PUBLIC HEALTH SERVICE

Meeting of the

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

October 31, 2001

National Institutes of Health
Bethesda, Maryland

Committee Members Attending

Dr. Allen Spiegel, NIDDK, Chairman
Dr. Paul Brown, NINDS
Dr. Judith Fradkin, NIDDK
Dr. Elizabeth Koller, FDA
Dr. Saul Malozowski, NIDDK
Dr. James Mills, NICHD
Dr. Robert L. Perlstein, FDA
Dr. Lawrence Schonberger, CDC
Dr. Diane Wysowski, FDA

Also Attending

Mr. John Condray, NIDDK
Dr. Jane DeMouy, NIDDK
Dr. Richard Farishian, NIDDK
Ms. Sharon Pope, NIDDK
Dr. Elizabeth Thuresson, NIDDK

Committee Members Absent

Dr. Snider, CDC

Dr. Spiegel chaired the meeting, which began at 1:00 p.m.

1. Welcome

Dr. Spiegel welcomed the group and asked that those present introduce themselves to the other members of the group.

2. Discussion/Approval of Minutes of the November 2000 Meeting, and draft 17th Report

Dr. Schonberger stated that the number of individuals who were not in the originally defined study cohort may be about 1,400 separate individuals, but there is much uncertainty about this estimate. This uncertainty should be noted in the language used in the draft minutes of the November 2000 meeting, and draft 17th report.

Dr. Schonberger also suggested that the number of 1998 deaths given in the Epidemiology Study Status Report section of the minutes for 2000 be revised from 27 to 28 to include one death that had been reported, but not verified, at the time of the meeting. As a result of this change, the total of deaths, including the 28 for 1998, should be revised to 506, and the number of deaths for the 1990s (a period which Dr.

Schonberger suggested be described specifically as 1990-1998) should be revised to 219 Dr. Schonberger also suggested that the draft minutes from the November 2000 meeting, which state that there were no reports of CJD cases in the cohort with onset of symptoms since October 1998, should instead state that there were no reports of CJD cases in the cohort who died after October 1999, or who had onset after June 1998.

Dr. Schonberger noted that under "Mortality International," the report stated that the 74 CJD deaths in France were persons treated during the period from 1983 to mid-1984. Although these individuals were treated during that period, they may also have been treated before or after this time period and that this point should be clarified in the minutes and report.

The minutes and Report were approved provisionally, pending incorporation of the requisite changes.

3. Epidemiology Study Status Report

Dr. Fradkin presented the hGH Followup Study Progress Report received from Westat, dated October 11, 2001. (TAB A)

Dr. Schonberger noted that Westat continues surveillance for deaths in the cohort of the 6,272 identified and confirmed National Hormone and Pituitary Program (NHPP) hGH recipients. In January 2001, Westat screened the approximately 5,700 members of the cohort not previously known to have died using the National Death Index (NDI) for deaths occurring in 1999. The results of the NDI screen determined that there were probably 28 deaths of known NHPP hGH recipients during 1999. Westat is trying to get hospital records and death certificates for all the deaths. They now have death certificates on 26 of the 28 deaths. Two deaths will not be considered confirmed until Westat has the actual death certificates to verify that the deceased is a member of the NHPP cohort.

Dr. Schonberger reported that the NDI search for deaths occurring in the cohort in 1999 revealed no CJD deaths beyond the two in the cohort that were previously known to the Committee. In addition, there have not been any new CJD cases identified in U.S. recipients of human growth hormone since the Committee's last meeting.
While Westat is very successful in obtaining death certificates, Drs. Fradkin and Schonberger noted that Westat is having increasing difficulty obtaining the medical records of the patients in the cohort who are known to have died. Early in the study Westat obtained the medical records for 60 to 80 percent of cohort members who had died. Since 1994, the retrieval rate has dropped to 40 to 60 percent. An analysis of the reasons for the decline in retrieval rates shows each of the following account for about one third of those for whom records are not retrieved: 1) family members cannot be located to give consent; 2) the family refuses consent and 3) the family does not reply although the letters are sent under Dr. Fradkin's name on NIH stationery.

