New Research on EMS Contaminants
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Stephen Naylor Ph.D. of NEMSN's Medical Advisory Panel is extensively investigating a heretofore not identified contaminant in Showa Denko L-Tryptophan. It also appears to be present (not yet confirmed) in some of today's commercially available L-Tryptophan supplements. The specific contaminant that caused EMS in 1989 has never been identified. EMS seems to be still occurring from current supplements though not in epidemic proportions. Although Dr. Naylor's current work doesn't point quickly to new medicines or therapies for EMS patients, it is in the category of research that must be completed before any new treatments for our disease can be developed.

Dr. Naylor's article for NEMSN is below. It is an overview of the current understanding of EMS from a toxicological point of view. It does contain some very technical terms and information, but the meaning of the article is clear even for those of us without an understanding of the chemistry. This article is meant to be read in conjunction with Gerald J. Gleich's article from 2016, "Eosinophilia Myalgia Syndrome", an overview of EMS.

1. INTRODUCTION

All of you are familiar with the outbreak of Eosinophilia Myalgia Syndrome (EMS) that occurred in 1989. Many of you continue to suffer from health issues after taking contaminated Showa Denko K.K. L-Tryptophan associated with EMS onset. Some of you have experienced EMS-like symptoms after taking other brand-name L-Tryptophan, 5-Hydroxytryptophan (5-HTP) or Melatonin. My first conversations about EMS occurred when meeting Dr. “Jerry” Gleich in Rochester, Minnesota. I had been recruited by Mayo Clinic as a research professor in 1991, and was fortunate enough to encounter Dr. Gleich in 1993. As most of you know, he was one of the first physicians to diagnose the condition and recognize that there was a new disease associated with elevated levels of a specific white blood cell called the eosinophil. This disease ultimately became known as EMS.

At the time, Dr. Gleich had an active research program at Mayo Clinic investigating the cause of EMS, and he introduced me to those issues, as well as to many members of NEMSN. Dr. Gleich and I began what has developed into an approximately 25-year collaboration. Our intent has always been to try and understand what actually caused EMS onset in patients who took Showa Denko L-Tryptophan. Any comprehension of what occurred may ultimately help prevent further harm to anybody taking dietary supplements in the future. In this article I will try to provide you with my perspective on
EMS in terms of past, present and future. It is written in a way to complement Dr. Gleich’s excellent article that provides a medical perspective of EMS, and is available on the NEMSN website [1]. Here I try to provide a contaminant/toxicological perspective for you to consider, as well as our future plans for trying to solve the mystery of what actually caused EMS in patients who took Showa Denko L-Tryptophan.

2. EMS CONTAMINANTS-HISTORY

The beginning of the EMS outbreak was first recognized in October 1989 when three women in New Mexico were identified with similar clinical symptoms after consuming L-Tryptophan supplements. After widespread media publicity additional cases in both the USA and elsewhere were identified. Epidemiological studies were initiated and it was subsequently demonstrated that a strong association existed between the consumption of L-Tryptophan supplements and EMS onset [1].

2.1 Epidemiological Studies: A national surveillance program was initiated by the US Centers for Disease Control (CDC) to investigate and understand the causation of EMS. In addition as a precautionary measure, the US Food and Drug Administration (FDA) issued a nationwide warning (November 11th 1989) to stop consumption of manufactured L-Tryptophan food products and required a nationwide recall of all L-Tryptophan dietary supplements sold over-the-counter. As Dr. Gleich has described previously in detail, “initial case control studies showed an association between consumption of manufactured L-Tryptophan as a major risk factor for EMS.” [1]. In these studies, consumers of L-Tryptophan supplements were classified as either case patients (those who had EMS) or controls (non-EMS L-Tryptophan users), and the L-Tryptophan lots consumed by each group were traced to determine the L-Tryptophan source. At the time of the epidemic, and to the best of my knowledge, six Japanese companies manufactured all L-Tryptophan supplements. Analyses of the L-Tryptophan source for case patients and controls showed a strong association between EMS and the consumption of L-Tryptophan manufactured by a single company, namely Showa Denko K.K. (Tokyo, Japan).

