Creutzfeldt-Jakob disease in United Kingdom patients treated with human pituitary growth hormone

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Abstract—*Objective:* To investigate risk factors for Creutzfeldt-Jakob disease (CJD) in patients in the United Kingdom treated with human pituitary growth hormone (hGH). *Methods:* Incidence rates of CJD, based on person-year denominators, were assessed in a cohort of 1,848 patients treated with hGH in the United Kingdom from 1959 through 1985 and followed to the end of 2000. *Results:* CJD developed in 38 patients. Risk of CJD was significantly increased by treatment with hGH prepared by the Wilhelmi method of extraction from human pituitaries. Risk was further raised if this treatment was administered at ages 8 to 10 years. The peak risk of CJD was estimated to occur 20 years after first exposure, and the estimated lifetime cumulative risk of CJD in Wilhelmi-treated patients was 4.5%. *Conclusions:* Size-exclusion chromatography, used in non-Wilhelmi preparation methods, may prevent CJD infection. Susceptibility to CJD may vary with age, and susceptibility may be present in only a few percent of the population.

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Treatment of short stature with human pituitary growth hormone (hGH) was begun in 1958.[1] Treatment in the United Kingdom started in 1959 as a clinical trial, and after 1976 was a centrally administered health service activity. In 1985, four cases of Creutzfeldt-Jakob disease (CJD) in patients treated with hGH were reported from the United Kingdom and United States,[2,3] and as a consequence all hGH treatment in the United Kingdom was stopped in May 1985. A cohort study was then initiated of UK patients, and results were published describing the cohort and the cases of CJD incident up to 1990.[4] Studies in the United States[5] and France[6-8] also found substantial numbers of cases of CJD after hGH treatment. However, these studies did not calculate CJD risks in relation to person-years at risk, which is needed to give valid comparison of risks in different subgroups—by duration of treatment, type of hGH preparation, and age of subjects. We therefore studied the UK hGH cohort, to analyze the person-year based risks of CJD associated with hGH.

Patients and methods. During the operation of the national schemes for distribution of hGH, registers of treated patients were compiled at the coordinating center, but the information held on these registers about treatment was considerably incomplete. Therefore, with appropriate ethical committee agreement, we undertook extensive new data collection to ensure, as far as possible, that all patients who had been treated in the country were included, and that their treatment histories were complete and accurate.

The sources searched were as follows: computer databases and paper records held by the national coordinating center; local listings at the 21 clinics in the country where the patients had been treated, and, as far as they had been retained, the endocrinology case notes of these patients; at two of the three largest clinics, separate research records that had been kept to record auxologic variables and hGH treatment; for treatments since December 1980, records from the central distribution center detailing supplies of hGH for individual patients as they were sent to local clinics around the country; records kept by the central steering committee of authorizations for individual patients to start treatment, and notifications to this committee by the responsible clinicians when treatment ceased; detailed treatment logs kept at one clinic for each patient treated there; at some clinics, local pharmacy records; and a list of all patients in the United Kingdom under treatment in May 1985, which had been compiled then in order to implement national discontinuation of hGH treatment when the risk of CJD was realized. Integration of information from these various sources was complex, and was conducted clerically case by case, because legitimate discrepancies could occur as well as erroneous ones; for instance, the dates recorded by the central distribution center tended to be weeks before those shown in the local case notes for the same treatments, because of the time taken to send out and use the hGH.

Using the data from all the above sources, we compiled a list of all treated patients and the preparations they received on each date, aggregating treatments received by the same patient at different centers, and deleting duplicate reports of the same treatment. We excluded from the cohort patients resident outside the United Kingdom, because we could not gain follow-up for these. We also excluded patients treated solely with commercially prepared hGH (there were about 40 of these in the United Kingdom),[4] because they were not treated via the national system, and consequently we did not have details on them. (The number of patients in the cohort is less than in the publication by Buchanan et al.[4] because of exclusion of 28 nonresidents, 31 subjects for whom there is no secure evidence that hGH was received, and duplicated records.)

Identification information about all cohort members was sent to the National Health Service Central Registers in Southport (for England and Wales) and Edinburgh (for Scotland), and the Cen-

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tral Services Agency for Northern Ireland, which are effectively national population registers, to obtain follow-up information ("flagging") on deaths and emigrations. In addition, such follow-up was obtained from clinical sources. Follow-up for incidence of CJD was obtained from notifications by endocrinologists, neurologists, general practitioners, pathologists, patients, and the patients' self-help group to the national hGH coordinating center, and from surveillance by the National CJD Surveillance Center. Also, death certificates for cohort members received from the flagging process were examined for diagnoses that might indicate CJD.

