



National EMS Network Newsletter

EMS Twenty Years Later: Words from our Medical Advisory Panel

By Lois Vierk

In this second "Twenty Years Later" issue, NEMSN presents articles just written for the EMS community by our Medical Advisory Panel: Edward Belongia, M.D., Luis R. Espinoza, M.D. and Gerald Gleich, M.D. The previous newsletter issue featured reflections of EMS patients -- what we ourselves have to say about surviving, managing and living with eosinophilia myalgia syndrome for these twenty years since the 1989 outbreak. Now our medical advisors write to us about EMS and research, about concern over another possible outbreak, and about the question of the safety of dietary supplements today, including L-tryptophan, which since 2001 is legally sold again in the US after the temporary ban by the FDA right after the big EMS outbreak.

NEMSN is proud to have this group of doctors on our Medical Advisory Panel. They have been involved in EMS research and treatment of patients since the early days of the outbreak. Unlike many in the medical community, they are still interested in understanding the disease and treating it. They are still interested in us.

Our medical advisors are well known in their fields. Edward Belongia, M.D. is Senior Epidemiologist/Director of the Epidemiology Research Center, Marshfield Clinic Research Foundation in Marshfield, Wisconsin. As the center's website (www.marshfieldclinic.org) states, "Epidemiology research focuses on population health issues. The Marshfield Epidemiology Research Center emphasizes consequential epidemiology – applied research that has a positive effect on public health and disease prevention." Dr. Belongia has published extensively on antibiotic resistance, vaccine-preventable diseases and tick borne diseases as well as on other topics, including EMS. NEMSN vice-president Jinx Engstrom writes of Dr. Belongia's early work with EMS patients, "He was an epidemiologist here in Minnesota when the initial outbreak hap-

pened in 1989. He was a huge help in determining what was making so many people sick. Then after that was determined, he was generous to our support group. When he was presenting information at the University of Minnesota for medical staff, he allowed us to attend, so we were in on what was known early on in the epidemic. He was also very patient to explain things in terms we could understand."

Luis R. Espinoza, M.D, our next medical advisor, is Chief, Section of Rheumatology, Department of Medicine, at Louisiana State University in New Orleans. Over the years Dr. Espinoza has treated many EMS patients. He has authored research articles on EMS and on many other topics in rheumatology. His articles have been published in numerous medical journals. Dr. Espinoza has recently been elected president of the Pan-American League of Associations for Rheumatology. Besides bringing you the the article that Dr. Espinoza just wrote for us, NEMSN also recommends his excellent article from 1999 which appears on our website: "Eosinophilia-Myalgia Syndrome--Long Term Complications" (www.nemsn.org/Articles/Espinoza2.htm).

And finally, Gerald Gleich, M.D, our other distinguished medical advisor, is recognized as one of the world's foremost experts on the eosinophil and on eosinophilia of all sorts. From 1965 to 2001 he was a researcher at the Mayo Clinic, Rochester, Minnesota. At present he is Research Professor of Dermatology and Medicine at the University of Utah, Salt Lake City. He lists his medical interests on the University of Utah website (<http://uuhsc.utah.edu/derm/bios/facultybios/ggleich.htm>) as including "diseases associated with eosinophilia, such as the hypereosinophilic syndrome, Churg-Strauss syndrome, the eosinophilia myalgia syndrome, the Spanish

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To The Editor...

A sincere thank you to Sandy Kintz and the board of directors for all of their efforts regarding the periodic publication of the NEMSIN newsletter. I really do appreciate each and every one of you who works on the board, or in any other capacity that deals with helping, or even just remembering EMS victims/survivors. It's so nice that all of you are still keeping up with the research, newsletters, web sites, etc. Believe it or not...I actually have remembered all of you in my prayers from time to time, as all of us need you and a sincere "thank you" for being there for all of us for so many years now.

Sincerely,
Sherry Fletcher
An EMS victim/survivor

Thank you for finally addressing the severe intestinal/esophageal problems that I still am suffering from and are life threatening to me to this day. This last issue is the first time I recall it being mentioned in any of the newsletters to this time.

Linda Remais

EMS Twenty Years Later
by Lois Vierk

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toxic oil syndrome, and the syndrome of episodic angioedema and eosinophilia . . ." Dr. Gleich's research papers and articles have been published in many medical journals.

