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THE FIRST WORD/

L-TRP'S LESSON: THE PROCESS IS THE PRODUCT

The product is the process; the process is the product. Recent research seems to confirm that seemingly minor purification changes in an L-tryptophan (L-Trp) production process may have killed scores of people and sickened thousands. It certainly threatened biotechnology's good name.

In 1989 and 1990, several thousand people around the world began reporting horny deformities of the skin, body aches, and general inflammation—elements of eosinophilia-myalgia syndrome (EMS).

In 1990, medical investigators linked EMS with L-tryptophan manufactured by Showa Denko, specifically to batches produced after October 1988, when the company introduced a new, high-output bacterial fermentation process. That process featured, among other changes, a recombinant strain of *Bacillus amyloliquefaciens.*

As soon as the word "recombinant" appeared in the public record, Jeremy Rifkin and the Foundation on Economic Trends ("pat upon the instant like the catastrophe in the old play") petitioned the U.S. Food and Drug Administration to halt all "genetic engineering manufacturing processes" producing "human drugs, animal drugs, foods, food additives, and nutrients" of whatever kind.

That was in August 1990. This fall, FDA properly and soberly rejected Rifkin's petition. Showa had, the regulators noted, introduced other process changes along with the recombinant microbe. Perhaps most important, as E.A. Belongia noted in the New England Journal of Medicine and FDA reiterated, Showa had "reduced quantities of powdered carbon in a purification step.... The high correlation between the reduction in the amount of powdered carbon and the use of *B. amyloliquefaciens* Strain V limits our ability to assess the independent contribution of the bacterial strain to the risk of [EMS]." (NEJM **323**:361-365, 1990.)

Well, much more independent assessment has now been done. EMS correlated with one specific contaminant of the Showa Denko product, Peak 97 or Peak E. It took much of a year for researchers to identify the substance as a condensation product of L-Trp and the acetaldehyde (common in microbial fermentations, FDA noted) formed by oxidation of ethanol. Related compounds are fairly well known ("Eat brussels sprouts and boil your urine through alcohol," observes one researcher wryly), even though it can go by a bewildering variety of names. Early reports referred to DTAA (ditryptophan aminal of acetaldehyde). More recently, researchers have preferred EBT (1,1'-ethylidene bis[L-tryptophan]).

At two meetings this fall—Neuroscience and the American College of Rheumatology—a group of U.S. researchers drawn from the National Institute of Mental Health, Centers for Disease Control, and FDA reported the latest and perhaps clearest demonstration that mixtures of non-recombinant EBT and L-Trp do indeed produce most (though not quite all) of the physiological changes associated with EMS, changes that go far beyond those produced by either compound alone.

The data strike us as decisive, plainly showing that the villain was too little filtration, not too much biotechnology.

Some of the NIMH-CDC-FDA researchers, though, think that would be jumping to conclusions.

"The story is very complex, and it doesn't get anybody off the hook," says NIMH's Esther M. Sternberg. (Sternberg entered the field in the late 1970s, when a group of patients developed EMS-like symptoms after receiving L-5-hydroxytryptophan to boost their serotonin levels.) The EMS debacle does, after all, have its biotechnology component: EBT forms most readily in very high L-Trp concentrations, like those attained in bio-tweaked processes.

But, Sternberg agrees, the chief lessons are to be learned further downstream. "A drug is a drug is a drug," she says, even if it is marketed as a food supplement. Proper purity and process controls are vital.

On that point, we heartily agree. Pharmaceutical good manufacturing practice would likely have prevented the L-tryptophan EMS problem altogether, and at very least would have caught the error before damage was done.

—Douglas McCormick