Mystery Disease at Lake Tahoe Challenges Virologists and Clinicians

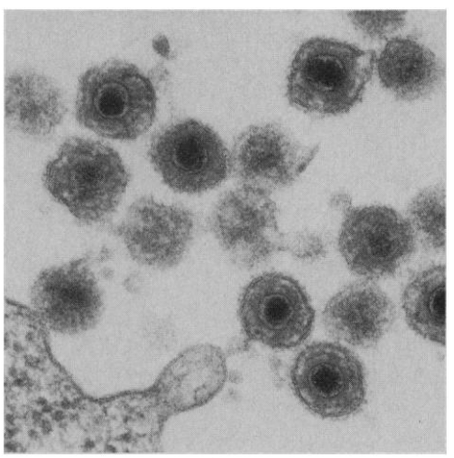
Outbreaks of a chronic mononucleosis-like syndrome, a disease that has yet to be well defined, are leading scientists to search for possible causes, which may include herpes-like viruses

It reads like a detective story. A mysterious illness breaks out in the Lake Tahoe area for no apparent reason. The first scientists on the scene link it to Epstein-Barr virus (EBV), which persistently infects more than 90% of American adults and sometimes causes mononucleosis. Although the symptoms of the Lake Tahoe patients are similar in some respects to those of mononucleosis, the mysterious disease differs in its long duration and clustered outbreaks. So what link—if any—does EBV have to the Lake Tahoe epidemic? Did something else trigger the disease?

The emerging answer is a likely yes, but it is still too early to know whether there are one or more causes of the disease and what those agents might be. Some researchers think that herpes-like viruses may trigger the chronic mononucleosis-like syndrome, one of which may be Epstein-Barr virus. Other researchers in Robert Gallo's laboratory at the National Cancer Institute (NCI) and their collaborators are investigating the possibility that a newly characterized virus, human B-lymphotropic virus (HBLV), reported in this issue on pages 596 and 601, may somehow be associated with the disease. It is even possible that a nonbiological agent triggers the disease. But because scientists are "still in the throes of data analysis and manuscript writing," as physician Paul Cheney of Incline Village, Nevada, puts it, they cannot yet be certain about what causes the chronic syndrome.

The search for possible causes of chronic mononucleosis-like syndrome is complicated by the fact that the disease is still not well defined clinically, nor has it been described in any major review. Its symptoms vary greatly, although the most striking are chronic severe fatigue lasting more than a year, and neurological problems. The syndrome may have existed for some time in isolated cases, but is now regarded as unusual because it occurs suddenly in clusters of people. Still, some researchers are not convinced that reports of the illness, from the Lake Tahoe area as well as from several other areas of the country, are even accounts of the same disease.

Between the fall of 1984 and the fall of 1985, Cheney and his clinical partner, Daniel Peterson, diagnosed 150 patients with chronic mononucleosis-like syndrome or chronic Epstein-Barr virus syndrome, as the Lake Tahoe disease was also called. About 70% had higher than normal antibody levels for Epstein-Barr virus, according to Cheney. But 5% had no detectable EBV antibodies and the remaining 25% had normal levels. Because almost all adults in the United States are infected with EBV, finding a large number of Lake Tahoe patients with antibodies to the virus was not very surprising.



Human B-lymphotropic virus particles erupting from a B cell in tissue culture. [*Courtesy of Zaki Salahuddin, National Cancer Institute*]

Last fall, at the urging of the Nevada clinicians, Gary Holmes and Jon Kaplan of the Centers for Disease Control (CDC) in Atlanta went to Lake Tahoe to investigate the strange disease. "As far as I'm concerned, EBV cannot be proven as the cause of the Lake Tahoe epidemic," says Holmes. "We ended up with 15 patients who met our case definition. It was difficult to determine which patients really had the syndrome because many of the symptoms are fairly common. And when we tried to identify a threshold antibody titer for Epstein-Barr virus, we couldn't do it. There was too much overlap between the case group and a control group."

In addition, the CDC investigators found elevated levels of antibody against several other viruses, including cytomegalovirus, herpes simplex types I and II, and even measles virus, making a specific disease link to EBV even more tenuous. But because they investigated the disease very early in the course of the outbreak, many patients had been ill for only a few months, which made it difficult to define the disease clinically and even more difficult to identify a cause.

Still, reports published early in 1985 by Stephen Strauss of the National Institute of Allergy and Infectious Diseases and James Jones of the National Jewish Hospital and Research Center in Denver gave credibility to the hypothesis that EBV was a probable culprit in the chronic mononucleosis-like syndrome. There are several reasons for this: EBV causes mononucleosis; many of the patients with the chronic mononucleosis-like syndrome have elevated antibody levels against EBV, particularly antibodies against so-called early antigens that may signal a new or recently activated EBV infection; and the modes of transmission of mononucleosis and the chronic syndrome are similar. But there is no general agreement that the chronic mononucleosis-like syndrome and chronic EBV syndrome are one and the same thing.

Jones now says, "I think that there is a specific syndrome and that EBV is one of the agents that can induce the syndrome." He also notes that many patients have symptoms of classical allergy, which may be a sign of immune system perturbation or may point to a genetic predisposition for the chronic mononucleosis-like syndrome. He also cites certain limitations of the CDC study and advocates a more thorough analysis of possible causal agents, including Epstein-Barr virus, in patients who have been ill for one or more years.

Meanwhile, Robert Gallo, Zaki Salahuddin, Dharam Ablashi, and Steven Josephs, of the National Cancer Institute (NCI) and their colleagues were working on another line of research. About a year ago they began to isolate virus from the blood of patients with different lymphocyte disorders

to see what might cause lymphoid tumors, which sometimes occur in patients with AIDS (acquired immune deficiency syndrome). The NCI group found that HBLV, rather than EBV, was a common viral denominator in six patients with disorders that affect B-cell production, two of whom were also infected with the AIDS virus.

