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 the uses to which his company's Taq is put by individual customers, but he's adamant that his company has been "squeaky clean." Heffernan points out that the Promega catalog contains a disclaimer stating clearly that its Taq is not licensed for PCR. But Agnieszka Junosza-Jankowski, PCR licensing manager at Roche's headquarters in Basel, maintains that the Swiss company will prove that Promega has violated the terms of its license. "They are not enforcing [the] disclaimer in a way that is sufficient for our purposes," she says.

Although Roche has gone after Promega in a U.S. court, insiders speculate that the primary target may be Europe, where Perkin-Elmer now commands less than half of a Taq polymerase market valued at $26 million in 1991 (see table). Analysts say that the aggressive marketing stance taken by alternative Taq suppliers in Europe reflects the fact that the European Patent Office (EPO) hasn't yet issued any patents covering PCR. But that is about to change: Roche got word from EPO in November that its first PCR patent has now been granted and will take effect later this month. Other patents are expected to follow in a matter of months.

So far, Roche has only gone after the suppliers of Taq polymerase, not the scientists who use unlicensed supplies of the enzyme for PCR. And Douglas McQuilkin, vice president for business development with Roche Molecular Systems—a U.S. subsidiary that's handling Roche's PCR business—says his company has no plans at present to target researchers directly. But many researchers in Australia, where Roche's basic PCR patent was granted in April, are complaining that they have already come under heavy pressure to stop buying Taq polymerase from sources other than Perkin-Elmer.

This pressure hasn't come from Roche, but from Perkin-Elmer itself. John Bignall, general manager for Perkin-Elmer in Australia, says the company's policy has merely been "gently to remind users that there are patents that apply to this technology." But staff at leading Australian biomedical research centers say that the clear implication has been that institutes may be prosecuted if they refuse to switch to AmpliTaq. Helen Croll, purchasing officer at the Royal Children's Hospital in Melbourne, says Perkin-Elmer representatives had led her to believe that "the hospital could be involved in unpleasantness" if she continued to order Taq from other suppliers. A 7 April letter from Bignall, addressed to the general manager of Melbourne's Walter and Eliza Hall Institute for Medical Research, made a similar point: "It is our belief that, unless you can obtain a written disclaimer from your alternative supplier, it is your organization that would be in breach of any patents covering the use of the technology."

If Perkin-Elmer adopts the approach it has taken in Australia in other countries, it would risk a backlash from the research community. "That sort of thing doesn't sit well with scientists," says geneticist Norton Zinder of Rockefeller University in New York. "It would be a very bad policy....They would lose the constituency." And that could soon be a major concern for Roche and Perkin-Elmer. For the time being, PCR is the only serious game in town when it comes to rapid and accurate gene amplification, but a rival DNA amplication technique, the ligase chain reaction (*Science*, 26 November 1991, p. 1292), is currently being readied for the market by Abbott Laboratories in Illinois. With alternatives possible, Roche and Perkin-Elmer will have to tread carefully to avoid upsetting the core users of their technology.

–Peter Aldhous

HUMAN GENOME PROJECT

NIH Takes New Tack on Gene Mapping

For several years, the U.S. Human Genome Project has followed a piecemeal approach to genome mapping, dividing the research pie chromosome by chromosome—say, chromosome 5 for one group, 21 for another. Now such strict balkanization is giving way to a more global approach. Leading the way are two NIH-funded centers—a new one headed by Jeffrey Murray at the University of Iowa and an expanded version of Eric Lander's existing center at the Whitehead Institute and the Massachusetts Institute of Technology (MIT). Both are embarking on projects to map the entire genome in one fell swoop.

The chromosome-by-chromosome approach was scientifically and politically attractive, providing a way to divide up the work and the credit. But Daniel Cohen's stunning success at the Centre d'Etude de Polymorphisme Humain (CEPH) in Paris earlier this year in creating giant clones that span the entire human genome prompted considerable rethinking (*Science*, 2 October, p. 28). To at least one prominent U.S. researcher, Cohen's success shows that "the U.S. approach never made any sense at all." Others, though, vehemently disagree.

In the newly expanded Whitehead/MIT center, funded at about $24 million for 5 years, Lander and colleagues from Princeton, the Jackson Laboratory, and CEPH will map both the mouse and human genomes. For the mouse, the first goal is a high-resolution genetic linkage map—essentially an abstract representation of the genome, with DNA markers spread out along the chromosomes. The Whitehead group completed a low-resolution map earlier this year with 1000 of these markers; they now plan to add 5000 more.

At the same time the group will construct physical maps—albeit relatively crude ones—of both human and mouse genomes. Physical maps, which are needed to actually pull out a gene, consist of cloned pieces of DNA with markers in each piece that are used to line them up in the right order. Detailed physical maps of several human chromosomes are already under way, but "this chromosome by chromosome approach has not yet addressed two-thirds of the chromosomes," says Lander.

The building blocks for the human map will be Cohen's megaclones, known as YACs (for yeast artificial chromosomes). Lander and his colleagues, who include Cohen, will try to align the YACs with a new type of marker called a sequence-tagged site, or STS—a short unique stretch of DNA that can be easily detected by PCR. The goal is 10,000 of these markers—roughly one every 300 kilobases—a tall order since fewer than 1000 STSs have been mapped so far. Even that will be an intermediate map, says Lander. While the whole genome approach offers advantages in speed and cost, it can't provide the degree of detail that will ultimately be needed, says Lander. "There is a mistaken perception that it can replace chromosome-specific efforts. It can't."

At the Iowa center, funded at $15 million for 4 years, Murray and his colleagues at the Fox Chase Cancer Center, Harvard, and the Marshfield Medical Research Foundation in Wisconsin are working on a fine-resolution genetic map of the human genome. They will build on the "index" map already being constructed, chromosome by chromosome, by teams around the country. When complete in 1994, the index map will consist of very "informative" or useful markers spaced roughly every 2 million to 5 million bases. Murray and colleagues plan to push the resolution up to about 4000 markers, or one every million bases, which would greatly speed the task of cloning disease genes.

Both Lander and Murray say they are committed to getting their data out to the community promptly. Not only will both publish their PCR primer sequences, which will enable others to synthesize the markers, but both will follow a strategy Lander pioneered at his center. The group contracted with a company to synthesize the primers in bulk and then took only half for their own use. The rest were sold to the mouse community for just a handling charge—$12 for each pair of primers versus $220 to synthesize them from scratch. Says Lander: "It is instant access at affordable prices." The Whitehead investigators have now gone one step further, explicitly agreeing to make data available prior to publication, as soon as it is confirmed, and not to seek patents on the clones, markers, or maps, which they consider basic infrastructure for the scientific community.

–Leslie Roberts