PUBLIC HEALTH SERVICE

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

December 17, 2004

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

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

Dr. Spiegel chaired the meeting, which began at 9:00 a.m.

1. Welcome

Dr. Spiegel welcomed the group.

2. Discussion/Approval of Minutes of the December 2003 Meeting

It was noted that under "Foreign cases of CJD" of the 2003 minutes, the parenthetical sentence on case confirmation refers to a date in December 2004. Dr. Spiegel suggested that the parenthetical sentence be eliminated and replaced with, "This, however, could not be independently confirmed by the Committee."

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

3. Epidemiology Study Status Report (including status of death follow-up and Westat contract)

Dr. Leschek distributed a document to the Committee pertaining to the Westat contract and to recently confirmed and possible CJD deaths in the cohort. She began by recommending that from this time forward, to avoid confusion, all documentation regarding confirmed cases will be referred to using the Westat identification number as well as the individual's initials and CJD case number. For purposes of summary in the minutes, the initials and date of death will be redacted to preserve patient confidentiality.

Two cases previously listed as possible CJD have been confirmed in the last year. For Case 25, CJD was listed as cause of death on the death certificate. No specimens were submitted for 14-3-3 CSF and PrP evaluations, but slides from brain tissue were reviewed by two neuropathologists participating in the study review group, and both reported that the specimens were of good technical quality. The first neuropathologist concluded that the tissue pathology was consistent with probable CJD, and no alternative neurologic diagnoses were identified. The second neuropathologist concluded that the brain tissue was definitely consistent with a diagnosis of CJD.

According to the death certificate, Case 26 died from CJD and cardiorespiratory failure. An autopsy was performed and microscopic examination of the brain revealed neuronal loss and pathology consistent with CJD. Specimens were sent to the National Prion Disease Pathology Surveillance Center, where CSF 14-3-3 positivity and PrP^{Res} immunostaining were confirmed. Brain slides were reviewed by two of the study review group neuropathologists, and both reported that the specimens were of good technical quality. The first neuropathologist concluded that CJD was probable, with no alternative diagnosis. The second neuropathologist listed the diagnosis of CJD as definite.

Two cases from last year remain under consideration for possible CJD. The first, Westat ID 1290-0718, died at age 33. On the death certificate, causes of death were listed as gastrointestinal bleed, cardiac arrest, and Alzheimer's disease. Very limited medical records were available for review (no information was available for the period between ages 8 and 33 years), and the details are described in the 2003 Minutes. Overall, it was felt that the medical records were consistent with a severe neurological disorder, but definitive tests and samples were unavailable to draw any conclusions. The family, primary care physician, and neurologist have been contacted by mail requesting additional and specific information about the time between ages 8 and 33 years. A response is pending.

The patient in the second case, Westat ID 1270-1157, died at 40 years of age. The death certificate listed cause of death as acute respiratory failure and pancerebellar dysfunction. Detailed medical records were obtained, but an autopsy was not performed, and samples appropriate for confirming CJD were never obtained. Early in 2004, the records were reviewed independently by two neurologists from the study review group, and both pointed out that the observed worsening of the patient's ataxia and mental functioning shortly before death were consistent with CJD. The first neurologist considered CJD highly probable (90-99 percent chance), but the second neurologist regarded CJD as possible but unlikely (1-9 percent chance). In November 2004, a third neurologist agreed to serve as an additional member of the Neurologic Review Group (NRG). He will review the records when Westat finalizes his consultancy agreement.

In another case, Westat ID 1440-0147, the patient died in 2001 at 31 years of age with cause of death listed as glioblastoma. Review of medical records uncovered a worsening ataxia over the three months prior to death, although this symptom was likely due to the pontine/cerebellar location of the tumor. The medical records will be sent to the NRG for review.

Dr. Major asked about the particulars of the protocol when possible cases arise. Dr. Fradkin stated that when the NIH is contacted by the family prior to death, we maintain communication with them and their physician, and try to obtain a CSF test and ensure that there is an autopsy, as in cases 25 and 26. The other way that possible CJD cases are identified is through searching the National Death Index (NDI) for individuals from the hGH cohort. Death certificates are obtained, and where indicated, medical records and further information is sought, as in the cases under consideration which are discussed above.

Dr. Leschek reported that interactions with Westat have been going smoothly, and that nothing had changed in the contract since last year.

