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Case report

Contaminated Human Growth hormone as a cause of Creutzfeldt–Jakob disease

M.N.G. Dukes
Trosterudveien 19, 0386 Oslo, Norway
Tel.:+47 22 49 40 58; Fax: +47 22 92 11 35

Abstract. Eleven plaintiffs vs. The United Kingdom Medical Research Council (First Defendant) and the Secretary of State of Health (Second Defendant). High Court of Justice, Queen's Bench Division, No. 1994-N-06806. Judgement by Mr. Justice Morland, London; unrevised text, July 24th, 1996.

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1. Events

The essential events leading to this case were as follows:

Between 1959 and 1985 almost 2,000 children in the United Kingdom were treated with Human Growth Hormone (HGH) extracted from the pituitaries of about 940,000 cadavers. The treatment was designed to treat pituitary deficiency in the children and in particular deficiency in the secretion by the child's pituitary of growth hormone, with resultant dwarfism. Physically, the treatment was highly successful.

The HGH treatment of the recipients was carried out under the auspices of the First Defendants, i.e., the Medical Research Council (MRC). From the beginning until July the 1st, 1977 the responsibility for the collection of human pituitaries, their processing to obtain HGH and the allocation of HGH to nominated recipients was also the responsibility of the MRC. After that date and until 1985 the latter responsibility was that of the Second Defendants, i.e., The Secretary of State for Health (the Department) although responsibility for the collection and processing of pituitaries remained with the MRC until 1980. In the MRC phase the HGH programme was a Clinical Trial, but by 1976 because of the large number of child recipients it had effectively become a therapeutic programme. It was for that reason that responsibility was assumed by the Department.

In both phases of the programme, the technical responsibility for its conduct in effect passed progressively to a number of voluntary advisory committees of experts, supported by the scientific staff of MRC or the Department.

The UK programme ended on May the 9th, 1985 following the deaths from Creutzfeldt–Jakob disease (CJD) in the preceding months of three American recipients of HGH produced in the USA and the consequent withdrawal of the programme in that country. The first death of a British recipient

occurred on the 16th of February, 1985 when a woman died at the age of 22. In all, since 1985 and up to the date of the judgement, 16 of the UK recipients of HGH have died of CJD, four of them dying in 1995.

2. Proceedings

Proceedings in negligence were initiated by two groups of plaintiffs. Group A comprised 8 representatives of recipients who had died of CJD, as well as 3 plaintiffs themselves treated with HGH and currently suffering from diagnosed CJD. The dates of their treatment differed, the earliest courses starting in 1972 and the last doses in some cases being administered shortly before the termination of the programme in 1985. Group B comprised 87 plaintiffs who were recipients of HGH but had not up to the time of the proceedings contracted CJD. A preliminary Court Order obtained in 1994 consented to the current proceedings being conducted for the Group A plaintiffs only, with the provision that findings of fact in those proceedings would also bind the claims of the Group B plaintiffs should these be heard later.

For the purposes of this litigation only, the defendants admitted that the CJD suffered by the recipients of HGH was caused by an infectious CJD agent which had contaminated the dosages of HGH with which they were injected. The case therefore turned upon the issue whether the defendants had been sufficiently diligent in making themselves aware of the fact that this risk existed, whether they had identified and employed adequate means to reduce or eliminate it, and whether it was defensible, in view of the risk, to continue the programme throughout the period when plaintiffs were treated.

The 85-page judgement by The Hon. Mr. Justice Morland laid especial emphasis on the question of emergent knowledge; only by determining how and when knowledge of the risk had originated, and how and in what manner that knowledge could or should have been available to the defendants can one hope to determine what would have been a proper course of action at various points in time and assess the question of their having deviated from that standard.

The Court considered in turn the proper standards by which the handling of risks in an experimental or therapeutic programme should be assessed, the way in which in this instance basic relevant knowledge had been built up in the literature and elsewhere, the means of collection, storage and extraction of pituitary glands, the awareness within the programme that serious risks to recipients might be involved, and questions relating the procedures followed.

