Virus Scare Halts Hormone Research

Three deaths attributed to a brain virus have halted distribution of human growth hormone and other products of the pituitary gland

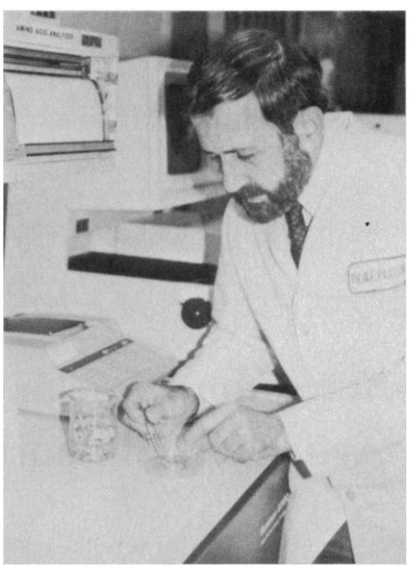
Early in March, officials at the National Institutes of Health (NIH) received a letter from a Stanford University physician that contained some disturbing information. Autopsy reports, the letter said, had confirmed that a young man who died last November had been a victim of Creutzfeldt-Jakob disease, a rare and mysterious viral infection of the brain for which there is no known cure. The source of his infection was believed to be growth hormone, extracted from human pituitary glands, with which he was treated between 1966 and 1976.

The letter sparked a series of events that have brought to a halt the distribution within the United States of growth hormone to treat certain types of dwarfism. It has also brought to an end, for an indefinite period, clinical research on all hormones extracted from pituitary glands, and placed in doubt the future of the National Hormone and Pituitary Program, a 20-year federal program that produces a variety of hormones for research and distributes growth hormone free of charge to patients in the United States.

About the only potential winners in all this are biotechnology companies that are poised to market synthetic versions of growth hormone derived from recombinant DNA techniques. Their products now have no competitors. Genentech of South San Francisco and KabiVitrum, a Swedish company, have been conducting clinical trials of a biosynthetic version of the hormone and Genentech is expected soon to receive approval from the Food and Drug Administration (FDA) to market its product in the United States.

These actions have provoked some controversy. "What we have is panic, what we have is jitter, what we have is supercaution," says Albert Parlow, an endocrinologist at Harbor-UCLA Medical Center who since 1977 has extracted and purified pituitary hormones under contract to NIH. "It is a major tragedy," he says. Erol Caglarcan, a spokesman for Serono Labs, one of two commercial suppliers of natural human growth hormone in the United States, says, "We think the [federal government] acted much too hastily."

Others argue that the government had no choice. When he received the letter from Stanford, Mortimer Lipsett, director of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, which runs the national pituitary hormone program, immediately called a meeting to determine what action to take. It was decided to halt all clinical experiments with pituitary hormones that do not involve therapy. Then in the following few weeks, NIH learned of two more suspected cases of Creutzfeldt-Jakob disease in patients who had received growth hormone in the 1960's and 1970's. One died in February but no autopsy was performed. The second died in April and the diagnosis was tentatively confirmed by autopsy.



Albert Parlow

Research with pituitary hormones could be destroyed.

"That clinched it," says Lipsett. NIH promptly sent out a notice halting distribution through the federal program of new batches of growth hormone. FDA also put pressure on Serono and KabiVitrum, the two commercial suppliers of the hormone in the United States, to halt distribution as well. "I don't think NIH had any choice," says Stanley Prusiner of the University of California at San Francisco who is an expert on the class of viruses that includes Creutzfeldt-Jakob. "These kinds of degenerative diseases in young people are extremely uncommon," he notes. Caglarcan of Serono points out that doubts have been expressed about the diagnoses in the three cases, but Prusiner says that is not at all unusual with this disease. The consensus seems to be that the autopsy reports provide strong evidence in at least those two cases.

All three victims received hormone through the federal program at a time when the preparations were relatively crude. The material is extracted from pituitary glands taken from the brains of donors—usually accident victims—and put through a series of purification procedures. Before 1977, the final product was only between 25 percent and 50 percent pure, the remainder being a variety of unknown proteins. The supposition is that if any of the glands were infected with virus, the purification techniques may not have been rigorous enough to keep it out of the final product.

More recent techniques produce a product that is about 95 percent pure, however. Parlow and Caglarcan argue that there is no evidence that the highly purified versions of the hormone pose any danger of contamination with Creutzfeldt-Jakob virus.

The halt in distribution of the hormones is supposed to be temporary while tests are run to determine what the risks, if any, are. But in fact it could take years before supplies of natural pituitary hormones can be proved safe to everybody's satisfaction. In the meantime, biosynthetic versions of growth hormone are likely to enter the market and distribution of the natural version may never be resumed in the United States. If that were to happen, the National Hormone and Pituitary Program, which currently processes some 50,000 pituitary glands a year could be wound up. This would mean that a variety of pituitary hormones for which there are no alternative sources could remain permanently unavailable for clinical research. "We could be facing the destruction of research with hormones of the pituitary gland," says Parlow.

