The Truth About Tryptophan

**This article first appeared in the
May/June, 1993 issue of VRP's Nutritional News**

by A. S. Gissen

L-tryptophan had been commercially available in the United States for fifteen years until its recall by the Food and Drug Administration in late 1989. It is an essential, naturally occurring amino acid that is a precursor for serotonin biosynthesis. Since serotonin is a neurotransmitter implicated in numerous psychiatric and neurologic disorders, dietary tryptophan supplementation has been investigated as a possible treatment for a number of conditions attributed to alterations of serotoninergic neurotransmission. These conditions include depression], aggression[2], obesity[3], hypertension[4], obsessive-compulsive disorder[5], and seasonal affective disorder[6]. Its widest use, however, was in the treatment of insomnia, where it was found to be effective in inducing sleepiness and sleep[7].

Prior to its association with the nationwide outbreak of Eosinophilia- Myalgia Syndrome (EMS) in 1989, few adverse effects had been reported with L-tryptophan, even when taken in doses of up to 8 grams a day for extended periods of time. These adverse effects did include muscle stiffness, blurred vision, dry mouth, tremor, and ataxia[5]. In actual use, however, L- tryptophan was considered quite safe. Prior to its recall, up to 2 percent of all households in the United States contained at least one person who consumed L-tryptophan on a regular basis[8]. The Wall Street Journal of November 21, 1989 estimated yearly retail sales to be over $60 million dollars. Thus, it came as quite a shock that such a widely used food product could be associated with a debilitating and potentially lethal syndrome that resulted in dozens of deaths, and may have injured more than 5000 people.

L-tryptophan-induced Eosinophilia Myalgia syndrome was first recognized in October l989, by three physicians in the Santa Fe, New Mexico area, when they notified the New Mexico State Health Department of three patients with a mysterious and undiagnosable condition. The patients were previously healthy women who reported severe myalgia (muscular pain), and were found to have elevated eosinophil counts in their blood. After thorough analysis, it was discovered that all three women had been taking L-tryptophan supplements. This initial outbreak in New Mexico was investigated using a case study of L-tryptophan consumers, and results of this study strongly associated the use of L-tryptophan with the development of EMS[9]. Shortly after the results of the study were made public, studies in other parts of the country substantiated the findings. The Food and Drug Administration (FDA) subsequently issued its first recall of most L-tryptophan containing products on November 17, 1989. Strangely, this recall applied only to products containing more than 100 milligrams of L-tryptophan, as no reports existed of illness in anyone consuming less than 150 milligrams a day. On March 22, 1990, the FDA expanded its recall of L-tryptophan to include products of any dosage, as some EMS cases involving the consumption of less than 100 milligrams a day were discovered. Exempt from both recalls were some protein supplements, infant formulas, special dietary foods, intravenous and oral solutions, in which small amounts of L-tryptophan are needed for nutrient fortification. Ultimately, there would be cases of EMS in patients consuming these "exempt" products.

Eosinophilia-Myalgia syndrome is a heterogeneous, multi-organ disease that appears to have a sub-acute onset. The disorder is characterized initially by eosinophilia and severe myalgia. A host of other systemic systems may include, joint pain, weakness, fever, dyspnea, cough, fatigue, edema, rash, sclerodermaform skin changes, hair loss, and neuropathy. A common and distinctive long term complication in EMS patients is the presence of muscle cramps and spasms. Severe interstitial lung disease and pulmonary hypertension have also been described. Alterations of tryptophan metabolism are common, and patients have also developed neurocognitive deficits causing functional disability. The prevalence of symptoms in EMS patients has ranged from common to rare, with only myalgia being universallyrecognized[l0].

Immediately following the recognition of EMS as a new disease linked to L- tryptophan consumption, intense research efforts were taken to determine the cause of the disease. Although EMS appears to be a new

disease, there are several previously described syndromes with eosinophilia as a presenting symptom. Among these, Toxic Oil Syndrome (TOS) bears some striking similarities to EMS.

Toxic oil syndrome was an explosive illness that swept Spain in 1981. It affected over 20,000 people and ultimately led to over 300 deaths. It was associated with eosinophilia and multi-organ manifestations similar, though not identical, to EMS. Epidemiologic and chemical investigations have clearly linked the toxic oil syndrome to the consumption of rapeseed oil mixtures, denatured with aniline, and intended for industrial use. Aniline itself did not cause the disease, and despite intensive research efforts over the past decade, the agent(s) responsible for TOS has not been identified[ll].