Person-years at risk of CJD in cohort members by sex and 5-year age group were calculated. The start of risk was taken to be, in different analyses, either the date of first treatment (with hGH, or with a particular preparation in analyses relating to preparations) or the midpoint of treatment. The midpoint was the weighted average of the periods when treatment was actually received, giving zero weight to gaps in treatment, rather than the simple mid-date between first and last treatments. The end of risk was taken as the end of December 2000, or the date of first symptoms ("incidence") of CJD, death, or loss to follow-up, if earlier. Incidence rates of CJD in different subgroups of patients were calculated by dividing the numbers of cases in these groups by the person-years at risk; hazard (rate) ratios were then calculated using Cox regression analysis,[9] with Wald-based 95% confidence intervals,[10] to compare risks between analytic categories. As well as univariate analyses, multivariate analyses were conducted to examine the effects of the study variables adjusted for potentially confounding variables. For analyses of risks in relation to age at treatment, year of treatment, and hGH preparation type, most individuals contributed to more than one analytic category (e.g., were treated at several ages); we therefore analyzed risks in patients ever treated at each age (or year or preparation) compared with those never treated at that age (or year or preparation). This is conservative in that if there is a true effect encompassing more than one age/year/preparation, it will be underestimated by the analysis.

Incubation periods were estimated by fitting the time course of risk to several different mathematical models—the Weibull, log-logistic, gamma, and log-normal—that have frequently been used to model infectious disease epidemics.[11] These models take into account the number of new cases occurring at each point in time as a proportion of all patients at risk of disease at that time. We allowed for the possibility that not all patients would be susceptible to CJD by fitting a model that was a mixture of two distributions, with one component for those susceptible to CJD and one for those not susceptible. The relative weight of each component was estimated from the data,[12] rather than based on a presupposition. We fitted the mixture models using Proc IML in SAS.[13]

Results. We identified 1,849 UK residents treated with hGH in the UK national scheme from 1959 through 1985. All but one of these patients were found in the National Health Service Central Registers; this individual was excluded from analysis. Two-thirds of the cohort members (1,209) were male, and almost all were under age 20 at first treatment: <10 years (39%), 10 to 19 years (60%). The causes of growth hormone deficiency were mainly idiopathic GH deficiency (53%) and intracranial neoplasia (26%).

The patients were treated with 10 to 20 IU of hGH weekly, given in two or three IM injections. Stocks of hGH were given to the patients at clinic visits, usually 3 monthly, and it was for these treatment consultations that preparation information was recorded: there were 22,616 such episodes, an average of 12.2 per patient. We managed to ascertain definite dates of starting treatment for all patients and dates of ending it for all but 10, whom we counted as ending treatment after their last known treatment. Preparation type was identified for all but 1,836 (8.1%) of the treatment episodes; 255 of these occurred in the period before 1970, when hGH prepared by the Raben method was the only preparation available, and we therefore counted these as Raben. Of the total person-time between start and end of treatment for all cohort members combined, 8.1% was spent with no recorded growth hormone treatment. For many of the periods concerned there were positive records that the patient was off treatment, but for some it was unknown whether the patient was untreated or the treatment had gone undetected despite our multiple data sources.

During follow-up to December 31, 2000, 38 patients developed CJD, all of whom have now died. The diagnosis of CJD was confirmed by expert neuropathologic examination including histochemistry in all but one case; in the latter, the clinical diagnosis was unambiguous. A total of 207 (11.2%) other patients are known to have died and 28 (1.5%) emigrated or were otherwise lost to follow-up. In total, 39,147 person-years of follow-up were accumulated, a mean of 21.2 years per patient. Fifty-eight percent of the patients have now been followed beyond 20 years from first treatment, and 8% beyond 30 years. The average age of patients still alive at the end of 2000 was 34.2 years.

Risk of CJD did not differ significantly according to the sex of the patient or diagnosis leading to hGH treatment (table 1). Greatest risk in relation to preparation of hGH was for that made by the Hartree-modified Wilhelmi method (referred to hereafter as Wilhelmi). All cases had received this preparation, significantly more than expected from the distribution of use of Wilhelmi in the cohort ($p < 0.001$) (see table 1). There was also a significantly raised risk in the univariate analyses for receipt of the Lowry preparation (but see the multivariate analyses below), and for receipt of hGH of unknown preparation type.

