THE SEVENTEENTH

REPORT OF THE PHS INTERAGENCY COORDINATING COMMITTEE ON

HUMAN GROWTH HORMONE AND CREUTZFELDT-JAKOB DISEASE

November 2001

The Seventeenth Report

of the

PHS Interagency Coordinating Committee on Human Growth Hormone and Creutzfeldt-Jakob Disease

TABLE OF CONTENTS

The Seventeenth Report

of the

PHS Interagency Coordinating Committee on Human Growth Hormone and Creutzfeldt-Jakob Disease

I. INTRODUCTION

This is the Seventeenth Report of the PHS Interagency Coordinating Committee on Human Growth Hormone and Creutzfeldt-Jakob Disease, which was established on May 29, 1985, by the then Acting Assistant Secretary for Health. This Report primarily reflects the deliberations of the Committee at its meetings of November 4, 1999, and November 6, 2000. A list of the agencies and representatives participating in the Committee follows below. Dr. Allen M. Spiegel, Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), presides as Chairman of the Committee.*

A. Background

During the period from late February to early April of 1985, officials of the Public Health Service (PHS) were notified of the deaths of three people who had received medical treatment with human growth hormone (hGH), distributed by the National Hormone and Pituitary Program (NHPP). The clinical course of each individual was reported to have been compatible with Creutzfeldt-Jakob Disease (CJD).

Officials of the National Institutes of Health, the Food and Drug Administration, and the Centers for Disease Control immediately responded to these reports by outlining a strategy to address the situation. Within a week of notification of the first case, distribution was halted for pituitary-derived hormones used for purely experimental, non-therapeutic purposes. A week after notification of the second and third cases, a decision was made to halt temporarily the distribution of hGH for all clinical use, except to patients with life threatening hypoglycemia, and to initiate epidemiological studies to assess the full extent of the problem.

To facilitate the scientific review of this issue, the then Acting Assistant Secretary for Health formally established the Interagency Coordinating Committee on Human Growth Hormone and Creutzfeldt-Jakob Disease. The purpose of the Committee is to advise the Assistant Secretary for Health regarding a coordinated PHS response to the scientific questions surrounding hGH distribution in relation to CJD. The Committee originally reported at three-month intervals, and it now reports annually or as significant new information becomes available.

*Dr. Spiegel replaced Dr. Phillip Gorden, who was reassigned from the NIDDK Directorship, which included his position as Chair of the PHS Interagency committee on hGH-CJD, on Nov. 15, 1999.

The PHS Interagency Coordinating Committee provides updated information to recipients of pituitary-derived human growth hormone supplied through the NHPP to keep them informed of the progress of the study and of new developments with regard to growth hormone administration and CJD.

B. Goals of the Public Health Service Related to hGH-CJD

The PHS is expending maximum efforts to answer the scientific and public health questions raised by the reported deaths. The PHS objective has been and continues to be to protect the public from health risks through the following actions:

--To inform physicians who have administered pituitary hGH and their patients of the current state of knowledge about health risks associated with pituitary hGH;
--To determine which NHPP products may have been contaminated by the CJD infectious agent;
--To ensure the continued availability of NHPP hormones for non-human research purposes; and
--To bring to bear the relevant expertise available on these issues from throughout the scientific community in the most expeditious and well coordinated manner.

Another objective of the PHS when the Coordinating Committee was formed was to assure uninterrupted supplies of growth hormone to children with need. This goal was met when the FDA approved recombinant hGH in 1985.

C. Roster of Committee Members

Agency	Representative
National Institutes of Health	
National Institute of Diabetes and Digestive and Kidney Diseases	Dr. Allen M. Spiegel, Chairman Dr. Judith Fradkin Dr. Saul Malozowski
National Institute of Neurological Disorders and Stroke	Dr. Paul Brown
National Institute of Child Health and Human Development	Dr. James Mills
Centers for Disease Control and Prevention	Dr. Lawrence B. Schonberger Dr. Dixie Snider
Food and Drug Administration	Dr. Diane Wysowski Dr. Elizabeth A. Koller

II. OVERVIEW

A. Creutzfeldt-Jakob Disease (CJD)

Creutzfeldt-Jakob Disease is a rare neurological disease that occurs in the general population at a rate of one in one million per year, affecting predominantly persons over 54 years of age. CJD is caused by an infectious agent with a long interval from the time of infection until symptoms first appear. These symptoms include progressive dementia, involuntary movements (myoclonus), visual and speech abnormalities, and lack of coordination. This rare disease can occasionally be clinically confused with other dementias, particularly Alzheimer's disease. There is no cure or treatment for CJD currently available; the illness progresses invariably to death, usually within three to six months of onset.

