PUBLIC HEALTH SERVICE

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

November 4, 1999

National Institutes of Health
Bethesda, Maryland

Committee Members Attending

Dr. Phillip Gorden, NIDDK, Chairperson
Dr. Judith E. Fradkin, NIDDK
Dr. Lawrence B. Schonberger, CDC
Dr. James Mills, NICHD
Dr. Diane Wysowski, FDA
Dr. Beth Koller, FDA
Dr. C. J. Gibbs, Jr., NINDS
Dr. Paul Brown, NINDS
Dr. Saul Malozowski, FDA

Committee Members Absent
Dr. Dixie Snider, CDC
Dr. Solomon Sobel, FDA
Dr. Richard Eastman, NIDDK

Other NIDDK Attendees

Dr. Richard Farishian
Dr. Jane DeMouy
Ms. Betsy Singer
Ms. Nola Whitfield
Ms. Winnie Martinez
Ms. Joan Chamberlain

The seventeenth meeting of the PHS Interagency Coordinating Committee on Human Growth Hormone (hGH) and Creutzfeldt-Jakob Disease (CJD) was convened by Dr. Phillip Gorden, Director, NIDDK, and Chairman of the Committee.

Dr. Gorden acknowledged the presence of representatives of each of the PHS components that participate on the Committee. Dr. Gorden noted that the Committee meets once per year to review information collected on patients who received pituitary-derived hGH that was distributed through the NIH-funded National Hormone and Pituitary Program. The Committee is responsible for analysis of this information to determine the extent of the problem of transmission of CJD through contaminated pituitary growth hormone, and subsequent dissemination of this information to hormone recipients, their families and physicians, and to the PHS.

Dr. Gorden informed the Committee that Dr. Ruth Kirschstein, Acting Director of the NIH, formally instructed the Committee to transmit its annual report solely and directly to the Director, NIH. This submission must receive approval from the Director, NIH

before it can be made available to the public.

1. Approval of Minutes of the last hGH/CJD Meeting and the Sixteenth Report
Minutes from the meeting of the PHS Interagency Coordinating Committee on Human Growth Hormone and Creutzfeldt-Jakob Disease of September 25, 1998, were previously approved by all Committee members by e-mail on April 29, 1999, and were incorporated into the Sixteenth Report (September 1999) of the Committee. Dr.Gorden thanked the Committee members for their prompt responses. The Committee will continue to be asked for e-mail approval of the minutes in order to allow for more timely dissemination of information.

Minutes from this meeting (November 4) will be incorporated into the Seventeenth Annual Report on hGH and CJD, which will be submitted to the Director, NIH, and subsequently transmitted to the PHS.

2. Epidemiology Study Report

Dr. Schonberger, representing the Centers for Disease Control and Prevention (CDC), reported on the Committee's follow-up study of hGH recipients and CJD cases. He said that over the past year, the number of confirmed CJD cases increased from 18 to 19. In addition, there are three additional suspected, but currently unconfirmed, cases under investigation that could increase the total number of cases to 22.

With concurrence from the NIH Office for Protection from Research Risks, and the CDC, the Committee previously decided that the CDC Institutional Review Board (IRB) would review and approve this study annually on behalf of all the PHS components participating. Dr. Schonberger reported on implementation of recommendations from the IRB on improved communications with hGH recipients. Specifically, the Board suggested simplifying the language in our questions and answers format Fact Sheet. This was accomplished with the help of the NIDDK's Office of Communication and Public Liaison (OCPL). They also requested that a toll-free phone number be provided to all recipients, which has also been accomplished through OCPL.

Dr. Schonberger also reported on a meeting that some members of the Committee had with Dr. Paul Stolley of the University of Maryland. Dr. Stolley is a distinguished epidemiologist who had provided expert scientific guidance about the design of the study at its inception. The focus of the meeting was how best to accurately convey to the public information on the risk of CJD in subsets of the cohort treated with hGH produced by different methods and at different times. This is a complex issue given the long incubation time of CJD. Committee members reviewed with Dr. Stolley time trends for the rate of occurrence of CJD. Specifically, there was an average of 0.9 cases per year between 1983 and 1989, and 1.7 cases per year between 1990 and 1998. As previously reported, all cases have occurred in patients who began therapy before or during 1977. There still have been no cases in patients treated exclusively with hormone produced by

the improved purification method introduced in 1977 that incorporated a column chromatography step. Dr. Stolley suggested revisions in the Fact Sheet that were incorporated into the most recent version.