2.2 Showa Denko L-Tryptophan Manufacturing: The L-Tryptophan manufactured by Showa Denko K.K. was produced by a genetically engineered bacterium using a fermentation process. The bacterium, Bacillus amyloliquefaciens, had been progressively modified over a period of several years to increase the production of L-Tryptophan. The fermentation process used by Showa Denko utilized a large vat/container filled with nutrients, which was seeded with the Bacillus bacteria. As the bacterial colony grew, it began to produce large quantities of L-Tryptophan along with a number of other components using its own internal molecular processes. The large quantities of L-Tryptophan produced were then subjected to a multistep purification protocol. During manufacture from October 1988 to June 1989, some of the fermentation batches bypassed a filtration step and, in some cases, quantities of powdered activated carbon used to purify L-Tryptophan were reduced. Retrospective analyses of these changes in the process showed an association between the development of EMS and the “contaminated” L-Tryptophan produced with the lower quantity of charcoal and the use of the new strain of the bacterium. Showa Denko K.K. ultimately used this confusing situation to their “advantage” since the causal nature of EMS onset in patients was thereby obfuscated.
However, as Dr. Gleich has noted, “taken together, epidemiological and clinical findings in the EMS patients could be explained by changes in the manufacturing process of L-Tryptophan from 1985 until 1988, which resulted in sporadic contamination of the product with increased quantities of contaminants in 1989.” [1]

2.3 Showa Denko L-Tryptophan Contaminants: As noted above, epidemiological studies had demonstrated a clear correlation between consumption of only Showa Denko K.K. L-Tryptophan and onset of EMS. In addition it is noteworthy that the epidemic was essentially curtailed when the FDA removed the L-Tryptophan from the retail market. Analysis of the Showa Denko K.K. L-Tryptophan by high performance liquid chromatography (HPLC) and HPLC coupled on-line with mass spectrometry (LC-MS) revealed the presence of over sixty contaminants! Careful and exhaustive epidemiological studies as well as lot analyses of contaminated L-Tryptophan revealed that “six individual contaminants” were identified as being case-associated with the onset of EMS. In other words, these six contaminants had some higher probability of being responsible for the causation of EMS. These case-associated contaminants were labeled as Peaks UV-5 (also known as PAA), E, 200, C, FF and AAA, as determined by their unique HPLC retention. Scientists at the CDC, namely Hill and Philen, concluded that contaminants Peak E and Peak AAA “should receive a high priority for isolation and identification”.

Dr. Gleich has described his initial work on the structure determination of one of these contaminants, namely Peak E. He wrote, “Arthur Mayeno, a skilled analytical chemist working in our laboratory, set about testing L-Tryptophan from the various companies and from various lots produced by Showa Denko K.K. Arthur had the critical samples needed to find the contaminant, and he employed HPLC to dissect the L-Tryptophan. But what was peak E? Mayeno focused his chemical skills and soon had a structure for Peak E, which consisted of two tryptophan molecules linked together by another molecule, acetaldehyde”.[2]

Since that original work, another four of the six the case-associated contaminants have been identified by Dr. Gleich, our collaborators and myself. We have used powerful analytical instruments such as Nuclear Magnetic Resonance (NMR), mass spectrometry (MS), combined HPLC-MS and tandem mass spectrometry (MS/MS) in order to carry out such tasks. Peak UV-5 was identified as 3-(phenylamino)alanine (PAA) after isolation of the contaminant from Showa Denko K.K. L-Tryptophan. Peak 200 has been identified as 2-(3-indolylmethyl)-tryptophan using, both NMR, and HPLC-MS with MS/MS. Peak C was characterized as 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]-indole-2-carboxylic acid. Peak FF was also subjected to the same analytical protocols as Peak C and identified as 2-(2-hydroxy indoline)-Trp [3,4]. In the case of the “high priority” contaminant peak AAA, until very recently no complete structure determination had been reported (see below). The reason for the hiatus was that both Dr. Gleich and I left Mayo Clinic to pursue other opportunities. We presented some of our preliminary findings on the structure of “AAA” at a meeting in Los Angeles in 2000, but we were not confident enough at the time that we had completely solved the structure. Thankfully we did not try to publish this early work in a peer-reviewed journal since we were actually wrong in our initial analysis!
2.4 Other Contaminants- Toxic Oil Syndrome: In 1981 the ingestion of cooking oil fraudulently sold by Spanish street-vendors as olive oil, caused an outbreak of what became known as Toxic Oil Syndrome (TOS). Causation was attributed to the ingestion of adulterated rapeseed oil (also known as canola oil) used widely in Spanish cooking at the time. In this case the oil had been deliberately contaminated with a mixture of industrial aniline derivatives [5]. The clinical symptoms manifested by TOS patients closely resembled those of EMS patients and were characterized by incapacitating myalgias and elevated peripheral eosinophils. The human impact was traumatic since in excess of 20,000 individuals were affected and over 300 people died in the first twenty months of the TOS epidemic. It was further estimated that it also led to the premature death of approximately another 1690 people during the time period 1983-1997.