B. The National Hormone and Pituitary Program

The National Pituitary Agency (the present National Hormone and Pituitary Program) was established in 1963 by the then National Institute of Arthritis and Metabolic Diseases (the present National Institute of Diabetes and Digestive and Kidney Diseases, NIDDK) with support from the College of American Pathologists. Until 1985, it provided pituitary hormones for both clinical and laboratory research. Since 1985, it has supplied materials for laboratory research only.

The NIDDK's Hormone Distribution Program makes available to the research community human and animal pituitary hormones, antisera against these hormones, and selected other hormonal and biological products. Upon request, these materials are distributed to research scientists who use them in research projects which enhance understanding of endocrine and metabolic processes and diseases. The program is an outgrowth of the research community's perceived need for high quality, standardized research materials. Through this program, scientists have access to hormones and antisera of known composition and potency. Most of the products are unavailable commercially. Currently, approximately 170 research materials are distributed. Approximately 7,000 individual vials of human and animal hormones and antisera are awarded to investigators annually for immunochemical research.

In 1992, after 23 years at the University of Maryland at Baltimore, the contract for distribution of these endocrine reagents was awarded to Ogden Bioservices in Rockville, Maryland. At the expiration of this contract in December, 1997, the distribution of these materials was consolidated with the primary source laboratory, Dr. Albert Parlow at Harbor-UCLA Medical Center in Torrance, California. Through an innovative agreement with Dr. Parlow, the endocrine community has ready access to many additional materials as well as the scientific and technical expertise that Dr. Parlow has accumulated through a career of research on pituitary hormones. Dr. Parlow has already been instrumental in bolstering the inventory of recombinant hormones through contacts with the pharmaceutical industry. Working

with the project officer, Dr. Parlow has added other reagents of value to the research community, such as leptin and recombinant mouse pituitary hormones.

III. UPDATE ON ISSUES

A. Cases of Creutzfeldt-Jakob Disease in Pituitary Hormone Recipients Worldwide

United States
In October 2000, the Committee identified a total of 22 CJD cases among the U.S. recipients of the NHPP hGH hormone.

Seventeen of these 22 cases of CJD occurred in the originally-defined study cohort of 6,272 hormone recipients whose treatment was confirmed based on information from treatment centers. There have been 506 total deaths in this cohort.

--By the beginning of 1980, there was one confirmed CJD case, albeit preclinical, in the first 72 cohort deaths (1.4 percent). This case-patient died from a non-neurologic illness; the patient's CJD brain lesions were diagnosed years later upon re-examination of autopsy tissue.
--During the 1980s, there were five CJD cases among the 215 deaths that occurred among the originally-defined cohort (2.3 percent).
--From 1990 through 1998, there were nine CJD cases among the 219 deaths that occurred in the cohort (4.1 percent).

In 1999, there were two reported CJD deaths in the originally-defined study cohort; the most recent of these occurred in October.

Five additional CJD cases--one in 1991, two in 1993, one in 1998, and one in 1999--occurred in U.S. hGH recipients who were not in the originally-defined study cohort because they were not identified before 1989 as confirmed hGH recipients. The precise number of such U.S. recipients of hGH who were not initially identified for the study cohort is unknown, but is believed to be about 1,400 persons.

In the U.S., all cases of CJD have so far occurred in people who began hGH treatment before 1977, when a new method of purification that included chromatography was introduced.

Foreign Cases
United Kingdom: The United Kingdom has reported 35 cases among 1,900 human growth hormone recipients.

France: No new additional cases have been reported since 1998. France has reported 74 cases among approximately 1,700 hGH recipients.

Australia: No recent hGH-associated CJD cases have been reported in Australia. Australia had previously recorded one death believed due to CJD in an hGH recipient, and four in pituitary-derived gonadotropin recipients.

New Zealand: A total of five CJD cases were previously reported in New Zealand. All five cases occurred among 46 people who received hGH produced in the U.S. by one of the three laboratories that supplied National Hormone and Pituitary Program hGH prior to 1977.

Brazil: One case was previously reported in an hGH hormone recipient who received hormone produced in a U.S. laboratory that also produced hormone for the National Hormone and Pituitary Program.

Holland: In 1998, Holland reported one hGH-associated CJD case. No new cases have been reported since that time.

B. Epidemiology Study

A major goal of the epidemiology study is to provide hGH recipients the best information possible about their risk of contracting CJD.