The highest rates of CJD have occurred in the patients treated at the earliest times after the National Hormone and Pituitary Program began distributing hGH (before 1970). Some patients treated during that time period are now 30 years beyond exposure to hGH. It is possible they may now be emerging from the incubation period during which they were vulnerable.

It was noted that CJD accounts for only three percent of deaths that were observed and analyzed in the overall cohort. Most 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. Deaths from other causes, which occurred before the presumptive incubation time of CJD had passed, effectively reduced the size of the population at risk for CJD. Currently, CJD death rates are increasing--while the deaths from other causes in this population are decreasing--because deaths from hypoglycemia and serious organic causes of growth hormone deficiency tended to occur earlier. Mortality rates in this population now better reflect the rates in the general population. Thus, CJD is increasing as a proportion of total deaths in the cohort in recent years.

CDC staff has been working with Westat, Inc., to improve data management for this study. Dr. Fradkin complimented and thanked Dr. Schonberger for his effort. In the course of this effort, ten possible duplicate patients were discovered in the data set. This reduces the cohort of confirmed hGH recipients to 6,272.

Westat, Inc., has changed the personnel assigned to this project. Ms. Ruth Thompson is no longer the project director. She will be a consultant to ensure continuity. Ms. Margaret Camarca, a nurse, has been assigned to direct the project. Drs. Fradkin and Schonberger reported that Ms. Camarca appears well qualified for her new role. Mr. Stephen Durako, the Westat, Inc., Vice President who has provided supervision and scientific leadership for the project, will continue in this role.

3. Update on Mailings to Growth Hormone Recipients

Dr. Fradkin reported that the most recent letter and Fact Sheet were sent to hGH recipients, parents, and physicians on June 21, 1999. The letter incorporates material developed in response to a number of questions received after the previous mailing, as well as suggestions from the CDC Institutional Review Board, Dr. Paul Stolley, and members of the Committee. Compared to the previous mailing, the NIDDK received many fewer calls and letters with questions and concerns after this mailing.

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.

Dr. Gorden noted that an individual not affiliated with the Federal government had formally asked to participate in the hGH-CJD Interagency Committee annual meetings. Under the Federal Advisory Committee Act, if the meetings include any non-Federal employees, the NIH must advertise these meetings in the Federal Register and the meetings must be open to the public. Such open meetings may be problematic for the Committee in conducting its business, which includes discussion of confidential information related to contracts for the support of the study. Committee members noted that several public meetings were held at the inception of the study. If there were sufficient interest, the Committee could hold an open session as part of an annual Interagency Committee meeting or a separate public meeting. However, many interested parties are not in the immediate Washington area and may be better served by the availability of telephone contacts with PHS officials responsible for the conduct of the study.

Dr. Gorden discussed a request from several hGH recipients that the PHS organize support groups for hGH recipients. Since recipients are located throughout the U.S., it was felt that the PHS did not have the ability or resources to directly organize such groups. In response to this request, 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.

An hGH recipient asked the PHS to transmit a letter to all other hGH recipients asking them to contact him for creation of a support group. The Committee agreed that it would not be appropriate to send such a letter. Members noted that, according to many hGH recipients, each communication update from the PHS renews concern about the risk of CJD. If the PHS were to transmit one such letter and then accede to subsequent similar requests, hGH recipients might be subjected to substantial unnecessary and anxiety-provoking correspondence. It was agreed that anyone who wished to be contacted by this individual and/or other hGH recipients had the opportunity to do so through the MAGIC Foundation. Preliminary information from the MAGIC Foundation indicates that notification of this opportunity through the mailing resulted in very few responses from hGH recipients wishing to contact or be contacted by other recipients. Committee members expressed appreciation to the MAGIC Foundation for its help in providing this opportunity.

Dr. Fradkin asked for suggestions for improving the NIDDK web site to enhance the

provision of information on CJD and other issues of concern to hGH recipients. She noted that this site now includes not only the latest version of the Fact Sheet, but also links to other sources of information on CJD, links to relevant voluntary groups and references to relevant scientific publications. The online version of the Fact Sheet will be revised when a new case of CJD is confirmed in this population or when other significant information becomes available. The date of the last revision is prominently displayed. Thus, hGH recipients do not have to wait for a mailing or call the PHS to obtain the latest information on occurrence of CJD in this population.