Figure 1 shows dates of treatment with each preparation type, and of CJD incidence and death, for the 38 patients in whom CJD occurred. The shortest incubation period between treatment and first symptoms of CJD was in the range 2 years 3 months to 11 years 9 months, depending on when during treatment infection is assumed to have occurred, and on the same basis the longest incubation period so far was in the range 20 years 7 months to 32 years 1 month. The cases occurred at ages 20 to 43 (mean 28.8) years. To encompass all cases of CJD that have occurred to date, the infected hGH would have to have been used at least over the period May 1974 to May 1981. Two cases (nos. 23 and 25) had been treated solely with Wilhelmi, from May 1975 to June 1979 and January 1977 to September 1978, respectively, implying that this preparation at some point during these years was infected. To explain all cases by Wilhelmi, this preparation would need to have been infected at least over the period April 1972 to July 1981; 93% of all Wilhelmi treatments occurred during this period. Twenty-nine cases were known to have received Lowry hGH; three of the nine other cases had been treated with an unknown preparation type during the period when Lowry was available.

Table 2 shows risks of CJD in relation to age, year, and duration of hGH treatment analyzed for all hGH treatments, and restricted to Wilhelmi treatments. Significant risks in relation to hGH overall were found for treatment at ages 8 to 14, and treatment during 1977 through 1982, but in analyses restricted to Wilhelmi treatment, the only ages with significantly raised risk were 8 to 10 years and there were no significantly raised risks by year of treatment. (The greater risk for treatments in 1977 through 1982 than at other times accords with the greater propor-

Table 1 *Risks of CJD by sex, diagnosis leading to treatment, and hGH preparation type*

Factors	No. of hGH-treated patients	Person-years at risk	No. of cases of CJD	Rate ratio (95% CI)
Sex				
Male	1,209	25,787	28	1.0
Female	639	13,360	10	0.7 (0.3–1.5)
Diagnosis*				
Idopathic GH deficiency	973	21,799	26	1.0
Intracranial solid neoplasm	475	8,968	7	0.7 (0.3–1.7)
Other	393†	8,219	5	0.6 (0.2–1.5)
				heterogeneity $p = 0.40$
Preparation type‡				
Raben	481	12,923	12	0.6 (0.3–1.4)
Wilhelmi	1,195	26,588	38	∞ (4.6–∞)§
Lowry	773	15,217	29	3.7 (1.7–8.1)¶
Modified Lowry	1,088	18,646	23	1.9 (0.9–3.8)
Commercial, NHS pit.	521	8,885	9	0.9 (0.4–2.0)
Commercial, com. pit.	238	4,280	7	1.5 (0.6–3.3)
Unknown	625	12,835	21	2.1 (1.1–3.9)
All nonchromatographed	1,285	29,738	38	∞ (3.1–∞)§
All chromatographed	1,348	24,765	29	1.9 (0.9–4.3)

* Excluding seven patients with unknown diagnosis.
† 214 multiple pituitary hormone deficiency, 51 short normal, 40 Turner syndrome, 23 histiocytosis X, 65 other known.
‡ Rate ratios for patients ever receiving each preparation compared with those never receiving it.
§ $p < 0.001$.
¶ $p < 0.01$.

CJD = Creutzfeldt-Jakob disease; hGH = human pituitary growth hormone.

tion of treatments that were Wilhelmi then than at other times.) Similarly, for hGH treatment overall there was a highly significant relation of risk to duration of treatment ($p = 0.007$), but within Wilhelmi treatments there was no such trend ($p = 0.84$). There was also no trend of risk with duration of Lowry treatment (not in the table). Treatment with hGH of unknown preparation type was largely of short duration (not in the table). In accord with the above evidence that the effect of duration of treatment in the overall dataset might be a consequence of confounding by preparation type, cross-tabulation of these two variables (not in the table) showed that 98% of patients treated for 5 years or more had received Wilhelmi compared with only 22% of patients treated for less than 2 years.

In multivariate analyses of CJD risk in Wilhelmi-treated patients, examining the effects of age at treatment, year of treatment, and receipt of Lowry preparation (i.e., those factors that tables 1 and 2 suggested had the potential to be risk factors independent of Wilhelmi) (table 3), only age at treatment was a significant risk factor and the effect of Lowry hGH almost disappeared.

Figure 2 and table 4 show the time course of the CJD epidemic in hGH-treated patients, using the Weibull and log-normal models, assuming that infection occurred at the start (see figure 2A) or the midpoint (see figure 2B) of hGH treatment. The results for the gamma and log-logistic models (not shown in the table) were intermediate between those for the two models shown. Considering hGH treatment overall, under all models the peak risk occurred at around 19 to 22 years from the start of treatment, with 40 to 50% of cases occurring by 20 years, and more than 90% by 30 years. From the midpoint of treatment, the peaks ranged from 16 to 18 years, and the percentages of cases reached by 20 and 30 years were more than 55%, and at least 90%, respectively. The hypothetical eventual cumulative risk of CJD after indefinite (unlimited) follow-up was around 3.5%, ranging from 3.3% to 4.0%. Considering solely Wilhelmi treatments made only a small difference in the results, with some reduction in the dispersion of the epidemic under the Weibull model, and eventual cumulative risks of 4.1 to 5.0%. For infections occurring at ages under 11, the peak of the epidemic was up to 3 years earlier and the eventual cumulative risk was greater than after infection at older ages; this was true both if Wilhelmi preparations alone were considered (see table 4) or for all hGH treatments (not in the table).