The surveillance procedure used in the epidemiology study continues to be identification of all deaths in the cohort of 6,272 identified National Hormone and Pituitary Program (NHPP) hGH recipients through the National Death Index (NDI). The match of NHPP hGH recipients with the NDI has been completed for all deaths through 1998. Although there is an inherent delay in the identification of deaths through the NDI, the Committee believes that the awareness of the CJD problem in the medical community, as a result of publications and presentations at major medical meetings, would likely yield more rapid ascertainment of CJD cases, including cases among recipients who may not have been included in the originally identified study cohort. This has proven to be the case. Of the 22 identified U.S. hGH recipients with CJD, including the 17 cases in the originally-defined cohort, all but two were ascertained prior to the NDI searches by direct reports from physicians or family members.

The follow-up study has been successful in obtaining death certificates for nearly all deaths, but has experienced difficulty in obtaining releases to obtain and review medical records of some deceased members of the cohort identified through the NDI. Written requests are sent to verified addresses of family members to obtain releases; when there is no response, follow up phone calls are made to further extend this effort. In some cases, family members decline to sign a release and in others they may agree to do so but fail to return it despite several contacts. In other cases, after considerable search, family members of these patients cannot be located to request consent to obtain and review records. The study also attempts to retrieve all available neuropathology specimens for review by neuropathologists who are consultants to the study.

Mortality, United States

Through 1998, the total number of deaths in the 6,272 hormone recipients that comprise the study cohort is 506. Of these deaths:

--491 were not due to CJD.

--15 (3.0 percent of the deaths in the cohort) were individuals who were known to have been infected with the CJD agent. Two additional cohort members died of CJD in 1999.

There had been 254 non-CJD deaths reported in this cohort in a 1991 publication that included the complete ascertainment of deaths through 1986 (*Journal of the American Medical Association* 1991; 265:880-884). The plurality of deaths were due to brain tumors and other medical problems, which had their onset prior to hGH therapy, and were the cause of the hGH deficiency.

As of 1998, the proportion of deaths in the cohort due to CJD during the 1990s had increased compared to earlier decades. However, since the three additional reported CJD deaths occurred in 1999, including two among the originally-defined cohort, no additional cases of CJD have been identified.

Five additional deaths attributable to hGH administration occurred in U.S. hGH recipients who were not in the originally-defined study cohort because they were not identified before 1989 as confirmed hGH recipients. This cohort is believed to consist of about 1,400 persons.

Thus, 22 deaths due to CJD have occurred in both cohorts, which total approximately 7,700 people.

As of October 1999, the total of 22 CJD deaths constituted 0.3 percent of the estimated total of NHPP hGH recipients in the U.S. Based on the study cohort, however, 0.8 percent of recipients whose treatment began before 1977 developed CJD. These proportions of recipients developing CJD were reported by members of the Committee (Drs. Brown, Fradkin, and Schonberger) and others (*Neurology* 2000; 55:1075-1081).

The separate analysis of recipients who began treatment before 1977 was presented because in that year, the laboratory of Dr. Albert Parlow at Harbor-UCLA Medical Center in Torrance, California, began producing NHPP growth hormone using a new method of production. This method was subsequently shown to substantially reduce CJD contamination in the starting material and no cases have yet occurred among the patients first treated after 1977.

Only 11 percent of patients from the originally defined cohort of 6,272 began treatment with hGH before 1970, yet most of the cases of CJD have occurred in this group. For patients starting treatment before 1970, the proportion developing CJD

is 2 percent. For patients who were known to have been first treated with hGH between 1970 and 1977 inclusively, the comparable proportion is 0.2 percent.

The same three laboratories produced NHPP hGH from the inception of the program in 1963 until 1977. It is not yet known whether the higher rates of CJD among patients treated before 1970 reflect primarily a higher risk of transmission from the earlier preparations or insufficient time for the more recently exposed recipients to develop CJD due to the long CJD incubation time. Some patients who completed treatment in the early 1970s are now approaching 30 years beyond exposure to hGH. It is probable that they are emerging from the incubation period during which they were potentially at greatest risk of developing CJD.

Of the 22 confirmed cases of CJD, six had onset during the last six years of the 1980s, and 15 had onset in the first nine years of the 1990s. (One case diagnosed retrospectively from neuropathologic study of brain tissue died of an unrelated illness in 1979 before she developed clinically apparent CJD.) Thus, the rate of occurrence of new cases of CJD in the U.S. averaged one case per year, 1984-1989; and 1.7 cases per year, 1990-1998.

The average duration of therapy of the confirmed cases was over nine years, while the average duration of therapy for the earlier cohorts (those who began treatment before 1970) was less than four years. Thus, as previously reported, duration of treatment is a major risk factor for development of CJD.

