Does Medical Mystery Threaten Biotech?

A petition with the FDA and a new animal model are the latest twists in the enigmatic disease known as EMS

A PUZZLING MEDICAL SYNDROME CAUSED by substances grown in a genetically engineered bacterium could have profound consequences for the entire biotechnology industry—if Jeremy Rifkin has his way. Rifkin, the controversial (some say trigger-happy) biotech critic, has filed a petition based on the eosinophilia-myalgia syndrome (EMS) with the Food and Drug Administration. In it, he asks that the FDA's review of all products made by genetic engineering techniques be suspended until strict new rules are in place to protect the public.

The problem is that no one yet knows whether the specific contaminant that has caused up to 5000 EMS cases and 27 deaths was actually the result of genetic engineering. It might well have been the result of problems with chemical purification steps that have little to do with molecular genetics. Until now there has been no way to resolve that uncertainty. But help is on the way—in the form of a recently published animal model of the disease that should eventually enable researchers to pinpoint the precise cause of the syndrome.

Those who acquired EMS, beginning last November, were found to have taken the amino acid L-tryptophan, which is marketed as a "natural tranquilizer" or sleeping pill. All the tryptophan linked to EMS cases came from a small series of lots manufactured by one Japanese company: Showa Denko. There is no question that the bacterium used to make the case-related L-tryptophan was genetically engineered.

Indeed, Showa Denko documents obtained by *Science* indicate that, contrary to previous reports, which suggested the genetic engineering was done by imprecise "shotgun" methods, the alteration was precise and purposeful. It was carried out in several steps aimed at increasing the amount of L-tryptophan the bacterial strain can make. One step involved the enhancement, or duplication, of the tryptophan operon and promoter, the cluster of genes that encode the amino acid and regulate its production. A further touch was the insertion of the gene for a rate-limiting enzyme from another bacterial strain.

Last month, Rifkin's Foundation on Economic Trends filed a petition requesting the FDA to take several measures to limit what it sees as the harmful potential of genetically engineered organisms. Those steps include requiring that new rules be established for the review of all products manufactured by recombinant DNA methods, that all those products be so labeled, and that studies be initiated "to establish a responsible predictive science for analysis of the safety of genetic engineering manufacturing processes."

In comments to *Science,* Rifkin said he plans to proceed to litigation against the FDA—which currently has no special procedures for handling genetically engineered products—as soon as legally possible. According to an attorney for his foundation, the FDA normally has 180 days to respond to a citizen's petition. But a suit could be launched earlier if there is clear evidence that human health and safety are at risk. The FDA refused to comment to *Science* on Rifkin's petition.

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EMS sleuth. *Esther Sternberg and her colleagues developed the first animal model for the puzzling eosinophilia-myalgia syndrome.*

Regardless of the legal details, the crux of the EMS case remains the issue of whether the disease is, in fact, due to genetic engineering. At the same time Showa Denko began using its new, genetically engineered bacillus (known as Strain V), it also reduced the amount of activated carbon used to filter the fermentation broth from 20 to 10 kilograms per batch—suggesting that inadequate filtration might have allowed impurities to pass through.

That possibility is discounted by scientists at Showa Denko, says Richard Hinds, a Washington lawyer who represents the Japanese firm. The amount of powdered carbon used for filtration had varied before without ill effect, and it was not unusual for it to dip this low, Hinds says. Yet neither Showa Denko scientists nor researchers at the FDA have yet offered a conclusive explanation for the EMS cases.

But in an article in the current *Journal of Clinical Investigation* long awaited by those who have been closely following the EMS saga, researchers report that they have reproduced several of the most distinctive features of the syndrome in rats. Esther M. Sternberg of the National Institute of Mental Health and the National Institute of Arthritis, Musculo-skeletal and Skin Diseases and Leslie Crofford of the NIAMS, with colleagues from the Centers for Disease Control and FDA, fed female Lewis rats the Showa Denko tryptophan from the lots associated with EMS. After 38 days the rats developed fasciitis and perimyositis, two types of inflammation linked to EMS. Control rats and those receiving non–Showa Denko tryptophan showed no symptoms.

Sternberg and her colleagues have now begun testing the substances associated with EMS to see which one—or which combination of them—is the culprit. The impurity that is the prime suspect (first called "peak E" or "peak 97") is the di-tryptophan aminal of acetaldehyde, or DTAA: an aberration consisting of two tryptophan molecules joined together. Many other biologically active impurities have been found in the Showa Denko tryptophan preparations, however, and the Sternberg group will also be testing them. Considerable attention is being focused on the extremely biologically active compounds known as beta carbolines, which have also been detected in the brew.

Sternberg's work will not, in itself, show whether genetic engineering is to blame for EMS. But by pinning down the exact cause of the disease, it could help to determine whether it was the chemical purification steps or the genetic engineering itself that was at fault. In any event, it seems likely that there will be a good deal more controversy before the strands of EMS—both scientific and legal—are fully unraveled.

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