PUBLIC HEALTH SERVICE

Meeting of the

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

November 6, 2000

National Institutes of Health
Bethesda, Maryland

Committee Members Attending

Dr. Allen Spiegel, NIDDK, Chairman
Dr. Paul Brown, NINDS
Dr. Judith Fradkin, NIDDK
Dr. C.J. Gibbs*, NINDS
Dr. James Mills, NICHD
Dr. Lawrence Schonberger, CDC
Dr. Diane Wysowski, FDA

Also Attending

Ms. Joan Chamberlain, NIDDK
Mr. John Condray, NIDDK
Dr. Jane DeMouy, NIDDK
Dr. Richard Farishian, NIDDK
Ms. Sharon Pope, NIDDK

Committee Members Absent

Dr. Malozowski, FDA
Dr. Snider, CDC

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

1. Opening Remarks

Dr. Spiegel welcomed the group, and acknowledged that this was his first opportunity to chair a meeting of this Committee, having been appointed NIDDK Director shortly after last year=s meeting. He echoed Dr. Phillip Gorden=s comments, as reflected in the minutes from the November 1999 meeting, that this is clearly one of the most serious and challenging responsibilities the Federal government faces, and he looks forward to working with the members of the group. He also noted that he has become familiar with the history of the problem and with the Committee=s activities.

* The Committee is saddened to report the death of Dr. C.J. Gibbs on February 16, 2001.

Dr. Spiegel mentioned that a former Committee member, Dr. Richard Eastman of NIDDK, has left the Institute, and has taken a position in the private sector. Dr. Eastman was Director of the Division of Diabetes, Endocrinology, and Metabolic Diseases. Dr. Judith Fradkin is now the Acting Director of the Division. (Note: Dr. Fradkin was appointed Director of the Division on December 3, 2000.)

2. Discussion and Approval of Minutes of the Nov. 1999 Meeting, and Draft Seventeenth Report

Dr. Fradkin noted that the Committee members have approved both the minutes of the November 1999 Committee meeting and the draft Seventeenth Report of the Interagency Coordinating Committee on Human Growth Hormone and Creutzfeldt-Jakob Disease. Dr. Schonberger requested a correction in the minutes (page 3), regarding the number of non-CJD deaths. He suggesting changing the sentence to read: AWhile the deaths from other causes in this population are relatively constant...@ and then continuing to the last sentence: AThus, CJD has increased as a proportion of the total cohort deaths in recent years.@ Committee members agreed that this change should be made.

Dr. Fradkin discussed the schedule of Committee reports, and noted that the draft Seventeenth Report would reflect activities of the Committee=s last two meetings, November 1999 and November 2000 (the current meeting). After finalizing the minutes of this meeting, the draft Seventeenth Report will be revised accordingly.

Dr. Schonberger noted that in the draft Seventeenth Report the number of confirmed recipients in the study cohort is estimated as 6,200, and the group for which growth hormone was awarded but treatment not confirmed or the recipient not identified is estimated as 1,400. Dr. Schonberger recommended that we should be as precise as possible for the confirmed recipients, because here a specific person (study individual) has been identified. The study has currently identified 6,272 confirmed recipients based on information from treatment centers. Occasionally a Aconfirmed recipient@ must be deleted from the study cohort; this can occur after investigation of a death in a Aconfirmed recipient@ reveals that the study individual was, in fact, not treated. Nonetheless,
Dr. Schonberger recommended that the committee use the number 6,272 instead of the estimate of 6,200.

Dr. Schonberger suggested that the Committee discuss the number that should be used as the best estimate of the total number treated. Dr. Fradkin offered insight into the difficulty the Committee has had in estimating the total number. She recalled that the original numbers were derived from a 26,000 Aline listing@ of individuals for whom growth hormone was awarded. However, no names of individuals were given, only treating institutions and some codes. It therefore was difficult to determine to what extent the list contained specific individuals multiple times. For a variety of reasons, including difficulties in identifying multiple entries for the same patient, the original number of 8,157 turned out to be an overestimate. In a recent AViews and

Reviews@ paper co-authored by several members of the committee (*Neurology* 55: 1075-1081, 2000) (TAB A), 8,000 was given as the estimated total number.

