PUBLIC HEALTH SERVICE

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

October 26, 2006

National Institutes of Health
Bethesda, Maryland

Committee Members Attending
Dr. Judith Fradkin, NIDDK
Dr. Ellen Leschek, NIDDK
Dr. Eugene Major, NINDS
Dr. James Mills, NICHD
Dr. Robert Perlstein, FDA (by speakerphone)
Dr. Griffin Rodgers, NIDDK, Chairman
Dr. Diane Wysowski, FDA

Also Attending
Dr. Jane DeMouy
Dr. B. Tibor Roberts, NIDDK
Ms. Marcia Vital, NIDDK

The meeting began at 12:10 p.m.

1. Welcome

Dr. Rodgers welcomed the group and asked Dr. Fradkin to lead the discussion.

2. Epidemiology Study Status Report (includes U.S. hGH/CJD cases, status of death follow-up and Westat contract)

Dr. Leschek reported that she will be initiating the process of renewing the Westat contract, which would otherwise end in June 2008.

At the 2005 Committee meeting, it was noted that, by WHO standards, a case can only be considered "confirmed" if a definitive post-mortem sample is available. Accordingly, a decision was made to classify the U.S. cases according to their level of certainty. Therefore, Dr. Leschek presented the Committee with a breakdown of the American hGH/CJD cases, divided into the following categories: I. Neuropathologically confirmed (13 cases); II. Clinically confirmed (13 cases); III. Clinically suspicious (1 case); and IV. Possible cases under investigation (6 cases).

Dr. Leschek noted that none of these are actually new since 2005. The 26 cases previously listed as "confirmed" are now divided into the first two categories. As discussed at length last year, there was no agreement among the members of the Neurological Review Group (NRG) concerning Case 1270-115, which is the one now listed as "clinically suspicious." Because no

additional information is available, the case will remain in this category, and will not be investigated further.

Two of the cases now in the "under investigation" category previously had been treated as closed. These preceded the tenure of many on the Committee, and were cases in which there was some suspicion of CJD by the NRG, but not enough to list them as clinically confirmed. Thus, they could in principle be listed in the new "clinically suspicious" category.

The first of these (Westat ID 1470-052) died with a diagnosis of a rare genetic condition. Neurological symptoms that occurred shortly before death were not inconsistent with CJD, however, and one of the two NRG reviewers considered CJD to be a possible cause of death; the other reviewer considered CJD unlikely. The second patient whose case had been closed, (Westat ID 0240-051,) had progressive ataxia and mental retardation that seemed to be worsening just prior to death. In this case the first reviewer thought CJD was unlikely and the second considered its probability to be around 50 percent. Since new members joined the NRG since these cases were investigated, both have been referred back to the NRG for review by the new member(s).

The remaining four cases under investigation were all discussed at the Committee's 2005 meeting. Westat ID 1290-071 was originally brought to the Committee's attention at the 2002 meeting; gastrointestinal bleed, cardiac arrest, and Alzheimer's disease were listed as causes of death. A neurologist's records from the last years of the patient's life were obtained this year. Although these records did not include information from the 5 months immediately preceding the patient's death, they were sent to the NRG. One reviewer concluded there was no evidence of CJD, the other considering CJD possible, because of cognitive decline, ataxia, and myoclonus that developed in the last eight months of life. This reviewer wished to speak with the patient's neurologist, and Westat has been asked to put the two doctors in contact. Pending the outcome of that discussion, the case may be referred to the third neurologist on the NRG.

The patient with Westat ID 0730-023 died in 2003, with cause of death listed as "CJD – End Stage." It appears no autopsy was performed. The patient was treated with hGH for 4.5 years beginning in late 1973. Unfortunately, despite multiple attempts to find the family, they have not been located, so medical records from this individual have still not been obtained. Westat will continue to search for the family.

The patient with Westat ID 1180-032 died September 2005. The patient's father later called to report that his son had been treated with hGH from 1976-1979, and had died of CJD. No autopsy was performed. The father has not released his medical records, and the death certificate is not yet available through the National Death Index. However, Westat will get the death certificate when it is available and will continue to try to obtain the father's consent.

"Craniopharyngioma" was listed as the cause of death on the death certificate of the patient with Westat ID 0400-058. The patient had had multiple surgeries and radiation for this condition, resulting in panhypopituitarism and seizures. A stroke left this individual aphasic, with a right field cut and other chronic issues, including gait abnormalities. In addition, a meningothelial tumor was removed. Both neurologists on the NRG indicated there was no evidence of CJD, but

both also noted that the records were missing information from the 3 years immediately prior to the patient's death. A request for those additional records is pending.

Dr. Leschek also reported that the total number of confirmed deaths in the cohort (not including the CJD deaths) is 662. A discussion ensued about the major causes of death in the cohort and whether anything can be gained from additional analyses beyond those already published. Dr. Fradkin expressed the opinion that the primary remaining question for the Committee to answer is whether individuals treated with growth hormone after 1977—when Dr. Albert Parlow's lab began purifying the hormone using size exclusion chromatography—are at risk of CJD. She noted that whereas countries that continued using ion exchange methodologies beyond 1977 have continued to see cases of hGH-related CJD, the U.S. has not. Significantly, those in our cohort who developed CJD all began their treatment prior to that year.

Dr. Major noted that a recent article in *Lancet* showed that some individuals may develop kuru after extremely long incubation periods (greater than 50 years), particularly if they are heterozygous for a common polymorphism at PRNP codon 129. It is therefore difficult to gauge how long the cohort needs to be followed in order to conclude that there is no danger to any particular sub-group. However, because the mode of transmission is oral in kuru, compared to hematogenous for hGH, it is difficult to know how directly these results can be compared. Because the incidence of CJD in patients treated pre-1977 seems to be decreasing, the Committee felt that if there have been no post-1977 cases by 2010, we may consider concluding that the chances of such a case are very small.

Dr. Fradkin noted, however, that even then there may still be benefit to maintaining the Westat contract, because Westat performs a variety of services for us, such as record storage, that may continue to be useful.

3. Report on CJD in Foreign GH Recipients

A report published this year in *Neurology* by Brown and colleagues reports that the total number of CJD cases outside the U.S. that are attributable to hGH is 168, with the following country-by-country breakdown:

France	107
United Kingdom	51
New Zealand	6
Australia	1
Brazil	1
Holland	1
Qatar	1
Total	168

4. Update on Website Fact Sheet for hGH Recipients

Dr. DeMouy distributed a draft revision of the "Information for People Treated with NHPP Human Growth Hormone" based on the numbers presented in the Brown *et al.* paper referenced

above. Because there were no objections, Dr. DeMouy will make the changes as described. Dr. DeMouy also noted that the number of calls and public inquiries has fallen to between one per week and two per month. Dr. Wysowski inquired about how often people are accessing the web site, and Dr. DeMouy replied that she would ask the people maintaining the website to see if they have statistics on traffic.

5. Brief highlights of progress in CJD research

Dr. Major referred the Committee to a recent review on the pathogenesis of prion diseases in *Nature Reviews Microbiology* by Adriano Aguzzi. Other recent papers include two in *Science*. One shows that chronic wasting disease (deer and elk equivalent of CJD) can be transmitted through saliva. The other, Saa et al., describes an experimental pre-mortem diagnostic test.

The meeting was adjourned at 1:20 p.m.

Griffin Rodgers

Griffin P. Rodgers, M.D.