Of the 27 CJD cases for whom prion protein codon 129 genotype was known, 14 (52%) were valine homozygotes, 1 (4%) was a methionine homozygote, and 12 (44%) were heterozygotes.[14] The mean incubation periods (from the start of GH treatment) were 17.1 (SD 2.8) years for the valine homozygotes, 13.4 years for the methionine homozygote, and 19.1 (3.5) years for the heterozygotes. If it is assumed that only Wilhelmi treatment was relevant, then the corresponding incubation periods were 16.6, 13.4, and 18.9 years. The mean ages at start of symptoms of CJD were 25.8 years for valine homozygotes, 20.0 years for the methionine homozygote, and 31.8 for heterozygotes.

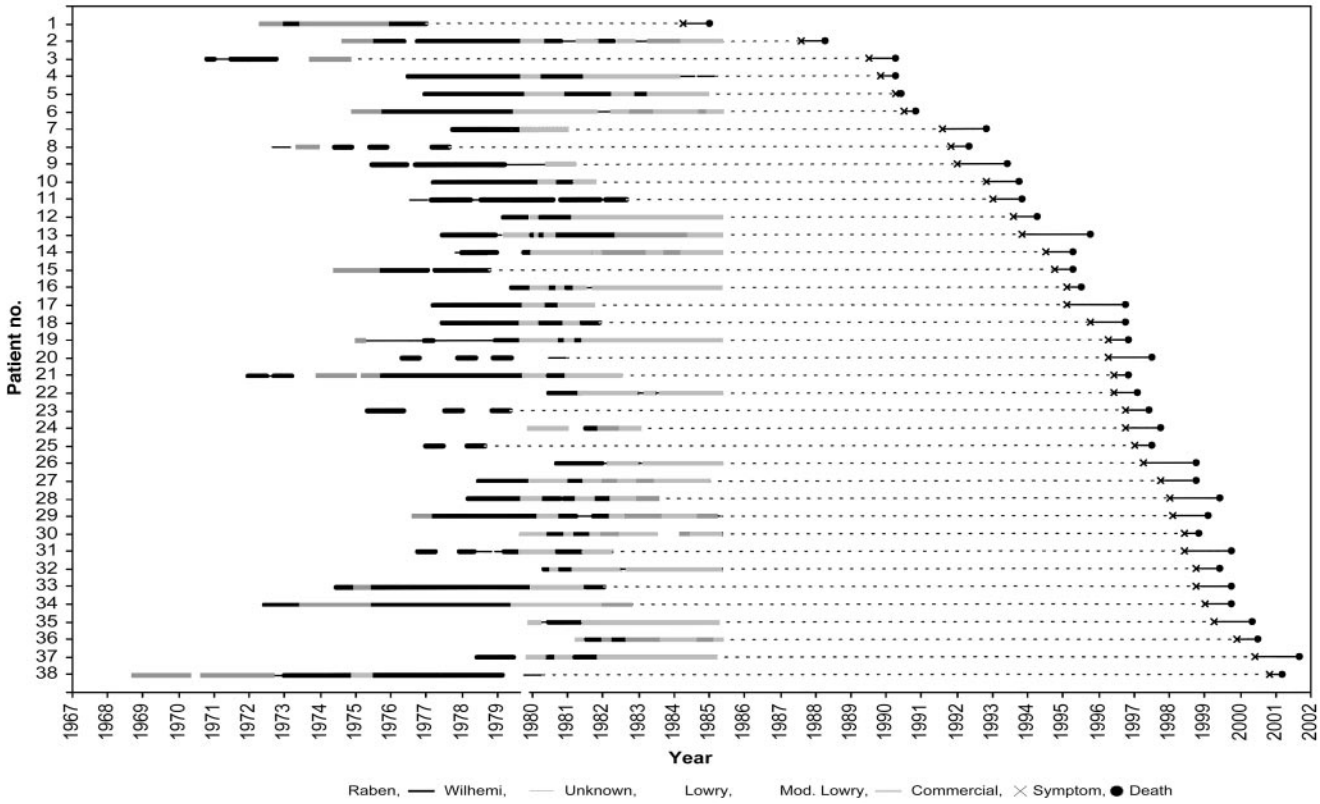

Figure 1. Histories of human pituitary growth hormone (hGH) treatment, Creutzfeldt-Jakob disease (CJD) incidence, and death in the 38 patients with CJD after hGH treatment.