Dr. Fradkin noted that the mailing and internet web site information place particular emphasis on the risk of death from hypopituitarism in hGH recipients. Unlike CJD, these deaths are preventable with proper information and precautions and the PHS has made every effort to make vulnerable patients and their physicians aware of the need for proper management of adrenal replacement therapy during acute illness in patients with adrenal insufficiency. She raised the issue of whether information on use of hGH in adults with growth hormone deficiency should be included. Dr. Gorden felt that there was insufficient information to make recommendations on this issue. It was noted that many National Hormone and Pituitary Program hGH recipients had brain tumors, and information is lacking on the effects of hGH therapy in such patients.

4. New Cases of Creutzfeldt-Jakob Disease

Dr. Fradkin reported there are three cases for which there is not yet complete information, and which are not formally considered confirmed, but are highly suspicious for CJD and likely to be confirmed in the near future. She reviewed the process of reviewing possible cases of CJD and designating confirmed cases.

Dr. Fradkin noted that she reviews available medical records for all deaths. She makes a determination of whether records should be further reviewed on the basis of the documentation of any neurologic signs or symptoms in the year prior to death. For example, if there are any neurologic problems, even if a brain tumor or other cause of neurologic dysfunction is well documented, the case is referred for evaluation to be sure concomitant CJD was not overlooked. However, if the death was due to trauma or some other sudden event and records indicate no neurologic problems prior to death, further evaluation is not obtained.

For deaths requiring further review, the study utilizes three consultants to review medical records. Each makes a determination on the probability an hGH recipient developed CJD. These include two outside university-based neurologist consultants and Dr. Paul Brown of National Institute of Neurological Disorders and Stroke.

Dr. Fradkin distributed the form used by these consultants: “Follow-up Study of Human Growth Hormone Recipients Neurologist Report” (TAB A), color coded blue, on which we ask the neurologist to indicate the presence or absence of signs and symptoms of CJD,

to provide a summary impression of the neurologic diagnosis and to rate the level of probability for CJD. In addition, for all deaths in which an autopsy was done and neuropathology specimens can be retrieved, two university-based neuropathologists review these. Dr. Fradkin distributed the form "Follow-up Study of Human Growth Hormone Recipients Neuropathologist Report" (TAB B), color-coded green, on which we ask for the neuropathologists' evaluation.

Dr. Fradkin summarized information from these forms we have received on recent cases that still have not formally been confirmed as CJD. She noted that for these cases the reviewers did not completely agree on the likelihood of a diagnosis of CJD. For one case, in which the patient died but an autopsy was never performed, a consulting physician who had evaluated the patient recommended additional tests to confirm the diagnosis of CJD. These tests were never performed and all available information had been evaluated by the three study consultants with differing assessments of the uncertainty of a diagnosis. One consultant rated the diagnosis of CJD as "confirmed," the second as "highly probable," and the third "possible/probable, 50 percent likelihood." The Committee decided to consider this case confirmed, even though one of the reviewers was undecided. The Committee also decided to consider confirmed a second case in which the consultants' opinions ranged from a "probable" case of CJD to be formally "confirmed." This particular patient had an autopsy report that was reviewed by our consultants, but we could not obtain release of the actual slides for review by study neuropathologists.

A third suspected case was reported verbally directly to PHS physicians by the treating physicians, but family members have not provided authorization to obtain medical records for review by our consultants. Dr. Malozowski of the Food and Drug Administration (FDA) suggested that, according to a 1972 regulation, the FDA should have access to the patient record. Dr. Wysowski reminded the Committee that the FDA has regional offices around the country, and these offices could be contacted for assistance in this regard. Committee members noted that, in the past, consent has not been required to obtain medical records on patients who are deceased, but policies about privacy and confidentiality are being re-evaluated. Dr. Brown said that if we show caring and compassion for the family in a gentle way, we should be able to get whatever cooperation we need from the patient. In this case, he said, he thinks that by working with the patient's wife, we will be able to accomplish that. Dr. Gibbs offered to talk with the family in this case and try to obtain the information we need.

