

PART 1

FOODBORNE and MICROBIAL TOXINS

COPYRIGHTED MATERIAL

PART 1 FOODBORNE and MICROBIAL TOXINS

I	Chemical Contamination and Additives	5	15	<i>Clostridium botulinum</i> (Botulism)	103
	by Cyrus Rangan, MD, FAAP				
1	Food Contamination	5	16	<i>Clostridium perfringens</i>	114
2	Food Additives and Sensitivities	22	17	<i>Escherichia coli</i>	120
			18	<i>Listeria monocytogenes</i>	133
II	Staples and Spices	34	19	<i>Salmonella</i>	141
3	Akee Fruit and Jamaican Vomiting Sickness (<i>Blighia sapida</i> Köenig)	34	20	<i>Shigella</i> Species (Shiga Enterotoxins)	150
4	Cinnamon (<i>Cinnamomum</i> Species)	39	21	<i>Staphylococcus aureus</i>	156
5	Cyanogenic Foods (Cassava, Fruit Kernels, and Cycad Seeds)	44	22	<i>Streptococcus</i> Species	162
6	Cycad Seeds and Chronic Neurologic Disease (<i>Cycas</i> Species)	54	23	<i>Vibrio</i> Species	167
7	Djenkol Bean [<i>Archidendron jiringa</i> (Jack) I. C. Nielsen]	59	24	<i>Yersinia enterocolitica</i>	174
8	Grass Pea and Neurolathyrism (<i>Lathyrus sativus</i> L.)	62	B	Other Microbes	181
9	Nutmeg (<i>Myristica fragrans</i> Houtt.)	67	25	Cyanobacteria	181
10	Pepper and Capsaicin (<i>Capsicum</i> and <i>Piper</i> Species)	71	26	Protozoa and Intestinal Parasites	191
11	Potatoes, Tomatoes, and Solanine Toxicity (<i>Solanum tuberosum</i> L., <i>Solanum lycopersicum</i> L.)	77	27	Gastrointestinal Viruses	202
12	Rhubarb and Oxalosis (<i>Rheum</i> Species)	84	IV	Seafood	212
III	Microbes	89	28	Amnesic Shellfish Poisoning and Domoic Acid	212
A	Bacteria	89	29	Azaspiracid Shellfish Poisoning and Azaspiracid Toxins	218
	by Cyrus Rangan, MD, FAAP		30	Diarrhetic Shellfish Poisoning and Okadaic Acid	222
13	<i>Bacillus cereus</i>	89	31	Neurotoxic Shellfish Poisoning and Brevetoxins	227
14	<i>Campylobacter jejuni</i>	96	32	Paralytic Shellfish Poisoning and Saxitoxins	231
			33	Ciguatera Fish Poisoning and Ciguatoxins	238
			34	Puffer Fish Poisoning and Tetrodotoxin	247
			35	Red Whelk and Tetramine	253
			36	Scombroid Fish, Scombrot toxin, and Histamine	256

I Chemical Contamination and Additives

Chapter 1

FOOD CONTAMINATION

CYRUS RANGAN, MD, FAAP

Records of outbreaks of human illness caused by toxic contaminants in foods appeared at least several centuries BC, when mad honey poisoning was associated with an illness among troops under the command of the Greek historian and mercenary, Xenophon.¹ One of the first recorded foodborne outbreaks of ergotism occurred in Limoges, France during the Capetian Dynasty in 994 AD.² The ingestion of rye bread contaminated with ergot alkaloids during this epidemic caused the deaths of approximately 20,000–50,000 victims. Numerous episodes of ergotism have occurred throughout history. Although ergotism is a possible explanation for the bizarre behavior that occurred before and during the Salem Witch Trials of 1692, there is no definite evidence that ergotism was a contributing factor.³ In the 1950s, mining operations in the Toyama region of Japan released cadmium into the Jinzu River. The use of this water for drinking and for irrigation of nearby rice fields resulted in a disease called *itai-itai* (translation: “ouch-ouch”), manifest by osteoporosis and renal dysfunction primarily in middle-aged women.⁴ In the same decade, numerous neonates born near Minamata Bay, Japan, developed birth defects and neurological abnormalities after pregnant women were exposed to seafood contaminated by methyl mercury released into the bay from a local factory. A methyl mercury-based fungicide caused an outbreak of mercury poisoning in Iraq in 1971 after grain seeds treated with the fungicide were inadvertently used for food manufacturing instead of plant-

ing.⁵ Prominent outbreaks of illnesses associated with chemical contamination of cooking oils include tri-*ortho*-cresyl phosphate-induced neuropathy (Morocco, 1959),⁶ yusho (“rice oil disease,” Japan, 1968), yu-cheng (“oil disease,” Taiwan, 1979), toxic oil syndrome (Spain, 1981), and epidemic dropsy (India, 1998). Some contaminants are unavoidable in food manufacturing. In the United States, the Food and Drug Administration (FDA) imposes “Current Good Manufacturing Practices” (CGMP) on food manufacturers. These mandatory codes enable the FDA to cite food products as *unfit* if an unavoidable contaminant poses a risk of harm by violating a standard or action level for that unavoidable contaminant (e.g., aflatoxin). Food products are considered *adulterated* when concentrations of avoidable contaminants (e.g., pesticides) exceed established standards, sometimes prompting food recalls after sale and distribution.

Metal contaminants such as lead, mercury, arsenic, and cadmium come from factory emissions, mining operations, and metal-containing industrial products used in food production. Methyl mercury found in commercially sold seafood is deemed an unavoidable contaminant because contamination preexists in the raw material; therefore, the contamination does not result from food processing or distribution. Fish and shellfish acquire methyl mercury primarily from microorganisms that methylate environmental inorganic mercury compounds released primarily from industrial sources.

YUSHO and YU-CHENG

HISTORY

The first known case of yusho (rice oil disease) involved a 3-year-old girl in northern Kyushu, Japan, who had an acute onset of an acneiform rash (chloracne) in June, 1968. Her family members, followed by other familial clusters, presented to a single clinic with complaints of acneiform rash, hyperpigmentation, and eye discharge over the next 2 months. By January 1969, 325 cases were reported. After a small minority of patients initially identified rice oil as the causative agent of yusho, Kyushu University convened the *Study Group for Yusho* to investigate yusho; about 2,000 afflicted patients were subsequently identified. The clinical features of yusho included fatigue, headache, cough, abdominal pain, peripheral numbness, hepatomegaly, irregular menstrual cycles, nail deformities, and hypersecretion of sebaceous glands. A field survey of canned rice oil associated the disease with the use of “K Rice Oil” produced or shipped by the K Company on February 5–6, 1968.⁷ The yu-cheng epidemic involved over 2,000 individuals in Taiwan in 1979, when an accidental leakage of thermal exchange fluid resulted in the contamination of rice-bran oil with polychlorinated biphenyls (PCBs), dibenzofurans (PCDFs), and quaterphenyls (PCQs).⁸ The clinical features of yu-cheng and yusho were similar.

EXPOSURE

Source

Polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) are thermal heat exchanger compounds used in food processing machinery. Leakage of these compounds into rice oils during manufacturing led to the yusho and yu-cheng outbreaks.