The Committee agreed that the current best estimate is that 7,700 individuals were given growth hormone supplied by the National Hormone Pituitary Program (NHPP). This reflects continued analysis in which the previously reported 1,873 individuals who could not be identified or confirmed as treated when the cohort was established have now been revised downward to 1,420. The 1,420 unconfirmed recipients is less reliable than the 6,272 confirmed recipients and Dr. Schonberger suggested than an estimate of 1,400 unconfirmed recipients be used. The Committee agreed that the total number of NHPP hGH recipients should now be estimated at 7,700.

The minutes were approved provisionally, pending incorporation of the requisite changes. The Seventeenth Report will be updated to include new information presented at this meeting.

3. Epidemiology Study Status Report

Dr. Schonberger reported that during the past year, Westat conducted the National Death Index (NDI) search for 1998, and determined that there were 28 deaths in the study cohort in that year. Two new deaths due to CJD in 1998 were identified in people in the confirmed recipient study cohort. For 1999, there was also one CJD death in the non-cohort group of NHPP recipients, and two additional CJD deaths within the cohort. Medical records are now being retrieved and reviewed for all deaths identified through the NDI search.

Including the 28 deaths during 1998, the total number of deaths among the 6,272 hormone recipients that comprise the study cohort now stands at 506, including 15 (3.0 percent) who were known to have been infected with the CJD agent. An additional two cohort members died of CJD in 1999. (The other five cases of CJD in NHPP hGH recipients occurred in the individuals for whom hGH was awarded but who could not be identified or confirmed as treated when the cohort was established.) Thus, the fraction of total deaths due to CJD has risen over time. By 1980, there was one confirmed CJD case in the first 72 cohort deaths (1.4 percent). This case-patient died from a non-neurologic illness. Her CJD brain lesions were diagnosed years later upon re-examination of her autopsy tissue. There were five CJD cases of the 215 deaths that occurred in the1980s (2.3 percent). There have been nine CJD cases in the 219 deaths that have occurred in the cohort between 1990 and 1998 (4.1 percent). During the past year, Westat, with Dr. Fradkin, has been working on the Aall cause@ mortality manuscript, and has updated the manuscript to include data through 1996.

Westat also worked with CDC to reverify some of the data and made corrections to improve our estimate of the number of NHPP hGH recipients. Westat compiled a data set with all the available information on the group of patients who were Aunknown@ or who were unidentifiable by physicians or treatment centers, including patients whose receipt of NHPP hormone could not be confirmed. It is from this file that it has been estimated that there may be about 1,400 separate individuals.

Up until now, physicians have reported almost all hGH CJD cases before the PHS identified them through the NDI search. There are no reports of CJD cases in the cohort who died after October 1999, or who had onset of symptoms after June 1998. However, it remains too early to be assured that the outbreak is waning based on the absence of more recent cases.

Westat has made some staff changes, specifically in the positions of Study Manager, with Denise Derick replacing Maureen McTide. Ms. Derick has been with Westat for 16 years, and is experienced in data base management, NDI searches, and data retrieval. She is being assisted by Elizabeth Wood, a new hire, in data inquiries and procurement.

The article published on May 21 in the *Los Angeles Times* (TAB B) brought with it a flood of inquiries. Some of the inquiries were from people who believed they may have received NHPP growth hormone. To assist in providing information in response to such inquiries Westat reviews the original Aline listings@ of all awards of hGH to the physician or institution where the patient may have been treated to see if we can match the individual with an award for which the recipient was not identified by the treatment center or with a confirmed recipient that we were not able to locate and inform about the problem of hGH and CJD. Many individuals who called after reading about transmission of CJD through hGH were treated for growth problems with substances other than hGH.