Dr. Gleich and I were, and still are, of the opinion that contaminants in the L-Tryptophan and in the rapeseed oil were involved in the onset of eosinophilia and other related symptoms, in both EMS and TOS, respectively. Therefore we looked for evidence that EMS and TOS causation may have a common etiological contaminant trigger. In an effort led by Arthur Mayeno we demonstrated that a known TOS contaminant, 3-phenylamino-1,2-propanediol (PAP), was metabolized in both rat and human liver tissue to produce PAA, a known case-associated contaminant of Showa Denko K.K. L-Tryptophan implicated in EMS onset [6]. In addition a number of other case-associated TOS contaminants have been identified, and they include the fatty acid esters of PAP, namely the 1-oleyl-ester (O-PAP) and the 1,2-di-oleyl ester (OO-PAP) [5].

2.5 Other Sources of Contaminants- 5-HTP & Melatonin: For over 25 years now there have been numerous, albeit sporadic reports of EMS-like symptoms apparently caused by taking either 5-HTP supplements or Melatonin supplements. These two other supplements have been used to facilitate sleep and control weight gain. In addition the chemical structures of both supplements are very similar to L-Tryptophan in that all three compounds contain an indole ring. All these compounds are also found naturally in your brain and are part of the serotonin pathway that controls many aspects of mood and other important functions.

After the temporary withdrawal of L-Tryptophan as an over-the-counter supplement, 5-HTP was marketed and promoted as a safer, superior replacement. The increased usage of 5-HTP and vigilance over the possible role of contaminants in EMS onset prompted a report in 1994 that three members of a Canadian family using 5-HTP manifested EMS-like symptoms. The mother was exposed to 5-HTP in 1991 by inhalation and/or by contact with the skin as she made a fine powder preparation of 5-HTP for her young children. The two infants ingested the 5-HTP as part of a medical treatment that included tetrahydrobiopterin and L-dopa/carbidopa, for tetrahydrobiopterin deficiency. The children developed asymptomatic eosinophilia. Their mother was diagnosed with 5-HTP related EMS. The children’s symptoms ceased when they stopped consuming the contaminated 5-HTP. The mother required treatment with prednisone to alleviate her symptoms. Analysis of the case-implicated product by HPLC with ultraviolet (UV) detection in 1994 revealed the presence of a unique contaminant, designated as Peak X. Dr. Gleich and I ultimately identified case-associated Peak X as 4,5-tryptophan-dione (4,5-TD) and detected its presence in a number of commercially available 5-HTP supplement brands [7.8]. Our findings were subsequently confirmed by independent
analyses carried out by the USA Food and Drug Administration.

There have been numerous reports from a variety of sources, including NEMSN, that taking Melatonin can cause EMS-like symptoms. Such reports from NEMSN began around 1996. In a clinical study in 1993 where Melatonin was being evaluated as an anti-cancer agent, several patients developed eosinophilia. Based on these reports Dr. Gleich and I analyzed three commercially available Melatonin supplements bought from a local pharmacy in Rochester, Minnesota. Analysis of these Melatonin tablets by LC-MS/MS enabled the structure determination of seven contaminants. The reason that these data were so interesting was because of the structural similarity to the L-Tryptophan case-associated contaminates [9]. Two of these contaminants were identified as hydroxymelatonin isomers, which closely resemble the structure of Peak C in Showa Denko L-Tryptophan. The other Melatonin contaminants were identified as formaldehyde adducts. This was an even more significant observation, as these Melatonin-formaldehyde condensation products were structural analogues of peak E. As you will recall this is one of the more important case-associated contaminants in Showa Denko L-Tryptophan [9].