3. General standard of assessment

The Judge noted that a Court "must be very cautious in condemning a clinical trial or therapeutic programme. Too ready a labelling of an act or omission as negligent by the courts could stultify progress in medical and scientific research and render eminent experts reluctant to serve on Committees voluntarily. However, during the clinical trial of a new drug or form of treatment, and especially when the clinical trial is becoming a general therapeutic programme, all reasonably practical steps should be taken to minimise dangers and side effects. To discharge this duty constant alert and inquiring evaluation of the trial or programme is required. I do not accept that a Government Department or a quasi-Governmental Agency such as the MRC can discharge this duty by a lower standard of care than a commercial pharmaceutical company..."

4. Accumulation of basic relevant knowledge

Evidence leading to the conclusion that a human pituitary extract might carry the infectious agent (prion) inducing Creutzfeldt–Jakob disease did not arise acutely or in a simple manner. Over a long period there was a progressive accumulation of data having greater or lesser relevance and it came to the fore in different circles, including findings on the apparently related conditions known as kuru (occurring in traditionally cannibal populations in New Guinea) and scrapie (affecting sheep).

The Court cited some relevant dates, notably the following:

- In 1920, CJD was first described by Creutzfeldt, and in 1921 by Jakob.
- In 1959, Hadlow published an overview of knowledge of scrapie and kuru in the Lancet.
- In 1972, Roos et al. "reported the clinical characteristics of 47 CJD patients including cases where inoculated brain tissue transmitted the same disease to primates".
- In 1959, Gibbs reported on the transmission of scrapie and kuru to the chimpanzee.
- In 1972, Gadjusek and Gibbs published an authoritative overview of the infectious "Sub-Acute Spongiform Virus Encephalopathies", basing their portrayal of this group of diseases on evidence relating to scrapie, kuru and CJD.
- In 1974, Duffy described in the New England Journal of Medicine "Possible Person to Person Transmission of CJD" via a corneal transplant.
- Also in 1974, Bernoulli published in the Lancet evidence that in two patients CJD infection had been transmitted on insufficiently sterilized brain electrodes.
- In 1975, Matthews in the United Kingdom set the incidence of new cases of confirmed CJD in Britain at 0.09 per million population, an estimate now realized to be "a gross underestimate".
- In 1977, Brown in the New England Journal of Medicine reviewed evidence that "all tissues of patients with CJD must be considered potentially hazardous", noting earlier evidence of the resistance of this class of slow viruses to acetone treatment.

The Court considered that as late as the 1960s or 1970s "only the first glimmers of knowledge and understanding about CJD being caused by an infectious agent were emerging" and "even today doctors and scientists are still at the frontiers of knowledge..."

5. Collection of pituitaries

Pituitaries were collected throughout the programme from autopsy subjects. As early as 1958, the Secretary of the relevant MRC committee, appealing to consultant pathologists to provide this input, noted as far as selection was concerned that "All or a fraction of any post-mortem pituitaries which are not the seat of primary disease will be useful", a statement which was repeated literally in 1974; more stringent selection criteria were not issued until 1980. Evidence was given to the Court that some mortuary attendants never received any more specific instructions on selection than those issued by the authorities.

A payment of 20p per gland was to be made, and it seems clear that these sums became a perquisite of mortuary attendants who at the time were poorly qualified and poorly salaried. Despite the financial incentive, and although it seems that many pathologists were in fact insufficiently informed as to the disorder from which the deceased had been suffering, the Court concluded that almost all Mortuary Attendants and Pathologists would have done their best to exclude pituitaries which in their judgement

were unsuitable. More explicit selection criteria for pituitaries, which in fact had been drafted internally by 1977, should in the Court's view have been issued earlier than 1980. These would not however have entirely eliminated risk since even frank CJD would not always be diagnosed, nor would cases in a late incubation phase of the CJD virus have been recognized, but the Court considered it negligent not to introduce this warning in 1977.

