PUBLIC HEALTH SERVICE

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

November 8, 2002

National Institutes of Health
Bethesda, Maryland

Committee Members Attending
Dr. Allen Spiegel, NIDDK, Chairman
Dr. Paul Brown, NINDS
Dr. Judith Fradkin, NIDDK
Dr. Saul Malozowski, NIDDK
Dr. James Mills, NICHD
Dr. Robert L. Perlstein, FDA
Dr. Lawrence Schonberger, CDC
Dr. Diane Wysowski, FDA
Dr. Dixie Snider, CDC

Also Attending
Ms. Joan Chamberlain, NIDDK
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 and asked that those present introduce themselves to the other members of the group.

2. Discussion/Approval of Minutes of the October 2001 Meeting

The Committee noted that 1999 was the year that Westat screened for previously unknown cohort deaths using the National Death Index (NDI), as stated in the October 2001 meeting minutes, second paragraph, of the Epidemiology Study Status Report. The minutes will be modified to reflect this change.

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

3. Epidemiology Study Status Report

As of 2001, of the 6,272 patients enrolled in the study, 573 (9.1 percent) are known to have died. Of these 573 deaths in the cohort, 22 were attributable to CJD.

Dr. Schonberger noted that Westat is in its fifteenth year of identifying and following up on the vital status of the 6,272 members of the cohort. The procedure that Westat uses for identifying Creutzfeldt-Jakob Disease (CJD) deaths through the NDI begins with the NDI providing Westat with death certificate numbers that match with cohort patients. In each case, Westat then contacts the state vital statistics office to obtain the death certificate to learn the cause of death.

In 2002, Westat added two CJD deaths of cohort members; these are cases 23 and 24. Information regarding the new CJD cases is included in Westat's listing in the CJD National Report.

In addition to these two new cases, another likely cohort case of CJD was reported to Dr. Fradkin by the patient's endocrinologist. The patient was still living as of September 2002. This case will be added to Westat's continuing study as "under investigation," as case TR.

Westat reported two additional cohort deaths possibly related to CJD. These cases, uncovered when Westat checked cohort members against the NDI, are also under investigation. The cause of death was not diagnosed as CJD by a physician in either case. One of the patients (called case SW) is being investigated because the death certificate indicates that the patient died in August 2000 at the age of 33 of Alzheimer's disease. Westat's records indicate that the woman's family declined an interview for a 1980's follow-up study and, therefore, key data on this patient are not available.

The other case lists progressive cerebellar dysfunction as the cause of death. Westat's records indicate that the patient had a tumor that caused a pituitary hormone deficiency. This patient (called case GS) is not on Westat's listing of confirmed or likely CJD cases under investigation because the evidence for CJD is considered very weak.

Since the Committee's last meeting, Westat has completed searches for NDI cohort deaths for the year 2000 and extending back to the period 1985 through 1999. The purpose of this search was to provide greater assurance of the completeness of ascertainment of cohort deaths; both the NDI and Westat databases are periodically updated with more deaths and/or patient identifiers. In addition, Westat performed a search of the Social Security Agency's (SSA) records for deaths that occurred during 1985-2000. Westat determined that eight additional cohort deaths occurred between 1985 and 1999. None of the newly discovered deaths in the cohort occurred during the earliest five-year period of this search. No more than two deaths were added to any single year. The SSA search accounted for one of the eight deaths identified.

Westat's report for the year 2000 leads to the conclusion that there were probably 29 deaths among the cohort that year, although death certificates for two of the probable matches with the NDI index were not yet received to confirm the match. The death of another cohort patient was reported by a family member in 2001.

It was agreed at the October 2001 meeting that Westat will not try to obtain medical records on all cohort members who die. The procedure decided on was that Dr. Fradkin would first review the death certificates for possible cases of CJD or leukemia. Westat would then try to obtain the medical records on these cases. Dr. Schonberger noted that according to Westat, medical records are becoming increasingly more difficult for Westat to obtain. In February, Westat updated its mailing list using the National Change of Address process. It also performed additional tracing for about 90 persons for whom no forwarding address was available. During the past year, Westat fulfilled the IRB renewal requirements that are needed to obtain death certificates in four states and New York City, where special submissions were required.

