tists and clinicians studying it, is that it's very unlikely that there is a single etiologic agent," he says. "It's a syndrome that probably has multiple triggers." But CDC's Gunn doesn't agree: "I have trouble buying this thing about multiple causes, because when you look for them they're not there." Gunn believes that researchers will ultimately find a single, major causative factor, and he would not be surprised if it turned out to be a retrovirus, since that class of virus has already been shown to attack both the immune system and the brain.

Skepticism persists

The failure to nail down the cause of CFS is, however, fueling the skepticism of researchers who argue that it would be more profitable to focus on the psyche than the immune system of CFS patients. "I don't think that there is any solid, reliable, reproducible evidence that patients with chronic fatigue syndrome are in any way immunologically, virologically, or biochemically different from any other patients with a chief complaint of chronic fatigue," says Peter Manu, an internist at the University of Connecticut. Manu says that at the time they are diagnosed with the syndrome, at least three-quarters of all CFS patients have a psychiatric disorder that is a sufficient explanation for their symptoms. "I am not saying that the psychiatric disorder that all of us have noted in these people is the sole cause of Chronic Fatigue Syndrome or of chronic fatigue," he says. "But it is the only diagnosable one."

Manu goes on to argue that the search for a single viral agent is pointless. "I do not think there's any reason for going for such an arcane etiology," he says. "I cannot see any infection that will predominantly affect middle-aged, college-educated white women. It just doesn't make any epidemiologic sense to me."

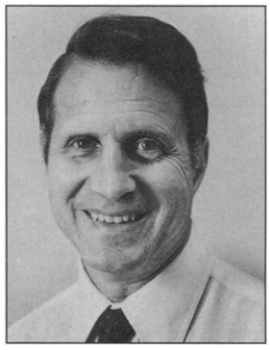
While Gunn admits that the majority of patients the CDC is seeing are white women, he says the experience in other countries—notably Australia—suggests that CFS is equally distributed between men and women. As for the suggestion that a psychiatric disorder explains most CFS symptoms, Gunn says that at least half of the patients referred to CDC neither have a diagnosable psychiatric disorder at the time they are diagnosed with CFS, nor do they subsequently develop one.

There will clearly be plenty of room for doubts about the nature of CFS unless a causative agent is identified—just as there was in the early days of AIDS. But even if a CFS virus is found, there will likely be many questions left unresolved. Like AIDS, it could be years before all the pieces of the CFS puzzle fall into place. ■ JOSEPH PALCA

A "Jumping Gene" Caught in the Act

Researchers have identified a transposon before and after it jumped; they now have a working transposon to study

WHEN GENETICIST HAIG KAZAZIAN and his colleagues at Johns Hopkins University School of Medicine analyzed the factor VIII genes of a large number of hemophilic children in the late 1980s, they got a surprise. Sitting in the middle of the gene in two patients, and disrupting its ability to produce the blood-clotting factor VIII was a stretch of foreign DNA that looked suspiciously like a transposon—a so-called jumping gene. Transposons had been widely observed to jump from place to place in the genomes of lower organisms, but nobody had witnessed one moving around in a mammalian genome before.



Serendipity. *Haig Kazazian wasn't strictly looking for transposons.*

Now, beginning on page 1805 of this issue of *Science*, Kazazian, director of the Center for Medical Genetics, and his collaborators report compelling evidence that they have indeed caught a jumping gene in the act. They have found where the transposon disrupting the factor VIII gene of one of the patients came from. The progenitor appears to be a type of transposon known as a LINE on chromosome 22 of the child's parents. "This is the first demonstration that transposable elements can cause human genetic disease," says yeast geneticist Jef Boeke, one of Kazazian's collaborators. And that's not all. A second Johns Hopkins team working in collaboration with Kazazian, headed by molecular biologist Abram Gabriel, reports that the transposon contains a functioning copy of a gene that codes for reverse transcriptase—an enzyme that plays a key role in the process of transposition.