A group discussion ensued regarding the original purpose for obtaining the medical records and the value of continuing to pursue them. The medical records are reviewed to identify cases that may have been unrecognized CJD deaths. When medical records are received, Dr. Fradkin reviews them for completeness and to determine if there are any neurological signs or symptoms in the year prior to death. If there are neurologic manifestations, Westat sends medical records for review to Dr. Brown and to other neurologists with expertise in CJD. Many patients did not have a neurologic exam in the year prior to death, and those that did often had brain tumors and other neurologic problems that were the cause of the GH deficiency. No case of CJD has been identified by neurologists' reviews that was not reported directly to the Public Health Service or identified on a death certificate. The Committee members agreed that the value of the medical records is not sufficient to justify continuing to contact bereaved family members for consent and is not commensurate with the effort required to obtain them. The Committee agreed that after 1999 deaths medical records will no longer be routinely obtained. There was agreement that Westat should continue getting the death certificates. If anything suspicious for CJD is noted on the death certificate, such as dementia, then a concerted effort can be made to obtain the medical records.

Despite the fact that Westat will not be contacting families to obtain consent for review of medical records, the Committee agreed it was important to be able to contact patients and families in case there is new information that should be provided to them. Therefore Westat will be instructed to do annual postmaster checks to update addresses.

The contract with Westat has been supported under a Memorandum of Understanding providing for transfer of funds from NIDDK to CDC to administer and support this contract. Dr. Fradkin expressed great appreciation for CDC's help and noted that Dr. Schonberger's expertise has been essential to the success of the follow-up study. The fifth year of the third consecutive five year contract to Westat has just begun. Because there have been no new cases of CJD, fewer analyses than anticipated have been required and substantial funds remain unexpended. It is anticipated that at least a sixth year could be supported through a no-cost extension. A conference call with Drs. Fradkin and Schonberger and the contract officers from the CDC and the NIDDK will determine the best mechanism by which the contract could be extended.

4. New Cases of CJD, United States and Foreign

Dr. Brown reported on new cases of CJD resulting from hGH administration. There have been no new deaths from CJD in the U.S. since October 1999. The total number of cases remains at 22. Since the Committee's last meeting, France had six new cases for a total of 80 and the United Kingdom had four new cases for a total of 39. Japan had 12 more cases resulting from dura mater grafts, bringing the total number of CJD cases in Japan from this source to 79. The number of cases in all other countries is unchanged.

5. Report on Mortality in hGH Recipients

Information on mortality is covered in the hGH Followup Study Progress Report dated October 11, 2001 (TAB A). Refer to discussion in the Epidemiology Study Report, Item 3. Dr. Mills has taken over first authorship of a manuscript on mortality.

6. Report on Studies of Animals Injected with hGH

There are no new developments in studies of animals injected with hGH since last year's meeting. In the study involving squirrel monkeys injected intra-cerebrally with hGH, only one animal in 200 tested positive for CJD. This study has been completed and the single finding of transmission was previously reported in the *New England Journal of Medicine.* Dr. Farishian will follow-up with Dr. Gibbs' assistant regarding the Committee obtaining a final report on the animal studies that was in preparation at the time of Dr. Gibbs' death.

7. Update on hGH Contacts and Inquiries, etc.

Dr. DeMouy reported that the most recent contacts have come from people who have read articles about hGH on the NIDDK website and have called to make general inquiries requesting information. Additionally, NIDDK has received calls from people asking if there was any new information. These people are told that there have been no new cases to report.

8. Update on Mailings to Growth Hormone Recipients

The Committee agreed an update should be sent to recipients informing them that there have been no new cases since the previous update. Instead of 19 confirmed cases and three probably but not fully confirmed cases, there are now 22 confirmed cases. Also, the number of recipients will be changed to reflect last year's minutes. Dr. Fradkin suggested that we inform mailing list recipients that the website will be updated with current CJD information, provide the URL and ask them if they wish to continue to receive mailings versus accessing the website for information.