NEMSIN extends sincere and warm thanks to Dr. Belongia, Dr. Espinoza and Dr. Gleich for writing these articles for this newsletter. Thank you for

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Happy Holidays
& a Healthy New Year
from the
NEMSIN Board
of Directors

Mission Statement

The National Eosinophilia-Myalgia Syndrome Network, Inc., is a non-profit organization dedicated to helping EMS survivors and their families by offering educational information and peer support. NEMSIN is also committed to encouraging research to improve treatment for L-tryptophan-induced EMS and to increasing awareness of the cause and effects of the disease.

DISCLAIMER

The NEMSIN does not engage in the practice of medicine or law & does not claim to have legal or medical knowledge. All persons should seek the advice of their own lawyers & medical professionals. Opinions expressed by individual writers herein are those of the writers and not necessarily those of the NEMSIN Board of Directors or its committee or subcommittee heads, nor of the Editor. Information is intended merely to inform readers. Drugs & treatments & legal issues should be discussed with readers' own physicians & attorneys.

Could EMS have been Prevented? Will Future Outbreaks be Prevented?

By Edward Belongia, M.D.

EMS took everyone by surprise in 1989. Now that 20 years have passed, it is useful to revisit the question as to whether the EMS epidemic could have been prevented, and what has been done since then to protect consumers from unsafe dietary supplements? In the 1980s there was no regulatory oversight of companies that manufactured amino acids and other food supplements, yet these products were widely sold and consumed for their pharmacologic effects. L-tryptophan in particular was widely promoted and used because multiple studies had shown that it was beneficial for insomnia, premenstrual syndrome, and other problems. It was the pre-internet era, but books, magazines and news articles amplified these findings and promoted them to the general public. The product labels made no therapeutic claims--they didn't need to because all the advertising was done through the media and word of mouth.



In 1989 the FDA issued a recall of L-tryptophan when the link to EMS was first demonstrated by studies in Minnesota and New Mexico. It remained off the market for several years, but the situation changed in 1994 when Congress passed the Dietary Supplement Health and Education Act (DSHEA). Under this law, manufacturers of dietary supplements are responsible for determining that their products are safe before they are marketed, but there are no standards or requirements. Premarketing approval by FDA is not required. In 2001 the FDA issued a position paper that specifically stated that L-tryptophan could be marketed, and the manufacturers are responsible for ensuring that the products are safe. But how can that be done? The specific contaminant that triggered EMS has never been proven, and we know it was present in extremely low concentrations. I don't think a manufacturer can determine that L-tryptophan is safe when there is no way to test for the causative agent. We have some good candidates, but it's hard to prove that any of them caused EMS because the syndrome cannot be reproduced in animals. Although it was Showa Denko L-tryptophan that

caused the 1989 epidemic, we have no way of knowing whether the same contaminant might occur in the manufacturing process at another company. People who take L-tryptophan now are choosing to participate in a natural experiment on the safety of manufactured L-tryptophan. No company or government agency can verify the safety of these products.

DSHEA defined 'dietary supplements' so broadly that it included amino acids, extracts, herbs, and other biologically active products (think melatonin and DHEA) that are used almost exclusively for therapeutic effect. Yet they are not regulated as drugs even though they are clearly marketed and purchased for their pharmacologic effects. In addition, virtually nothing is known about the interactions of these substances when people consume many different types of supplements. Drug-drug interactions are carefully evaluated in the world of pharmaceuticals, but interactions among different dietary supplements are largely unpredictable.

More than a decade after DSHEA, the FDA finally implemented standards for good manufacturing practices of dietary supplements. Since 2008, dietary supplement manufacturers and distributors have been required to monitor and document the production process for quality assurance, and perform laboratory analysis of raw materials and finished products to document product purity and the absence of contaminants. This is a meaningful step forward, but it does not guarantee another EMS-like epidemic will not occur. The number and variety of dietary supplements or 'nutraceuticals' is enormous, and the burden of evaluating safety and efficacy still falls on the consumer.

At least one private laboratory, ConsumerLab (www.consumerlab.com), now offers independent test reports for dietary supplements from different manufacturers. Their tests can determine if the product label accurately reflects the actual amount of active ingredient in the product, and they evaluate product purity and the presence of trace contaminants. The downside is that they

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Eosinophilia Myalgia Syndrome Revisited -- 1989-2009

By Luis R. Espinoza, M.D.