YUSHO

Epidemiological studies revealed that 95.7% ($p < 0.01$) of surveyed patients recalled consumption of rice oil from K Company in Western Japan.⁷ A case-control study revealed rice oil as the only associated etiologic factor, and a cohort study demonstrated a 64% risk of yusho in K rice oil consumers compared with no risk for nonexposed individuals.⁷ Food engineers confirmed the leakage of dielectric thermal exchange fluid (Kanechlor

400) containing PCBs into the rice oil. This contaminant contained PCB compounds, primarily tetra-chlorinated biphenyls. In 1969, the Study Group initially concluded that PCBs caused yusho.⁹ However, a lack of similar symptoms (besides chloracne) in PCB workers who had significantly higher tissue burdens (mean blood PCB level: 45 ppb) contradicted this conclusion. Furthermore, the dermatological lesions could not be reproduced in animals following the oral administration of PCB compounds or by Kanechlor 400, and the severity of the clinical features of yusho did not correlate to serum concentrations of PCB compounds. Therefore, other compounds (e.g., polychlorinated dibenzofurans) in the adulterated rice oil probably contributed to the development of yusho.^{10,11}

YU-CHENG

As with the yusho incident, the suspected causative agents of yu-cheng were PCDFs rather than PCBs.¹² Contamination of the cooking oil occurred when PCBs used for the indirect heating of rice-bran oil leaked into the cooking oil. Repeated heating of the partially degraded PCBs produced PCDFs, as well as polychlorinated terphenyl and polychlorinated quaterphenyl compounds.¹³

Food Processing

High temperatures ($>200^{\circ}\text{C}$) in dielectric thermal exchange fluid during the deodorization step of oil refining contributed to the development of yusho and yu-cheng by degrading PCBs in the contaminated rice oil to PCDFs, PCDDs (polychlorinated dibenzo dioxins), and PCQs (polychlorinated quaterphenyls).¹⁴

DOSE RESPONSE

Exposure to toxic contaminants in the rice oil from the yusho and yu-cheng epidemics was assessed by recording the lot numbers of purchased oil containers and comparison of the volume of oil purchased to the volume of oil remaining in the containers retrieved from affected households. Consumption of the contaminated rice oil by household members was estimated by proportional distribution to each family member. Positive relationships were observed between estimated individual oil consumption and incidences of yusho and yu-cheng.^{15,16} The mean concentrations of PCBs, polychlorinated quaterphenyls (PCQs), and PCDFs in five samples of contaminated cooking oil from the yu-cheng outbreak were 62 ppm, 20 ppm, and 0.14 ppm, respectively.¹⁷ The congeners of these compounds were similar in the cooking oils from these two outbreaks, but yu-cheng cooking oil

samples contained about 10% of the concentrations of these compounds found in cooking oil from the yusho incident along with three to four times lower PCQs/PCBs and PCDFs/PCBs ratios.

A cross-sectional study of 79 patients with documented yusho demonstrated a dose-response relationship between estimated consumption of contaminated rice oil and the symptoms of extremity numbness, coughing, expectoration, and the sensation of “elevated teeth.”¹⁸ These symptoms were evaluated by self-administered questionnaires. Symptoms failing to demonstrate a dose-response relationship to the estimated ingestion of contaminated rice oil included fatigue, eye discharge, fever, headache, dizziness, abdominal pain, swollen joints, menstrual irregularities, and alopecia. The estimated mean total intake of PCBs and PCDFs by yusho patients was about 633 mg and 3.4 mg, respectively, compared with 973 mg and 3.84 mg, respectively, for yu-cheng patients.¹⁹

CLINICAL RESPONSE

Animal studies confirm a strong association between high concentrations of PCBs (i.e., at least 60% chlorination) in diets and the incidence of hepatic carcinomas. However, no human studies have confirmed an association between PCB exposure and cancer. Therefore, PCBs are listed as probable human carcinogens by the International Agency for Research on Cancer (IARC) and the US Environmental Protection Agency (EPA).²⁰

Yusho

Clinical features of this illness included fatigue, headache, cough, abdominal pain, peripheral numbness, hepatomegaly, irregular menstrual cycles, nail deformities, and sebaceous gland hypersecretion. The most common symptoms were eye discharge, hyperpigmentation (skin, mucous membranes, nails), acneform lesions, and weakness.¹⁹ Although the severity of these symptoms has decreased since the epidemic, follow-up studies of yusho survivors indicated that these symptoms persisted at least through 1993.²¹ The chloracne resolved relatively rapidly in children, but hyperpigmentation and hypertrichosis remained in some patients. Thirteen children born to yusho-affected mothers exhibited gray-brown skin discoloration at birth (“black babies,” “cola-colored babies”), but the discoloration spontaneously disappeared after several weeks. These babies exhibited no other symptoms consistent with yusho.²²

Yu-cheng

The clinical features of yu-cheng and yusho are similar. Clinical findings include chloracne, hyperpigmentation, edema, weakness, vomiting, diarrhea, and hepatomegaly. The acneform eruptions were open comedones, papules, and pustules with dark heads distributed on the axilla, extremities, and external genitalia.²³ Abnormalities in children of yu-cheng patients included low birth weights,²⁴ prematurity, neurobehavioral changes such as delayed autonomic maturity,²⁵ normal menarche with shortened menstrual cycles,²⁶ abnormal reflexes, dysfunctions in visual recognition memory,²⁷ and decreased intelligence scores.²⁸ A 24-year follow-up study of yu-cheng victims demonstrated increased mortality from chronic liver disease and cirrhosis in men, but not in women.²⁹ There was an increased incidence of systemic lupus erythematosus in exposed women in the later years. The mortality rates for cancers were similar between the exposed group and the background population.

DIAGNOSTIC TESTING

Analytical Methods

Gel permeation chromatography and high resolution gas chromatography/high resolution mass spectrometry detect and differentiate PCBs and PCDFs in oil samples and in human samples.³⁰ Methods that utilize high performance liquid chromatography/mass spectroscopy (HPLC/MS) or high performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) reliably detect the di-oleyl-phenyl amino propanediol ester (OOPAP) and other acylated phenyl amino propanediol derivatives (PAPs) in cooking oils.³¹ Methods to detect OOPAP in humans are not available.

Biomarkers

Rice oil from the yu-cheng epidemic contained approximately 3,000 ppm total PCBs. The mean blood concentration of PCBs in patients with chloracne and hyperpigmentation was in the range of approximately 5 ppb. There was a linear correlation between the severity of skin lesions and the total PCB concentrations in blood samples. Studies of human and animal subjects indicate that PCB concentrations in the range of 10–25 ppm cause similar skin abnormalities. Analysis of PCBs, PCDFs, and PCQs in contaminated rice-oil samples collected from factory cafeterias, school cafeterias, and the families of patients with yu-cheng ranged from 53–99 ppm, 0.18–0.40 ppm, and 25–53 ppm, respectively.³²