6. Storage and processing of pituitaries

From the start, simple instructions were issued to pathologists on storing the freshly harvested glands in excess acetone. The initial experiments in extraction were undertaken at Cambridge using the relatively mild (acetone) method developed by Wilhelmi, which appears to have had only a limited ability to destroy infective organisms; expert advice received in 1958 (from Prof. Wilson Smith) expressed optimism as regards infection, but noted that it was impossible to rule out the possibility of some hypothetical agent surviving the treatment. Soon thereafter Cambridge began production of HGH for the programme but now using the harsher Raben method, which included extraction in hot glacial acetic acid; this could be expected to eliminate harmful organisms but partly denatured the hormone, reducing the yield and producing antigens. In 1969, Cambridge therefore moved back to the milder Wilhelmi (acetone) method, though now modified by its own staff.

From 1975 onwards, extraction was also undertaken at St. Bartholomew's Hospital, London using frozen (rather than acetone-preserved) pituitaries and the Lowry Ross (chromatographic) extraction method which produced a highly purified HGH.

After the Department of Health took over responsibility for the Programme, production was progressively transferred to a Government laboratory at Porton Down which began to deliver HGH in 1980; here both the Cambridge and London extraction processes were used but additional steps were incorporated to produce a purer product.

All the known cases of CJD infection resulting from the programme to date have been found to have been associated with use of the Cambridge product, not with the use of the London or Porton Down batches.

In its judgement, the Court laid weight on the improved purification procedures introduced when the various methods were transferred to the Porton Down Laboratory in 1979/1980; there was in fact no reason why these improvements could not have been introduced when production was still based at Cambridge and London.

The Court further regarded it as a serious deficiency of the Programme's Steering Committee that the Directors of the two laboratories producing HGH were both members, and that no other members were qualified to monitor their work. There was no significant outside quality control.

7. Awareness of risk

In the view of the Judge the medical and scientific staff of the MRC and the Department had a duty to be alert to and aware of current medical and scientific knowledge and discoveries. In briefing the Chairman and members of committees "they were an obligation to alert committee members to such current knowledge and discoveries". Committee members themselves, volunteers though they were, had to be alert and inquiring.

The first direct warning that use of HGH might lead to CJD was in a telephone call to MRC staff in October 1976 from an agricultural scientist, Dr. Alan Dickinson. The staff reported the warning in detail to the Chairman of the relevant Committee and a discussion in the Committee followed. Further advice from Dr. Dickinson was to be sought, but the provisional impression of the Committee was that the London procedure might involve greater risks of infection (primarily to laboratory staff) than that used at Cambridge. In February 1977 Dr. Dickinson replied with a guarded statement as to possible risks; he suggested two additional studies to assess the risk, and some precautions to be taken, notably the exclusion of pituitaries from patients with dementia. Dr. Dickinson's advice was not sought on a proposal received as long ago as 1973 from Dr. Wilhelmi to add gel filtration to the extraction method which he had originally developed, in order to reduce viral risks. Only two of Dr. Dickinson's suggestions for action were in fact followed, and both much later. The Court noted a "failure to act with sufficient urgency" at this time, e.g., in implementing Dr. Dickinson's suggestions and in obtaining timely virological advice from other experts.

8. Procedures

The Court was critical of the poorly defined manner in which, from 1976 onwards, responsibility for the programme was transferred from the MRC to the Department of Health. The Steering Committee of the Medical Research Council remained for a long period responsible for collection and production, and bestowed little further attention on risks to patients, indeed deleting a passage dealing with the issue from the draft minutes of one of its meetings. The parallel "HSHGH" committee instituted by the Health Services to deal with actual use of the drug, though it consisted primarily of clinicians, would in the Court's view have been able to assess the question of risk but was not given the facts either by its secretariat or by the MRC. When two eminent virologists (Prof. Mimms and Prof. Wildy) were ultimately consulted regarding the risks advanced by Dr. Dickinson, the exhaustive replies received from them in December 1977 were, in the judgement of the Court, never laid before the HSHGH Committee. Nor was the issue adequately brought forward in meetings between the HSHGH and the MRC, which should have jointly examined the seriousness of the problem and decided on appropriate action.

