HUMAN GROWTH HORMONE

French Scientists May Face Charges Over CJD Outbreak

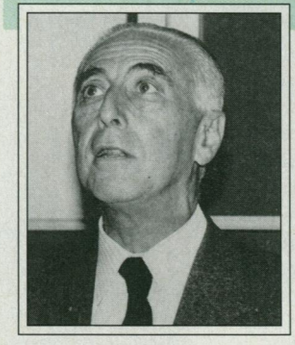
PARIS—These are perilous times for researchers who worked in the French public health system in the mid-1980s. A few days after a Paris court jailed Jean-Pierre Allain, formerly a senior scientist at the French National Center for Blood Transfusion, for failing to halt the distribution of HIV-contaminated blood clotting factors to hemophiliacs (*Science*, 23 July, p. 422), two more scientists have begun to feel the heat of French justice. Pediatrician Jean-Claude Job of the St. Vincent-de-Paul Hospital in Paris and Fernand Dray, a retired Pasteur Institute biochemist, were notified last week that they are being investigated for involuntary homicide in a case that bears an eerie resemblance to the contaminated blood episode.

The judicial inquiry—which is the first step toward possible formal criminal charges—stems from a public health tragedy in which children treated for dwarfism with human growth hormone have fallen victim to Creutzfeldt-Jakob disease (CJD), a rare, fatal neurodegenerative condition (*Science*, 4 December 1992, p. 1571). Before recombinant versions of the hormone were developed, it was derived from pituitary glands taken from cadavers. The CJD cases presumably were caused by contamination of hormone stocks with the infectious proteins, or prions, that are thought to cause the neurological disease. With 24 confirmed cases, France already has as many growth hormone-linked cases of CJD as the rest of the world combined, and new cases are emerging at the rate of one a month.

The accusations against Job and Dray are based on a scathing review of France's national growth hormone program by the inspectorate-general for social affairs (IGAS), released last Christmas. The two scientists were key players in the program: Job remains president of the Association France-Hypophyse, the agency responsible for collecting the pituitary glands; Dray's laboratory extracted and purified the hormone. The IGAS report concluded that precautions designed to ensure that pituitaries were not taken from neurologically diseased cadavers were "manifestly insufficient" and questioned the adequacy of Dray's purification procedures.

Much of the attention has focused on the operations of the French growth hormone program in 1985. In that year, the United States and Britain abruptly halted the use of cadaver-derived pituitary hormones, after the first cases of growth hormone-linked CJD were discovered. At the time, no French cases had emerged. But rather than follow the U.S. and British example by switching to recombinant hormone, French officials in June 1985 instead added an additional step to the purification procedure: treatment of pituitary extracts with an 8 Molar solution of urea. This has since been shown to reduce greatly—but not necessarily eliminate—prion infectivity. Several groups have reduced the infectivity of pituitaries deliberately contaminated with scrapie, a related disease of sheep, by more than 99% using concentrated urea. If this model holds true for CJD, the risk of contracting the disease from the urea-treated natural growth hormone would be small.

"Everywhere in the world, the collection of pituitaries was done in the same way."
–Jean-Claude Job



But given the availability of recombinant hormone, says neurologist Maurizio Pocchiari of the Higher Institute of Health in Rome, "maybe it is not a good idea to take even this low risk." Although the French program had completely switched to recombinant growth hormone by the end of 1988, the IGAS report criticized the decision not to halt use of pituitary-derived hormone 3 years earlier, and also contended that some stocks of hormone that had not gone through urea purification were not recalled from hospital pharmacies.

Dray declined to be interviewed, but Job vigorously rejects the IGAS report's criticisms. "Everywhere in the world, the collection of pituitaries was done in the same way," he asserts. Scientists involved in other national pituitary hormone programs cannot confirm whether the French procedures for excluding potentially infected pituitaries were as thorough as their own. But they point out that no screening program is likely to be 100% effective. Endocrinologist Judith Fradkin of the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, for example, says that the long incubation time of CJD—up to 35 years—makes it impossible, in many cases, to know whether a cadaver is diseased.

Whatever the reason, the French program apparently suffered problems not experienced elsewhere. Aside from the sheer number of cases, epidemiological data suggest that the majority of the French children became infected in or around a period from January 1984 to May 1985. In the United States and Britain, however, no cases have yet emerged in patients who started growth hormone therapy after 1977—the year in which a set of more refined techniques for extracting the hormone from pituitary glands came into general use worldwide.

Many CJD and growth hormone experts sympathize with the position of Job and Dray, who may soon be facing serious criminal charges in an atmosphere of angry public opinion, fueled by the AIDS-hemophilia cases. But several researchers contacted by *Science* last week were highly critical of the French decision to continue using pituitary-derived hormone after 1985, albeit with an extra purification step, when commercially produced recombinant growth hormone was available. "I just don't understand the logic," says endocrinologist Michael Preece of the Institute of Child Health in London. "Why take the chance?"

A series of letters written in 1985 by Job and other senior health officials, included in an annex to the IGAS report, make it clear that they were reassured by the fact that the British and U.S. cases derived from pre-1977 purification protocols and regarded the mid-1980s techniques—even without the additional urea step—as safe. Nevertheless, Job flatly denies the IGAS report's charge that some batches of hormone that hadn't been treated with urea were not recalled after June 1985—an accusation based on interviews with two hospital pharmacy officials. All stocks were "immediately destroyed or retreated with concentrated urea," he says.

Even if that were the case, however, the worrying possibility remains that the urea treatment may not have been a sufficient precaution against CJD transmission. Job can take comfort from the fact that so far, no cases have yet been found in French children whose growth hormone treatment began after June 1985. But given the disease's long incubation time, it will be decades before that possibility can be ruled out.

–Michael Balter

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