PUBLIC HEALTH SERVICE

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

December 11, 2003

National Institutes of Health
Bethesda, Maryland

Committee Members Attending
Dr. Allen Spiegel, NIDDK, Chairman
Dr. Paul Brown, NINDS (by speakerphone)
Dr. Judith Fradkin, NIDDK
Dr. Ellen Leschek, NIDDK
Dr. James Mills, NICHD
Dr. Robert L. Perlstein, FDA
Dr. Lawrence Schonberger, CDC
Dr. Diane Wysowski, FDA

Also Attending
Dr. Jane DeMouy, NIDDK
Dr. Richard Farishian, NIDDK
Ms. Sharon Pope, NIDDK

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

1. Welcome

Dr. Spiegel welcomed the group.

2. Discussion/Approval of Minutes of the November 2002 Meeting

The Committee noted that 2000 was the year patient SW died at the age of 33 of Alzheimer's disease, as stated in the November 2002 meeting minutes, page 2, paragraph 5, of the Epidemiology Study Status Report. The minutes will be modified to reflect this change.

The minutes were approved provisionally, pending incorporation of the change.

3. Epidemiology Study Status Report (update on human subject status)

Westat now has statistics through June 30, 2002. The 2002 meeting minutes reported that of the 6,272 Cohort members, 573 were known to have died. Seventeen of those deaths were caused by CJD; five additional CJD deaths occurred in hGH recipients who had not been originally identified as members of the cohort. Since that report, the total number of known deaths in the cohort has risen by 28. This brings the total number of Cohort deaths to 601 through 2002.

4. New Cases of CJD, United States and Foreign

United States Cases of CJD

Dr. Schonberger reported on the number of cases of CJD in the United States. From the 2002 Committee Report, there were 22 confirmed CJD deaths, one almost certain and two more likely CJD deaths in the United States. Since the 2002 Report, Dr. Schonberger reported the total of confirmed CJD deaths has risen to 24; the National Prion Disease Pathology Surveillance Center (NPDPSC) has obtained neuropathological evidence of CJD for case #24. In addition, likely case-patient #25 had a positive 14-3-3 CSF test performed at the NPDPSC and a compatible history. Slides of brain tissue from that patient are being sent to Westat from the University of California Los Angeles. The CDC has given verbal confirmation that in likely case #26 CJD was neuropathologically confirmed at the University of California San Francisco. The tissue was been shipped to Westat, then sent to Dr. Hedley-Whyte for a secondary confirmation.

Dr. Leschek reported on other cases that are under investigation for possible CJD. Two were discussed in detail:

- Case SW refers to an individual who was diagnosed with craniopharyngioma at eight years of age and treated with total brain irradiation. Treatment resulted in blindness, panhypopituitarism, diabetes insipidus, and a seizure disorder. Although records on this case were obtained at Dr. Fradkin's request, they are extremely limited. The records cover only the12 to 18 months prior to the patient's death. However, there are no records covering the time period from age eight to the last months of the patient's life. At some point during that period, the patient was reported to have mental retardation and Alzheimer's disease. However, all that is verifiable is that the subject had a severe neurological disorder. Westat is checking on the type of records that are available and whether or not there was an interview with the family. The Committee may make a request later that Westat contact the family for a phone interview.

- The records of Case GS include a very comprehensive note by the neurologist who followed her case for many years. At age 10, she had craniopharyngioma resected which resulted in blindness in one eye and central hypothyroidism. At age 23, she was diagnosed with cerebellar dysfunction. The cause of her death, at age 40, was listed as acute respiratory failure and progressive pancerebellar dysfunction. Dr. Leschek reported that it is unlikely that Case GS had CJD because her diagnosed pancerebellar degenerative disorder extended over 17 years without significant cognitive deterioration until within a month of her death. The case is now with the Neurological Review Group.

Foreign Cases of CJD

Dr. Brown addressed the Committee by speakerphone. He reported that there are no new confirmed foreign cases of hGH-related CJD. However, possible cases continue to arise in France. This information could not be independently confirmed by the Committee.