Westat reported that Ms. Elizabeth Wood, Assistant Study Manager, died. Her supervisor, Janet Pakowski, is assuming responsibility for the daily management of the studies.

At the end of FY 2002, Westat applied for and was given a no-cost extension of its contract through June 30, 2003.

4. New Cases of CJD, United States and Foreign

Dr. Fradkin discussed one of the new, confirmed CJD deaths in the cohort (case 24) and one of the additional cases under investigation for possible CJD (case SW). She stated that new CJD case 24 had been reported to her by the patient's physician and her presentation was typical of CJD caused by hGH. She also indicated that an autopsy had been approved by the family.

Case SW, a case under investigation, is the 33-year-old woman whose cause of death on her death certificate was reported as Alzheimer's disease. The family had previously declined to fill out one of our study questionnaires, but Westat was able to determine their address and phone number. The Committee discussed whether study personnel should now contact the family for permission to obtain and review the patient's medical records. It was decided that Dr. Fradkin would write a letter to the family explaining the benefits to the study and other cohort members of knowing whether this patient had CJD and requesting an interview with the family and/or permission to examine the patient's medical records. Dr. Fradkin will send a draft of the letter to Dr. Brown for his review before the letter is sent by registered mail to the family. A follow-up will be made to the family by phone.

Dr. Schonberger described new, confirmed case 23 who, in 2002, had been reported to NIH by the patient's wife and to the CDC by a hospital neuropathologist and a state epidemiologist. This case-patient was particularly difficult to diagnosis because of the

presence of three conditions, each of which produces neurologic signs and symptoms: Chiari malformation, spinalcerebellar ataxia type 8, and CJD. The patient had developed an unsteady gate in January 2000. Because symptoms could have occurred because of the Chiari malformation, an operation was performed in April 2001. Normal infection control procedures were used to decontaminate surgical instruments rather than the more stringent methods generally recommended for use when neurosurgical procedures are performed on patients with CJD. After the patient's death in March 2002, CJD was confirmed at autopsy. Following this confirmation, the hospital (in Pittsburgh, PA) notified approximately 1,000 surgery patients of the situation and encouraged them to contact their physician.

Dr. Schonberger also discussed case TR, a case under investigation, which was reported by his endocrinologist as having developed CJD. Years earlier, this patient had killed his mother and used CJD as his defense. At this time, we do not have any of his medical records and the case is under investigation.

New foreign cases reported brought the total number of cases in the United Kingdom to 40 cases and the total number of cases in France to 90 cases.

5. Report on Mortality in hGH Recipients (Dr. Mills)

The newly confirmed case brings the number of U.S. CJD cases to 24. In addition, cases TR and SW are under investigation. Although CJD is considered to be less likely, an effort will be made to further clarify the cause of death of patient GS (see page 2 of report).

The Committee discussed the U.S. not being able to compile hormone lot-specific statistics on U.S. cases precisely comparable to those in the British study.

A manuscript on the mortality experience of the hGH recipients in the U.S. was submitted to the *New England Journal of Medicine* and is under review. The Committee discussed the issue of Westat's having subsequently identified 25 addition deaths in the period covered by the manuscript. To make sure that these 25 deaths do not alter any of the manuscript's conclusions, Dr. Mills will review their reasons for treatment and their causes of death. The manuscript reports the fact that there continues to be no CJD in patients in the cohort who started their hGH treatment after 1977, when the purification procedure was changed.

6. Update on Reports of Cancer in Human Growth Hormone Recipients

Dr. Mills discussed an article published in *The Lancet*, entitled, "Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: A cohort study." (*The Lancet*. 360:273-77, 2002) (TAB A). The authors examined the risk of cancer in patients who were treated with human pituitary growth hormone before May 1985. The follow-up on these patients extended up to 40 years. Although the study found a significantly raised frequency of colon cancer within the cohort, the small

number of patients precludes a firm association. Since the NHPP follow-up ascertains only deaths, our data is of limited value in assessing the relationship between hGH and cancer.