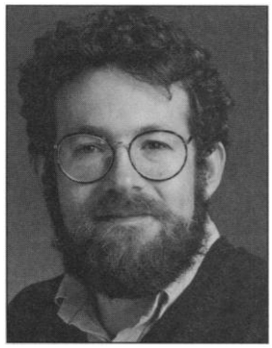
Researchers have long been anxious to get their hands on an active human transposon, with all its protein coding sequences intact, in order to understand how these strange genetic elements work. There are reckoned to be 100,000 LINEs scattered around the human genome, though all but about 4000 have massive deletion mutations and most of the full-length ones appear to be inactivated by point mutations. Nobody knows how they got into the genome in the first place—though some have speculated that they are remnants of retroviruses—how they move about, how frequently they jump, how often they cause disease, and how they may have shaped evolution. "They are obviously shaping our genomes in some way," says Kazazian. "But are they useful?"

Kazazian's discovery comes upon the heels of reports published in *Nature* (31 October) and the *Proceedings of the National Academy of Sciences* (15 December) that another mysterious molecular inhabitant of the genome, called an *Alu* sequence, had disrupted a neurofibromatosis type 1 gene and a cholinesterase gene. Like LINEs, *Alu* sequences are known to move about in the genome, but they lack the machinery to do it by themselves. One possibility, strengthened by the Hopkins work, is that the reverse transcriptase coded by LINEs may help *Alu* sequences relocate in the genome.

By identifying a LINE before and after it jumped, Kazazian's research may help shed some light on these questions. Ironically, however, he had not been searching for transposons. He had wanted to find out what causes new mutations. The factor VIII gene was a logical place to search, because it resides on the X chromosome. Males have only one copy of the X chromosome, which means that male carriers of defective factor VIII genes are inevitably hemophiliac. In the past, few became fathers. Therefore, compared with, say, mutant hemoglobin genes, defective factor VIII genes are less frequently handed down over generations like some cursed heirloom. About one-third of cases of hemophilia A are caused by fresh mutations, says Kazazian.

Once they had identified the cause of the mutation as a LINE insertion, Kazazian's group then set out to find its source. The fact that they were able to distinguish the progenitor from the other 100,000 LINEs in the genome is no mean feat. Kazazian's colleague geneticist Alan Scott had developed a "consensus sequence" for the human LINE by comparing the sequences of 20

elements and filling in each position of the consensus sequence with the base that most commonly occupied it. Beth Dombroski, a postdoctoral fellow in Kazazian's laboratory, then searched for the biggest distinction she could find between the child's transposon and this consensus sequence. One 20-base stretch had three base changes, a difference of 15%. Human LINEs typically vary by no more than 5%. She had her handle.



Working gene. *Abram Gabriel showed that reverse transcriptase is produced.*

Using this 20-base sequence as a probe, Dombroski found five LINEs in the mother's DNA that closely matched the transposon sitting in the child's factor VIII gene. The child's transposon proved to be a truncated version of one of these, a full-length LINE on chromosome 22. They are identical in all bases that had not been deleted. Dombroski subsequently found this LINE in the same position on the father's chromosome 22. "As far as we know, everybody's got it in that location. We've even found it in the same location in chimps and gorillas, which means it's been at the same place in the genome for at least 6 million years," says Kazazian. It's impossible to say whether the mother's or the father's transposon was the progenitor, he adds.

The next step was to see whether the transposon could make reverse transcriptase. Active LINE elements are copied into RNA, which is then converted into a DNA copy by reverse transcriptase. The DNA copy is then inserted into a new place in the genome. Gabriel, along with graduate student Stephen Mathias and associate professors Scott and Boeke, tested the transposon's reverse transcriptase gene by splicing it into the equivalent region of a yeast transposon, and then showing that particles taken from the yeast cytoplasm have reverse transcriptase activity. They nailed down the proof by making a point mutation in the reverse transcriptase gene, which disabled the protein.