Although the specific compound associated with yusho or yu-cheng remains unknown, PCDDs are more appropriate biological biomarkers for the severity of yusho and yu-cheng than other polychlorinated hydrocarbons because the presence of PCDDs in blood samples indicates exposure to these compounds or parent compounds as PCDDs do not occur in nature.³³ These compounds persist in the blood for years.³⁴ Clearance of PCDFs and PCBs in humans is nonlinear with faster elimination rates at higher concentrations. In blood samples from 3 yu-cheng patients, the whole blood elimination half-life of two persistent toxic congeners, 2,3,4,7,8-pentachlorodibenzofuran (PnCdf) and 1,2,3,4,7,8-hexachlorodibenzofuran (HxCdf) was approximately $2\frac{1}{2}$ years.³⁵ The calculated blood elimination half-lives of the same PCDF congeners in yusho patients were more variable with median values near 10 years. In a follow-up study of 359 patients with yusho, the serum concentrations of PnCdf and PCBs remained significantly elevated over 35 years after the incident.³⁶ The mean blood concentration of PnCdf in exposed patients was 177.50 pg/g lipids compared with 15.2 ± 8.9 pg/g lipids in the blood of healthy controls. The blood PnCdf concentration in these patients correlated to some clinical symptoms of yusho including acneform eruption, comedones, oral pigmentation, constipation, numbness in the extremities, and body weight loss. Follow-up studies indicate that the blood elimination half-lives are shorter (i.e., about 1–5 years) for PCB congeners than PCDF congeners. Follow-up studies of blood samples from yusho patients 34 years after the incident indicate that PCDFs contribute about 65% of the remaining total toxic equivalents of dioxins (non-*ortho* PCBs, mono-*ortho*-PCBs, PCDDs, PCDFs).³⁷ In particular, the mean concentration of some PCDF congeners were substantially higher than controls including 1,2,3,6,7,8-HxCdf (3.9 times), 1,2,3,4,7,8-HxCdf (12 times), and PnCdf (11.3 times). The blood samples from 165 yu-cheng patients collected 9–18 months after the onset of poisoning contained 10–720 ppb PCBs with a mean value of 38 ppb.⁸

Abnormalities

Yusho and yu-cheng patients occasionally had mild elevation of serum hepatic aminotransferase concentrations, but results of most laboratory studies were within normal ranges.³⁸ Hepatorenal function is usually normal.

TREATMENT

The treatment for yusho and yu-cheng is supportive. Dermatologic changes may persist for several months,

and topical or systemic medications typically do not alter the time-course of these lesions. Yusho and yu-cheng patients require long-term follow-up for the development of liver dysfunction and malignancy.³⁸

TOXIC OIL SYNDROME

HISTORY

In the early 1980s, Spanish laws banned the importation of rapeseed oil for human consumption to protect the Spanish olive oil market.³⁹ These laws required the denaturation of imported rapeseed oil with aniline, methylene blue, or castor oil as a means to make this imported oil unfit for human consumption. During late 1980 and early 1981, a substantial amount of aniline-denatured rapeseed oil imported from France was fraudulently diverted for human consumption through Catalonia. These oils were diluted with other edible oils, refined, and resold through a network of distributors and itinerant salesmen. Although these oils contained aniline, the toxic oil syndrome was apparently not associated with the aniline.

During the first quarter of 1981, an oil distributor based in the center of Madrid named RAELCA entered the illicit oil sales market with mixed aniline-denatured rapeseed oil. In March 1981, RAELCA purchased five lots of aniline-denatured rapeseed oil from two French food oil companies, and they shipped three lots to the ITH oil refinery in Seville.⁴⁰ The other two lots went to the Danesa Bau refinery in Madrid. Although the denatured oils were intended for industrial use, roadside vendors sold the oils as “olive oil” to residents over a 2-month period.⁴¹ Most of the cases of toxic oil syndrome appeared in the period from May to August 1981. Figure 1.1 displays the number of cases of toxic oil syndrome diagnosed in 1981. Epidemiological studies concluded that the ITH oil refinery was the point source for the epidemic.⁴²

EXPOSURE

Source

The exact causal agent in the contaminated oil involved with toxic oil syndrome remains unknown, in part, because of the many potential toxins in denatured aniline compounds associated with this illness. In a study of toxic oil syndrome-associated oils, fractionation of

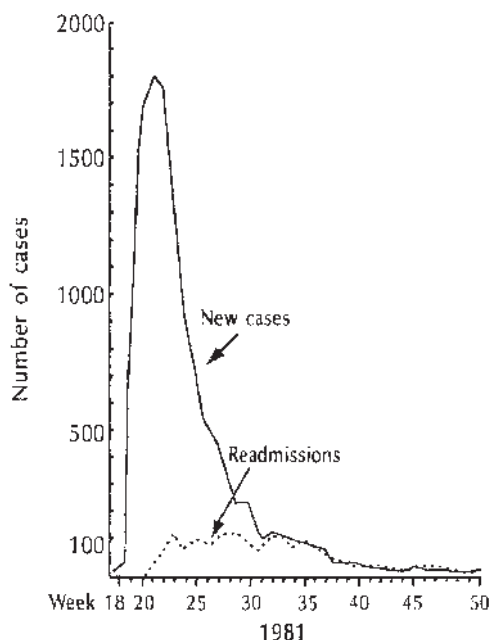


FIGURE 1.1. Onset of cases of toxic oil syndrome in Spain during 1981. From Philen RM, et al. Toxic oil syndrome and eosinophilia-myalgia syndrome: May 8–10, 1991, World Health Organization Meeting Report. *Semin Arthritis Rheum* 1993;23:106. Reprinted with permission from Elsevier.

the oils by high performance liquid with ultraviolet detection (HPLC/UV) and analysis by high performance liquid chromatography/atmospheric pressure chemical ionization/ tandem mass spectrometry (HPLC/APCI/MS/MS) demonstrated 115 aniline derivatives from nine aniline-related families of chemicals.⁴³ Toxic oil syndrome is a unique combination of vasculitis, thrombosis, and immunologic changes (e.g., T-lymphocyte activation, cytokine release) that differs from the toxicity previously associated with refinery products, additives, or contaminants.⁴⁴ The full spectrum of toxic oil syndrome has not been reproduced in experimental animals.³⁹ The two suspected groups of toxic compounds are fatty acid anilides and amino-propanediol derivatives (fatty acid mono- and di-esters).⁴⁵ Analysis of contaminated oil samples indicates that pentachlorophenol and pentachloroanisole were not etiological agents of toxic oil syndrome.⁴⁶

Food Processing

In contrast to other illicit rapeseed oil distributors, RAECA mixed the denatured rapeseed oil with other oils *after* the refining process. All other illicit refiners of denatured rapeseed oil in Catalonia mixed the denatured and edible oils *before* refining the adulterated oils. The processing of the fraudulently diverted rapeseed oil probably contributed to the formation of toxic com-

pounds in the oil. High temperatures during deodorization catalyzed the reaction of 2% aniline with triglycerides in the rapeseed oil associated with toxic oil syndrome.⁴⁷ In experimental studies, the yield of 3-(*N*-phenylamino)-1,2-propanediol (PAP) esters in toxic oil syndrome is highest at 250–300 °C (~480–570 °F), similar to those temperatures achieved during the deodorizing step of oil refining.⁴⁸ These studies indicate that the heating of denatured oil samples stored for 3 weeks yields higher concentrations of potentially toxic PAP esters compared with samples stored for 1 week. Distillations times did not significantly affect the formation of fatty acid anilide compounds. The development of toxic oil syndrome following the ingestion of denatured rapeseed oil stored for about 1 year suggests that the toxic compounds in these contaminated cooking oils are stable for at least 1 year.⁴⁹

DOSE RESPONSE

Dose response in toxic oil syndrome was evaluated by a case control study known as the “Toxi-Epi Study,” which followed sales and distribution chains of the fraudulently distributed rapeseed oils using the chemical markers, oleyl-anilide and di-oleyl-3-phenylamino-1,2-propanediol (OOPAP). The content of these compounds varied several fold in different samples of contaminated cooking oil. Cooking oil containers with a characteristic shape purchased by residents were traced back to the ITH oil refinery in Seville in southern Spain. Analytical studies showed a linear statistical correlation between the concentration of the chemical markers detected in the refinery’s oil and the log of the odds ratio for dose-response.⁵⁰ Rapeseed oil concentrations of oleyl-anilide and OOPAP traced to this plant were 1900 ppm and 150 ppm, respectively.

