ANNEX 2

NIDDK Fact Sheet

Human Growth Hormone and Creutzfeldt-Jakob Disease

In 1958 scientists demonstrated that children who were deficient in growth hormone began growing when treated with human growth hormone (hGH) extracted from pituitary glands. At the time, human pituitaries were the only source of the hormone. Pituitary hGH was used effectively for more than 20 years to help growth hormone deficient children.

From 1963 to 1985 a government funded program distributed pituitary hGH to children with short stature from hGH deficiency. This program was called the National Pituitary Agency until 1983 when the name was changed to the National Hormone and Pituitary Program (NHPP). The NHPP was set up to coordinate the collection of pituitary glands removed at autopsy and to distribute hGH and other hormones extracted from these glands. It is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a part of the Federal Government's National Institutes of Health (NIH). About 7,000 patients have been treated with the NHPP-distributed growth hormone.

In late February and early April of 1985, government health officials were notified that first one, and then two more men in their twenties and mid-thirties who had been treated years before with human growth hormone supplied by the NHPP, had died. All three men had symptoms of a neurologic disorder called Creutzfeldt-Jakob disease (CJD). Pathologists confirmed this diagnosis in all three cases by careful microscopic examination of brain tissue from the men. Because CJD is so rare in young adults, the reports of three deaths from CJD in this patient group led scientists to conclude that the men who died had contracted CJD due to inadvertent contamination of growth hormone. The government's distribution of hGH was stopped.

Two commercial companies, Serono and KabiVitrum, also distributed pituitary-derived hGH in this country during the past decade. The methods used by the private companies to make hGH were similar to those that the NHPP used to produce hormone after 1977. At least 2,500 to 3,000 individuals are estimated to have received hormone from commercial sources. (Many of these people also received NHPP hormone.) Shortly after the NHPP stopped distribution of hGH, these companies also ceased distributing the hormone in the U.S.

Since the first three cases of CJD were identified in U.S. recipients of growth hormone, two additional cases have been reported in this country and two overseas. Both Americans had received NHPP hormone. One died of CJD, while the other died of unrelated causes but was later found to have CJD infection based on microscopic examination of the brain. One overseas case involved a person who had received pituitary hGH prepared in a laboratory supported by the British government. The other overseas case involved a person in New Zealand who had received hGH processed in a U.S.

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laboratory that produced hormone for the NHPP. A pooled supply of pituitary material was used to prepare hormone for distribution in the United States and New Zealand.

What is Creutzfeldt-Jakob disease?

Creutzfeldt-Jakob disease or CJD is a nervous system or brain disease. It is transmitted by a particle similar to a virus. This particle, or infectious "agent," is different from the viruses most of us are familiar with. In fact, it has not yet been completely characterized. Unlike most viruses, a person infected with the CJD agent may harbor the agent for many years before becoming ill. For that reason, CJD is called a "slow-virus" disease.

What are the effects of CJD?

CJD may progress differently in different people, and it may mimic other neurologic diseases. Symptoms that may be seen in CJD include difficulty in balance while walking, loss of muscular coordination, slurred speech, failing vision, and muscle jerking, rigidity or stiffness.

These physical changes--as opposed to mental ones have been prominent in the cases of CJD reported in hGH recipients. Changes in behavior and mental capacity also occur. These changes may include dementia, inappropriate or abnormal behavior, progressive memory loss, and confusion. (Headaches are not usually a symptom of the disease.)

The symptoms of CJD are unmistakably severe and progressive. Therefore, mild, transient clumsiness, irritability or forgetfulness should not be a cause for worry. In most people with CJD, these changes progress rather rapidly over a period of several months, and the disease is usually fatal in less than a year.

Is there any treatment for CJD?

There is no treatment that will cure or slow the progress of CJD.

How is CJD transmitted?

A few people have been infected by direct contact with contaminated tissue or instruments in the course of surgical treatments. For example, CJD has been reported in an individual who received a transplant of the cornea (the clear front covering of the eye) from a person who was later found to have the disease; in a person who received a transplant of dura mater, a tissue that covers the brain and spinal cord; in people who had electrodes implanted in brain tissue, after the electrodes had been similarly implanted in the brain of a patient with unrecognized CJD; and in a few people who underwent neurosurgical procedures in which infection probably occurred from contaminated instruments.

In the vast majority of cases the mode of transmission of CJD is unknown. It is known, however, that it is not transmitted through casual contact or through sexual intercourse, because husbands and wives of patients with CJD are not at increased risk of developing the disease.

Why do we believe that CJD is associated with growth hormone?