Twenty years have elapsed since a newly recognized systemic inflammatory disorder of epidemic proportions, eosinophilia myalgia syndrome (EMS), began to unravel in the United States of America and several other countries worldwide. The CDC defined EMS on the basis of three laboratory and clinical criteria: a) presence of peripheral blood eosinophilia greater than 1000 cells/ul; b) incapacitating myalgias (muscle pain); and c) absence of infection or malignancy that could account for the previous findings. By July 1991, 1543 cases had been reported by the US Centers for Disease Control and Prevention (CDC) in Atlanta. Epidemiological and clinical observation made by several astute clinicians, however, rapidly led to the conclusion that EMS was secondary to the intake of L-tryptophan containing trace amounts of several contaminants and, more specifically, with particular lots of tryptophan that contained the trace contaminant 1,1'-ethylidenebis (tryptophan) (EBT) and another trace contaminant ("peak UV-5") 3-(phenylamino) alanine (PAA). Patients with EMS ingested significantly higher amounts of both EBT and PAA than did control tryptophan users. Of great interest and importance is the fact that PAA is chemically similar to 3-phenylamino-1,2-propanediol, an aniline derivative isolated from samples of oil that were consumed by persons from Spain in whom the toxic oil syndrome developed.

[Editor's note: Toxic oil syndrome broke out abruptly in Spain in 1981. The disease has symptoms similar to EMS and was found to be caused by contaminated cooking oil.]

From its initial description in 1989 to subsequent follow-up it became clearly established that EMS was associated with a relatively high morbidity and mortality. The overwhelming majority of patients (>97%) were white, most (>80%) were female, and age of occurrence was between 35 and 60 years. Early stages of the disease (lasting 3 to 6 months) were characterized by the presence of severe generalized myalgias, fatigue, weakness, edema, and skin rash. During the acute illness, over 30% of patients required hospitalization for incapacitating myalgias, muscle cramps, or pulmonary involvement. Late clinical stages



were characterized by the presence of a multitude of ill-defined complaints including paresthesias [skin sensations such as tingling, numbness, burning, etc.], muscle cramps, and alopecia [hair loss]. Long-term follow-up exceeding a year demonstrated that most EMS patients continued to be symptomatic with fatigue, cognitive dysfunction, arthralgias [joint pain], myalgias, alopecia, and skin rash as main clinical manifestations. Follow-up over 5 years has shown that a significant proportion of EMS patients have exhibited significant improvement of their major complaints, although a large proportion remains symptomatic but with a tendency for a gradual and slow recovery. A significant high mortality was seen during the early stages in some epidemiological studies, and by July 1991, 31 deaths had been reported. Most deaths were secondary to severe neurologic and cardiovascular involvement, and also to superimposed infection.

Epidemiological studies have conclusively demonstrated that the most important and reproducible risk factor for EMS was the dose of contaminated L-tryptophan consumed. In addition, the severity of symptoms experienced by individual patients and degree of disability were directly related to the daily dose of L-tryptophan ingested (individuals taking doses higher than 4000 mg/day were more predisposed to develop definite EMS).

What have we learned from this epidemic?

The similarity of EMS and other contaminated foodstuff products-related disorders such as the toxic oil syndrome (TOS) highlights the potential for environmental agents to induce autoimmune disorders, particularly systemic sclerosis and related disorders.

Secondly, the precise identification of the causative agent is difficult to be determined despite intense investigation.

Thirdly, the development of EMS and TOS reminds us that even developed countries are not exempt from being affected by large epidemics of environmental origin.

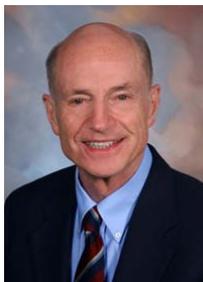
Lastly, although disease activity in a large proportion of

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EMS Disappointments

By Gerald Gleich, M.D.

It was late in October 1989. Three women in New Mexico had become ill with a devastating illness that was associated with marked increases in blood eosinophils. All of them had ingested a popular health food, L-tryptophan. Shortly thereafter, other cases came to light prompting the Centers for Disease Control to track down the cause of epidemic. By early November the Minnesota Department of Health had linked the illness and the eosinophilia to L-tryptophan ingestion. By mid-November the Food and Drug Administration banned the sale of L-tryptophan, and existing supplies were removed from the shelves of drug stores across the country.



In our laboratory at the Mayo Clinic in Rochester Minnesota, the activity level was high. The disease, now termed the eosinophilia myalgia syndrome (EMS), was a serious systemic illness with marked increases in eosinophils in the blood and with striking fibrosis in affected individuals. Because the link to L-tryptophan was so strong, it seemed that investigation of this link would be important in understanding how EMS occurs. However, L-tryptophan itself was an unlikely cause of the disease because L-tryptophan is part of our diet and a normal body constituent. Therefore, it seemed that an L-tryptophan contaminant must be responsible for the disease. If so, then the bottles of L-tryptophan being removed from the shelves of drug stores should be useful as a tool for EMS investigation.