The fact that the child's transposon is a truncated version of that of its parents' suggests that the deletions so common among mammalian LINEs are acquired during jumping. "That answered a question as to whether the degeneration is something that happens in the course of evolution or whether it is part of the process of transposition," says Maxine Singer, president of the Carnegie Institute of Washington, a longtime expert in this field. Some researchers think that these crippling mutations may be nature's way of controlling the population of transposons.

Perhaps the biggest unanswered question is what role transposons play in the human genome. Many researchers think they are genetic parasites, whose presence in the genome is harmful to the organism. But some think that organisms may have become dependent upon them over the course of evolution. "There is something interesting about the fact that all mammals have retained these sequences, in spite of the fact that they are mutagenic," says Singer.

An interesting angle for future research, suggests Singer, is the possibility that LINEs may play an important role as a source of reverse transcriptase in the genome—a role that may help *Alu* sequences move around and, in turn, might be a major factor in the evolution of the genome. Because *Alu* sequences (and similar sequences in other organisms) lack reverse transcriptase genes, they have no obvious means of transposing themselves to new places in the genome. But the research at Johns Hopkins suggests that LINEs could be providing the enzyme. "There is no other known consistent source of reverse transcriptase in mammalian genomes," says Singer, though endogenous retroviruses may occasionally provide the enzyme. "It is very possible, since we know that various pieces of DNA have arisen in the genome through reverse transcriptase, that this is the enzyme that did it," she adds.

The scattering of *Alu*, LINE, and other repetitive sequences around the genome may play a role in duplicating genes in the genome, which is thought to be important in the development of whole families of genes such as the hemoglobins, the individual members of which have somewhat different functions from one another. (Duplicate genes can develop new functions because mutations in one won't kill off the host organism.)

Duplication can occur during meiosis, when an unequal genetic cross-over takes place between two paired chromosomes. In a normal cross-over, the chromosomes trade genes, but in an unequal cross-over, one chromosome can end up with two copies of a gene, leaving the other with none. That's where repetitive sequences come in. If a gene is flanked on both sides by repetitive sequences, base pairing between these sequences can occur so readily that it pulls the DNA into a configuration that leaves both copies of a gene on one chromosome. Without reverse transcriptase, *Alu* sequences could not have multiplied in the genome to the point where genes are sometimes surrounded by them. LINE elements may complete this story. ■ DAVID HOLZMAN

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HIV Risk Higher for First-Born Twins

For twins born to HIV-infected mothers, the first child delivered is more than twice as likely to be infected with the virus as the second. That's the remarkable—and potentially controversial—result of an international study published last week (*Lancet*, 14 December, p. 1471). The finding strongly suggests that in most instances, the AIDS virus is transmitted from mother to infant at birth. If it were transmitted across the placenta earlier in pregnancy, birth order should make no difference in the incidence of transmission.

The study compared 66 pairs of twins delivered either vaginally or by Caesarean section. For vaginal births, 50% of first-born twins were infected with HIV, compared to 19% of second-born twins. In Caesarean births, the effect was smaller and not statistically significant: 38% for the first born twin, and again 19% for the second born twin. James J. Goedert, a member of the viral epidemiology section of the National Cancer Institute and senior author of the study, postulates that the first-born infant must come in contact with some maternal fluids released at birth that contain infectious virus. But in the process of delivery, most of that fluid is swept away, so the second infant is less likely to be exposed to infection. Goedert says that simply cleansing the birth canal may reduce the transmission rate of the virus from mother to infant.

But others are not convinced that the majority of transmission occurs at birth. William Lyman, associate professor of pathology at the Albert Einstein College of Medicine in the Bronx says he finds a 30% infection rate in second trimester fetuses carried by HIV-infected mothers. Lyman acknowledges that infection across the placenta may be enhanced in his patient population because many of the mothers he studied were also crack-cocaine users. Cocaine use is associated with vasculitis, which may permit leaks between the fetal and maternal blood supply.

Goedert is accruing more patients and plans to take an additional look at infection rate and birth order in about a year to see if the results hold up. ■ JOSEPH PALCA