In 2016 working with Dr. Gleich and Dr. Klarskov (Sherbrooke University), we identified the contaminant Peak X in samples of both Showa Denko L-Tryptophan as well as commercially available L-Tryptophan. Recall that Peak X (see above) was the case-associated contaminant identified from the 5-HTP sample associated with EMS-like symptoms in the Canadian family. Hence Peak X has now been found in Showa Denko L-Tryptophan, in the 1991 5-HTP which made the Canadian family sick, and in currently available commercial L-Tryptophan. Our work on this is in the process of being submitted to a journal for publication. However the relevance is that many of the original case–associated contaminants of both L-Tryptophan and 5-HTP seem to be present in all three indole ring supplements, namely L-Tryptophan, 5-HTP, and Melatonin. Is this a coincidence or has it some relevance to causal onset of EMS in patients taking these supplements?

2.6 Importance of Contaminants: All of the contaminants described above have complex names and equally complex chemical structures. The determination of the chemical structures of such compounds is both expensive and complicated. These efforts require access to analytical instrumentation that can cost millions of dollars and requires many years of specialized training. So why go to such efforts to determine the structures of these contaminants? The structure of a molecule, particularly a contaminant, can provide valuable insight into how disease symptoms such as those in EMS occur. In other instances the structure and shape of a molecule determines how it interacts with the body. For example, everybody is familiar with the analgesic Aspirin, as well as the cholesterol reducing drug Statin. These widely used drugs have very different chemical structures and thus react with different parts of your body in order to bring about the effects we are all familiar with after taking them. The same principle applies to contaminants; by determining their structures it may be possible to unravel the mechanism by which they harm your body. Once we have such an understanding then it is both possible to prevent further damage as well as possibly treat the effects of the contaminant(s).
2.7 Animal Models: Once a contaminant structure is determined, then typically it is evaluated in an appropriate animal model such as a rat or mouse. The intent is to try and mimic some of the same symptoms manifested by EMS patients upon administering the contaminant to the animal. Unfortunately simple administration of the Showa Denko L-Tryptophan into mice, rats, monkeys and other animals for the most part has failed to reveal anything of significant value [1]. These same negative findings have been mirrored in the toxic oil animal studies associated with TOS [3]. Finally Dr. Gleich and I were awarded a grant (funding research from 1998-2000) from the World Health Organization while we were both still at Mayo. We evaluated a number of animal models and administered separately, both Showa Denko L-Tryptophan and toxic oil. In all cases we did not observe any detectable adverse effects from either the L-Tryptophan or the toxic oil. All these disappointing efforts have led to a general abandonment of efforts to try and find a cause for EMS or TOS onset. Not least because as Dr. Gleich has noted “…. failure to have an animal model and the failure to develop an in vitro test for the contaminants involved in EMS and TOS is crucial. The implication from this failure is that these diseases will likely occur again because we have no way of identifying the critical contaminants”. [1] However, we now believe that declaring there is no way of identifying the critical contaminants may be somewhat premature, and this issue is discussed more below.

3. CONTAMINANTS- CURRENT PERSPECTIVES

EMS is a neglected and forgotten disease state. Few clinicians are aware of its existence and how to diagnose and treat the disease. In part this is because EMS is a relatively rare disease that does not occur widely in the general public, but it is also because our understanding of onset and causation is still very limited. Nevertheless, based on anecdotal information from NEMSN, as well as on occasional reports in medical literature, EMS-like symptoms continue to be reported by patients worldwide.

3.1 Continued Occurrence of EMS: The efforts of NEMSN in publicizing EMS as well as providing a website of information content and a focused contact source has continued to facilitate individual reports from patients exhibiting EMS-like symptoms. These reports typically involve the use of L-Tryptophan (now available again in the USA), 5-HTP and Melatonin. In addition on the NEMSN website there is a page that lists more recent literature reported occurrences of EMS [10]. Briefly they include: 1). The journal *Arthritis & Rheumatism* published an article in 2011 that detailed a “new” 2009 case of EMS after taking L-Tryptophan. The article is entitled "Post-epidemic eosinophilia-myalgia syndrome associated with L-tryptophan". 2). The medical journal *Case Reports in Rheumatology* published an article in 2012 entitled "Severe Eosinophilic Syndrome Associated with the Use of Probiotic Supplements: A New Entity?" The abstract of the article details two current cases of an EMS-like illness from taking probiotic supplements. 3). The medical journal *Reactions Weekly* published an article in 2013, describing new EMS cases in France from 2001-2012, attributed to taking 5-HTP supplements.

