The Eosinophilia-Myalgia Syndrome: Lessons From Germany

During the autumn of 1989, an epidemic of a new disease occurred in the United States. This novel illness, characterized by blood eosinophilia and severe muscle pain, was termed the eosinophilia-myalgia syndrome (EMS).1 EMS was initially recognized in October 1989 in three women from New Mexico, all of whom had consumed L-tryptophan before the onset of their illness.2 Epidemiologic studies by the health departments of New Mexico and Minnesota demonstrated a clear-cut association between ingestion of L-tryptophan and the occurrence of EMS.2,3 As a result of these investigations, the US Food and Drug Administration initially issued a nationwide warning advising consumers to discontinue the use of supplements and subsequently issued a nationwide recall of L-tryptophan. After tryptophan was removed from the consumer markets, the number of new cases of EMS rapidly diminished. Nonetheless, more than 1,500 persons were afflicted, and many patients still suffer from the disease. The toll from EMS would almost certainly have been higher, except for the alertness of physicians who linked the new disease to ingestion of tryptophan, the epidemiologic investigations by the state health departments and the Centers for Disease Control and Prevention, and the prompt recall of L-tryptophan-containing products by the Food and Drug Administration.

Epidemiologic Data.—Use of tryptophan was widespread in the United States in 1989, and in Oregon and Minnesota, approximately 2% of household members surveyed had ingested tryptophan at some time between 1980 and 1989.3,4 The most common reasons for consumption of tryptophan were insomnia, premenstrual syndrome, and depression. In the United States, tryptophan was available to consumers without a prescription; thus, a very large number of persons were at risk. As of June 1993, 1,511 cases of EMS (and 37 related deaths) had been reported to the Centers for Disease Control and Prevention.6 The case definition included the following factors: (1) an eosinophil count of 1,000/μL or more, (2) generalized debilitating myalgia, and (3) no evidence of infection or neoplasm to explain the clinical findings. National surveillance data from July 1990 showed that 84% of affected patients were female, 97% were non-Hispanic white, and 86% were older than 34 years of age (median age, 49).7 Probably, the actual prevalence of EMS was considerably higher than that estimated by these surveillance reports because persons with mild disease were excluded by the surveillance case definition, and many cases may have gone unreported.

Source of Tryptophan.—After initial case-control studies associated consumption of tryptophan and EMS, investigations were initiated in Oregon and Minnesota to examine this relationship.4,5 Consumers of tryptophan were classified as cases (patients with EMS) or controls (users of tryptophan without EMS), and the lots of tryptophan consumed by these groups were traced to determine the source of the tryptophan. Tryptophan ingested by the cases and controls had been manufactured by six companies, all in Japan. Analyses of the sources of tryptophan used by cases and controls showed a strong association between EMS and consumption of tryptophan manufactured by a single company, Showa Denko K.K., a large petrochemical firm in Tokyo. In Oregon, 98% of cases had ingested tryptophan manufactured by Showa Denko in comparison with 44% of controls.5 In Minnesota, 29 of 30 cases (97%) had ingested tryptophan that was traced to Showa Denko K.K. in comparison with 21 of 35 controls (60%) (odds ratio, 19.3; 95% confidence interval, 2.5 to 844.9).4 High-performance liquid chromatographic analysis of the tryptophan ingested by the one Minnesota case that was not traced to Showa Denko revealed a chromatogram characteristic of that company’s product, an indication that the tryptophan was indeed produced by Showa Denko.

Attack Rate.—Data from a cohort of persons who ingested tryptophan in the practice of a psychiatrist in South Carolina provided an estimate of the attack rate of EMS for persons who ingested relatively large quantities of tryptophan. These persons consumed a single brand of tryptophan from only three lots of Showa Denko material. Among the 157 persons, 29% fulfilled the surveillance definition of EMS, and an additional 23% were classified as “possible cases” because they had some clinical findings of EMS, such as eosinophilia without myalgia, but did not meet the strict surveillance case definition. Thus, the pooled attack rate of both definite and possible cases was 52% among those who ingested these lots of Showa Denko L-tryptophan. Interestingly, among those who consumed more than 4 g of tryptophan, the definite attack rate was 59%, and the pooled attack rate (definite and possible cases of EMS) was 84%. These results suggest that all persons who ingest sufficient quantities of the etiologic agent are susceptible to having EMS. Furthermore, in this cohort, the attack rate for male and female subjects was identical.