Dr. Schonberger reported on the CDC's Morbidity and Mortality Weekly Report, entitled "*Update: Creutzfeldt-Jakob Disease Associated with Cadaveric Dura Mater Grafts --Japan, 1979—2003*" (MMWR 52(48); 1179-1181) that Japan has reported 97 cases of dura graft-associated CJD and another five suspected cases are under investigation (TAB A). The method of production of the dural grafts (LYODURA^R) (commingling of grafts and the use of irradiation for sterilization) and the unusually high frequency of the use of this product most likely account for the large number of dural graft-associated cases of CJD in Japan. Although LYODURA^R grafts were not intended by the manufacturer for distribution in the United States, in 1987 a Connecticut patient was diagnosed with CJD after receiving a graft supplied through a Canadian distributor.

As new cases appear, the mean incubation time is increasing. The initial case of dura mater-associated CJD had an incubation time of 19 months; however, the upper limit of the latency period now exceeds 22 years. This extensive latency period may create difficulty because of the need to take protective measures long before the existence or extent of a problem is known.

Bovine spongiform encephalopathy (BSE) has a latency period of two-to-eight years or more. As with CJD, this presents the need for instituting measures to prevent the spread of this disease before the extent of the problem is known. In light of the recent Canadian case and the fact that an estimated one-half million cattle crossed the border between Canada and the United States in 2002, the USDA and FDA are considering strengthening preventive measures in order to further protect US residents from possible exposure to BSE.

5. Publication on CJD in U.K.

Two articles have recently been published on hGH recipients in the U.K. One of the articles, entitled "Risk of Cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: A cohort study" (Swerdlow, DM, et al. *The Lancet* 360:273 (2002), was presented at last year's meeting by Dr. Brown and is included in the November 8, 2002 minutes (TAB B). The article analyzes data from a cohort of patients who received hGH prior to May 1985, and were followed for up to forty years. Although the study found a statistically significant increase in the frequency of colon cancer, the cohort was limited in size. The Committee noted that it would not be possible to perform a similar study on the U.S. Cohort because the NHPP follow-up study only recorded data on the deaths of cohort members. (Also, see 6, "Report on Mortality in hGH Recipients," below)

The second article, "Creutzfeldt-Jakob disease in United Kingdom patients treated with human pituitary growth hormone" (Swerdlow, DM, et al. *Neurology* 61:783-791 (2003)), expands on the previous study of the U.K. cohort, extending the analyses through 2000 (TAB C). The study determined that the risk of CJD significantly increased when patients were treated with hGH prepared by the Wilhelmi method of extraction and indicated that exclusion chromatography used in non-Wilhelmi preparation methods may prevent CJD infection. The risk of CJD increased when treatment was administered to patients between the ages of eight and ten. The article concluded that susceptibility may be present only in a small percent of the population and may vary with age. It would not be possible for the Committee to conduct a comparable study because the U.S. cohort members did not received exclusively either Welhelmi preparations or

hGH purified by other methods. It was noted that the findings of the current U.K. study did not confirm the Committee's previously published finding that duration of treatment was a major risk factor for CJD.

6. Report on Mortality in hGH Recipients

Dr. Perlstein reported on cancer deaths that have occurred in Cohort members. There have been 136 deaths since 12/30/1996 when the last mortality analysis was reported. Of those 136 deaths, 39 were attributable to cancer. Westat ran a line listing of the 39 cancer deaths. The majority of these were "expected" deaths, in the sense that they were caused by pre-existing tumors, or secondary neoplasms resulting from cancer treatments or prior malignancies. None of the deaths was caused by colorectal cancer or non-Hodgkin's lymphoma, and only one was caused by leukemia. Dr. Perlstein suggested that the Committee may want to publish an article on cancer deaths occurring in the Cohort, reporting that there are no clusters of colorectal cancer or any other unexpected cancers in this group. A discussion was held on the advisability of preparing such an article.