CJD is extremely rare. Worldwide, there is about one case per year per million people, and nearly all of these cases are in older individuals. Prior to the reports of CJD connected with growth hormone, there had been only nine cases of the disease known to have occurred in patients younger than 30 years old.

Over the years, approximately 7,000 Americans have received hGH through the NHPP for growth hormone deficiency. Because CJD is so rare in younger people, the chances of CJD occurring by coincidence in 5 out of 7,000 individuals who received growth hormone are vanishingly small (less than 1 in 1 trillion).

There is very little doubt that the five young adults who died were exposed to the CJD agent through injections of pituitary hGH. One important goal of current scientific studies is to determine whether cases of CJD in hGH recipients will be limited to those already reported.

How would the CJD particle have gotten into supplies of hGH?

For over 20 years, the only source of hGH was human pituitary glands. The pituitary is attached to the brain, the primary target of CJD. The glands were collected from cadavers, and the growth hormone was extracted using chemical procedures. Individual pituitary glands yield only small amounts of growth hormone, so that hundreds or even thousands of glands are used to make one batch of distributed hormone. While CJD is extremely rare, we believe that one or more individuals from whom pituitaries were taken to make hGH had undetected CJD. Although efforts were made to exclude pituitaries from individuals with certain infectious brain diseases such as encephalitis and meningitis, CJD was not a specific criterion for exclusion. Also, someone infected with CJD could have died of unrelated causes with no symptoms of CJD.

Does it make any difference whether someone received pituitary hGH prepared before or after 1977?

Around 1977, scientists began using methods of extracting pituitary hGH that yielded a more highly purified hormone than was produced before 1977. All five people in the United States in whom CJD was identified received hGH that was produced before 1977. One of these patients received hormone produced after 1977 as well.

While the methods of preparation of pituitary hGH used since 1977 yield a product that is more than 95 percent pure, there is no certainty that the modern preparation is safer than the hormone extracted before 1977. It is important for medications to be as highly purified as possible. The more effective the purification process, the less likely a medication is to cause allergic or toxic reactions. The infectious particle that causes CJD, however, is very small and extremely difficult to destroy or inactivate. The particles resist treatment with chemicals like formalin, hydrochloric acid, and alcohol. Extraction methods that result in 95 percent chemical purity still may not remove or inactivate the CJD agent.

In an effort to determine whether hormone extraction methods would eliminate the CJD agent, the British Medical Council performed an experiment in 1980 in which they deliberately introduced a slow virus similar to the CJD agent into growth hormone preparations. (They used the infectious particle for scrapie, a disease of sheep.) Then they purified the preparation using routine procedures for hGH preparation similar to those used by the NHPP since 1977, and the product was tested in scrapie-susceptible animals. No infection resulted, indicating that the purification steps had indeed removed most or all of the scrapie particles. Although encouraging, this study is not a guarantee that all the infectious particles had been removed or that all pituitary hGH produced after 1977 is safe.

Is there a diagnostic test for CJD?

There is no test that can determine whether a healthy person is incubating the disease. One of the goals of research on CJD is to develop a diagnostic test that can detect infection in someone with no symptoms. A spinal fluid test has recently been developed that may aid in the diagnosis of patients with symptoms of CJD. At this time, however, this test can only help confirm the diagnosis of CJD in someone who already has symptoms that suggest the disease.

Why don't we know more about CJD?

Only in the late 1950's did scientists begin to suspect that certain neurologic disorders might be transmitted by an infectious agent distinct from any known virus. It was not until the late 1960's that CJD was recognized as a condition that was transmitted by a virus-like agent. Several teams of scientists are working to identify the infectious particle that causes CJD, as well as other slow-virus diseases. There is evidence that such an infectious particle may be smaller than and unlike any virus known up to this time. Scientists are studying transmission of the disease, developing accurate methods of detecting it, and searching for methods to inactivate the slow-virus agent.

I (or my child) have been treated with pituitary hGH. What should I do now?

Stay in touch, if possible, with the physician who prescribed the growth hormone. If that is not possible, contact one of the organizations that has an interest in hGH and hGH research. The addresses of the Human Growth Foundation and the Parent Council for Growth Normality are listed at the end of this fact sheet. These groups will relay new information to members. You can also call the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland, with questions. The number is (301) 496-3583.

You can help obtain answers to questions of patients and their families about the long-term results of treatment with pituitary hGH by participating in an epidemiology study described starting on p.4 of this fact sheet. This study is likely to be the most valuable means we have of gathering information on hGH treatment and CJD.

Are there any measures a recipient of pituitary hGH may take to protect his or her health or that of others?

