HUMAN GROWTH HORMONE

French Officials Panic Over Rare Brain Disease Outbreak

Lightning, it seems, can strike twice in the same place. In late October, three senior physicians were convicted by a Paris court for failing to prevent the distribution of HIV-infected blood clotting factors to hemophiliacs (*Science*, 30 October, p. 735). Now, even as moves are under way to indict former ministers who may have been involved in that affair, the French government is wrestling with another potential public health scandal, which —at least superficially—involves similar circumstances: Again, patients treated in the mid-1980s have contracted an incurable disease after receiving medication derived from human tissues.

This time, the disease is a rare neurodegenerative condition called Creutzfeldt-Jakob disease (CJD)—one of a class of diseases that are thought to be caused by mysterious infectious agents called "prions," an altered form of a naturally occurring protein. The patients were children suffering from congenital dwarfism, and the source of their infection is believed to be human growth hormone extracted from the pituitary glands of cadavers. Eighteen probable cases of CJD in growth hormone recipients have so far been identified—roughly equal to the number believed to have been infected through growth hormone therapy in all other countries combined. Of the 18, nine have died, and their fate seems even more horrific—if that is possible—than that of the hemophiliacs now dying of AIDS. Before killing its victims, CJD robs them of their mental faculties.

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> **–Paul Brown**

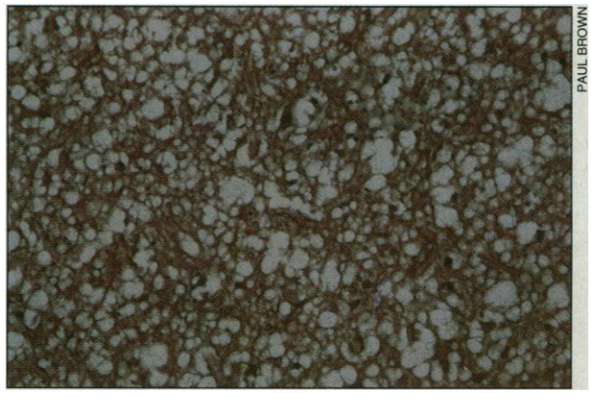
The inspector-general for social affairs has already launched an investigation that is believed to be focusing on whether France was unduly slow in switching from natural growth hormone to the recombinant version, which became available in the mid-1980s, and whether adequate precautions were taken to purify the natural product. At this point, researchers outside France who are familiar with the situation there believe there's little or no evidence of negligence. The French program, they believe, may just have been unlucky.

But that hasn't stopped the French government from panicking: In July, the health ministry imposed restrictions on the use of recombinant human growth hormone, even though it couldn't possibly contain the CJD agent. The French government is "firing off in all directions," says endocrinologist Michael Preece from the Institute of Child Health in London. The inspector general's report is expected to be completed sometime in December, but in the meantime, researchers are trying to reverse the decision to restrict the use of recombinant growth hormone.

Undue delay? For the French government, potentially the most explosive issue in this affair is whether health officials were too slow in phasing out the production of natural growth hormone when problems with CJD began showing up in the mid-1980s. U.S. and British officials banned the use of cadaver-derived pituitary hormones in 1985, after they identified the first few cases of CJD in growth hormone recipients —interrupting the treatment of many children for several months until recombinant growth hormone became widely available (*Science*, 7 June 1985, p. 1176). But in France, recombinant hormone didn't completely replace the natural product until the end of 1988. (Some other countries, including Japan, were even more sluggish in switching to recombinant products.) French researchers are understandably reluctant to discuss the matter until the inspector-general's report is completed. But Jean-Claude Job, a pediatrician who heads France Hypophyse—the agency that in the mid-1980s ran the pituitary hormone program, and now oversees the use of recombinant growth hormone—says he was concerned at the time because some patients treated with early batches of recombinant growth hormone produced antibodies to the drug.