The immediate problem, however, is that treatment for an estimated 3500 children and adolescents with pituitary disorders who were being supplied with

growth hormone is in jeopardy. Some 2300 were receiving growth hormone through the federal program and the remainder were being treated with commercially produced material at a cost of between $5,000 and $10,000 per year. (Exactly how many are being treated is uncertain. Serono says it is supplying hormone for at least 1500 children, but there may be overlap with those receiving at least part of their supplies through the federal program.) Although physicians are free to use supplies they already have on hand, the halt in distribution of new material will dry up availability of the hormone within 2 months, federal officials believe. The impending unavailability of growth hormone will put intense pressure on FDA to approve Genentech's application. But even if biosynthetic versions are soon available, those who have been receiving hormone free through the federal program will be faced with potentially enormous costs of buying it commercially.

The chief reason why it will take so long to determine the safety of pituitary extracts is that Creutzfeldt-Jakob virus is extremely difficult to detect and work with. It has a long incubation period, which appears to increase as the initial dose is decreased. Thus a very low level of contamination of hormone samples will be very hard to confirm and even more difficult to discount completely.

As a first step, NIH is planning to inject samples of every batch of growth hormone ever distributed by the National Hormone and Pituitary Program—fortunately such samples have been retained—into squirrel monkeys to see whether they come down with Creutzfeldt-Jakob disease. It will take perhaps 18 months to obtain a positive result, but even longer to say with certainty that the animals were not infected.

At the same time, NIH is hoping to do an epidemiological study of those who have received growth hormone through the federal program. Such a study could take at least a year, according to federal officials. Serono has already conducted a study of 300 people in Switzerland who have been treated with its hormone, but found no evidence of Creutzfeldt-Jakob disease, according to Caglarcan.

Finally, some tests may be run using scrapie virus, which produces a disease in sheep similar to Creutzfeldt-Jakob, to get some indication of whether the new purification techniques are effective in screening out these types of viruses. Such a test would involve spiking pituitary glands with scrapie virus, running them through the extraction and purification processes, and testing the product for presence of scrapie virus. The final tests would involve injecting the products into hamsters, which should show symptoms within about 3 months, according to Prusiner.

Similar tests with scrapie virus were in fact conducted in Britain in the late 1970's, and they indicated that no virus was present after the pituitary extracts had been purified. "This is very encouraging, but we don't feel it is conclusive," says Judith Fradkin, head of the endocrinology branch at the arthritis institute. Even if a repeat of the British tests produces similar results, there is some uncertainty about extrapolating the findings to Creutzfeldt-Jakob virus. Prusiner says it would be at best "a good first approximation." According to Fradkin, a meeting will soon be held to design such tests and determine whether they would be worth doing.

Unless biosynthesized growth hormone is approved soon, treatment for some 3500 patients will be in jeopardy.

In the meantime, clinical research with pituitary hormones is on hold. Most of the research involves growth hormone—in fact, all the people being treated through the National Hormone and Pituitary Program were participating in clinical studies. As Salvatore Raiti, the director of the program points out, "We know that human growth hormone works, but we still don't even know the optimal dose." The program was, however, about to make some other pituitary hormones available for clinical research. (All the materials are extracted and purified by Parlow at UCLA. He supplies them to the national program, which is based at the University of Maryland Medical School in Baltimore, and they are distributed from there to researchers. The whole operation is funded by NIH.)

For example, some 7 grams of highly purified prolactin are available for the first time. Prolactin stimulates milk production in lactating women, but it is also produced in substantial quantities by males for purposes that have not been determined. Mark Molitch of Northwestern University Medical School had just begun some initial pharmacology studies with the material, and several investigators were planning experiments, according to Raiti. There are no alternative sources of pure prolactin.

Similarly, the program was about to announce that highly pure thyroid-stimulating hormone (TSH) is ready for clinical investigations. The material should be useful for studying thyroid function and may eventually prove valuable in treating thyroid tumors. An alternative, bovine TSH, is available only in relatively crude extracts and causes an immune reaction, according to Parlow.

The sex hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), have also been prepared individually in pure form. These hormones are also extracted from the urine of postmenopausal women, but this produces a mixture of the two which is unsuitable for some research applications. According to Raiti, these hormones have been unavailable from the program for several years, but sufficient quantities had just been accumulated to make them available again.

Clinical studies with pituitary hormones can only be resumed when it has been determined that there is no danger of viral contamination. The national program's supporters worry, however, that the program itself will be abandoned before that happens.

Concerns about the program's future were, in fact, already being expressed even before the Creutzfeldt-Jakob scare. The problem is that, in distributing growth hormone free of charge, the program has been competing with commercial suppliers. Although this has not presented problems in the past because demand for the hormone has exceeded supplies, once biosynthetic versions come on the market, there is likely to be pressure on the federal government to stop competing with the private sector.

Raiti argues that the program is "an enormous bargain." He points out that it costs just $1.2 million a year and is providing growth hormone to 2300 patients—a cost of about $500 per patient. And that calculation does not even include the benefits from providing other hormones for research. In contrast, treatment with commercially produced growth hormone costs $5,000 to $10,000 a year.

If the production and distribution of growth hormone is halted indefinitely, will it be worth processing 50,000 pituitary glands a year to produce small quantities of the other hormones for research, even if the products are eventually pronounced safe? "I don't know," says Lipsett. The future of the program is now being looked at, he says.

—COLIN NORMAN