4. New Cases of CJD

United States Cases of CJD

Dr. Leschek distributed the most recent quarterly report from Westat. In summary it reports a total of 614 deaths from the original 6,272 member cohort. Twenty-one of these are known to have had CJD at death; five additional CJD deaths were of hGH recipients from outside the original cohort. As described above, two more of the 614 deaths are being investigated for possible CJD. The newly confirmed or possible cases were all known prior to this past year (2004), and all began treatment with pituitary-derived hGH prior to the change in purification procedure that occurred in 1977. Of the subjects who eventually developed CJD symptoms, the mean incubation time from midpoint of hGH treatment to onset of symptoms is 249 months, or almost 21 years. The longest incubation time from midpoint of hGH treatment to onset of symptoms was 332 months (more than 27 years).

Foreign Cases of CJD

Dr. Fradkin informed the Committee that a colleague with INSERM had put her in touch with a contact for French CJD information, Dr. Jean-Philippe Brandel of Cellule Nationale de Référence des MCJ, Hôpital de la Salpêtrière. Dr. Brandel reports that there are currently 99 confirmed cases of hGH-related CJD in France. This number represents roughly 10 percent incidence among those treated with French-produced hGH between December 1983 and June 1985. In France CJD risk was concentrated during that time. The finding that cases are continuing to arise in France 20 years after this high risk period of treatment provides information about the incubation time of CJD transmitted by hGH with implications for the U.S. cohort. It should be noted that the method of hGH preparation in France between 1983 and 1985 did not include the procedures instituted in the U.S. in 1977.

Dr. Schonberger reported that through personal contacts he estimates a total of at least 176 hGH-related CJD cases worldwide: the 99 from France; one each from Australia, the Netherlands, and Brazil; six from New Zealand (which represents one more than previously known); one from either Norway or Sweden; and 41 from the United Kingdom, along with the 26 confirmed U.S. cases. About 19 percent of these cases come from hGH produced in the U.S. (the domestic cases as well as those from Brazil and New Zealand). Dr. Schonberger noted that the six New Zealand cases represent fully 13 percent of the recipients known to have taken hGH from the U.S. in that

country, greatly in excess of the incidence here, where it is just under 1 percent to date among persons treated through the National Hormone and Pituitary Program prior to the purification change in 1977.

Dr. Fradkin suggested that since the retirement of Dr. Brown it would be worthwhile to put another person in charge of tracking international hGH-related CJD incidence, and suggested that Dr. Schonberger with his multiple international contacts would be a logical choice. Dr. Major indicated that his group also has valuable contacts who may be helpful.

Dr. Spiegel requested that Dr. Fradkin put Drs. Major and Schonberger in contact with Dr. Brandel, so that we may hopefully gain a more complete picture of the international situation. Dr. Spiegel went on to note that we are unlikely to have international information that is as accurate and detailed as what we have in this country, but that the purpose of the global information is to get a better sense of the hGH-CJD incubation period, and to provide better and more valuable information to the U.S. hGH cohort. Dr. Fradkin noted that a large proportion of the European hGH recipients received hormone made by the method used post-1977 in this country; therefore if cases were to arise from among those European patients, it would have significant implications for the group of American recipients who were treated between 1977 and 1985. Dr. Schonberger noted that because the U.S. was among the first countries to begin administering hGH therapeutically, our data may itself be more informative with regard to incubation period than what is available from the rest of the world.

Dr. Mills pointed out that because U.S.-produced hGH yielded the high frequency of CJD in New Zealand noted above, knowledge of lot-specific information might allow us to identify a high risk group from among our population. Dr. Fradkin indicated that a great deal of effort has been expended to address that question, but that the available records were unfortunately unenlightening.

Dr. Schonberger also mentioned that, again according to unofficial personal communications, the number of dura mater graft-associated CJD cases around the world is now about 169, including an official number of 112 from Japan. Dr. Spiegel noted that information on dura mater transmission was primarily of academic interest, because it does not help us establish risks and incubation periods for recipients of pituitary-derived hGH.

5. Report on Mortality in hGH recipients

Dr. Mills provided a reprint of the paper, "Long-term mortality in the United States cohort of pituitary-derived growth hormone recipients" (Mills et al. *J Pediatr* 144, 430-436 (2003), TAB A) A central conclusion of this paper is that many of the patients in this cohort were dying not of iatrogenic CJD, but rather of preventable causes related to adrenal insufficiency. Dr. Spiegel noted that this type of information is of tremendous interest to our study population and their health care providers, and that it is a very good thing that these data have been made available and have been well reported.