Whatever the reasons for the delay, the evidence so far suggests that it did not contribute to the outbreak: No CJD cases have yet showed up in France among patients whose treatment with cadaver-derived material began after June 1985. The date is significant because that's when a team led by Fernand Dray of the Pasteur Institute in Paris, which supplied the growth hormone for the national program, added a new step to its production process—treatment of the pituitary extract with an 8 Molar solution of urea —to inactivate the CJD agent. Subsequent experiments have shown that urea can't completely remove prion infectivity from a heavily contaminated sample, but the additional step probably did reduce the risk of contracting CJD to a negligible level. "My guess is that not one of the cases in France were infected in the 3-year period after 1985," says Paul Brown, a prion disease researcher at the National Institute of Neurological Disorders and Stroke in Bethesda.

Unlucky break, or lapse? Epidemiologists are now focusing on a period between January 1984 and May 1985, during which all of the 18 French CJD victims identified so far were receiving growth hormone therapy. "Why France should have so many cases is, at the moment, unanswerable," says Brown. The number of cases is not the only unusual aspect, however: Most of the victims are children in their teens or younger, whereas growth hormone recipients in other countries who have been struck down with CJD mostly developed symptoms in their twenties or later —about 15 years after they presumably received contaminated injections. "The fact that it's a shorter incubation period would argue for a higher titer of inoculum," says Judith Fradkin, an endocrinologist at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, who's leading a follow-up study of U.S. growth hormone recipients. In other words, contaminated hormone preparations used in France presumably contained more of the CJD agent than contaminated batches used elsewhere. There are two leading hypotheses to explain this: bad luck or a processing error.



PAUL BROWN

Prion lesions. Brain tissue showing spongy degeneration characteristic of Creutzfeldt-Jakob disease.

The first hypothesis is that one or two extremely heavily contaminated pituitary glands were somehow included in a batch from which growth hormone was extracted—despite a policy of excluding material from patients with obvious neurological problems. There's no evidence yet to implicate a particular batch of growth hormone in the French outbreak, but if this is the explanation, most CJD researchers say that the French

program experienced an unfortunate problem that could have occurred anywhere, because it is not always possible to identify potentially infectious pituitary glands. Moreover, even the most elaborate procedures for purifying the material could not have removed infectivity completely from samples heavily loaded with the CJD agent.

The second possibility is that there was some lapse in the procedure for extracting and purifying growth hormone around 1984, which allowed larger quantities of the infectious protein to contaminate preparations used to treat growth hormone-deficient children. It may not be possible 8 years after the event to determine definitively what, if anything, went wrong, however. And in the charged atmosphere left after the AIDS/hemophilia trial, that's a worrisome prospect for the scientists who ran the program back in the mid-1980s.

Poisoned atmosphere. The political fallout from the AIDS case has not just affected those researchers who were directly involved with the natural pituitary hormone program, however. The health ministry's decision to slap controls on the use of recombinant growth hormone is widely seen as a political overreaction. The ministry has decreed that—although the treatment of growth hormone-deficient children can continue—no new clinical trials involving recombinant growth hormone can start in France and no new patients can be enrolled into trials already under way. The ministry has yet to spell out its reasons for this move, and officials were unavailable for comment last week.

Not surprisingly, the companies that produce the biosynthetic hormone are up in arms. "There is no scientific reason to do what they have done," says Anne Marie Kappelgaard, vice president for medical affairs with Novo Nordisk, a Copenhagen-based supplier. And the French health ministry has further annoyed the companies' executives by asking them to help evaluate the risks and benefits associated with their products. "We haven't done it," says one industry source. "You can't assess benefit versus risk if there is no risk."

On 9 December, many of the world's leading authorities on growth hormone and CJD will assemble in Paris at a meeting organized by Jean-Louis Chaussain, a pediatric endocrinologist at the St. Vincent-de-Paul Hospital in Paris, to go over the data on the French CJD outbreak and review the safety of the biosynthetic hormone. The relevant officials from the health ministry have been invited. Researchers hope that the meeting will make the ministry see sense. But Chaussain says that in the tense political climate following the AIDS/hemophilia scandal, researchers must tread cautiously. "We have to be extremely careful," he says. "The aim of this meeting is to establish the scientific facts and no more."