Discussion. The risk factors for CJD in patients treated with hGH are of importance both to the patients who received this treatment and to understanding of CJD transmission generally. Previous publications on CJD occurrence after hGH[4-8,15] have not calculated rates in relation to person-years at risk. They may consequently have underestimated risks at long periods of follow-up, because person-years are needed to censor follow-up for patients who die or are otherwise lost and are needed to account for the difference in dates of starting treatment between patients, such that not all patients, even if alive, have yet reached longer follow-up periods. These potential biases must be considered when comparing previous with the present results.

Follow-up of the UK cohort was over 98% complete, and it is likely that all cases of CJD occurring in the cohort were detected from the multiple sources of information used: certainly, no cases have been ascertained at death who had not previously been notified. Of course, if a patient with early CJD died fortuitously from another cause before CJD symptoms and signs were sufficient to lead to diagnosis, then such a case might have been missed. Diagnostic accuracy of CJD diagnosis was secure, based on expert neuropathology in all but one case. As the incidence of CJD in the UK general population is less than 1 per million per year,[16] and none of the cases in the study cohort had features suggestive of vCJD or were in families with known other cases, it is highly improbable that any of the study cases were not due to infection from hGH. Infection from contaminated surgical instruments during surgery for cranial tumors is an alternative hypothetical source, but very unlikely because such cases are extremely rare.[17] Furthermore, the rate of CJD was not greater in patients who had been treated for brain tumor than in those with other initial diagnoses.

hGH treatment in the United Kingdom (with the exception of preparations from commercially obtained pituitaries used to treat 238 patients in this study) was prepared from pituitary glands taken at routine autopsies in the United Kingdom, with a policy of excluding patients known to have died from infectious or neurologic diseases. About 10 to 20 IU of hGH was obtained per pituitary, and batches of hGH were derived from hundreds or thousands of pituitaries. Based on the person-weeks of treatment we have documented in the cohort, the known dosage schedules over time, and amount of hGH extracted per pituitary, we estimate that 400,000 pituitaries were used to produce hGH in the United Kingdom, of which 197,500 produced Wilhelmi hGH. About 1 in 10,000 deaths in the United Kingdom may be due to CJD,[3] so about 40 infected pituitaries in total may have been used in hGH manufacture, depending on the success of the policy of excluding neurologic disease deaths and the extent to which material was used from people with CJD undiagnosed at death.

Before 1978, all hGH was made by the Raben[1] and

Table 2 *Risks of CJD by age at treatment, year of treatment, and duration of treatment, for all hGH treatments and for Wilhelmi treatments*

	All hGH treatments			Wilhelmi treatments
Factor	Person-years at risk	No. of cases of CJD	Rate ratio (95% CI)	Rate ratio (95% CI)
Age, y*				
<7	6,897	5	0.7 (0.3–1.9)	0.8 (0.3–2.4)
7	7,594	10	1.4 (0.7–2.9)	1.8 (0.9–3.8)
8	9,138	17	2.3 (1.2–4.4)†	2.3 (1.2–4.6)†
9	10,402	20	2.6 (1.4–4.8)‡	2.5 (1.3–4.8)‡
10	12,177	21	2.2 (1.2–4.2)†	2.1 (1.1–3.9)†
11	13,573	24	2.5 (1.3–4.8)‡	1.5 (0.8–2.9)
12	14,547	26	2.7 (1.4–5.4)‡	1.3 (0.7–2.5)
13	15,468	27	2.6 (1.3–5.3)‡	1.2 (0.6–2.3)
14	16,295	31	4.2 (1.9–9.6)‡	1.0 (0.5–2.0)
15	16,636	25	1.7 (0.9–3.3)	0.8 (0.4–1.5)
16	15,810	20	1.0 (0.5–1.9)	0.9 (0.5–1.8)
17	13,741	16	0.8 (0.4–1.6)	0.7 (0.3–1.4)
18	10,943	12	0.8 (0.4–1.5)	0.4 (0.2–1.1)
≥19	7,966	5	0.4 (0.2–1.0)	0.4 (0.2–1.2)
Year of treatment§				
<1975	11,954	9	0.5 (0.2–1.1)	0.6 (0.2–1.4)
1975	9,454	12	1.0 (0.5–2.1)	0.7 (0.3–1.5)
1976	10,660	16	1.5 (0.7–2.6)	0.7 (0.4–1.5)
1977	11,987	25	3.1 (1.6–6.2)‡	1.9 (1.0–3.7)
1978	13,219	26	2.9 (1.5–5.9)‡	1.8 (0.9–3.6)
1979	14,859	27	2.7 (1.3–5.5)‡	1.4 (0.7–2.8)
1980	15,926	31	4.5 (1.9–10.4)‖	1.8 (0.9–3.5)
1981	16,147	29	3.3 (1.5–7.2)‡	1.5 (0.8–2.9)
1982	15,182	25	2.3 (1.2–4.7)†	1.2 (0.6–2.6)
1983	14,319	20	1.6 (0.8–3.1)	1.4 (0.2–10.3)
1984	14,606	18	1.5 (0.8–2.9)	—
1985	12,966	17	1.8 (0.9–3.6)	—
Duration of treatment, y				
<2	12,952	1	1.0	1.0
2–4	14,918	14	7.2 (0.9–54.9)	1.2 (0.6–2.3)
5–9	9,519	17	9.6 (1.3–72.7)†	1.0 (0.3–3.5)
≥10	1,757	6	13.9 (1.7–116.5)†	—
			p trend = 0.007	p trend = 0.84