I contacted the local drug stores and soon had cartons of L-tryptophan bottles littering my office. However, later information would show that the contaminants most strongly implicated in the causation of EMS were in relatively low concentrations in those particular bottles. Furthermore, as information from the CDC and the various state health departments accumulated, it seemed likely that EMS had peaked in October and was decreasing by mid-November. By early 1990, after studies by state departments of health, especially in Minnesota, New York and Oregon, L-tryptophan produced by Showa Denko and not by any of the other Japanese companies was clearly

the culprit. The way seemed clear to utilize the Showa Denko L-tryptophan to identify the critical contaminants and to determine their role in EMS.

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. Our laboratory had forged a strong link to the Minnesota Department of Health, and Arthur was in daily contact with Michael Osterholm, Craig Hedberg and Ed Belongia, epidemiologists investigating EMS. With their help, Arthur had the critical samples needed to find the contaminant, and he employed high performance liquid chromatography to dissect the L-tryptophan and to determine which of the many contaminants marked EMS. One day, Arthur called a meeting in our laboratory conference room and showed the data. One constituent, which we called peak E, was particularly prominent in Showa Denko L-tryptophan consumed by EMS patients. Ed Belongia then summarized the epidemiological data from the Minnesota Department of Health's efforts, and his paper in the New England Journal of Medicine showed the link to Showa Denko and the existence of Peak E. But what was peak E? Arthur Mayeno focused his chemical skills and soon had a tentative structure. Although his solution was challenged, Arthur proved that the structure he had identified was the correct one. Peak E consisted of two tryptophan molecules linked together. So the stage appeared to be set for a series of critical experiments linking peak E to EMS.

Our optimism was limitless at this point. Because EMS resembled other diseases associated with fibrosis, particularly scleroderma, it seemed that we had a wonderful opportunity to not only understand the mechanism of EMS but also to begin to understand why scleroderma occurs. We applied for a grant from the National Institutes of Health, and the grant was awarded. Hirohito Kita was a visiting scientist from Japan and a skilled bench scientist. Hirohito began experiments testing whether blood from normal individuals and individuals with EMS could be stimulated by the various L-tryptophan and Peak E preparations we had accumulated.

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Could EMS have been Prevented? Will Future Outbreaks be Prevented?

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charge a subscription fee to view their reports and test results, but I think it is a worthwhile service since the FDA is not doing this testing. Unfortunately, this still does not guarantee the safety of any particular product, since we have learned from EMS that a dietary supplement can be over 98% pure and still contain deadly contaminants. In addition, a product may be pure and still cause unanticipated health effects due to lack of safety testing.

The bottom line is that we have made some progress but we still have a long way to go. Hopefully the current FDA leadership recognizes this and will make greater efforts to protect consumers from unregulated products that are widely purchased and used for therapeutic purposes.

Eosinophilia Myalgia Syndrome Revisited -- 1989-2009

By Luis R. Espinoza, M.D. continued from page 4

affected individuals continues to lessen, the ultimate consequences of their disease are not well-defined and need further study.

NEMSN suggests you read the above article by Dr. Espinoza along with his article on our website (www.nemsn.org/Articles/Espinoza2.htm), "Eosinophilia-Myalgia Syndrome -- Long Term Complications".

In the website article Dr. Espinoza compares major studies of long-term outcomes for EMS patients, one of which shows milder long term effects and others of which demonstrate more major long term symptoms.

EMS Disappointments

By Gerald Gleich, M.D. continued from page 5

At first our results indicated that certain batches of L-tryptophan were particularly active, and we thought we had a bioassay to detect the contaminants. However, as we proceeded, it became clear that the reactive factor in L-tryptophan was a well known contaminant, endotoxin, that is the bane of research scientists utilizing biological systems. [Editor's note: Endotoxin is known as a dead end to research experiments since it falsifies results.] By this time, implicated L-tryptophan from Showa Denko had been injected into animal species from rats to mice to guinea pigs and to monkeys, and, although the animals may have become fat, they did not become ill. Moreover, although we persisted in our studies on the blood from patients with EMS, the results were unproductive; none of the methods we employed to stimulate blood was fruitful.