The epidemic nature of EMS, identified in late October 1989, was determined largely in retrospect. Cases had been occurring at low levels for months to years prior to a sudden increase in incidence during the spring and summer of 1989. The epidemic peaked in October 1989, and rapidly subsided after the FDA's recall of November 17, 1989.

This epidemic nature of EMS, coupled with a lack of cases in countries where the distribution of L-tryptophan is carefully regulated as a pharmaceutical (such as Canada), immediately pointed to a contaminant or by-product as the likely cause of the EMS epidemic.

When the EMS epidemic occurred, bulk L-tryptophan was produced by several manufacturers, each located in Japan. Following importation, this tryptophan was repackaged into thousands of different products, and distributed by hundreds of different companies. The development of EMS, however, was ultimately associated with the ingestion of L-tryptophan from only one of the primary manufacturers, Showa Denko K.K., Tokyo[12]. The possibility of a source-point contaminant was further suggested by findings that the EMS- implicated L-tryptophan causes the secretion of cytokines, including granulocyte/monocyte colony-stimulating factor (GM-CSF) and Interlukin 6, in vitro[13,14]. No such effect was found with non-implicated L-tryptophan. Additionally, a syndrome with some features similar to EMS has been induced in rats using implicated, but not non-implicated L-tryptophan[15,16]. Interestingly, pure L-tryptophan, manufactured by companies other than Showa Denko, was incapable of inducing any abnormalities in vitro or in vivo.

The production of L-tryptophan involves a bacterial fermentation process in which multiple secondary metabolites are formed. Before a pharmaceutical grade of L-tryptophan can be obtained, various purification steps are required. These include contact with activated carbon and reverse-osmosis filtration, in order to remove impurities, by-products, and cellular debris. Analysis of the manufacturing procedures at Showa Denko revealed several simultaneous changes in manufacturing protocols between December l988 and June 1989. These included the introduction of a new bacteria strain (strain V) of Bacillus amyloliquefaciens that had been genetically altered to increase the production of L-tryptophan. Additionally, the purification procedure was altered. Reverse-osmosis filtration was partially bypassed, and the amount of activated carbon was reduced by about one-half. A significant correlation was subsequently found between the development of EMS and the reduction in powdered activated carbon[8].

Analysis of the EMS-implicated L-tryptophan lots by high-performance liquid chromatography (HPLC) revealed the presence of numerous peaks besides L-tryptophan. Ultimately, almost 60 different impurities were detected in the implicated lots of L-tryptophan, with significant lot to lot variations[17-18]. These impurities were not found in pure, non-implicated L-tryptophan. One particular peak was consistently found in EMS-implicated L-tryptophan lots, and was labeled peak E by investigators at the Mayo Clinic and peak 97 by the Centers for Disease Control (CDC)[19]. The structure of this impurity was ultimately determined to be 1,1 '- ethylidenebis [tryptophan] (EBT)[20]. Additionally, the breakdown product of EBT was found to be a consistent contaminant in implicated lots. This chemical was determined to be 1-methyl-l,2,3,4-tetrahydro-beta-carboline-3-carboxylic acid (MTCA)[21]. EBT is a novel amino acid, composed of a tryptophan dimer, with two L-tryptophan molecules joined together by an ethylidene bridge between the two indole ring nitrogens.

The consumption of implicated L-tryptophan was not uniformly associated with the development of EMS. In one study, about half of the patients consuming more than 4 grams a day of L-tryptophan originating from Showa Denko developed EMS, while the attack rate from lower consumption was substantially less,

suggesting a critical threshold of exposure was necessary to precipitate EMS[22]. Interestingly, many people consumed more than 4 grams of the implicated L-tryptophan and didn't become ill, thus individual predisposition and genetic factors also played a role in determining a person's risk of developing EMS. No confirmed cases of EMS from the consumption of L-tryptophan from any manufacturer other than Showa Denko has been reported, and L-tryptophan from other manufacturers continues to be used around the world, both in supplement products and clinical research trials. EBT and MTCA are thought to be the contaminants related to the outbreak of EMS, and are currently the subject of intensive research.