Dr. Spiegel noted that a minor illness, such as gastroenteritis, could precipitate the need for even more cortisone by pituitary-insufficient members of the hGH cohort, or inability to take the

regular replacement. It is therefore important to monitor these people, and to be certain that they receive adequate supplemental adrenal corticosteroids, particularly during intercurrent illness. Dr. Leschek commented that during her review of medical records, she often found that the health care providers of individuals who appeared to have died of adrenal crisis were not aware that their patients were hypo-adrenal.

6. Update on Fact Sheet for hGH Recipients

Dr. DeMouy reported during the last meeting that some people had misunderstood the adrenal crisis health alert, believing that their having been treated with hGH rendered them subject to adrenal crisis. To address this misconception, a variety of changes have been proposed, which were summarized in a document she distributed to the Committee, asking for comments.

Dr. Spiegel indicated that there are two important facts that must come through in this document: that GH-replacement therapy is not itself the cause of adrenal crisis, and the paragraph on why patients should know about adrenal crisis should explicitly state that only a subset of hGH patients—those who have hypo-pituitarism—are at risk for adrenal crisis. Drs. DeMouy, Leschek, and Fradkin will craft that message carefully. Dr. DeMouy pointed out that the new version of the alert will not be distributed to the cohort, but rather will be available on the website.

Two other changes were proposed for the fact sheet. The statement on how many people treated with hGH have developed CJD was modified to explicitly state not only that cases have come exclusively from individuals who began treatment prior to 1977, but also that this is when the laboratory of Dr. Albert Parlow began producing hGH for the NHPP. The second change modifies the section on blood donation to mention that there have now been two confirmed cases of vCJD transmission through blood, and also to draw a distinction between the vCJD that was transmitted this way, and that which has occurred in hGH recipients, for whom the blood transmission danger is theoretical.

7. Highlights of new basic and clinical information about CJD

Dr. Major reported that in late 2001, HHS Secretary Thompson established the Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathy (BSE/TSE) Action Plan, which highlights the role of HHS agencies in managing prion related diseases. NIH is the lead agency in HHS that focuses on research and to that end there was a recommendation to establish a TSE Reagent Repository so that investigators can deposit materials such as antibodies, molecular clones, even prion-containing samples of tissues. The TSE Repository has been established in a joint effort between the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Allergy and Infectious Diseases (NIAID), using the already established and successful AIDS Reagent Repository as a model. As the TSE Repository grows over the next number of years, it will include not only laboratory samples and reagents but also transgenic mice that carry various prion genes. The Program Directors involved in this effort are Drs. Christopher Beisel of NIAID and Michael Nunn of NINDS.

Dr. Major also reported that the White House Office of Science and Technology Policy, Committee on Science, recommended and then authorized an Intra-agency Working Group Committee (IWG) on Prion Science. The committee will be composed of members from all federal agencies that have a portfolio or activity on prions and the diseases they cause. Dr. Major co-chairs the committee with Dr. Caird Rexroad, of the Agricultural Research Service, USDA. The IWG on Prion Science will help coordinate information flow among all federal agencies and provide a forum for discussion of significant issues on managing prion diseases such as BSE, TSE and chronic wasting disease.

Dr. Major also noted that one of the major areas of work on prions is the establishment of biological standards for the development of highly sensitive and specific pre-mortem diagnostic assays. There are several large research groups working in this area with the hope that further technical advances along with shared resources among investigators will lead to uniformity and accuracy of testing. This is a significant priority in prion research.

Dr. Schonberger referred the Committee to two recent papers concerning transmission of vCJD via blood transfusion. The first describes a cohort of 48 individuals identified as having received labile blood components from 15 donors who later developed vCJD. One recipient developed symptoms of vCJD 6.5 years after transfusion. The corresponding donor had developed symptoms 3.5 years after the donation (Llewellyn et al. 2004 Lancet **363**:417-421).

The second paper reports on a preclinical case of vCJD in a patient who died from an unrelated disorder five years after receiving a blood transfusion from a donor who developed vCJD 18 months after the donation. The transfused patient showed no evidence of CJD pathology in brain slices and in other organs including the tonsil, appendix and large intestine, but PrP^{Res} was found in follicular dendritic cells of the spleen and within a cervical lymph node. Perhaps more importantly, the patient was heterozygous Val/Met at codon 129 (as indicated by RFLP analysis, not direct sequencing.) vCJD patients have to date all been homozygous for the methionine allele, although the heterozygous condition is more common in the general population. These data could indicate that Val/Met heterozygosity is associated with longer vCJD incubation times than Met/Met homozygosity, and that there is therefore a large population of people with preclinical vCJD (Peden et al. 2004 Lancet **364**:527-529).

The meeting was adjourned at 10:15 a.m.

Allen M. Spiegel, M.D.