In addition there have been several other reports and developments that include the following cases. There was a recent report (2016) of a case of a 59-year old female who started a special weight-reducing diet regimen that included excessive cashew nut
ingestion. She presented several months after consumption of the cashew nuts with peripheral blood eosinophilia and constitutional symptoms. She was diagnosed with EMS due to extreme L-Tryptophan intake, a compound found in the cashew nut oil. She responded well to cashew nut withdrawal and steroid therapy. In the follow-up period she remained stable with a normal eosinophil count and there was no need for any specific therapy [11].

In a follow up investigation in 2015 of Melatonin, eight L-Tryptophan related contaminants were detected and their structures determined. This was actually due to the PRESENCE of L-Tryptophan in the Melatonin. Most of the commercially bought samples (11/17) incorrectly listed the amount of Melatonin by 1.0–15% less than declared on the label. In addition the majority of Melatonin tablets tested actually contained L-Tryptophan. The researchers had been interested in evaluating the purity of the Melatonin supplements, yet they made the surprising discovery that L-Tryptophan, along with L-Tryptophan contaminants, were actually found in the Melatonin supplements. One Melatonin supplement tested listed L-Tryptophan on the label as an ingredient, but the rest of the samples tested did not! [12].

3.2 Alternative Theories of "Contaminants": Causal onset of EMS efforts has focused primarily on the actual case-associated contaminants of Showa Denko L-Tryptophan. However there have been alternate suggestions as to the cause of EMS, as follows.

3.2.1 Quinolinic Acid: Quinolinic acid (QA) is a downstream product of L-Tryptophan metabolism that occurs by the well-described kynurenic pathway. QA has been shown to be a potent neurotoxin and has been suggested as a key compound involved in a number of psychiatric disorders as well as neurodegenerative diseases. In 2006 an Australian research scientist performed an unusual experiment. He injected himself with QA in order to show that it was a causative agent in eosinophilia. Here he describes in his own words what he did in the name of science! “The principal author (Noakes) received a series of subcutaneous injections of Quinolinic Acid. A total of 1200 mg was administered over a 1-month period. Peripheral blood eosinophil counts were monitored and biopsies taken for H&E and immunohistochemical stains. Over the 1-month period the eosinophil count rose from 0.3x10^9/l to 0.8x10^9/l before falling to 0.4x10^9/l approximately 5 weeks later. H&E sections showed a mixed infiltrate of eosinophils and neutrophils extending through the reticular dermis and septa of the panniculus. No deep fascia was obtained on biopsy. The immunohistochemical stain for transforming growth factor beta 1 showed staining of endothelial cells and dendritic cells. The interleukin-5 stain was negative. Our results suggest that Quinolinic Acid may play a role in cutaneous eosinophilic disorders” [13].

3.2.2 Uncontaminated L-Tryptophan: In 1999 Gross and colleagues [14] evaluated if uncontaminated L-Tryptophan alone could cause EMS-like symptoms in a rat model. They took three-month-old female rats and fed them at 3,6,12 weeks on a diet containing 20% protein diet derived from casein and supplemented with 1%, 2% or 5% L-Tryptophan. On the last week of feeding, half of the animals fed on a control diet and half of the animals fed on the L-Tryptophan diet were injected with para-chlorophenyl alanine (p-CPA), an L-Tryptophan hydroxylase inhibitor. This causes L-Tryptophan metabolism to occur primarily via the kynurenic pathway described above. The authors concluded
“that a cumulative dose of L-Tryptophan and the duration of exposure appears to be important in induction of pathological changes in some tissues. Induction of the kynurenic pathway by injection of p-CPA augments some of the pathological changes and might increase mortality rate. The present observation also confirms previous literature postulating a role of L-Tryptophan and its metabolites in induction of fibrosis and inflammatory reaction.”[14]. This was far from a compelling result but appeared to suggest that the kynurenic metabolic pathway may play a role in the manifestation of some of the symptoms of EMS.