"It's particularly impressive when a patient says, 'My life has changed. I caught what seemed to be a cold and have never recovered from it.'" Anthony Komaroff

The human B-lymphotropic virus that the NCI group now reports is a DNA virus that resembles EBV and other herpes-like viruses in its appearance, but differs in several respects. It has a specific affinity for freshly isolated B lymphocytes and "does not transform B cells as EBV does," says Salahuddin. "HBLV virus particles are dispersed throughout the Golgi bodies of an infected B cell rather than being clustered like cytomegalovirus, another member of the herpes family. And many mature healthy virus particles are produced from HBLV-infected cells, which is something you don't see with EBV." Does HBLV cause chronic mononucleosis-like syndrome? "It's being investigated," says Salahuddin.

In fact, the possible connection between HBLV and the chronic mononucleosis-like syndrome is being investigated to the extent that the NCI researchers are collaborating with Cheney and many other investigators—in Boston, New York, Houston, Fort Lauderdale, and Miami, for example—who report similar disease outbreaks. But before he identifies any link between HBLV and the chronic syndrome, Gallo wants to test sera from a large number of people who do not have the disease, to see how many of them might be infected with HBLV.

Anthony Komaroff of Brigham and Women's Hospital in Boston and a member of the collaborative network, points to several possible causes of the chronic syndrome he is studying in the New England area. "Is there a new variant of EBV?" he asks. "Is some other virus reactivating a latent EBV infection? Or might there be some other force, some environmental toxin, perhaps? This disease may have a number of causes, and even stress could be an activating factor." With respect to the possibility that HBLV may be linked to the chronic mononucleosis-like syndrome, Komaroff says that the data are too preliminary to interpret.

Komaroff indicates that many of the symptoms of the illness—chronic fatigue, headaches, recurrent sore throat, recurrent fevers, swollen lymph glands, inability to concentrate, some memory impairment, and sleep disorders—could occur with other kinds of infections. But he says, "it's particularly impressive when a patient says, 'My life has changed. I caught what seemed to be a cold and I have never recovered from it.' We've heard that over and over." The prognosis for patients with the chronic illness is still uncertain.

Another intriguing aspect of the chronic disease involves its neurological complications, which in many respects resemble those seen in some AIDS patients. Paul Levine of NCI recently interviewed more than 70 people from Nevada and California who complain of the chronic syndrome and was struck by the fact that many patients are now unable to perform mental tasks that were once routine for them. Perhaps different herpes-like viruses, including HBLV, act in concert to produce nervous system damage as well as B-lymphocyte abnormalities.

More women than men suffer from the chronic syndrome, which Cheney explains on the basis of more women holding jobs that put them in frequent contact with infectious agents. Some patients are completely debilitated by the disease and lose their jobs. Most go on with their lives, often at a reduced level of activity.

Chronic mononucleosis-like syndrome is not a lethal disease, but like mononucleosis it seems to be highly infectious. Epstein-Barr virus, which causes mononucleosis, is present in saliva and can be spread by kissing, sharing food, dishes, or bathrooms, or coming in contact with someone who is sneezing or coughing. The chronic syndrome has a similar pattern of transmission through casual contact. The new human B-lymphotropic virus also seems to be fairly infectious.

But whether HBLV, EBV, or any other virus or nonbiological agents or combinations of agents cause outbreaks of chronic mononucleosis-like syndrome is far from proven. ■ **DEBORAH M. BARNES**

ADDITIONAL READING

J. F. Jones *et al.*, "Evidence for active Epstein-Barr virus infection in patients with persistent unexplained illnesses: elevated anti-early antigen antibodies," *Ann. Intern. Med.* **102**, 1 (1985).

S. E. Straus *et al.*, "Persisting illness and fatigue in adults with evidence of Epstein-Barr virus infection," *ibid.*, p. 7.

Briefing:

What Does it Mean to Be "Rare" or "Likely"?

Frederick Mosteller, a statistician at Harvard University, would like to know what people think they mean when they use ordinary expressions such as "rare" or "likely." His goal, he says, is to decide whether there are unwritten but implicitly agreed upon definitions for these probabilistic terms and, if so, to publish them in the hope that people will eventually come to use the words more meaningfully. If they do, he says, there might be better communication between scientists and laypeople, and between doctors and patients.

When a doctor tells a patient that the side effects of a medication are "rare," do the doctor and the patient have the same conception of what "rare" means? And does rare always mean the same thing to the same individual? One study by R. E. A. Mapes found that more than half of a group of doctors surveyed think that a rare side effect of a beta blocker is one that occurs less than 1 in 1000 times, whereas only about one-fifth of the doctors said that an antihistamine's side effects are rare when they occur less than 1 in 1000 times. The side effects of an antihistamine are mild compared with those of a beta blocker.

Mosteller began this project when he noticed himself using terms such as "infrequent" or "common" in his own published papers in order to avoid writing down the same numbers over and over again to describe the likelihood of an event. "It is very hard to keep writing the same numbers. I found myself wanting to use other expressions," he says.

But these probabilistic expressions are never formally defined. So, in the first stage of his study, Mosteller and his colleagues contacted hundreds of physicians and medical sudents by means of a computer network, based at Massachusetts General Hospital. The investigators asked these respondents what, numerically, they think various expressions of probability mean and compared their results to those of others who had conducted similar studies in the past.

Their conclusion, published in the 18 September issue of the *New England Journal of Medicine*, is that there does seem to be a common, unstated, understanding of what these expressions mean. Medical professionals think "almost certain," for example, means about 95% likely and "very likely" means that an event is about 90% likely to occur. ■ **GINA KOLATA**