9. Advances in Understanding the Biology of CJD

Prion Structure. Dr. Brown showed a diagram of the prion protein's structure (Zahn, R. Liu, A., Lührs, T., Riek, R., von Schroetter, C., García, F.L., Billeter, M., Calzolai, L., Wider, G. and Wüthrich. K. NMR solution structure of the human prion protein. *PNAS* 97, 145-150 (2000)) (TAB B). The normal conformation of the protein—a harmless, soluble protein—is mostly alpha-helical with some beta sheet. The function of the normal prion protein is unknown. Some studies suggest that the prion protein may be involved in neurotransmission as it is concentrated at the synaptic region. There have also been a number of papers suggesting that the prion has effects on diurnal rhythms and effects on excitatory impulses in nerve cells in culture. Mouse knock-outs have yielded no dramatic consequences, indicating that the protein is redundant in mice and is not

essential for normal neurologic function. If the mouse data translate to humans, and the human protein is also redundant, genetic engineering therapy may be a viable option for CJD patients if it ever becomes a feasible form of therapy.

Just as the function of the normal protein remains unknown, the mechanism by which the abnormal protein causes damage and death in CJD is unknown. These do not seem to be caused by a lack of the normal protein. The abnormal, insoluble amyloid form of the prion protein is thought to have a greatly increased percentage of beta sheet compared to the normal protein.

Recently, scientists reported that the normal form of the prion protein crystallized as a dimer (Knaus K.J., Morillas M., Swietnicki W., Malone M., Surewicz W.K., Yee V.C. Crystal structure of the human prion protein reveals a mechanism for oligomerization. *Nature Structural Biology* 8(9), 770-774 (2001)) (TAB C). Interestingly, almost all of the pathogenic mutations occur at the backbone of the dimer. Studies have also indicated that transformation of the normal protein form into the disease-causing form occurs in a series of steps involving a number of soluble intermediates before transformation into the insoluble, amyloid form.

Infectivity in the blood and diagnostic tests. Despite numerous experiments CJD infectivity in human blood is disputed and may not occur at all. If infectivity in human blood does occur in patients with CJD, it only occurs occasionally and is barely detectable. Epidemiological data bear out the notion that blood is not at risk. However, experimental animal models do indicate that blood is infectious in animals that are clinically ill from CJD. Three different transmissible spongiform encephalopathy agents have been used: Gerstmann-Straussler-Scheinker, which is responsible for the familial form of CJD in humans, adapted to the mouse; Scrapie, adapted to the hamster; and bovine spongiform encephalopathy adapted to the mouse. The levels of infectivity found in clinically ill animals were all in the same broad range between zero and 20 infectious units per milliliter of plasma. Buffy coat (lymphocyte fraction of whole blood composed of leukocytes and platelets) was found to be about 10 times more infectious than plasma, with the greatest infectivity for both plasma and buffy coat being at 18 weeks post-inoculation.

There is a worldwide effort to develop a blood screening test, using the prion protein as a marker for early disease. However, if infectivity occurs in humans, clinicians and researchers are not able to detect it in a practical manner at this time. Using hamster models, researchers have found that CJD-diseased rodents had between zero and 20 infectious units per milliliter of plasma, or, an average of one picogram of prion protein per milliliter of plasma. No prion protein screening test can detect protein levels in this range. The best candidate screening tests for prion protein are the Western Blot, Capillary Elecrophoresis, Conformation-Dependent Antibody Binding, Double Antibody ELISA and the Scan for Intensely Fluorescent Targets. Although researchers have been unsuccessful in identifying low levels of prion as a definitive marker for early disease, they are progressing in making the prion assay more sensitive.

There are currently two other studies aimed at understanding CJD that are promising but have yet to be replicated. One involves the conversion of large amounts of normal prion protein to the abnormal variant by seeding normal protein with a small amount of abnormal protein. The other describes the identification of hybrid proteins of the normal and abnormal prion in the urine of animals that are clinically ill with CJD and some that are only in the incubation stage.

In addition to studies aimed at understanding the pathology of CJD and detecting infection, there has been renewed interest in pharmacological agents against CJD. There have been about 55 drugs over the past four years evaluated for use in CJD, none of which had any practical consequence. Drugs that eradicated CJD in tissue culture have not proved efficacious when given after clinical disease occurred. No drug has proven effective when administered singly. Effective agents continue to be sought.

10. New Business and Information Items

There were no new business and information items to report.

The meeting adjourned at 2:45 p.m.

Allen M. Spiegel, M.D.

Attachment
TAB A: hGH Follow-up Study Progress Report from Westat