CLINICAL RESPONSE

The first cases of toxic oil syndrome were reported on May 1, 1981 in central and northwestern Spain. Initial epidemiological studies demonstrated clustering in incidence and mortality for toxic oil syndrome in households distributed along transportation routes throughout the affected regions. In July 1981, Spanish health officials announced that a fraudulently distributed, industrial oil sold as edible cooking oil was the etiology of this illness, initially termed pneumonic paralytic eosinophilic syndrome.⁵¹ The Spanish government subsequently initiated a consumer exchange program for olive oil, and they stockpiled the contaminated oil for further study.⁵² In 1983, the World Health Organization named the illness toxic oil syndrome.⁵³ The official census originally consisted of records of patients with clinically suspected toxic oil syndrome that did not necessarily fulfill the case definition of the 1981 Spanish

Clinical Commission. A 1987 review of these records by the World Health Organization Regional Office for Europe Scientific Committee for the Investigation of the Toxic Oil Syndrome indicated that about 20,000 people were affected with over 10,000 hospitalizations.⁵⁴ Although during the first few years about 300 patients died of toxic oil syndrome, the overall mortality of the cohort with toxic oil syndrome was not elevated after the first year of the epidemic when compared with the general Spanish population.⁵⁵

Toxic oil syndrome is a progressive multisystemic disease with three distinct clinical phases (acute, intermediate, chronic). The average latency period was about 4 to 7 days after the ingestion of the contaminated oil with a maximum of about 10 days.⁵⁶ The basic underlying pathological lesion is a nonnecrotizing vasculitis with associated thrombotic events. Common initial symptoms of toxic oil syndrome included fever, cough, dyspnea, and chest pain. Other acute symptoms included urticarial rash, pruritus, abdominal cramping, and headache. The differential diagnosis for toxic oil syndrome includes other autoimmune disorders such as eosinophilia-myalgia syndrome, eosinophilic fasciitis, systemic sclerosis, scleroderma, and systemic lupus erythematosus.⁵⁷ Porphyria cutanea tarda did not occur in these patients.

Acute (Pulmonary)

The characteristic manifestation of the acute phase is the development of noncardiogenic pulmonary edema with dyspnea, alveolar-interstitial infiltrates with or without pleural effusions, peripheral eosinophilia, fever, and rash. Most patients recovered from this early pneumonic phase of the illness. Deaths during this phase occurred from respiratory insufficiency initially from degeneration of type I and type II pneumocytes and later from thromboembolic complications.⁵⁸ During the acute phase (i.e., first 2 months), the primary lesion occurs in the endothelium of multiple organs with the exception of the central nervous system.⁵⁹ Severe myalgias and muscle cramps occur at the end of the acute phase.³⁹

Intermediate (Thrombotic)

About 60% of the patients with the acute phase progress to the intermediate phase that involved the development of sensory peripheral neuropathy along with intense myalgias, dermal induration, and weight loss. More serious complications during this phase began about 2 months after the onset of illness, including pulmonary hypertension and thromboembolism of large vessels. In severe cases, histological examination demonstrated proliferation of the intimal lining of the vessels along with fibrosis and thrombosis.

Chronic (Neuromuscular)

Approximately 2 months after the onset of the intermediate phase, the chronic phase of toxic oil syndrome began, characterized by sclerodermiform changes, motor neuropathy, musculoskeletal contractures, muscle wasting, myalgias, muscle cramps, weight loss, limited joint mobility, peripheral eosinophilia, hepatomegaly, pulmonary hypertension, and Sjögren syndrome.⁶⁰ Some patients developed this chronic phase without experiencing the acute pneumonic phase.⁵⁸ The most common persistent symptoms were cough and dyspnea with about 20% of affected patients developing reduction in the carbon monoxide diffusing capacity.⁶¹ Mortality in the chronic phase was primarily due to infectious complications of respiratory insufficiency secondary to neuromuscular weakness, thromboembolism, or pulmonary hypertension with cor pulmonale.^{62,63} A minority of toxic oil syndrome patients developed severe pulmonary arterial hypertension during exercise over 20 years after exposure.⁶⁴ Long-term follow-up studies of survivors suggest reduction in the quality of life of these patients with elevated rates of depression (odds ratio [OR] = 9.66), functional disabilities (OR = 4.74), and psychosocial disabilities (OR = 2.82).⁶⁵

Mortality was high during the first year, with a significant decline in mortality rates in subsequent years.⁵⁵ Most of the decline in mortality was observed in elderly populations; however, the mortality rate in women <40 years of age increased as a result of complications from pulmonary hypertension.⁶⁶ Concurrent clustering of incidence and mortality in toxic oil syndrome suggested that a genetic predisposition determines the severity of toxic oil syndrome. Linkage mapping of the human genome revealed increased mortality in patients with a chromosome 6-associated risk factor for the HLA-DR2 phenotype.⁶⁷ Studies in enzyme mechanics implicate a role for impaired hepatic acetylation in mediating individual susceptibilities to toxic oil syndrome.⁶⁸

DIAGNOSTIC TESTING

Analytical Methods

Analytical methods to identify and quantify OOPAP and other PAPs in contaminated cooking oil samples include high performance liquid chromatography/atmospheric pressure ionization/tandem mass spectrometry (HPLC/API/MS/MS) and HPLC/MS.^{31,69}

Biomarkers

The analysis of contaminated oil was complicated by poor identification markers on cooking oil bottles during

the recall process. Two case control studies suggested a dose-related association between the presence of three fatty acid anilide compounds (oleyl, linoleyl, palmityl) and the risk of developing toxic oil syndrome.^{50,70} Of these fatty acid anilide compounds, oleyl anilide occurred in the highest concentration. Subsequent analyses suggested that 3-(*N*-phenylamino)-1,2-propanediol (DEPAP), a by-product of the same reaction of aniline with triglycerides, is an equally sensitive and a more specific biomarker of toxic oil syndrome than fatty anilide compounds.⁷¹ Animal studies suggest that the liver converts fatty acid mono- and diesters of 3-(*N*-phenylamino)propane-1,2-diol to 3-(4'-hydroxyphenylamino)-propane-1,2-diol, which generates the electrophilic metabolite quinoneimine intermediate-2 (QI-2).⁷² However, the specific chemical causing toxic oil syndrome has not been identified.