<u>United States</u>

Including the three cases discussed above, two of which were considered confirmed based on the discussion at this meeting, there are now 21 confirmed cases, and one suspect case for which records are being sought. In addition, two deaths were identified by the Neurology Review Group as possible CJD, but the likelihood of a diagnosis was felt to be less than 50 percent based on available information.

Foreign Cases

The Committee reviewed information on transmission of CJD from pituitary hormone in other countries:

United Kingdom: The United Kingdom has reported 27 cases among 1,900 human growth hormone recipients. No new additional cases have been reported since our last meeting.

France: No new additional cases have been reported since 1998. France has reported 55 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. No new cases have been reported since the last meeting of this Committee.

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.

5. Report on Mortality in hGH Recipients

Identification of deaths among members of the cohort using the National Death Index was completed through calendar year 1997. The search identified 25 new non-CJD deaths in 1997. This raises the total to 474 non-CJD deaths. Two hundred twenty deaths have occurred since those reported in the *Journal of the American Medical Association* publication in 1991. Death certificates were obtained for all except three deaths, and additional medical information on cause of death or health status in the year prior to death was obtained for 190 of these 220 additional deaths. A manuscript on causes of mortality in this population is in preparation.

6. Report on Studies of Animals Injected with hGH

Dr. Gibbs provided updated information on follow-up of non-human primates inoculated with 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.

Dr. Fradkin reminded the Committee that we have very little information on specific lots of hGH people actually received because this information was not usually recorded. The lot that caused disease in the one squirrel monkey was not a lot that was known to have been received by any patient who contracted CJD. Based on records of distribution of that lot to treatment centers, only two patients who contracted CJD could possibly have received that lot, and neither of them was known to have received it. 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 continued to be followed for more than ten years. All animals were examined for evidence of CJD upon death. Upon closing of the laboratory, all of the surviving experimental animals (one-third of those originally inoculated) were sacrificed and are undergoing testing for CJD. Each animal's brain is divided into six areas, and each of the six areas is assayed for prion protein and evaluated histologically and immunohistochemically.

7. Update on HGH Contacts and Inquiries, etc.

These were discussed under item 3 above.

8. Advances in Understanding the Biology of CJD

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. At present, five different methods are being studied, and one or more of them may achieve this goal in the foreseeable future.

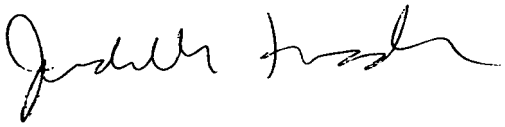
9. New Business and Information Items

Dr. Schonberger reported on identification of 47 cases of new variant CJD in the United Kingdom--one in Ireland and one in France.

Dr. Gorden informed the group that this was his last meeting with the Committee, and

that the Institute was in the process of making the transition to a new Institute Director. He recalled that he was introduced to this group when he became Director ten years ago. He felt that this PHS Committee was an example of the Federal government at its best--responding to human tragedy with the highest level of integrity, sensitivity, and judgment. He further said that he believed the scientific excellence and thoroughness shown in investigating this problem went a long way to help heal the emotional trauma resulting from CJD. He complimented the group for its progress and accomplishments in the science of CJD. The Committee members in turn expressed their appreciation to Dr. Gorden for his leadership, dedication and sensitivity in dealing with this issue.

The meeting adjourned at 2:50 p.m.



Judith E. Fradkin, M.D. November 4, 1999
(for Phillip Gorden, M.D.)

Attachments

Handouts at the meeting

TAB A - Follow-up Study of HGH Recipients-Neurologist Report Form

TAB B - Follow-up Study of HGH Recipients-Neuropathologist Report Form

TAB A

Revised 2/92

ID_____

FOLLOWUP STUDY OF HUMAN GROWTH HORMONE RECIPIENTS

NEUROLOGIST REPORT

DATE MATERIALS RECEIVED: |_|_| |_|_| |_|_|

RECEIVED: |_| NRG Neuropathologist Report (No. |__|)

|_| Pathology Report from Hospital

|_| Autopsy Report from Hospital

|_| Clinical Report from Hospital

|_| Other (Specify_____)

COMMENTS:

_____

_____

_____

DATE MATERIALS RETURNED TO WESTAT |_|_| |_|_| |_|_|

A. REVIEWING NEUROLOGIST:_____

B. DATE OF REVIEW: |_|_| |_|_| |_|_|

C. SOURCES USED FOR REVIEW:

|_| Pathology Report

|_| Autopsy Report

|_| Clinical Report

|_| Discussion with patient's physician(s)