4. Requests by non-Government Individuals to Attend hGH-CJD Interagency Coordinating Committee Meetings

Ms. Chamberlain was contacted by an individual who asked to attend meetings of the Committee. She told the person that she would ask the Committee to address this issue at its next meeting. Dr. Fradkin related that several non-Government individuals have requested this in the past. The chief technical barrier is that many issues that are routinely discussed in these meetings are confidential in whole or in part, for example issues relating to the contract under which the follow-on study is conducted. The Committee could offer to meet with interested individuals or, alternatively, there could be a special Committee meeting that could include a host of non-government participants.

It wasn=t clear to Dr. Spiegel how non-government individuals would be helped, or what they would gain, by attending Committee meetings, over and above the extensive information that is already available to them. Dr. Spiegel noted that questions NHPP hormone recipients have about the hGH-CJD association are very well handled either by the abundant information produced and distributed by the NIH (Fact Sheets, etc.), or by direct communication with NIH staff or by the patient=s physicians. The NIDDK Web site has links to many other sources of information about CJD and growth hormone replacement therapy. Moreover, NIH staff are available to speak directly with individuals to answer specific questions relating to the hGH-CJD association. Dr. Spiegel said that to allay concerns, people who make requests to attend the meetings should be given a description of what the Committee=s activities involve and do not involve. The Committee is doing an ongoing epidemiologic study, gathering data, and

monitoring mortality of the cohorts. In addition, each year the Committee evaluates the research developments that have occurred in the areas of diagnostic indicators and possible prophylatic treatments for CJD. Dr. Fradkin noted that parents and recipients were involved in the design of the follow-up study to ensure that their questions were addressed as effectively as possible.

5. New Cases

As noted in Section 3, there are no reports of CJD cases in the cohort who died after October 1999, or who had onset of symptoms after June 1998.

6. Report on Mortality in hGH Recipients

Drs. Brown and Schonberger reported that through August 2000, deaths from CJD stand at 22 in the U.S. (0.3 percent frequency overall; 0.8 percent frequency for pre-1977 treatment), including the one Aprobable@ case for which the family has not agreed to release medical records to allow the PHS to confirm the diagnosis; five from New Zealand (10.9 percent frequency for pre-1977 treatments); 35 in the United Kingdom (1.9 percent frequency); and 74 in France (5.9 percent frequency). The French cases all received some hGH treatment between January 1983 and mid-1984. Purification methods were discussed as possibly accounting for the sharply higher increased risk of CJD in France. Post-1977, the French used a broad cut from DEAE (ion-exchange) chromatography as opposed to a narrow cut from size exclusion chromatography that was employed in the U.S. post-1977. Dr. Brown remarked, however, that any kind of chromatography removes contaminants if a narrow cut is taken. (In the U.S., all cases of CJD have so far occurred in people who began hormone treatment before 1977 when a new method of purification including chromatography was introduced.) One suspected case of CJD in Brazil and the five cases in New Zealand received hormone prepared in the U.S. in the laboratories that produced NHPP hGH prior to 1977.

Dr. Schonberger said that the one Aprobable@ U.S. case among the 22 U.S. cases is being investigated. The PHS received information that this individual was thought to have CJD from the family, but the family did not consent to provide medical records. This individual has died, and Westat is in the process of obtaining the Death Certificate. If the PHS is not able to obtain medical records or neuropathology for review, the committee agreed it would consider this a case of CJD based on a death certificate diagnosis.

7. Report on Studies of Animals Injected with hGH

The animal study was initiated to identify possible Ahot@ lots of hGH at high risk of transmitting CJD. Dr. Gibbs reported that all squirrel monkeys injected with hGH have been sacrificed, and the brains of over 200 animals were extracted for analysis of prion protein. Squirrel monkeys, it was noted, are particularly sensitive and susceptible hosts, almost as sensitive as chimpanzees. Moreover, the monkeys were injected intra-cerebrally which greatly increased the risk of transmission. Only one preparation transmitted CJD to one animal. This has previously been reported in a letter to the NEJM. No human cases of CJD could be definitively associated with

this preparation. None of the patients who developed CJD is known to have received this preparation; it is possible but unconfirmed that two of the 22 cases of CJD might have received this preparation. Thus, the animal study did not yield useful clues about the hormone lots in terms of which may have been Asafe@ on the one hand, or particularly problematic on the other.