These data led to what is an ongoing drumbeat suggesting that high doses of uncontaminated L-Tryptophan were solely responsible for the onset of the EMS epidemic. Dr. Gleich organized a one-day symposium, sponsored by NIH and held on October 21st 2004, to discuss the “current” status of our understanding of EMS. Both Dr. Gleich and I attended and presented, as well as a number of then NEMSN board members [15]. One presentation in particular was intriguing in that Dr. Lori Love (FDA) appeared to argue and suggest that high doses of L-Tryptophan alone were the possible likely cause of EMS onset. This idea was reinforced and presented in a paper by Smith (FDA) and Garrett (University of Virginia) in 2011. They argued “reliance on a finite impurity from one manufacturer is both unnecessary and in-sufficient to explain the etiology of EMS” [16]. They artfully suggested that excessive histamine activity induced blood eosinophilia and myalgia. They went on to suggest, “overloads of tryptophan supplements cause – among other relevant side-effects – an increased formation of formate and indolyl metabolites, several of which inhibit the degradation of histamine”. Finally they suggested, “a final common pathway for syndromes characterized by eosinophilia with myalgia is now evident” [16]. However, it is difficult to reconcile their findings with the original epidemiological work carried out and the subsequent conclusions of Hill and Philen, on Showa Denko-L-Tryptophan. This is discussed in more detail below.

3.3 L-Tryptophan Contaminants-AAA: As we noted above, six compounds present in the Showa Denko L-Tryptophan were reported to be case-associated contaminants. However, “one” of these compounds, Peak AAA has remained structurally uncharacterized, despite the fact that it was described by the CDC as “the only statistically significant (p=0.0014) contaminant”. Recently, we used LC-MS and MS/MS technologies to determine that Peak AAA is in fact two structurally related isomers. Peak AAA1 and Peak AAA2 differed in their HPLC retention times. By comparing the LC-MS and LC-MS-MS retention times and spectra with authentic synthetic standards that my Canadian colleagues at the University of Sherbrooke made for us, Peak AAA1 was identified as the intermolecular condensation product of L-Tryptophan with anteiso 7-methylnonanoic acid, to afford (S)-2-amino-3-(2-((S,E)-7-methylnon-1-en-1-yl)-1H-indol-3-yl)propanoic acid. Peak AAA2 was determined to be a condensation product of L-Tryptophan with decanoic acid, which produced (S)-2-amino-3-(2-((E)-dec-1-en-1-yl)-1H-indol-3-yl)propanoic acid.

The structure determination of the two isomers, AAA1 and AAA2, finally completed the identification of the “six” original case-associated contaminants identified by Hill and Philen. One of our colleagues who is a food chemist in Germany, Dr. Simat, has argued that the fermentation process used to manufacture L-Tryptophan produced six different types of contaminants that include i. metabolites; ii. oxidation products; iii. carbonyl
condensation compounds; iv. 2-substituent–Tryptophan derivatives; v. 1-substituent-Trp derivatives and vi. PAA and related compounds. AAA₁ and AAA₂ are actually type iv) 2-substituent-Tryptophan derivatives. However the presence of the fatty acid derived aliphatic chains in AAA₁ and AAA₂ will result in very different metabolic and distribution pathways through the body of a person consuming SD L-Tryptophan. Whether this is of relevance in ascertaining the causal onset of EMS is still to be determined.

The presence of the anteiso aliphatic chain in AAA₁ indicates that *Bacillus amyloliquefaciens* was under cellular stress during the fermentation process. In order to control bacterial cell viability, *Bacillus* species change membrane fluidity and permeability by altering fatty acid composition, chain length, and the ratio of branched-to-linear chain structural isomers. An increase in the anteiso-to-linear or iso-to-linear ratio results in an enhanced fluidity and permeability of the cell membrane. Such a change would facilitate an increased transportation of excess L-Tryptophan from within *Bacillus amyloliquefaciens* out into the fermentation broth, through the more permeable cell membrane. Finally the presence of AAA₁ and AAA₂ indicate that the production of at least these contaminants was due to the fermentation conditions themselves, not as previously stated an inefficient purification process.