* Rate ratio for ever-treatment vs never-treatment at this age.
† $p < 0.05$.
‡ $p < 0.01$.
§ Rate ratio for ever-treatment vs never-treatment during this calendar year.
‖ $p < 0.001$.

CJD = Creutzfeldt-Jakob disease; hGH = human pituitary growth hormone.

Wilhelmi[18] processes at one laboratory in Cambridge, using acetone-preserved pituitaries.[19] The Raben method entailed hot glacial acetic acid extraction and the Wilhelmi method used weak alkaline extraction. Use of Raben GH virtually ceased after 1976, but Wilhelmi continued to be used greatly through to 1982. From 1978 through 1983 the Lowry method[20] at St. Bartholomew's Hospital and from 1982 through 1985 a similar commercial method was used, involving frozen non-commercially obtained pituitaries with purification by ion exchange plus G100 size-exclusion chromatography. In addition, commercially prepared GH from commercially obtained pituitaries was used on a lesser scale from 1977 through 1985; the preparation methods included one or more chromatographic steps. Finally,

Table 3 *Risks of CJD in patients receiving Wilhemi preparation by age at treatment, year of treatment, and whether Lowry preparation also received: multivariate analysis*

Factor	Person-years at risk	No. of cases of CJD	Unadjusted rate ratio (95% CI)	Adjusted* rate ratio (95% CI)
Treated at ages 8–10 y				
No	17,891	16	1.0	1.0
Yes	8,710	22	2.7 (1.4–5.1)†	2.2 (1.1–4.3)‡
Treated during 1977–1980				
No	7,436	3	1.0	1.0
Yes	19,165	35	3.7 (1.1–12.1)‡	2.6 (0.8–9.0)
Lowry				
No	11,829	9	1.0	1.0
Yes	14,772	29	2.2 (1.0–4.7)‡	1.3 (0.6–3.0)

* Adjusted for the other variables in the table.
† $p < 0.01$.
‡ $p < 0.05$.

CJD = Creutzfeldt-Jakob disease.

from 1981 onwards an increasing proportion of hGH, and from 1983 most hGH, was made at Porton Down by a modified Lowry method using G100 size-exclusion chromatography, mainly with acetone preserved glands. Inactivation of prion protein by 8 molar urea was not used in the United Kingdom.

There is no direct biologic evidence to identify which preparations or batches of hGH in the United Kingdom were infected with CJD. It is not likely that there was cross-contamination between different laboratories, but it is possible that once a preparation at a particular laboratory became infected, subsequent batches of the preparation were contaminated from it. All cases of CJD in the cohort were known to have received Wilhelmi treatment, so it is possible that this preparation alone was infected. This is supported by the much larger relative risk of CJD for Wilhelmi than any other preparation, and by experimental evidence,[21] although not conclusive,[22] that chromatographic purification by the Lowry method may largely or entirely have eliminated the risk of CJD. It would also accord with the pattern of hGH-related cases in the United States, where all cases of CJD so far have occurred in patients who started treatment before 1977, when size-exclusion chromatography was added to purification.[17] In France, risk appears to have related to a preparation method with a chromatographic step,[23] but this was DEAE ion exchange, not size exclusion. Risk in the UK cohort was not raised after Raben GH, which was made without a chromatographic step; destruction of the prion by hot glacial acetic acid extraction or chance absence of infected pituitaries are possible reasons. It has been suggested that frozen glands were responsible for the epidemic of CJD,[24] but this does not seem plausible from the risks we found for Wilhelmi, which was not made from frozen glands.