Abnormalities

Laboratory changes associated with toxic oil syndrome include peripheral eosinophilia, hypertriglyceridemia, and coagulation disorders in patients with liver involvement. Analytical studies of toxic oil syndrome patients demonstrate eosinophilia and a high concentration of mRNA for T-helper-2 cytokines, IL-4 and IL-5, in the lungs.⁷³ Antemortem sera from fatal cases of toxic oil syndrome also contained elevated serum IL-2R and total IgE concentrations along with a high frequency of HLA-DR2 on chromosome 6.⁷⁴ The sinus and atrioventricular nodes may exhibit dense fibrosis, hemorrhages, or cystic degeneration similar to findings in scleroderma and systemic lupus erythematosus. Coronary arteries may exhibit focal fibromuscular dysplasia and cystic myointimal degeneration with embolization. Histopathological analyses show lymphocytic inflammatory lesions of coronary arteries and the cardiac conduction system, similar to the findings in eosinophilia-myalgia syndrome. Cardiac lesions associated with eosinophilia-myalgia syndrome, however, are distinguished by cytotoxic T-cells directed against cardiac neural structures and sinus nodal myocytes, whereas toxic oil syndrome cardiac lesions are characterized by a prominence of B cells and T-helper cells.⁷⁵

Chest x-ray demonstrates an interstitial-alveolar pattern with progression to acute respiratory distress syndrome (adult respiratory distress syndrome or ARDS) in the acute phase of toxic oil syndrome.⁷⁶ Eosinophilia is a universal finding in toxic oil syndrome patients.⁷⁷ Hypoxemia, respiratory alkalosis, and an increased alveolar-arterial oxygen gradient (A-a gradient) as determined by arterial blood gases are common in patients with severe toxic oil syndrome-induced non-cardiogenic pulmonary edema during the acute phase.⁷⁸

TREATMENT

During the acute phase, respiratory compromise from ARDS is the most serious complications of toxic oil syndrome. Patients with toxic oil syndrome are also at increased risk of cardiovascular disease that may manifest several years after exposure. Echocardiography, cholesterol screening, and weight management are effective tools for the screening and detection of cardiovascular sequelae in patients with toxic oil syndrome.^{79,80} Long-term neuromuscular and articular complaints are prominent, and abnormalities are treated symptomatically.⁸¹ Patients should be monitored for the prominent risk factors most closely associated with early mortality: female <40 years old, liver disease, pulmonary hypertension, frequent pulmonary infections, motor neuropathy, and eosinophilia.⁸²

EPIDEMIC DROPSY

HISTORY

Although the first of several epidemics of epidemic dropsy was documented in 1877 in Calcutta, the most prominent epidemic dropsy epidemic occurred in Delhi, India during August, 1998.⁸³ The Indian Ministry of Health received over 2,552 reports of poisoning with 65 deaths from August to October 1998. The incidence of epidemic dropsy was higher in lower socioeconomic groups, probably as a result of purchasing less expensive, loosely packaged mustard oil from roadside vendors. Epidemic dropsy (argemone toxicity) is characterized by the pathological accumulation of lymph throughout the body along with gastrointestinal distress, erythrocytosis, sarcoid-like skin lesions, myalgias, paresthesias, and painful edema of the lower extremities.

EXPOSURE

Source

Argemone oil (Katkar oil) mixed with mustard oil and ghee (clarified butter) caused epidemic dropsy outbreaks in India, South Africa, and Nepal. *Argemone mexicana* L. (Mexican prickly poppy, Satyanashi [translation: *devastating*], Papaveraceae) is an invasive weed with a yellow flower similar to the mustard flower (*Brassica nigra* (L.) W.D.J. Koch). Indian mustard oil

merchants commonly remark to public health officials that argemone seeds are inadvertently harvested with mustard seeds because they thrive in similar climates, with potentially overlapping harvests (Mustard—February/March; Argemone—April/May).^{84,85} However, the canopy-like structure of the mustard plant does not permit concurrent growth of other plants in the same fields; therefore, mustard seeds are generally harvested in February, leading to the widely accepted theory that adulterations of mustard oil with argemone oil are intentional.

Argemone oil contains two toxic alkaloids: dihydrosanguinarine (CAS RN: 3606-45-9, $C_{20}H_{15}NO_4$) and much smaller amounts of sanguinarine (CAS RN: 2447-54-3, $C_{20}H_{14}NO_4$). Although the concentration of dihydrosanguinarine in argemone oil is greater than sanguinarine, the toxicity of the latter compound is greater.⁸⁶ The names originate from the bloodroot (*Sanguinaria canadensis* L.), which is the original source of this alkaloid.⁸⁷ These alkaloids are benzophenanthridine derivatives of glycosides that cause increased permeability of blood vessels, particularly in the heart, liver, eyes, gastrointestinal tract, and kidneys.⁸⁸ Figure 1.2 and Figure 1.3 demonstrate the chemical structure of dihydrosanguinarine and sanguinarine, respectively.

The exact mechanism of toxicity of epidemic dropsy is unknown. Sanguinarine and dihydrosanguinarine accumulate in the gastrointestinal tract, serum, and tissues after binding tightly to plasma proteins.⁸⁹ *Potentially* these toxic alkaloids cause damage by binding to $Na^+-K^+-ATPase$,⁹⁰ inactivating hepatic cytochrome P-450 enzymes,⁹¹ depleting hepatic glutathione,⁹² and

disrupting carbohydrate metabolism. The latter effect inhibits active transport of glucose across intestinal villi, resulting in increased glycogenolysis and the formation of excess glucose-1-phosphate, pyruvate, and lactate.⁹³ These processes lead to the formation of reactive oxygen species, causing oxidation of plasma proteins and lipids.⁹⁴

Food Processing

Mustard seeds are differentiated from the seeds of *Argemone mexicana* L. by physical appearance: mustards seeds are smooth and round; argemone seeds are creased with spiked edges. Batches of mustard seeds are visually inspected for argemone seeds during processing with the argemone seed discarded upon detection. The practice of sorting is painstaking and cost-prohibitive, as 1% adulteration of mustard oil by argemone oil is enough to cause symptoms.⁹⁵ The early harvesting of mustard avoids the contamination of mustard oil by argemone seeds. The toxic alkaloids in argemone oil are heat-stable to 240°C (~460°F). Consequently, consumers in endemic areas are advised to heat mustard oils to 240°C for at least 15 minutes to deactivate the toxic alkaloids present in argemone seeds.⁹⁶

DOSE RESPONSE

As little as 1% adulteration of cooking oil with argemone oil is probably sufficient to cause clinical toxicity.⁸⁶ Because sanguinarine and dihydrosanguinarine accumulate in human tissue, toxicity can result from subacute, low-dose exposure.

CLINICAL RESPONSE

The clinical features of epidemic dropsy begin approximately 1–3 weeks after consumption of contaminated oil with a variety of symptoms including nausea, vomiting, diarrhea, bloating, anorexia, hyperplastic lesions in the mouth and other mucous membranes, erythematous rash with bluish mottling (erythrocyanosis), nodular sarcoid-like skin lesions or telangiectasias,⁹⁷ bilateral glaucomatous findings,⁹⁸ anemia, muscle tenderness, numbness, tingling, and painful bilateral pitting edema, particularly of the lower extremities.^{99,100} Capillary leakage and congestion of gut mucosa epithelia cause watery gastrointestinal symptoms with occasional hematemesis, melena, or hematochezia. The ophthalmologic features of epidemic dropsy occur relatively late in the course of the disease. Ocular signs include increased ocular pressure and glaucoma from protein accumulation in the aqueous humor. Visual complications include subconjunctival hemorrhage, superficial

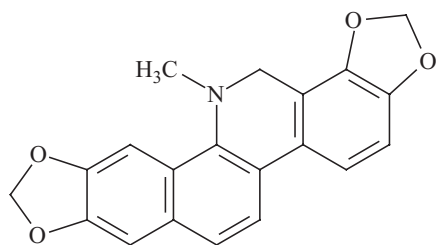


FIGURE 1.2. Chemical structure of dihydrosanguinarine.