There is no reason for a person who has received pituitary hGH to make any changes in day-to-day living, health habits, interaction with family members and sexual activity, or general attention to his or her own health because of fear of CJD.

The only exception to this advice relates to donation of blood or of other tissues and organs for transplantation. Because there is no way of testing to detect infection with CJD, blood banks will not collect blood from anyone who has been treated with pituitary hGH.

This recommendation reflects the great caution with which the blood banking community handles selection of blood donors. It is also recommended that pituitary hGH recipients not donate other tissues or organs for transplantation.

This recommendation has no bearing on an hGH recipient's day-to-day life and interaction with others. Experts in CJD believe there is no danger of infection to family members if a person were to be incubating CJD or had active disease. Husbands and wives of recipients have no increased risk of contracting the disease. CJD is not transmitted through sexual contact, and it is not transmitted from a mother to her unborn baby across the placenta.

In summary, there is no reason for someone to take any special precautions with a friend or family member who has received pituitary hGH.

What are the chances that someone who has received pituitary hGH over the years has been exposed to CJD and may become ill?

Unfortunately, there is no way for us to know that at this time. In order to answer this question, we need to know how likely it is that the CJD agent was present in the batches or lots of hGH. We need to know how likely it is that someone exposed to the agent will contract the disease and whether the dilution of the particle in growth hormone preparations affects the likelihood of infection. We also need to know if people differ in their susceptibility to contracting this disease.

To date, there have been five cases reported out of an approximate total of up to 10,000 people in this country who are believed to have received pituitary growth hormone from any source. One of the five died of causes unrelated to CJD but was found to have evidence of infection based on microscopic examination of the brain. Because CJD has a long incubation period, it is too early to tell whether additional cases of the disease will develop in persons who received pituitary hGH.

What is being done to answer these questions?

To help determine the extent of contamination of pituitary hGH by CJD, samples of all available lots of hGH used by the NHPP have been inoculated into experimental animals. The animals have been followed 2 1/2 years without signs of infection and will be watched for at least 5 years for signs of the disease. This kind of testing, called a bioassay, is the most reliable way to test for contamination with the CJD infectious agent. A negative result, however, may only mean that the particular vials tested contained no virus, whereas another vial in the same lot that was given to a patient could have contained virus.

The scientists carrying out this study are among the world's leading experts in slow-virus diseases. This group of scientists also used new techniques in an attempt to detect a protein-containing filament that is characteristic for CJD in hGH preparations and in blood taken from individuals who have had hGH. While no evidence of contamination has been found, these methods of detection are not as sensitive as the bioassay, and a failure to find contamination using them would not prove that there was no contamination.

Separate from this laboratory effort is an epidemiology study that is gathering information on the health status of as many people as possible who received hGH distributed through the NHPP. The study is aimed at determining if there have been any cases of CJD other than those that have already been identified. In addition, the study will also attempt to follow hGH recipients for several years in order to track any future cases of CJD in this group.

This study is possible because the physicians who distributed NHPP growth hormone had to keep records of patients who received the hormone. The commercial companies who marketed growth hormone once it was approved by the Food and Drug Administration (FDA) were under no obligation to keep records of the users of growth hormone--just as they are not required to keep records of users of other prescription drugs. However, many recipients of pituitary hGH from commercial sources may be traced through the epidemiology study because many of these individuals received NHPP hormone as well as the commercial product.

Through the epidemiology study, we hope to provide patients who received pituitary growth hormone with an estimate of their risk of developing CJD. Two of the NIH Institutes, the NIDDK and the National Institute of Child Health and Human Development, are funding this study.

Scientists from the government's Centers for Disease Control (CDC), the FDA, and NIH, together with a panel of advisors from the academic community who are experts in pediatric endocrinology, neurology, virology, and epidemiology, are participating in designing and

carrying out the study.

I understand that a biosynthetic form of hGH is available. How is it different from the previously used hGH?

Cells in the human body make hGH using inherited instructions. These instructions, or genes, are composed of the molecule DNA. Scientists have succeeded in inserting the DNA sequence that determines the structure of hGH into the DNA of bacteria. The bacteria are a type found normally in the human digestive tract. By a process called biosynthesis, the bacteria make hGH using the inserted human DNA as a blueprint. The hormone is purified so that no bacteria are present in the hormone used for treatment.

In 1985 the FDA approved the first biosynthetic growth hormone for use in children with growth deficiency. This hormone is identical to human growth hormone except for one extra amino acid. (Amino acids are links in the chemical chains that form proteins--hGH is a protein that is 191 amino acids long.) In March 1987, a second form of biosynthetic growth hormone that does not have the extra amino acid, became available commercially. Other companies are continuing to develop new biosynthetic forms of hGH.