An apparent argument against Wilhelmi as the sole source of infection was the significantly raised risk of CJD in relation to Lowry hGH. In analyses within Wilhelmi-treated patients, however, no independent effect of Lowry was seen, suggesting that the apparent risk from Lowry may have been due to confounding. (The alternative method to examine

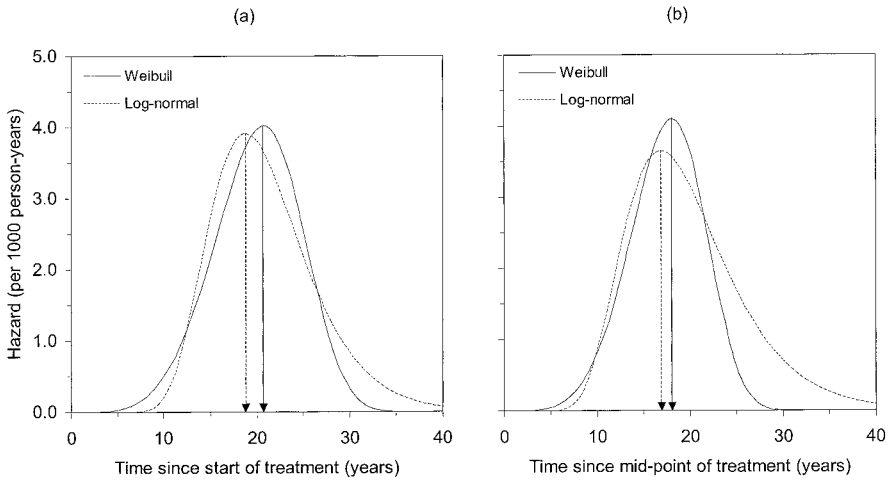

Figure 2. Risks of Creutzfeldt-Jakob disease over time in the human pituitary growth hormone cohort, from (a) start and (b) midpoint of Wilhelmi treatment: Weibull and log-normal models.

Table 4 *Estimated timing of peak risk of CJD, percentage of eventual CJD cases occurring by certain times, and eventual percentage cumulative risk of CJD, for various assumptions about the date of exposure, statistical models of the time-course, and ages at exposure*

Assumed exposure date, model	Peak (years after exposure)	Cumulative occurrence of CJD by various times after exposure, as percentages of cases by 60 y*			Eventual cumulative percentage of exposed patients who contract CJD†
		10 y	20 y	30 y	
Start of hGH treatment					
Weibull	21.8	1.7	40.0	97.1	3.99
Log-normal	19.4	0.1	44.8	93.0	3.92
Midpoint of hGH treatment					
Weibull	17.8	5.6	70.6	99.9	3.33
Log-normal	16.3	3.8	58.0	90.6	3.93
Start of Wilhelmi treatment					
Weibull	20.7	2.1	48.8	99.1	4.66
Log-normal	18.7	0.3	49.1	93.2	4.93
Midpoint of Wilhelmi treatment					
Weibull	20.0	3.9	73.6	100.0	4.06
Log-normal	16.8	2.2	59.0	93.3	4.97
Age at start of Wilhelmi treatment, y, Weibull model					
<11	20.4	2.8	50.1	98.6	8.30
≥11	21.2	1.2	44.5	99.5	3.32
Age at midpoint of Wilhelmi treatment, y, Weibull model					
<11	17.0	4.4	85.1	100.0	6.27
≥11	18.6	3.2	67.7	100.0	3.73

* Assuming all of cohort who are CJD-free survive to 60 years.

† Notional percentage of overall cohort/Wilhelmi-treated subjects who would contract CJD after indefinite follow-up if no deaths occurred from other causes.

CJD = Creutzfeldt-Jakob disease; hGH = human pituitary growth hormone.

confounding, by adjusting the Lowry risk for Wilhelmi treatment, is not possible because all CJD cases received the latter.) Thus it seems likely that Wilhelmi was the main source of the epidemic. It is possible that it was the sole source, and this would be compatible with the data, but it is not certain.

If Wilhelmi (or also Lowry) treatment was indeed the cause of the epidemic, then, very unexpectedly, the analyses showed that duration of relevant treatment was not material to risk. (The alternative hypothesis would be that duration of treatment with hGH is the underlying risk factor, and the association with Wilhelmi is secondary to this. This cannot be examined by statistical adjustment, because all cases of CJD had received Wilhelmi, but it does not appear plausible because if it were true then duration of treatment ought to have an effect on risk within Wilhelmi patients, which it did not.) An absence of effect of duration would suggest that all or almost all ampoules of Wilhelmi GH were materially infected, rather than that contamination was rare and random, because if each dose gave only a low probability of infection one would expect risk to rise with duration of treatment, whereas if the first dose alone was sufficient to cause disease in a susceptible person, then duration of treatment should not matter. That long durations of treatment may not be needed for infection is suggested by a recent Dutch case of CJD that occurred after administration of only 6 IU of hGH administered over 5 days[25] (although alternatively, this might have been a chance occurrence of sporadic CJD in a treated patient).