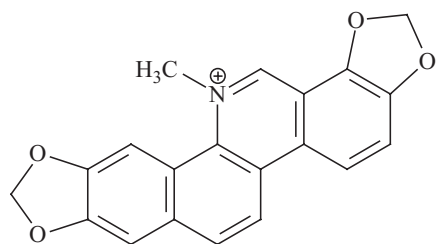


FIGURE 1.3. Chemical structure of sanguinarine.

retinal hemorrhages, retinal venous dilatation and tortuosity, subhyaloid hemorrhages, macular and papillary edema, central retinal vein occlusion, visual field defects, and rarely permanent visual defects from optic nerve damage.^{101–103} In a case series of 230 documented cases of epidemic dropsy, the incidence of intraocular pressures exceeding 22 mmHg was about 11% with most elevations of intraocular pressure returning to normal values within 12 weeks.¹⁰⁴ Inflammation of the anterior segment is usually absent.

Renal insufficiency with hypoalbuminemia and proteinuria may occur in serious cases of epidemic dropsy, resulting in acute renal failure.^{100,105} Bleeding occurs from sarcoidal lesions and telangiectasias on mucous membranes and gastrointestinal epithelial mucosa.^{106,107} Non-cardiogenic pulmonary edema and, rarely, cardiac failure develop in severe cases with hypoxemia, respiratory alkalosis, high-output cardiac failure, tachycardia, dyspnea, and increased A-a gradient. Death results primarily from cardiac arrest secondary to congestive heart failure, noncardiogenic pulmonary edema, or pericardial fluid accumulation.¹⁰⁸ Postmortem histological findings include venous congestion, extramedullary hematopoiesis, focal hemorrhages, proliferation of capillary endothelial cells, dilation of hepatic sinusoids, and mononuclear infiltration of the central veins in the liver.⁸⁶

DIAGNOSTIC TESTING

Analytical Methods

During an epidemic, samples of adulterated mustard oil are screened for sanguinarine by the addition of ferric chloride to the sample.¹⁰⁹ The appearance of a red-brown precipitate suggests the presence of $\geq 0.25\%$ argemone oil in the sample. The presence of sanguinarine in these samples is confirmed by HPLC with limits of detection in the range of 0.001% argemone oil in the sample.¹¹⁰

Biomarkers

In a study of 45 patients with epidemic dropsy during an outbreak in New Delhi, sanguinarine was detected in eight urine samples collected within 2–3 weeks of onset of dropsy with concentrations ranging between 0.4 and 3.6 $\mu\text{g}/100\text{ mL}$. Three of 18 serum samples in the same group were positive for sanguinarine with concentrations of 1.2, 1.6, and 3.6 $\mu\text{g}/100\text{ mL}$.¹¹¹

Abnormalities

Epidemic dropsy patients typically have hypoalbuminemia, hypocalcemia, proteinuria, and azotemia, similar

to nephrotic syndrome along with reduced concentrations of tocopherol and retinol secondary to depletion of antioxidants by reactive oxygen species.¹¹² Chest x-ray may reveal signs of pulmonary edema and right ventricular cardiomegaly. Case series suggest that the dyspnea associated with epidemic dropsy usually results from a restrictive ventilatory defect with reduced carbon monoxide diffusing capacity rather than a cardiomyopathy.¹¹³ The electrocardiogram may demonstrate ST-T wave changes and premature ventricular contractions.⁹⁶ Normochromic, normocytic anemia is a common finding despite expected hemoconcentration from intravascular fluid loss.¹⁰⁷

TREATMENT

Treatment for epidemic dropsy is supportive. Inpatient treatment includes compression stockings, protein-rich diet, correction of symptomatic hypocalcemia, and albumin infusions as indicated by the condition of the patient. Deficiencies in tocopherol and retinol may be corrected with supplementation, but there are inadequate clinical data to determine the clinical efficacy of the administration of antioxidants to patients with epidemic dropsy.¹¹⁴ Serial ophthalmologic examinations are necessary for several weeks to evaluate for the onset of glaucoma, which occurs in up to 11% of cases.¹¹⁵ Topical beta-receptor antagonists (timolol, levobunolol), α_2 receptor antagonists (brimonidine, iopidine) and parasympathetics (pilocarpine) may reduce intraocular pressures. Surgical intervention with trabeculectomy or laser trabeculoplasty may be necessary in severe cases. Patients should be followed for several weeks for signs of cardiac decompensation, cardiogenic and noncardiogenic pulmonary edema, and pericardial effusion. Digitalis and diuretics may improve the outcome of cardiovascular manifestations depending on the cause of reduced cardiac output (e.g., pericardial effusion or right-sided heart failure). Full recovery generally occurs within 3 weeks to 3 months, with a 5% mortality rate.¹¹⁶

EOSINOPHILIA-MYALGIA SYNDROME

HISTORY

In 1980, Sternberg et al. reported a scleroderma-like illness with eosinophilia in a patient treated with L-5-

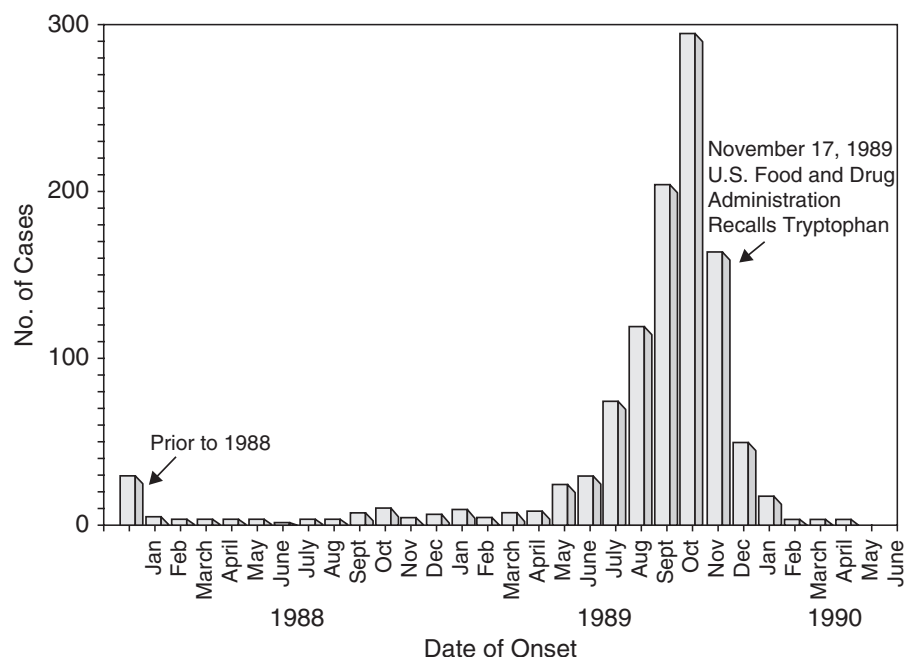


FIGURE 1.4. Onset of cases of eosinophilia-myalgia syndrome, 1988–1990. From Philen RM, et al. Toxic oil syndrome and eosinophilia-myalgia syndrome: May 8–10, 1991, World Health Organization Meeting Report. *Semin Arthritis Rheum* 1993;23:108. Reprinted with permission from Elsevier.

hydroxytryptophan and carbidopa.¹¹⁷ In the fall of 1989, the worldwide outbreak (United States, Canada, Germany, United Kingdom) of a disease with clinical features (eosinophilia, myalgias) similar to toxic oil syndrome appeared, primarily in the United States.¹¹⁸ This disease was subsequently called eosinophilia-myalgia syndrome. The first reported cases of myalgia and eosinophilia associated with L-tryptophan use occurred in three patients from New Mexico.¹¹⁹ The disease subsequently affected at least 1,500 people with about 30–40 deaths. Figure 1.4 displays the onset of cases of eosinophilia-myalgia syndrome during the 1989–1990 epidemic.