Name(s):_____

_____

_____

|_| Discussion with other NRG members

Name(s):_____

_____

_____

|_| Other, Specify Source:_____

D. FINDINGS:

	Not Present	Not Mentioned in Record	Course (Check one)				
			Duration	Resolving	Stable	Progressive	Other (Specify)
Mental deterioration							
Behavioral change							
Cerebellar signs							
Visual signs							
Myoclonus							

E. OTHER NEUROLOGICAL SIGNS:

1. EEG

|_| Done, relevant to diagnosis of CJD

|_| Done, not relevant to diagnosis of CJD

|_| Not Done

|_| Unknown

If done, results:

|_| Periodic 1 c/s

|_| Slow wave bursts

|_| Other (Specify)_____

2. CJD Protein Test (CSF)

|_| Done

|_| Not Done

|_| Unknown

If done, results:

|_| Positive

|_| Negative

F. DIAGNOSIS OF CJD:

1. Clinical Diagnosis:

If you had this same clinical information alone on each of 100 patients, how many would you expect to truly have CJD:

|_| Highly probable 90-100

|_| Probable 51-89

|_| Possible 1-50

|_| No evidence of CJD 0

|_| Insufficient data

2. Your interpretation of Neuropathology Reports from Hospital:

|_| CJD Confirmed

|_| CJD Uncertain

|_| No evidence of CJD

|_| Neuropathology not done

G. SUMMARY IMPRESSION BASED ON ALL INFORMATION RECEIVED FROM ALL SOURCES, INCLUDING NRG NEUROPATHOLOGICAL REPORT (IF DONE):

1. CJD

If you had this same overall information on each of 100 patients, how many would you expect to truly have CJD:

|_| Confirmed 100

|_| Highly Probable 90-99

|_| Probable 51-89

|_| Possible 10-50

|_| Unlikely 1-9

|_| No evidence of CJD 0

|_| Insufficient data

2. Alternative Neurologic Diagnosis:

|_| Confirmed (Specify):___ _____

|_| Probable (Specify):_____ _____

|_| Unknown

H. COMMENTS

Please specify details on the major factors which influenced your summary impression.

_____

_____

_____

_____

TAB B

ID_____

FOLLOWUP STUDY OF HUMAN GROWTH HORMONE RECIPIENTS

NEUROPATHOLOGIST REPORT

DATE MATERIALS RECEIVED: |_|_| |_|_| |_|_|

RECEIVED: |_| Brain Slides (No. |_|_|)

|_| Other slides (No. |_|_|)

|_| Autopsy Report

|_| Pathology Report

|_| Other (Specify_____)

COMMENTS:

_____

_____

_____

DATE MATERIALS RETURNED TO WESTAT |_|_| |_|_| |_|_|

A. REVIEWING NEUROPATHOLOGIST: _____

B. DATE OF REVIEW: |_|_| |_|_| |_|_|

C. SOURCES USED FOR REVIEW: (Check all that apply)

|_| Stained Slides (No. Reviewed |_|_|)

|_| Unstained Slides (No. Reviewed |_|_|)

|_| Autopsy Report

|_| Pathology Report

|_| Other (Specify)_____

D. QUALITY OF SLIDES REVIEWED: (Check one)

|_| Slides technically adequate

|_| Significant artifact obscuring diagnosis (Specify)_____

|_| Slides technically inadequate

|_| Not applicable (no slides reviewed)

(SKIP ITEM

E. FINDINGS:

	Absent	Present				Location
		4+	3+	2+	1+	
Neuronal loss						
Gliosis						
Spongiform changes						

F. DIAGNOSIS OF CJD:

Check one of the following:

|_| Definite

|_| Probable

|_| Possible

|_| No evidence of CJD in specimens examined

Also, check all of the following that apply:

|_| Slides adequate for review

|_| Inadequate no. of slides

|_| Slides technically inadequate

G. ALTERNATIVE NEUROLOGIC DIAGNOSIS:

|_| Yes, Specify Diagnosis_____

|_| Definite

|_| Probable

|_| Possible

|_| No

H. SUMMARY AND CONCLUSIONS

_____

_____

_____

_____