Dr. Wysowski informed the Committee that she had requested recombinant growth hormone manufacturers to submit information from their studies on individuals who received recombinant hGH. The data Dr. Wysowski received was minimal. A major concern that was addressed is the risk of secondary neoplasms developing in hGH recipients who had been treated for cancer. Pfizer Inc. presented incidence rates that, as expected, were fairly high. The incidence of second neoplasm following malignant neoplasms of the brain and nervous system in pediatric patients who received rGH and were followed to January 2003 in Pfizer's KIGS (Kabi International Growth Study) was 31/10,000. The incidence of second neoplasms following leukemia was 53.9/10,000. Compared to data from Cancer Incidence in Five Continents (Vol. VII, International Agency for Research on Cancer, World Health Organization, 1997), the standardized incidence ratio of second neoplasm following brain and nervous system neoplasms in pediatric patients who received rGH was 25 (95 percent confidence interval: 14.5-41.4).

Dr. Wysowski also commented on article, entitled "Risk of Disease Recurrence and Second Neoplasms in Survivors of Childhood Cancer Treated with Growth Hormone: A Report from the Childhood Cancer Survivor Study" (Sklar, CA, et al. *J Clin Endocrinol Metab* 87, 3136-3141 (2002) (TAB D). This study was co-funded by the National Cancer Institute and the Genentech Foundation for Growth and Development. The study found that the relative risk of recurrence of secondary neoplasms for GH-treated survivors compared with those not treated with GH was 3.21 (95 percent confidence interval, 1.88–5.46). Dr. Wysowski expressed concern about a statistically significant 56-fold increased risk of osteosarcoma in acute leukemia/lymphoma survivors who had received growth hormone compared with those who had not received growth hormone. The 56-fold relative risk was based on 3 of 122 leukemia/lymphoma survivors who developed osteosarcoma after receiving growth hormone compared with 2 of 4,545 leukemia/lymphoma survivors who developed osteosarcoma and had not received growth hormone. (These data were calculated from the discussion section on page 3140 of the report by Sklar et al.)

The manuscript that describes the mortality experience (through 1996) of the cohort of pituitary-derived human growth hormone recipients was submitted to the *Journal of Pediatrics*. Dr. Mills has received verbal acceptance for its publication.

7. Update on Mailings to Growth Hormone Recipients

Dr. Schonberger reported to the Committee that approximately five percent of NIH mailings were returned as "not deliverable." Westat is running special traces for the unknown addresses consisting of credit bureau searches, postmaster letters, and internet searches, to see if updated addresses can be obtained.

Dr. DeMouy reported on a successful April 2003 mailing to the cohort and their physicians. The comments that were received in response to the mailing were both positive and negative. There were 110 substantive inquiries and a number of address changes. The Health Alert that was sent out was interpreted by a number of individuals as implying that, because they had received hGH, they were now subject to adrenal crisis. Dr. DeMouy explained that although an effort is made to word alerts as clearly as possible, some people misinterpret them and, therefore it is necessary to have a knowledgeable person available to speak with those individuals. The NIDDK Office of Communications and Public Liaison was able to alleviate the concerns that arose from the recent mailing.

There were two to three requests to obtain assistance in contacting other members of the cohort. These included a mother, who is also a social worker, of a child who is suffering extreme duress due to the risk of CJD. The mother wanted a channel to communicate with others who are at risk for CJD, or their family members, to ask how the knowledge of CJD risk has affected their lives. Another request for access to the group was made by David Davies, a recipient who is a journalist. In the past, The Magic Foundation agreed to facilitate interaction among members of the cohort; however, membership dues must be paid before the Foundation will assist in these matters. Consequently, this resource has not been satisfactory to recipients.

8. Status of Westat Contract

Dr. Schonberger reported that Westat completed its third five-year CDC-funded contract on September 29, 2002. At that time, the contract was modified to extend the performance period to June 30, 2003.

Following completion of the extended contract, Westat was awarded a new five-year contract funded by the NIDDK, with Dr. Leschek as the new Co-Project Officer. Funding for this contract is on an incremental basis depending on the ability of NIDDK to fund it and a desire to continue the contract. Westat has been authorized to bill up to $156,000 during the first year of the new contract. The total cost of the 5-year contract is $852,480 and the scope of work under the new contract is the same as for the previous one. Westat continues to monitor the cause of cohort deaths and to follow-up on CJD cases by periodically searching the National Death Index and reviewing available death certificates, medical records, and neuropathological tissues. Additional activities include obtaining IRB approval in several states in order to continue receiving death certificates from those states.