Is biosynthetic growth hormone as effective as pituitary hGH?

In order for a drug, in this case biosynthetic hGH, to be approved by the FDA, the firms that market the drug perform clinical tests to establish that it is both effective and safe. In tests in which patients with growth hormone deficiency were treated with one or the other type of biosynthetic hGH, biosynthetic growth hormone stimulated growth in exactly the same manner and to the same extent as pituitary hGH.

Is biosynthetic hormone safe?

Because biosynthetic hGH is not made from human tissue, there is no chance of contamination with the CJD infectious particle.

Clinical tests of biosynthetic hGH before it was marketed sought to identify any adverse effects associated with the hormone. In particular, it was important to know whether recipients would react to the extra amino acid in the first available form of biosynthetic hormone, or to the minute amounts of impurities left after the biosynthetic process in either type of biosynthetic hGH.

A person's immune or disease-fighting system can recognize substances that are not identical to anything the body itself produces. The immune system may respond to a foreign substance, such as a hormone, by making antibodies to remove or inactivate it. There was some concern that antibody response might inactivate the biosynthetic growth hormone.

Although antibody formation sometimes occurs, only very rarely do the antibodies interfere with the growth-promoting effect of biosynthetic growth hormone. Antibody formation stops when biosynthetic hormone is stopped. (Antibody formation also occurred with pituitary hGH, usually without effect, but occasionally interfering with the hormone's ability to promote growth.)

As research continues, production methods improve. The biosynthetic hormones now being used are more highly purified than the first such hormone that was clinically tested. In other words, they contain more hormone relative to the very small amount of material that remains from the biosynthetic process. Children in the clinical tests of these more highly purified hormones have had lower levels of antibodies to injected hGH than were found in the first clinical trials with biosynthetic hGH.

In summary, no major or health-threatening side effects have been associated with biosynthetic hGH use.

We were told that pituitary hGH was safe, too. How can we be sure that biosynthetic hGH is safe?

When the FDA approves drugs for use, the decision is based on the best available knowledge of the risks and benefits of the medication. This judgment is made within the limits of the capabilities of clinical testing and current understanding of how medications work. Unfortunately, it is not possible to guarantee that any medication will be 100 percent safe.

However, at least 6 years of records beginning from the first patient tests of biosynthetic hGH are now available. From this evidence, there is no reason to believe that biosynthetic hGH will cause serious or long-term health problems.

Will the NHPP distribute biosynthetic hGH at no charge for patients in research studies as the program did with pituitary hGH?

No. When the NHPP was established, the only source of hGH was human pituitaries. Because of the limited supply of human pituitaries, a central resource was needed to ensure that the largest possible number of glands were collected and that hormone were systematically extracted and made available

to patients for treatment under approved research protocols. With the development of biosynthetic hGH, the supply of hGH is no longer limited.

Years of clinical research have documented the effectiveness of hGH in stimulating the growth of children with hypopituitarism. There are still important needs for research with growth hormone, and NIH continues to support research in this area. NIDDK continues to distribute pituitary-derived growth hormone to scientists for nonclinical laboratory research. NIDDK does not plan to purchase biosynthetic growth hormone for distribution for clinical research. Drug companies provide biosynthetic hGH to scientists who are working on specific clinical research projects.

Can biosynthetic hGH be covered under Medicaid or private health insurance?

Human growth hormone is an FDA-approved drug. Under Federal guidelines, approved drugs can be covered under Medicaid benefits. Each state has its own guidelines for eligibility for health benefits. The best way to investigate this coverage is to contact the state health or social services department, or Medicaid office.

Private insurance coverage depends on the individual policy. If you have not already done so, discuss insurance coverage of biosynthetic hGH treatment with your insurance carrier and the doctor responsible for your child's treatment.

Additional Reading

A list of papers published in the scientific literature on hGH and CJD is available on request from the National Institute of Diabetes and Digestive and Kidney Diseases (see address below).

Other Resources

If after reading this fact sheet, you have concerns or questions, please call:

National Institute of Diabetes and
Digestive and Kidney Diseases
Building 31, Room 9A04
Bethesda, Maryland 20892
(301) 496-3583

Other resources on the subject include:

Food and Drug Administration
Division of Metabolism and
Endocrine Drug Products
(HFN-810)
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857
(301) 443-3510

Human Growth Foundation
Montgomery Building
4720 Montgomery Lane
Bethesda, Maryland 20814
(301) 656-7540

Parent Council for Growth
Normality
2899 Camelia Drive
Opelousas, Louisiana 70570
(318) 942-9700