Typically, patients developed intense myalgias, peripheral eosinophilia, and dermatological lesions. The onset of eosinophilia-myalgia syndrome was associated *mostly* with the ingestion of contaminated L-tryptophan manufactured by a single Japanese manufacturer (Showa Denko K.K., Tokyo, Japan).¹²⁰ Case reviews of patients who ingested L-tryptophan produced by other manufacturers (e.g., Optimax®, Merck & Co., Inc., Whitehouse Station, NJ) did not support the diagnosis of eosinophilia-myalgia syndrome in these patients.¹²¹ Since 1991, the current surveillance system has detected a few cases of eosinophilia-myalgia syndrome. The occurrence of nontryptophan-related cases of eosinophilic-myalgia

syndrome now is similar to the rate before the 1989–1990 epidemic.¹²²

EXPOSURE

Source

To date, analysis of case-associated L-tryptophan from Showa Denko revealed the following six contaminants: peak AAA, (undefined); peak E, (1,1'-ethylidenebis[L-tryptophan]); peak 200, [2-(3-indolylmethyl)-L-tryptophan], peak C, (3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2-3b]-indole-2-carboxylic acid); peak FF, [2-(2-hydroxy-indoline)-L-tryptophan]; and peak UV-5, [3-(N-phenylamino)-L-alanine].^{123,124} The concentrations of these compounds in the L-tryptophan preparations were very low, and these concentrations did not exceed purity specification for the United States Pharmacopeia. Analysis of aniline-contaminated rapeseed oil from the toxic oil syndrome suggested a *possible* link between toxic oil syndrome and eosinophilia-myalgia syndrome, based on the structural similarity between the latter contaminant [3-(N-phenylamino)-L-alanine] and 3-(N-phenylamino)-1,2-propanediol in contaminated rapeseed oil.¹²⁵ Rodent studies indicate that metabolism of 3-(N-phenylamino)-1,2-propanediol

produces 3-(*N*-phenylamino)-L-alanine.^{126,127} *In vitro* studies suggest that the biotransformation of 3-(*N*-phenylamino)-L-alanine by human liver microsomes produces a toxic metabolite (4-aminophenol) similar to the metabolism of the toxic biomarker (3-(*N*-phenylamino)-1,2-propanediol) associated with toxic oil syndrome.¹²⁸ Potentially, the formation of this toxic metabolite causes the release of hazardous carbonyl species. However, animal studies have not reproduced eosinophilia-myalgia syndrome following administration of implicated tryptophan lots or case-associated contaminants (peak E, peak UV-5).¹²⁹ Consequently, the identities of the responsible contaminant or contaminants remain unconfirmed. Isolated case reports have associated eosinophilia-myalgia syndrome with the ingestion of 5-hydroxytryptophan and lysine unrelated to the L-tryptophan associated with eosinophilia-myalgia syndrome.^{130,131} The inability to identify specific contaminants in cases of eosinophilia-myalgia syndrome and the lack of dose-response relationships between L-tryptophan and eosinophilia-myalgia syndrome suggests that the cause of eosinophilia-myalgia syndrome is multifactorial.¹³² The cause of eosinophilia-myalgia syndrome remains controversial.¹³³

Food Processing

The association of eosinophilia-myalgia syndrome with the ingestion of L-tryptophan from a single Japanese company suggests that contamination of the L-tryptophan products occurred during the fermentation process with genetically modified strains of *Bacillus amyloliquefaciens*.¹³⁴ This manufacturer purified and isolated the tryptophan from the fermentation broth by using ion exchange resins followed by processing through an activated charcoal column prior to crystallization of the product. Before the epidemic of eosinophilia-myalgia syndrome, the fermentation and purification processes underwent several modifications including a reduction in the amount of activated charcoal and a change to *B. amyloliquefaciens* strain V.¹³⁵

DOSE RESPONSE

The risk of developing eosinophilia-myalgia syndrome increased with increased consumption of L-tryptophan Showa Denko products, suggesting a dose-response effect. In a cohort of 157 individuals from a psychiatric practice using Showa Denko L-tryptophan, the number of patients developing definite eosinophilia-myalgia syndrome increased from 13% in persons using 250 mg–1500 mg/daily to 50% in persons receiving >4,000 mg/daily.¹³⁶

CLINICAL RESPONSE

Following the index cases of eosinophilia-myalgia syndrome in New Mexico, the US Centers for Disease Control (CDC) established a voluntary national surveillance system to monitor the course of eosinophilia-myalgia syndrome. The CDC defined a case of eosinophilia-myalgia syndrome as follows: 1) peripheral eosinophil count $\geq 1,000$ cells/mm³, 2) generalized myalgias severe enough to disrupt the patient's usual daily activities, and 3) absence of any infection or neoplasm that accounts for the patient's symptoms.¹³⁷ Based on this relatively specific case definition, two case-control studies linked the ingestion of Showa Denko L-tryptophan with the development of eosinophilia-myalgia syndrome.^{137,138} Although most authors accept the causal link between contaminated L-tryptophan and eosinophilia-myalgia syndrome, these studies have been criticized for methodological flaws including diagnostic, recall and reporting biases, bias in the inclusion and exclusion of cases and controls, inequalities between cases and controls, failure to ensure that L-tryptophan exposure preceded the illness, and failure to exclude other illness.^{139,140}

The onset of eosinophilia-myalgia syndrome occurs over days to weeks, primarily in Caucasian, middle-aged women. Clinical features associated with eosinophilia-myalgia syndrome include diffuse myalgias, fatigue, headache, skin lesions (peau d'orange, fasciitis, erythematous, maculopapular rash), sicca syndrome, and sensorimotor neuropathy. These effects are similar to, but less intense than the clinical features associated with the toxic oil syndrome. For most patients, the acute phase begins with the abrupt onset of intense myalgias and peripheral blood eosinophilia along with variable degrees of weakness, edema, cough, dyspnea, paresthesias, and induration. The fingers and toes are spared, and the myalgias and weakness typically involved the proximal muscles. After a few weeks to several months, a chronic phase develops, manifest by persistent myalgias, peripheral neuropathy, cognitive dysfunction, and varying degrees of dermal sclerosis. Follow-up studies of patients with eosinophilia-myalgia syndrome suggest that the number and severity of symptoms diminishes with time.¹⁴¹ Although most patients remain symptomatic, a few patients develop new symptoms one year after onset of the disease.¹⁴² Histological features of eosinophilia-myalgia syndrome include increased collagen deposition and perivascular accumulation of eosinophils, plasma cells, and lymphocytes in affected tissue. The differential diagnosis of eosinophilia-myalgia syndrome includes relatively rare diseases, such as eosinophilic myositis, Churg–Strauss syndrome, Loeffler's syndrome, hypereosinophilic syndrome, eosinophilic gastroenteritis, and toxic oil syndrome.

