PUBLIC HEALTH SERVICE

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

November 9, 2005

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. Lawrence Schonberger, CDC (by speakerphone)
Dr. Allen Spiegel, NIDDK, Chairman
Dr. Diane Wysowski, FDA

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

The meeting began at 10:40 a.m.

1. Welcome

Dr. Spiegel 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 the Westat contract was proceeding smoothly, and that it is scheduled to continue through June 2008. She noted in the upcoming year we would have to make a decision on whether to renew the Westat contract.

Dr. Leschek noted that there are no new confirmed cases of CJD and discussed possible CJD cases and other deaths under investigation in 3 categories: "Possible Cases of CJD—Follow-up from December 2004 Meeting"; "Possible Cases of CJD—New Since December 2004 Meeting"; and "Other Cases Under Investigation".

The follow-up-from-2004 category includes two cases, both patients who died in 2000. (For more extensive details about both of these cases, see the 2004 minutes.)

The first, Westat ID 1290-0718, was originally brought to the Committee's attention at the 2002 meeting. The individual died at age 33 with causes of death listed as gastrointestinal bleed, cardiac arrest, and Alzheimer's disease. Despite extensive efforts, no new information on this

individual has been identified in the last year. The decision was therefore made to refer this case to the Neurological Review Group (NRG).

The second follow-up case, Westat ID 1270-1157, died at age 40 of acute respiratory failure and progressive pancerebellar dysfunction. As of the December 2004 Committee meeting, the records from this case had been reviewed by two NRG neurologists. One indicated that CJD was possible but unlikely (1-9%) while the other felt that CJD was highly probable (90-99%). A third neurologist was therefore recruited, who assessed the case as probable CJD (51-89%).

As with the confirmed cases, the hGH treatment in this case was entirely prior to 1977. Dr. Fradkin noted that determining whether people treated after 1977 were at risk of CJD is perhaps the most important remaining function of the study, and this question has relevance not only for subjects who received NHPP hormone but also for those who received commercial hormone prepared using protocols similar to those used by NHPP after 1977. Dr. Spiegel agreed and also noted that the lack of evidence that individuals treated post-1977 were at risk bears on the question of how long to continue follow-up of the cohort.

Dr. Fradkin suggested that the 1270-1157 case be reported as a "probable" case, since it appeared that further investigation in an attempt to yield a definitive diagnosis would not be fruitful. This prompted a discussion of the criteria for the various categories reported as outcomes of the investigation of deaths in the NHPP cohort. Since definitive autopsy results are often unavailable, cases have been considered to be confirmed, for our purposes, when available clinical data are highly consistent with CJD. Dr. Schonberger pointed out that by World Health Organization standards, such cases would be listed as probable.

> **Action Item**: For the next meeting, Dr. Leschek should provide a breakdown of all cases according to level of certainty of CJD diagnosis. These should include those that are neuropathologically confirmed; those that are not but which have overwhelming clinical evidence to support the diagnosis, as reflected by agreement of the NRG; and those for which the evidence is not unanimously considered unequivocal by the NRG. How to most accurately convey information about the likelihood that CJD was the cause of death will be considered at the next meeting. This breakdown and other meeting materials should be emailed or FAXed in advance to any members of the Committee participating by teleconference.
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> **Action Item**: In the interest of full disclosure the website (http://www.endocrine.niddk.nih.gov/pubs/creutz/update.htm#1) should reflect that in addition to the 26 "confirmed" cases there is a significant chance that case 1270-1157 represents a case of CJD.

Dr. Leschek then discussed "Possible Cases of CJD—New Since December 2004 Meeting". Westat ID 0730-0239 died in 2003 at age 42, 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. The impression is of possible CJD, and the plan is for a complete review of medical records.

Westat ID 1180-0323 died September 2005 at 35 years of age. The patient's father later called to report that his son had been treated with hGH from 1976-1979, and had died of CJD. The impression is of possible CJD; it appears that no autopsy was performed. The plan is for a complete medical record review.