Westat informed the Committee that Ms. Janet Bykowski, Data Management Supervisor, is retiring. Ms. Lesa Houser will replace her.

9. Advances in Understanding the Biology of CJD

Dr. Brown presented the scientific article, entitled "RNA molecules stimulate prion protein conversion" (Deleault, NR, Lucassen, RW, and Supattapone, S. *Nature* 425, 717-720 (2003). The authors reported the successful amplification of misfolded prion protein using a modified version of the protein-misfolding cyclic amplification method and that the amplification of misfolded prions requires specific RNA molecules. The authors proposed that host-encoded stimulatory RNA molecules may have a role in the pathogenesis of CJD. *In vitro* amplification of prions may provide a mechanism whereby small numbers of prions in blood samples could be amplified and used in PrP^{Sc} screening tests. (TAB E)

A commentary entitled, "Conformational exposure: a new handle on prions" (Brown DR. *The Lance* 362, 929-930 (2003) (TAB F), reviews an article by Paramithiotis et al., entitled "A protein prion epitope selective for the pathologically misfolded conformation" (*Nature Medicine* 9, 893-899 (2003)). The authors recently developed antibodies against three amino acids, Arg-Arg-Tyr, that are exposed when PrP refolds into a protease-resistant form (PrP^{Sc}). The antibodies were shown to selectively identify PrP^{Sc} using *in vitro* animal testing. An advantage of this assay is that proteinase K digestion is not required. Thus, there is potential for these antibodies to be useful in developing screening tests and in treating prion disease. Dr. Paul Brown, who is working with this Canadian group, stated that there is the possibility for a human anti-PrP vaccine to be developed as an extension of this work. However, two potential problems that can arise with this type of vaccine are: 1) as with other vaccines it could cause death by severe allergic reaction; and 2) it might fail to cross the blood-brain barrier. (TAB G)

Dr. Brown reported that there have been no new developments regarding the Baxter blood testing. The only case of CJD being transmitted by blood remains the study of a chimpanzee inoculated intracerebrally with purified white cells taken from a pre-symptomatic CJD-infected chimpanzee. Dr. Brown suggested that transfusion may be a more effective means of transmitting CJD than intracerebral injection, simply because it is possible to deliver a much larger sample into blood, even if it causes infection less efficiently. However, a distinction should be made between transfusion of labile blood components and blood plasma products.

Recipients of components from the blood collected from individuals who were healthy and subsequently developed a classic form of CJD are being followed in an American Red Cross/CDC study. So far, none of them has developed CJD. Although the risk, if any, must be extremely low, the risk may not be zero. There are over a hundred individuals that survived at least 5 years after receipt of a transfusion from a patient who later developed CJD. In accordance with the American Red Cross and CDC IRBs, the transfusion recipients in the ongoing study have not been informed of their receipt of blood from a CJD donor because the risk of transmission of classic CJD is theoretical and more harm to the patient than benefit could result from such notification. At this time, there have been no human cases of classic forms of CJD being transmitted by transfusion.

10. New Business and Information Items

Dr. Schonberger inquired about how NIDDK and FDA were responding to the Freedom of Information Act request (FOIA) for hGH/CJD files as he too has received the FOIA. Dr. Fradkin reported that NIDDK had all of their files copied a couple of years ago. The cabinets holding the copied files are locked, separating those files from any new documents that are accumulated, preventing the necessity for recopying the old files. Following the meeting, Drs. Fradkin, Schonberger, and Farishian went to meet with Ms. Lynell Nelson, who is responsible for the NIDDK hGH/CJD files.

The Committee discussed IRBs as they pertain to the work of the Committee. A determination was made by the Internal Review Board that an IRB is not required for the Committee's actions. This is because the follow-up information is on patients who have died and are no longer considered to be human subjects. At this time, notifications are no longer being sent to the Cohort unless a major event takes place such as the development of a new treatment procedure. Rather, information is being updated on the web and members of the Cohort can contact the Committee if they would like to receive a written copy.

The meeting was adjourned at 2:45 p.m.

Allen M. Spiegel, M.D.