For the people who previously benefited from the use of L-tryptophan, this entire episode has been particularly unsettling. Indeed, in a letter to the editor of the Canadian Medical Association Journal in 1990, ICN Canada Limited, the maker of the Canadian pharmaceutical form of L-tryptophan (Tryptan), urged physicians in Canada not to inadvertently discontinue tryptan therapy. Calling attention to the fact that L-tryptophan is an alternative to benzodiazapines in mild to moderate sleep disorders, as well as an effective mood-stabilizer, they pointed out that Tryptan is not associated with EMS, and that ICN Canada does not obtain raw material from Showa Denko [23] In addition to Canada, L-tryptophan remains available for specific uses in the U,. Sweden, and Switzerland. Even in the United States, L-tryptophan remains in use for infant formulas, parenteral products, and dietary enteral products. The conflict in logic here is obvious. If L-tryptophan is inherently dangerous, then the FDA is endorsing the reckless use of a potentially deadly ingredient, but only in certain products.

However, if only the Showa Denko product of particular batches produced in 1988 and 1989 is dangerous. then why is L-tryptophan still off the market for only over-the-counter dietary supplements? In conversation I had with the FDA and the CDC. I was surprised to learn that there is no criteria for the reintroduction of L-tryptophan as a food supplement.

In spite of the hard work of hundreds of scientists and physicians, and the passing of almost 4 years, there are more questions than ever in regard to EMS and the role that contaminated L-tryptophan played in the development of this widespread epidemic. To begin with, the responsibility of Showa Denko must be more adequately addressed. Showa Denko is the fourth largest chemical company in Japan. The fact that they could change numerous protocols in their production of L-tryptophan, and never determine that this "new" L-tryptophan product was contaminated with numerous microcontaminants, is certainly troublesome. Even more troublesome, the final contaminated product exceeded the FDA's standard for pharmaceutical grade (>98.5%) by more than a full percentage point (99.65). This strongly questions the logic of a system designed to ensure high product purity based solely on the percentage o the labeled product, and not on the types of additional chemicals in the product. Secondly, the question of why L- tryptophan is still off the market has not been adequately addressed by the FDA. The relation of L-tryptophan to the outbreak of EMS in 1989 has certainly been linked to the product of one company. If this is true, then why has L-tryptophan remained off the market? The FDA never recalled L- tryptophan for any reason other than its link to EMS. Other pharmaceutical recalled products that contain L-tryptophan were never part of either recall issued by the FDA, even when the FDA had no idea that Showa Denko's product was responsible for the problems with L-tryptophan. Why the FDA allowed some pharmaceutical products containing L-tryptophan to be sold after the link between EMS and L-tryptophan is certainly as extremely interesting question . We must assume that the FDA doesn't consider L-tryptophan inherently dangerous, but does consider it dangerous if it is in the form of an over-the-counter dietary supplement. The fact that EMS occurred in patients consuming these pharmaceutical products containing L-tryptophan from Showa Denko, and didn't occur in people consuming over-the-counter L- tryptophan supplements manufactured by companies other than Showa Denko, makes the FDA's recall actions appear much more political than scientific. It is also unclear if the FDA, after learning of the link between contaminated L-tryptophan and EMS, ever recommended that companies still packaging L-tryptophan containing products, exempt from the recalls, check their products and L-tryptophan stocks for the presence of the implicated contaminants.

The association or a nutritional/dietary/food supplement with a debilitating and potentially fatal disorder was used by the FDA as an opportunity to expand its regulatory status in the nutritional marketplace. This was made apparent by the comments of Dr. David Kessler, Commissioner of Food and Drugs, in a speech he made on April 24, 1991. The subject of the speech was food safety and the FDA's responsibilities for the food supply. Just before finishing his speech he brought up the issue of dietary supplements and stated, "the

recent problems with L-tryptophan...unequivocally demonstrates that dietary supplements, whose regulatory status has been in limbo, can harm people. To confront these problems I am establishing an internal FDA Task Force on dietary supplements. I have asked this group to take a completely new look at how these products should be regulated". In July 1990. However, almost a full year prior to Dr. Kessler's remarks of April 1991, published papers had clearly linked EMS with the consumption of L-tryptophan produced using biotechnology at one manufacturer in Japan. Indeed, the entire EMS epidemic was the result not of dangerous dietary supplements, but rather the lack of scientifically based FDA regulation of biotechnology and food supplements. This became apparent to the media in August 1990 when Michael Osterholm, one of the original investigators at the Minnesota Department of Health, publicly admitted what federal investigators had known for months: the implicated L-tryptophan had been produced by a genetically engineered bacteria. This information was initially not disclosed to the public because FDA officials were hoping to keep the genetic engineering link quiet until they could determine its role in the EMS outbreak. Furthermore, an FDA scientist was quoted as saying that the impact on the biotechnology industry was the reason for delaying the release of this information[24]. Yet, because of Dr. Kessler's statements, many dietary supplements and amino acids are now in peril of losing their food status. Surprisingly, no special task force is making new regulatory recommendations for the rapidly expanding biotechnology industry. The entire L-tryptophan incident does little to stimulate confidence in the FDA as a competent regulator of the biotechnology, food, or dietary supplement industries. The fact that a product which exceeded the FDA's requirement for pharmaceutical grade could contain almost 60 contaminants, cause thousands of people to become ill, and result in several deaths, should be a problem at the top of the FDA's agenda.