The Court also noted that although, from March the 9th, 1978 onwards, an expert group was convened elsewhere within the Medical Research Council to advise on the study of CJD as a disease, that Committee was not alerted at the time to the existence of the HGH Programme or to the current concern within that Programme regarding CJD. There was also a "Slow Virus Group" within the Department of Health which met from 1979 onwards but this too was scarcely confronted with the issue of HGH/CJD.

The Court therefore concluded that from 1976 onwards a "failure in communication" occurred, characterized by "the failure of the committees to be given the knowledge and their failure to seek it..." and this amounted to negligence. The Court noted specifically that, even after the Programme's Steering Committee had been alerted to possible CJD risks by Dr. Dickinson in 1976–1977 and was discussing his warning, there was failure to lay before the Committee the relevant papers by Bernoulli, Duffy and Gadjusek relating to transmissibility and resistance to sterilization. Similarly, when the merits of the various extraction procedures were under discussion, the Committee was not alerted to work showing the incomplete sterilizing effect of acetone (notably by Mould, 1965).

9. Conclusion

"I am satisfied that as from the 1st of July 1977 negligence is established against the Department including negligence on the part of the MRC for which vicariously the Department are liable. The programme should have been partially suspended on that date. I am satisfied that if a proper evaluation and re-appraisal of the programme by virologists, endocrinologists, scientists and clinicians had taken place the therapeutic programme would and should have been suspended for all new patients pending the results of Dr. Dickinson's experiments..."

Since recipients were not being inoculated with untreated HGH, but with treated HGH which was given not intra-cerebrally (as in published reports of human or animal transmission) but sub-cutaneously, "...I am satisfied that it would not have been unreasonable or irresponsible to have continued HGH treatment for those recipients such as those suffering from hypoglycaemia who would otherwise have suffered serious ill-health. Indeed that is what occurred in May 1985 when the programme was terminated, following the first CJD deaths, in the United States. It was advised that HGH be continued to be given to such patients pending the availability of the synthetic product."

In the light of the above, the Court allowed the action but only for plaintiffs who were admitted newly to the Programme after July the 1st, 1977. Since a careful evaluation at that time, had it taken place, would in all probability have resulted in a closely balanced conclusion, recommending continuance of the Programme for existing recipients, the action by plaintiffs already participating in the treatment on that date must fail.

10. Comments

This extensive judgement is in various respects a milestone in medico-legal jurisprudence. It provides a firm definition of the duties incumbent upon a governmental or government-backed organization when it engages in medical research with drugs or allied substances; their duties are held to be closely similar to those incumbent upon a pharmaceutical company. The facts of the case point to the existence of a situation where the bodies responsible for the programme were in various respects poorly structured to handle these duties, e.g., as regards the peer monitoring of production procedures, the internal flow of information, and the existence of means to take rapid action when necessary.

The judgement also squarely confronts the problem posed by emergent knowledge of risk–evidence which arises progressively over a long period and perhaps in entirely different fields of science and which may be pieced together and interpreted as a whole much too late to avoid harm being done. One may note that at the crucial date set by the Court (July the 1st, 1977) the risk here under discussion, i.e., the causation of CJD by contaminated Human Growth Hormone was still some years ahead of full recognition in the published literature; the full picture was in fact only portrayed in the medical journals in 1984/1985 and indeed mainly *following* the suspension of the treatment programmes in Britain and the USA. To that extent Mr. Justice Morland's judgement profiles the fact that any body imposed in therapeutic research has a duty to bestow careful attention on warning signals, look widely for emergent evidence of risk, and piece together all that is known or supposed in expert circles, irrespective of whether or not it has matured in published opinion.