Dr. Leschek then turned to "Other Cases Under investigation," noting that Westat ID 1440-0147 had been resolved by the NRG as a death due to glioblastoma, with no evidence of CJD. It will now be listed as negative. Records for Westat ID 0400-0584, for whom "craniopharyngioma" was listed as the cause of death on the death certificate, will be reviewed by the NRG.

Dr. Lescheck noted 621 people in the cohort are known to have died, not including the 21 confirmed to have died of CJD. Note that there are five other deaths considered confirmed hGH-related CJD among patients not in the original cohort.

3. Report on CJD in Foreign GH Recipients

Dr. Schonberger reported that the total number of cases, internationally, was 187, (counting 26 for the U.S.) distributed among eight countries. This includes increases in two countries: France, where the total is now officially 102 (up three from last year); and the United Kingdom where the total is now 49 (an increase of eight). The number of international dura mater transplant-related CJD cases increased from 169 to 180.

Dr. Fradkin, noting that Germany and Japan had exclusively used hGH prepared in the post-1977 manner, asked if there were yet any cases of hGH-associated CJD in those countries. Drs. Schonberger and Major both indicated that there are still no known cases from those countries.

Dr. Major noted that there was a valuable reference in Neurology that provides global statistics on CJD resulting from various causes, and that Dr. Schonberger had co-authored a valuable review on the health impact of CJD.

4. Update on Fact Sheet for hGH Recipients

Dr. DeMouy reported on the rewording of the on-line Health alert to members of the cohort, to clarify that the danger of adrenal crisis does not come from having taken hGH, but rather from underlying medical conditions common to many people who have hGH-deficiency. Other edits to the fact sheet included increasing the number of cases the PHS has "identified" to 26, and providing additional detail to the information on why blood and organ donation is not allowed by people who have received hGH.

Dr. DeMouy also noted that the number of calls and public inquiries have diminished considerably, and is now down to about 1 per week.

5. Highlights of new basic and clinical information about CJD

Dr. Major noted that current research of most direct interest to the Committee pertains to efforts to develop a pre-mortem test for CJD. He noted that most such ongoing efforts are pursuing

antibody-based approaches. However he noted that an intriguing alternative option is being developed using a series of peptides comparable to portions of PrP that undergo the conformational change that occurs during formation of PrP^{Sc}. CJD-positive blood or tissue samples induce a conformational change in the assay peptides that can then be instrumentally detected.

Dr. Schonberger reported on a paper by Chesebro et al. demonstrating that mice carrying a mutant version of PrP that does not undergo posttranslational modification with a glycosylphosphatidylinositol (GPI) membrane anchor can be infected by PrP^{Sc}. However, although abundant, infectious amyloid deposits result, there are minimal clinical manifestations of the disease in these animals.

Dr. Schonberger then described Silveira et al., in which the authors show that PrP particles of intermediate size (14-28 PrP molecules) are much more infectious than those that are either smaller or somewhat larger.

Dr. Schonberger noted a review by Weissman and Aguzzi on approaches to therapy for the transmissible spongiform encephalopathies (TSEs). The authors cite a lack of experimental evidence for the efficacy of quinacrine, even in animals. Amphothericin B, although it has been shown to extend life in TSE-infected hamsters, is notably toxic in humans, and was ineffective when used to treat a patient with CJD. Intraventricularly-injected pentosan polysulfate may hold promise as a treatment, however. It has been shown to lengthen life in infected mice even when administered late in disease. Moreover it is a drug used for other indications in people, though it has serious side effects; there are currently no published tests of efficacy in humans.

6. Information on changes to recombinant human growth hormone labeling

Dr. Pearlstein, although unable to attend the meeting, provided information on changes being made to labeling used for recombinant human growth hormone.

The meeting was adjourned at 11:50 a.m.

Judith Fradkin, M.D.