciences—DNA sequencing, neuroscience, and cellular development, for instance. The 1990s may see a renewed recognition of research with more immediate medical applications, suggests Deeda Blair, vice-president of the foundation. "It is easy to identify the men and women in basic science who are doing great work," she told *Science*, "but it is important that we get back to giving research in medicine due recognition, to highlight the human significance of work that is not necessarily molecular."

At 80 something (Lasker has always been reluctant to reveal her age) Mary Lasker's personal dominance of the nation's biomedical enterprise is fading. Thus, the foundation is counting on the prestige and visibility of its awards to bear the burden of its influence in medical affairs.

■ **BARBARA J. CULLITON**