Risk Factors.—Two risk factors for EMS have been identified—namely, the quantity of tryptophan consumed...
and the age of the person. As expected from the aforementioned results, the risk of occurrence of EMS increased with larger doses of tryptophan and with increasing age. The dose of tryptophan likely reflects the degree of exposure to the etiologic agent. The reason for the increased risk of EMS with advancing age is unclear; perhaps age-dependent physiologic changes in renal or, more likely, hepatic function alter the metabolism or the clearance of the toxin. No other host factors have been identified as altering the risk for EMS.

**Study in Germany.**—In this issue of the *Mayo Clinic Proceedings* (pages 620 to 625), Carr and associates present findings on EMS from Germany. A noteworthy difference between the use of tryptophan in Germany and in the United States is that tryptophan can be obtained only by prescription in Germany. Thus, all German patients who received l-tryptophan preparations were under medical supervision, and considerable information was available about the history of the patients with EMS. In general, the results obtained by Carr and colleagues substantiate the previous information obtained in the United States. For example, in the United States as in Germany, most patients with EMS were women. Furthermore, many patients had ingested tryptophan for long periods (10 years or more) before becoming ill in 1989. This observation makes the existence of an inborn error of tryptophan metabolism an unlikely cause of EMS and, thus, reinforces the concept that a contaminant in certain lots of tryptophan triggered the epidemic. In Germany, tryptophan was formulated by nine companies, and cases of EMS were associated with only two of these companies, both of which had used l-tryptophan obtained from Showa Denko. Although not stated explicitly, the authors imply that all tracebacks on the tryptophan ingested by the 105 patients who fulfilled the criteria for EMS led to Showa Denko; in contrast, no verified cases of EMS were traced back to other manufacturers. In 93 patients, concurrent use of medications or dietary supplements other than l-tryptophan could be assessed, and 45% of the 93 patients were taking one or more medications in addition to l-tryptophan. The two groups of patients—that is, those taking l-tryptophan only and those taking l-tryptophan as well as concurrent medications—did not differ significantly in median age, sex distribution, mean daily dose of l-tryptophan, or initial symptoms. Attempts to associate a particular medication, including tricyclic antidepressants, salicylates, multivitamins, estrogens, benzodiazepines, ß-adrenergic blocking agents, calcium channel antagonists, and diuretics, with EMS were unsuccessful. The authors concluded that the development of EMS does not seem to depend on the use of other medications concurrently with the l-tryptophan. This conclusion is consistent with prior observations. Carr and coworkers did not confirm the finding from the cohort of patients in South Carolina that the dose of tryptophan was the strongest predictor of EMS. In the German study, however, more than 90% of the patients with EMS had received less than 3 g/day. Most likely, different production lots had variable quantities of the EMS-associated l-tryptophan contaminants. Thus, the failure to find a relationship between the development of EMS and the dose of l-tryptophan may reflect lot-to-lot variation in the quantities of the contaminants in the l-tryptophan. Finally, one patient in whom EMS developed reportedly discontinued the use of l-tryptophan in May 1990 and had the onset of symptoms of EMS in May 1991, a latent period of 12 months—one of the longest latent periods reported to date.

**Etiologic Factors and Animal Models.**—A search for the cause of EMS continues, and several contaminants, including 1,1’-ethylidenebis(tryptophan) (EBT), 3-aniline derivatives were significantly associated with case-related samples. One contaminant, 3-phenylamino-1,2-propanediol (PAP), is chemically similar to the tryptophan contaminant PAA. The strong similarities between EMS and TOS suggest that they may share a final pathway that leads to neuromuscular damage, and the finding of a chemically related aniline derivative in tryptophan is suggestive of an associated cause. Thus, the possibility exists that PAP may undergo biotransformation to PAA in vitro; hence, the two diseases would be linked to a common chemical.

**Conclusion.**—During the past decade, two epidemics caused by food-associated contaminants have occurred. Although TOS was caused by illegally processed denatured rapeseed oil and, therefore, was avoidable, EMS resulted from tryptophan that had been manufactured reasonably.
carefully. The occurrence of these epidemics emphasizes the importance of rigorous quality control and a high degree of chemical purity of food supplements. New products should be initially tested for their safety in animals. In the absence of a faithful animal model, however, administration to humans on a trial basis and careful assessment of their responses, especially changes in the number of peripheral blood eosinophils, may be essential to evaluate safety. Currently, neither the mechanism nor the specific contaminant (or contaminants) that caused EMS or TOS has been unequivocally demonstrated, and the occurrence of another food-related epidemic similar to TOS and EMS seems likely.

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REFERENCES