7. Final Report on Studies of Animals Injected with hGH

Dr. Brown told the Committee that the last report on the squirrel monkeys inoculated with different lots of hGH was completed. Seventy-six lots of hGH were tested using a pair of monkeys per lot. A few monkeys died within the first year. Since this was too early to be considered as deaths caused by CJD, they were removed from the program. During the next 5½ years, one monkey developed CJD. The other monkey in the pair remained negative. In or about the year 2002, the remaining monkeys were sacrificed. Autopsies were performed on some of the monkey brains, but none was positive for signs of CJD.

8. Update on hGH Contacts and Inquiries, etc

Dr. Fradkin received an inquiry from an official from Ireland who wanted to know the methods used to obtain consent for obtaining pituitary tissues for the production of hGH. Dr. Fradkin did not have this information.

9. Update on Mailings to Growth Hormone Recipients

Dr. DeMouy told the Committee that several documents are being prepared to update the growth hormone recipients about data and issues related to the present study of the recipients. They will consist of a shorter, easier-to-read summary, as well as a longer, more comprehensive summary; an alert about the increased risk of death from adrenal crisis among the subjects observed in the study; and a letter to the physicians of the subjects in the study and a letter to the study participants themselves. The notification package of documents was seen by the Committee and will be reviewed by the IRB and by Dr. Paul Stolley. Dr. Stolley is a retired epidemiologist from the University of Maryland whose son was treated with hGH and who serves as a special consultant to the Committee.

10. Status of Westat Contract

Dr. Schonberger informed the Committee that the Westat contract is being extended six months, through the end of June 2003.

11. Advances in Understanding the Biology of CJD

"Three recent studies have attracted attention both inside and outside the scientific milieu of CJD:

Ma and colleagues reported on the occurrence of neurologic disease in mice that were genetically engineered to mimic the effect of drug-induced proteasome inhibition.

(Ma, J., Wollmann, R., and Lindquist, S. Neurotoxicity and Neurodegeneration When PrP Accumulates in the Cytosol. *Science* 298, 1781-1785 (2002). (Metabolic studies of normal and misfolded prions have emphasized the role of proteasomes in prion degradation. The reasoning is that if misfolded prions are the cause of disease, inhibition of their normal degradation pathway might provide clues to disease pathogenesis). They created transgenic mice expressing a cytosolic form of prion protein that in earlier studies had been shown to have some of the same biochemical characteristics as the pathologic prion protein, to accumulate under the influence of a proteasome inhibitor, and to be toxic to nerve cell cultures. To date, however, there is no evidence that the protein can transmit infection. (TAB B)

Zanusso, et al. ("Detection of Pathologic Prion Protein in the Olfactory Epithelium in Sporadic Creutzfeldt-Jakob Disease." *N. Engl. J. Med.* 348(8), 711-719 (2003) have shown that the olfactory nerve and associated nasal epithelium (but not the adjacent respiratory epithelium) contain large amounts of prion protein in autopsy tissue of patients dying of CJD. If ongoing studies show that the protein can also be detected in biopsies of living patients, the procedure could supplant brain biopsy in CJD cases or tonsil biopsy in vCJD cases as the easiest and most practical method to establish a pre-mortem tissue diagnosis, when it is desirable to do so. It may also have implications for neuroinvasion in environmentally acquired infections. (TAB C)

Safar, et al. ("Measuring Prions Causing Bovine Spongiform Encephalopathy or Chronic Wasting Disease by Immunoassays and Transgenic Mice." *Nature Biotechnology* 20, 1147-1150 (2002) continue to extend their studies of a prion detection method that depends upon the differential antibody binding of native and denatured prion protein (conformational dependent immunoassay, or CDI). They have shown that different strains of TSE (including chronic wasting disease and bovine spongiform encephalopathy) can be distinguished. They have recently reported the detection of prion protein in the blood of experimentally infected hamsters during the clinical stage of disease. It was reported that, "This represents a breakthrough in detection sensitivity, with the CDI method representing an important advance toward a pre-clinical blood screening test for TSE infection." (TAB D)

12. New Business and Information Items

There were no new business and information items to report.

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

Allen M. Spiegel, M.D.