Arthur Mayeno continued his chemical analyses and was able to link the contaminants in L-tryptophan to contaminants in the toxic oil responsible for a massive epidemic in Spain in 1981, referred to as the Spanish toxic oil syndrome (TOS). Remarkably, investigations of TOS had failed to generate an animal model or a bioassay, even though many animal species were exposed to contami-

nated oil. Thus, the same frustrations experienced by the TOS investigators were shared by our group (and many others) probing EMS. Both TOS and EMS scientists failed to identify any useful tools (such as a bioassay or an animal model) to determine which contaminants in the L-tryptophan and the toxic oil were the critical ones.

In retrospect, the epidemiologists obtained the most significant information about EMS. They showed the critical relationship to L-tryptophan ingestion and the link to L-tryptophan produced by Showa Denko. We were able to identify a series of contaminants in Showa Denko L-tryptophan, but without a bioassay or animal model we were not able to understand how the contaminants caused the disease or which contaminant(s) were the critical ones.

Sometime in the future, another epidemic related to TOS and EMS will likely occur. Hopefully, the experiences from these epidemics will allow future investigators to start where we ended. However, the failure to provoke either the Spanish toxic oil syndrome or EMS in experimental animals or stimulate reactions in patients' cells in test tubes may indicate that these diseases are uniquely human and related to a peculiar human biochemical or immunological characteristic.

When It Won't Go Away: Managing Chronic Disease *Take Charge of Your Symptoms and Your Care*

You are hurting, so you go to the doctor. The doctor diagnoses your problem and prescribes a medicine to take and lifestyle changes to make. You do everything the doctor said to, but you still hurt and the pain and discomfort is starting to interfere with all aspects of your life. Now what?

Chronic disease can be defined as a medical condition that can be treated but not cured. They typically have a slow onset, but their effects will be felt for a long time and will likely only increase in number and severity. While it may be impossible to reverse the effects of chronic disease, education coupled with lifestyle changes can help you manage symptoms and live a productive, happy life. The Healthy U Chronic Disease Self-Management Program is a six-week workshop that can help you learn skills and strategies to deal with your chronic disease. Call your [area agency on aging](#) at 1-866-243-5678 to find the nearest available program and other resources.

Chronic diseases, such as diabetes, arthritis and cardio-vascular disease, all have different causes and symptoms, but the problems they create are similar and connected. The effects of arthritis or stroke can limit the use of your hands. Pain or shortness of breath from a variety of causes can make it difficult to walk or exercise. The resulting inactivity can lead to loss of muscle strength and flexibility, making activity even more difficult and increasing the risk of falls.

Chronic conditions also take an emotional toll. People with chronic diseases often deal with depression, fatigue, loss of energy and sleeping problems. They may limit their social activities, which can lead to isolation and deeper feelings of depression. Chronic disease also can make a person more dependent on others, which can lead to concerns about their future independence.

Even though you are dealing with a chronic illness, life goes on. You still have to deal with a job, relationships and various other obligations. Things that you once took for granted can become much more complicated, requiring you to learn new skills to maintain your daily activities and enjoy life. You also need to manage the changing emotions brought on by your disease.

In the business world, managers make decisions and make sure these decisions are carried out. They may do some of the work, but they can't do it all. They achieve real success when they fully understand the tasks and factors

at play, take control of the situations and work with others to get the job done. As manager of your illness, your job is much the same.

The first step is to understand your disease. Learn its causes, effects and how treatments may affect you. The more you know, the better able you will be to communicate with your health care provider and others about your symptoms and form a partnership with your doctor in managing your illness. Information about your condition can be found on a variety of medical Web sites. Your insurance plan also may have a "nurse line" or other service you can call for information and advice.

Once you understand your condition and its symptoms, you can start to plan what you want to do to manage it and what help you'll need to do so. You also may need to develop three basic types of new skills:

- Skills needed to deal with the illness, including taking medicine, exercising, communicating with your doctor and changing diet;
- Skills needed to continue your normal life, such as how to use a cane or walker, use lift aids or other assistive devices; and
- Skills needed to deal with emotions, particularly negative emotions like anger, depression, frustration or isolation.

Once you have a plan and the skills you need, any successful work project requires regular evaluation and adjustment. Keep track of the symptoms you experience, rate their severity from day to day and situation to situation, and learn to spot trends (e.g., your joint pain is more intense when it rains). By doing so, you'll be able to anticipate pain and discomfort and take steps to prevent or lessen it sooner. You'll also be more likely to recognize, deal with and communicate new symptoms in a more efficient manner.

People who take an active role in the management of their own chronic pain and discomfort tend to have a better quality of life, reduce their perception of pain and feel more empowered. In addition to overcoming physical and emotional problems, you can learn problem-solving skills and how to respond to the effects of your disease.

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