Mortality, International

Mortality of CJD cases internationally is summarized as follows:

--New Zealand, five deaths, representing 10.9 percent frequency for pre-1977 treatment.

--United Kingdom, 35 deaths, representing 1.9 percent frequency.

--France, 74 deaths, representing 4.4 percent frequency, or 5.9 percent of persons treated during the period 1983 to mid-1984.

C. Conclusion of Studies of Animals Injected with Human Growth Hormone

The National Institute of Neurological Diseases and Stroke (NINDS) conducted studies in non-human primates to identify CJD infectivity in samples of 76 lots of growth hormone available from the NHPP. Each lot was inoculated by intracerebral, intravenous, and intramuscular routes into three squirrel monkeys. One of the three squirrel monkeys inoculated with one lot of growth hormone distributed between 1965 and 1968 was found to have clinical signs of progressive neurologic disease, which was verified histologically as CJD as previously reported in the *New England Journal of Medicine*. The remaining two squirrel monkeys inoculated with this lot did not develop disease. Hormone from this lot is not known to have been received by any patient who contracted CJD, although two cases of the 22 cases might have received this preparation. The Committee continues to believe that contamination was probably low level, random, and involved multiple hGH preparations, and that

there is no reason to believe that patients who may have possibly received hGH from the lot that transmitted CJD to the squirrel monkey are at increased risk compared to other hGH recipients treated during this time period.

These inoculated animals were followed for more than ten years. All animals were examined for evidence of CJD upon death. The NINDS reported that all squirrel monkeys injected with hGH have been sacrificed, and the brains of over 200 animals were extracted for analysis of prion protein. Squirrel monkeys, it was noted, are particularly sensitive and susceptible hosts--almost as sensitive as chimpanzees. Moreover, the monkeys were injected intra-cerebrally which greatly increased the risk of transmission. Only one preparation transmitted CJD to one animal. This has previously been reported in a letter to the *New England Journal of Medicine*. A final report on the animal studies is in process.

D. Communication with Growth Hormone Recipients

The most recent letter and Fact Sheet were sent to hGH recipients, parents, and physicians on June 21, 1999. The letter incorporated material developed in response to a number of questions received after the previous mailing, as well as suggestions from the CDC Institutional Review Board (IRB), Dr. Paul Stolley (a distinguished epidemiologist and consultant to the Committee), and members of the Committee. As recommended by the IRB, the PHS established a toll-free telephone number for hGH recipients and families to facilitate contact with PHS staff. This number was provided in the mailing and on an NIDDK website developed specifically to provide updated information to hGH recipients.

The PHS contacted the MAGIC Foundation, a voluntary group for support of people with growth disorders, which has chapters nationwide. This organization agreed to assist hGH recipients make contact with each other and form support groups. In the June 1999 mailing to hGH recipients, the NIH notified all hGH recipients that this opportunity was now available and encouraged those interested in joining such groups to contact the MAGIC Foundation for assistance. The NIDDK website for hGH recipients includes a link to the MAGIC Foundation and information about this opportunity.

E. Advances in Understanding the Biology of Creutzfeldt-Jakob Disease

Some of the world's leading researchers continue to focus their efforts on this disease, but at this point in time there is no effective treatment for CJD. There has been some progress toward developing more sensitive tests for the detection of the diagnostic prion protein, but none have so far been shown to be sufficiently sensitive to detect the protein in human blood or blood components, i.e., to be useful as a diagnostic screening test for preclinical or even clinical disease. Eight research groups have been unsuccessful thus far in identifying the prion as a definitive marker for early disease, but they are progressing in making the prion assay more sensitive.

Progress has also been made in prophylatic therapy against CJD. There is enough known biochemically about the prion protein now to begin to develop drugs to block the transition from prion protein to the development of insoluble amyloid protein, which is present in overt CJD. In fact, drugs have been developed that are effective in tissue culture and in animals.

Thus, vigorous efforts are being mounted and progress is being made. The timeline for useful tests and therapies, however, remains uncertain.

To date, there are three relatively specific diagnostic tests that can be performed on living individuals suspected of having the disease that do not involve a biopsy of tissue. These include examination of spinal fluid, magnetic resonance imaging of the brain, and an electroencephalography. These tests are less useful in the early stages of disease.

TAB A **Minutes of Meeting of the PHS Interagency Coordinating Committee on human Growth Hormone and Creutzfeldt-Jakob Disease, Nov. 4, 1999.**

TAB B **Minutes of Meeting of the PHS Interagency Coordinating Committee on human Growth Hormone and Creutzfeldt-Jakob Disease, Nov. 6, 2000.**