One cannot be completely sure about the lack of relation of risk to duration of treatment, however. It remains possible that only a few, or a limited range, of batches were contaminated (or at least contaminated with a dose sufficient to cause disease), and that the lack of relation to duration was due to chance or unexplained confounding. Future follow-up may help to clarify this.

Furthermore, if all or almost all Wilhelmi GH was infected, it would follow that either the great majority of patients must be resistant to the prion protein at the dose level received from hGH (because our models predict that only 4 to 5% of Wilhelmi-treated patients will ever contract CJD), or statistical models, based on experience of other infectious diseases[11] are inappropriate for predicting the CJD epidemic

beyond 20 years. A possible reason for inapplicability of the models would be that the epidemic to date may have occurred largely in subgroups of patients, by genotype or age, who have short incubation periods, and other subgroups may have later peaks not well represented in current follow-up. The available evidence suggests that this might occur, but not greatly. We found slightly shorter incubation periods in codon 129 homozygotes than heterozygotes. There was also evidence for this in hGH-related cases in France,[8,26] and it is implied by evidence of a lower age at onset for homozygotes than heterozygotes with sporadic CJD,[27,28] familial CJD,[29,30] and kuru,[31] although not in cases infected from dura mater.[17] There is evidence in mice for a slightly shorter incubation period after infection at older than at younger ages[32] and our data for humans showed the same. This was not thought to have been present for kuru[33] or hGH-related CJD in France,[8] but these were not analyzed in relation to person-years at risk.

As the lack of relation of risk to duration of (Wilhelmi) treatment is surprising, it needs testing by similar analyses in other countries. In the United States and France, the mean duration of hGH treatment was longer for CJD cases than other patients[5,34] but rates in relation to person-year denominators were not assessed, and the durations of treatment described were those of receipt of any hGH (for which we too found a duration-response relation) rather than for receipt of hGH during periods or of preparation-types in which infection was believed to be present.

Our results suggest that from the start of hGH treatment, the peak of CJD incidence risk occurs after an incubation period of about 20 years, and from the midpoint of treatment it is 1 to 3 years earlier. This is not greatly affected by whether one assumes that Wilhelmi alone or all hGH was infected, nor by the statistical model chosen. Analyses based on start of treatment equate with an assumption that virtually all doses of the treatment are infected and the first dose received is sufficient to cause eventual disease, whereas the midpoint would be appropriate if each treatment gave an equal, low chance of infection. The peak of CJD incidence in our cohort appears to be later than in France,[8] and more like that in the United States,[17] although the published analyses of the French and US data do not censor follow-up at death or loss to follow-up and therefore underestimate incubation periods, as discussed above. Another possible reason for an earlier peak in France is that the dose may have been greater there, and greater dose might be associated with shorter incubation periods.[8,17,23] In animals, transmission of CJD is highly dose-dependent.[17,35]

Our data suggested age variation in susceptibility to exogenous CJD infection, with greatest risk from exposure to Wilhelmi hGH at ages 8 to 10. A larger effect of young age on risk could potentially explain the young age of new variant CJD cases (these have on average died at age 29 years [SD 9.1], with only one case dying at age 55 years or greater).[36]

The near absence of methionine homozygotes at codon 129 of the prion protein gene among the CJD cases in the UK cohort is in contrast with the frequency of this genotype in people with vCJD (100%),[37] sporadic CJD in the United Kingdom (79%),[38] peripherally infected iatrogenic CJD in France (63%)[26] and the United States (64%),[39] and centrally infected CJD (74%).[17] Our cohort showed slight evidence of the relative protection from CJD in heterozygotes seen in previous studies, compared with the 50% heterozygosity in the general population in Western countries.[17] We did not have prion protein genotype information for all our cases, but there is no reason why availability should have been biased by genotype. The proportion of valine homozygotes in the United Kingdom cases (57%) was greater than in any of the above groups, or in the general population (about 10%).[17] At least in the comparison with sporadic cases, the explanation may lie in the young age of our cases. In sporadic CJD, the percentage of cases who are valine homozygotes varies significantly with age, and the proportion at young ages (41% at ages under 50 years)[40] is more similar to the cases in our cohort, all of whom were diagnosed under age 45. Alternatively, codon 129 genotype susceptibility might vary according to the strain of prion protein.

hGH-related CJD differs from other forms of the disease in route of transmission, species of the infected source, and variant of CJD, so our results cannot be directly transposed to other forms of CJD. The hGH results do represent, however, the only source of infection for which the dates of exposure are recorded and long follow-up is available for substantial numbers of people. They may therefore be relevant to consideration of the general biology and prevention of CJD—for instance, raising the possibility that only a few percent of the population may be susceptible, and that G100 size-exclusion chromatography can eliminate the prion. We intend future follow-up to estimate risks at longer periods after exposure.

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