Author's note: Due to the serious danger that contaminated L-tryptophan poses, be sure that you have destroyed all tryptophan stocks and products you may still have in your possession. Also, it has been reported that people have obtained L-tryptophan in other countries and become ill with EMS. Although it is unlikely that Showa Denko product from 1989 is still being marketed in any form, in any country, only the truly foolish would risk their life. Until the FDA resolves the L-tryptophan issue one way or another, take L-tryptophan supplements only if prescribed by a physician in a country that regulate L-tryptophan distribution by physician's prescription only, as in Canada and some European countries where a pharmaceutical form of L- tryptophan is available by prescription.

References:

1) S.E.Miller, C Kirk, P.Weiner, J Affective Disord 1980;2:47-59.
2) G.F.Wilcock, J.Stevens, A.Perkins, Lancet 1987;1: 929-930: J.Voluaka, M.Crowner, D.Boozer, et al. Biol Psychiatry 1990;28:728-732
3) N.Hrboticky, G.H.Anderson, Nutr Res 1985;5:595-607.
4) A.F.Sued, C.M.van Itallie, J.D.Fernstrom, J Pharmacol Exp Ther 1982; 221:329-332.
5) G.E.Pakes. Drug Intell Clin Pharm 1979;13:391-396.
6) R.E. McGrath, B.Buckwald, E.V.Resnick, J Clin Psychology 1990;51: 162-163
7) E.Hartman, C.L. Spinweber, J Ner Ment Dis 1979;167:447-449: E Hartman Psychiatric Res 1983;17:107-113; D.Schneider Helmert, C.I.Sphinweber, Psychopharmacology 1986;89:1-7.
8) E.A.Belongia, V.W.Hedberg, G.J.Glitch, et al. N Engl. J.Med 1990;323:357-366
9) P.A.Hertzman, W.C.Blevins, J.Mayer,et al, N Engl J Med, 1990:322:869-874
l0) Centers for Disease Control, MMWR l990;39:89-9l; E.M.Kilbourne, Epidemiologic Reviews 1992;14:16-36.
11) E.M.Kilbourne, M.Posada de la Paz, I.A.Borda, et al, J AM Coll Cardioll 1991;18:711-717.
12) L.Slusker, I.C.Hoesly, L.Miller, et al. JAMA 1990; 264:213-217.
13) J.J.Gurney, H.Kita, S.K.Lundy. et al, Clin Res 1991;39:250A.
14) Y.Yamaguchi, T.Jun-ichi, T.Suda, et al, Biochem Biophys Res Comm 1991;178:1008-1013.
l5) L.J.Crofford, J.I.Rader, M.C.Dalakis, et al, J Clin Invest 1990; 86:1757-1763.
16) K.DeSchryver-Kecskemeti, T.L.Gramlich, L. J. Crofford, et al, Modern Pathology 1991;4:354-357
17) L.D.Kaufman, R.M.Philen, Drug Saftey 1993;8:89-98.
18) T.Toyo'oka, T.Y.Yamasaki, T.Tanimoto, et al, Chem Pharm Bull 1991;39:820-822.
l9) Centers for Disease Control, MMWR 39:589-591.
20) A.N.Mayerno, F.Lin, C.S.Foote, et al, Science 1991;250:1707-1708
21) Centers forr Disease Control, MMWR 1990;39:78-790.
22) M L.Kam,. J.J.Murphy, J.L.Jones, et al, JAMA 1992;267:77-82.
23) A.Nickel. Can Med Assoc J 1990;43:1155-1156.

24) L. Roberts. Science 1990;249:988.

NEMSN Position Statement on Bio-Engineering of L-Tryptophan related to Eosinophilia-Myalgia Syndrome:

Even though the bacteria used to produce L-Tryptophan was genetically modified, there is insufficient evidence to prove that these modifications were solely responsible for the contaminants linked to the Eosinophilia- Myalgia Syndrome."