4. FUTURE AND CONCLUSIONS

In the past two years Dr. Gleich and I, along with Dr. Klarskov and Dr. Marsault (both at the University of Sherbrooke, Canada), have devoted considerable time and effort to the structure determination of “Peak AAA”. In addition we have been analyzing current commercially available L-Tryptophan and 5-HTP that has been taken by patients who subsequently manifested EMS-like symptoms. This latter effort has been undertaken with NEMSN board members who have identified individual patients who were then kind enough to provide original tablet samples. These new efforts have proved fruitful and interesting and offer some ways forward in terms of our possible understanding of causation of EMS.

4.1 Future Studies: As discussed above, the structures of AAA₁ and AAA₂ are completely different from any other L-Tryptophan contaminant reported. These structures resemble known metabolites in the body that cause eosinophils to migrate towards them wherever they are in the body. Therefore, we are now in the process of arranging to evaluate AAA₁ and AAA₂ in a variety of biological tests to determine if they played any role in causation of EMS patients who took Showa Denko L-Tryptophan. In addition we are testing current commercially available L-Tryptophan and 5-HTP to see if the contain AAA₁ and AAA₂. If these further studies prove successful, then the goal is to submit an NIH grant application for additional funds to more fully evaluate AAA₁ and AAA₂ in appropriate animal models.

4.2 Conclusions: The causal factors associated with EMS onset are still poorly understood. Indeed there continues to be an ongoing discussion as to whether contaminants of Showa Denko L-Tryptophan or high doses of L-Tryptophan caused the EMS epidemic. However, one compelling piece of evidence that suggests the Showa Denko L-Tryptophan contaminants caused the outbreak is as follows. In the late 1980’s
there were six Japanese companies manufacturing and providing L-Tryptophan to the US market. Hill and Philen at the CDC in their methodical and meticulous studies clearly demonstrated that it was only Showa Denko L-Tryptophan that caused EMS [17]. Patients had been taking high doses of L-Tryptophan manufactured by both Showa Denko as well as by the other five manufacturers. If high dose L-Tryptophan alone was responsible for EMS onset [16], then patients across the spectrum should have manifested symptoms. This was clearly not the case, and thus one concludes based on the epidemiological studies that something unique to Showa Denko L-Tryptophan caused the EMS epidemic.

It is however also clear that a simple relationship between ingestion of Showa Denko L-Tryptophan and onset of EMS does not exist. There have been a limited number of studies and suggestions that the genetics and immunological profiles of individual patients made some individuals more susceptible to EMS onset than others. Our understanding of this susceptibility is extremely limited. Part of our future studies would involve trying to unravel this added complexity. Finally, our ability to understand what caused EMS in patients will not, alas, alleviate the symptoms that you have lived with for many years. It will allow us to hopefully prevent any future outbreaks, as well as to possibly develop a therapeutic drug that could be used to treat patients in the early stages of eosinophilia, but that is for the future.

BIBLIOGRAPHY


BIO
Stephen Naylor PhD is a renowned biochemist/toxicologist and entrepreneurial founder of several biomedical specialty companies. He is the Founder and CEO of ReNeuroGen LLC, a virtual pharmaceutical company developing precision medicine drug therapies for the treatment of stroke, multiple sclerosis, sickle cell disease and cardiovascular protection. He is also a Founder and Chairman of the Board of iMBP, a biopharmaceutical company developing therapies for the treatment of hyperlipidemia related disorders. In addition he is the Founder, Chairman and CEO of MaiHealth Inc, a systems/network biology level diagnostics company in the health/wellness and precision medicine sector. He was also the Founder, CEO and Chairman of Predictive Physiology & Medicine (PPM) Inc, one of the world’s first personalized medicine companies. He currently serves as an Advisory Board Member of CureHunter Inc., a computational biology drug discovery company, and as a business adviser to the not-for-profit Cures Within Reach. He previously held professorial chairs in Biochemistry & Molecular Biology; Pharmacology; Clinical Pharmacology and Biomedical Engineering, all at Mayo Clinic in Rochester, MN, USA. He holds a PhD from the University of Cambridge (UK), and undertook a NIH funded fellowship at MIT located in the "other" Cambridge, USA.

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