8. Update on hGH Contacts and Inquiries, etc.

Dr. Fradkin reported that there is new litigation involving institutions where hGH was produced or distributed, but she is not aware of any litigation involving the Federal government directly. The NIH has received several requests through the Freedom of Information Act (FOIA) from the attorneys representing the institutions being sued, and it is possible that the NIH may get subpoenas to produce records. The NIH will retrieve these records, which now are contained on compact discs (CDs) produced by the Department of Justice several years ago when the Government was being sued. (The Government subsequently was dismissed as a defendant in CJD cases associated with NHPP growth hormone.) To protect patient confidentiality, all patient identifiers were redacted before transferring the records to the CDs. The NIH has requested the CDs but has not yet received them from the Department of Justice. Dr. Spiegel remarked that it is very important for the Committee to know what data exist in totality, where it is stored, and to catalogue it. This is in anticipation of FOIA requests the PHS is expected to receive for possibly years to come.

9. Advances in Understanding the Biology of CJD

Dr. Brown reported that there are a couple of aspects of the field that have advanced over the past year. There is an intense worldwide effort to develop a blood screening test for pre-clinical disease. Eight research groups have been unsuccessful thus far in identifying the prion as a definitive marker for early disease, but they are progressing in making the prion assay more sensitive.

Progress has also been made in prophylatic therapy against CJD. Dr. Brown said there is enough known biochemically about the prion protein now to begin to develop drugs to block the transition from prion protein to the development of insoluble amyloid protein, which is present in overt CJD. In fact, drugs have been developed that work in tissue culture and in animals.

Thus, vigorous efforts are being mounted and progress is being made. The timeline for useful tests and therapies, however, remains uncertain.

To date, there are three relatively specific diagnostic tests that can be performed on living individuals suspected of having the disease that do not involve a biopsy of tissue. These include examination of spinal fluid, magnetic resonance imaging of the brain, and an electroencephalography. These tests are less useful in the early stages of disease.

Dr. Gibbs urged that when people call the NIH with the suspicion they may have CJD, that they should be strongly advised to seek consultation with a neurologist to get an evaluation. Dr.

Fradkin replied that this was being done and that when necessary we have helped patients identify neurologists in their area with expertise in CJD. Dr. Spiegel agreed that this is one important way the government can assist in guiding patients to the care they may need. If warranted, the neurologist may then refer the patient to appropriate center for follow-up tests (MRI, etc.). Dr. Spiegel would like Dr. DeMouy and Ms. Chamberlain to develop a standard response to this effect that can be related to concerned callers.

10. New Business and Information Items

The Committee briefly discussed Emily Green=s article in the *Los Angeles Times* (TAB B), and various other media inquiries. Another article by David Davis is anticipated.

The meeting adjourned at 2:30 p.m.

Allen M. Spiegel, M..D.
Director, National Institute of Diabetes and Digestive and Kidney Diseases
and
Chair, PHS Interagency Coordinating Committee on Human Growth Hormone and Creutzfeldt-Jakob Disease

Attachments

TAB A B Brown P, Preece M, Brandel, J-P, Sato T, McShane L, Zerr I, Fletcher A, Will RG, Pocchiari M, Cashman NR, d=Aignaux JH, Cervenakova L, Fradkin J, Schonberger LB, and Collins SJ. Iatrogenic Creutzfeldt-Jakob disease at the millennium. *Neurology* 55: 1075-1081, 2000.

TAB B B Green, E. A Wonder Drug That Carried the Seeds of Death. *Los Angeles Times*, May 21, 2000.