–Peter Aldhous

POLYMERASE CHAIN REACTION

Roche Gets Tough on Illicit Sales of PCR Reagent

PCR users beware. If you have been capitalizing on the polymerase chain reaction—the revolutionary DNA amplification technique that has taken the world's genetics labs by storm since its debut in the mid-1980s—take a look at where your reagents are coming from. If your supplier of Taq polymerase, the key enzyme that drives the PCR reaction, isn't the Perkin-Elmer Corp., you'd do well to keep a close eye on a case in the U.S. District Court in New Jersey.

On 28 October, the Swiss-based drugs giant Hoffmann-LaRoche announced it was suing Promega Corp., a research biochemicals supplier headquartered in Madison, Wisconsin. The grievance? Roche alleges that Promega has breached a license agreement between the two companies that allows Promega to market the enzyme for only a limited range of applications—definitely not including PCR, for which Perkin-Elmer is the only licensed supplier of Taq. If Roche wins the case, PCR users could find it difficult to buy the bargain-basement Taq polymerase that Promega, and companies like it, is marketing. As thousands of cash-strapped academics know, Promega and others are currently undercutting Perkin-Elmer's prices for the enzyme by up to 60%. If researchers are forced to buy their Taq from Perkin-Elmer, "what it means is that the new water bath you wanted to buy next year will probably have to wait," says Ashley Dunn, a molecular biologist at the Ludwig Institute for Cancer Research in Melbourne, Australia.

Roche doesn't want to come off as the town bully. Its spokesmen say that it is just defending its legitimate rights. And Roche has a big investment to defend: In 1991, the Swiss company paid more than $300 million to Cetus Corp. for the worldwide rights to PCR, including those covering the production of Taq polymerase. Although Roche produces large quantities of the enzyme, it lacks a distribution network to market reagents to the research community, so it worked out a deal with Perkin-Elmer, which has an extensive network of contacts with research labs worldwide. In return for a cut of the profits, Perkin-Elmer has sole rights to sell Roche's Taq polymerase for PCR, which is marketed as AmpliTaq. A half-dozen other companies, including Promega, possess licenses to manufacture and sell the enzyme only for uses such as genetic sequencing.

In countries where Roche's patents have come into effect, researchers who want to use PCR are legally obliged to buy AmpliTaq from Perkin-Elmer. Although most other DNA polymerase suppliers are careful never to mention PCR in their promotional material, it's an open secret that up to 85% of their sales are to customers who use the enzymes for PCR. As a senior executive from one such company told *Science*, researchers certainly don't purchase large quantities of Taq polymerase "for sweetening their tea."

The European Taq Polymerase Market (1991)

Company	Market Share	Relative Price
Perkin-Elmer	45%	1.00
Amersham International	4%	0.70
Life Technologies Inc. (Gibco BRL)	10%	0.60
Integra Biosciences	2%	0.80
Boehringer Mannheim	8%	0.65
Promega (Serva in Germany)	25%	0.40
Others	6%	—

SOURCE: Adams Business Associates/Frost & Sullivan

Which is why Roche began to confront some suppliers of Taq earlier this year, initially targeting companies that have been selling the enzyme without any license at all—even for non-PCR uses. In late June, a small company called Biotech International, based in Perth, Western Australia, removed its Taq from the market after receiving a strongly worded letter from Roche. At about the same time, Cambio, of Cambridge, England, was also contacted by Roche. Again, Cambio—whose customers included the UK government's Forensic Science Service—stopped distributing its Taq polymerase.

Now, in taking on Promega, Roche is apparently trying to ensure that companies that have a valid license to sell Taq polymerase for non-PCR applications stay out of the PCR market. Jim Heffernan, managing director of Promega UK, admits that he can't vouch for