DIAGNOSTIC TESTING

Analytical Methods

Methods to detect and quantify contaminants in L-tryptophan preparations include high performance liquid chromatography (HPLC),¹⁴³ reversed phase HPLC (RP/HPLC),¹⁴⁴ and RP/HPLC with online ultra-violet detection and mass spectrometry.¹⁴⁵ The limit of detection of 1,1'-ethylidenebis(L-tryptophan) using RP/HPLC was 0.6 µg/g.

Biomarkers

Although at least six contaminants are associated with eosinophilia-myalgia syndrome, a specific contaminant responsible for eosinophilia-myalgia syndrome has not been identified. Therefore, to date there are no unique biomarkers for this disease.

Abnormalities

Case reports associated elevated serum aldolase, increased serum hepatic aminotransferases, and less frequently elevated serum creatine kinase concentrations with eosinophilia-myalgia syndrome. Antinuclear antibodies with a speckled pattern are occasionally detected. Marked peripheral eosinophilia may occur in the absence of symptoms.

TREATMENT

Treatment is supportive.

References

1. Biberoglu S, Biberoglu K, Komsuoglu G. Mad honey. *JAMA* 1988;259:1943.
2. Head T, Landes R. The peace of God: social violence and religious response in France around the year 1000. *Speculum* 1994;69:163–169.
3. Woolf A. Witchcraft or mycotoxin? The Salem witch trials. *J Toxicol Clin Toxicol* 2000;38:457–460.
4. Emmerson BT. “Ouch-ouch” disease: The osteomalacia of cadmium nephropathy. *Ann Intern Med* 1970;73:854–855.
5. Bakir F, Damluji SF, Amin-Zaki L, Murtadha M, Khalidi A, Al-Rawi NY, et al. Methyl mercury poisoning in Iraq. *Science* 1973;181:230–241.
6. Smith HV, Spalding JM. Outbreak of paralysis in Morocco due to ortho-cresyl phosphate poisoning. *Lancet* 1959;2:1019–1021.
7. Kuratsune M, Yoshimura T, Matsuzaka J, Yamaguchi A. Epidemiologic study of polychlorinated biphenyls. *Environ Health Perspect* 1972;1:119–128.
8. Chen PH, Wong CK, Rappe C, Nygren M. Polychlorinated biphenyls, dibenzofurans and quaterphenyls in toxic rice-bran oil and in the blood and tissues of patients with PCB poisoning (Yu-cheng) in Taiwan. *Environ Health Perspect* 1985;59:59–65.
9. Kuratsune M, Yoshimura H, Hori Y, Okumura M, Matsuda Y. Yusho—a human disaster caused by PCB and related compounds. Fukuoka: Kyushu University Press; 1996.
10. Yoshimura T. Yusho in Japan. *Ind Health* 2003;41:139–148.
11. Kunita N, Kashimoto T, Miyata H, Fukushima S, Hori S, Obana H. Causal agents of yusho. *Prog Clin Biol Res* 1984;137:45–58.
12. Kashimoto T, Miyata H, Fukushima S, Kunita N, Ohi G, Tung TC. PCBs, PCQs and PCDFs in the blood of Yusho and Yu-cheng patients. *Environ Health Perspect* 1985;59:73–78.
13. Guo YL, Lambert HG, Hsu C-C, Hsu MM. Yucheng: health effects of prenatal exposure to polychlorinated biphenyls and dibenzofurans. *Int Arch Occup Environ Health* 2004;77:153–158.
14. Asahi M. Clinical features and pathogenesis of Yusho (PCB poisoning). *J Univ Occup Environ Health* 1993;15:1–11.
15. Yoshimura T. Epidemiological analysis of “yusho” patients with special reference to sex, age, clinical grades and oil consumption. *Fukuoka Acta Medica* 1971;62:104–108.
16. Hayabuchi H, Yoshimura T, Kuratsune M. Consumption of toxic rice oil by Yusho patients and its relation to the clinical response and latent period. *Food Cosmet Toxicol* 1979;17:455–461.
17. Miyata H, Fukushima S, Kashimoto T, Kunita N. PCBs, PCQs and PCDFs in tissues of yusho and yu-cheng patients. *Environ Health Perspect* 1985;59:67–72.
18. Yoshimura T, Hayabuchi H. Relationship between the amount of rice oil ingested by patients with yusho and their subjective symptoms. *Environ Health Perspect* 1985;59:47–51.
19. Masuda Y. Health status of Japanese and Taiwanese after exposure to contaminated rice oil. *Environ Health Perspect* 1985;60:321–325.
20. Norback DH, Weltman RH. Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. *Environ Health Perspect* 1985;60:97–105.
21. Hirota Y, Tokunaga S, Kataoka K, Shinohara S. Symptoms and blood PCB level among chronic yusho patients, twenty-five years after outbreak. *Fukuoka Igaku Zasshi* 1997;88:220–225.
22. Yoshimura T. Epidemiological study on yusho babies born to mothers who had consumed oil contaminated by PCB. *Fukuoka Acta Medica* 1974;65:74–80.

23. Lu YC, Wong PN. Dermatological, medical, and laboratory findings of patients in Taiwan and their treatments. *Am J Ind Med* 1984;5:81–115.
24. Fein GG, Jacobson JL, Jacobson SW, Schwartz PM, Dowler JK. Prenatal exposure to polychlorinated biphenyls: effects on birth size and gestational age. *J Pediatrics* 1984;105:315–320.
25. Gladen BC, Rogan WJ. Decrements on six month and one-year Bayley scores and prenatal polychlorinated biphenyls (PCB) exposure. *Am J Epidemiol* 1988;128:912.
26. Yang C-Y, Yu M-L, Guo M-L, Lai T-J, Hsu C-C, Lambert G, Guo YL. The endocrine and reproductive function of the female yu-cheng adolescents prenatally exposed to PCBs/PCDFs. *Chemosphere* 2005;61:355–360.
27. Jacobson SW, Fein GG, Jacobson JL, Schwartz PM, Dowler JK. The effect of intrauterine PCB exposure on visual recognition memory. *Child Dev* 1985;56:853–860.
28. Rogan WJ, Gladen BC, Hung KL, Koong SL, Shih LY, Taylor JS, et al. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. *Science* 1988;241:334–336.
29. Tsai PC, Ko YC, Huang W, Liu HS, Guo YL. Increased liver and lupus mortalities in 24-year follow-up of the Taiwanese people highly exposed to polychlorinated biphenyls and dibenzofurans. *Sci Total Environ* 2007;374:216–222.
30. Hori T, Tobiishi K, Ashizuka Y, Nakagawa R, Todaka T, Hirakawa H, Iida T. Congener specific determination of PCBs in human blood using gel permeation chromatography (GPC) and high resolution gas chromatography/high resolution mass spectrometry (HRGC/HRMS). *Fukuoka Igaku Zasshi* 2005;96:220–226.
31. Calaf RE, Pena J, Paytubi S, Blount BC, Posada de la Paz M, Gelpi E, et al. Determination of aniline derivatives in oils related to the toxic oil syndrome by atmospheric pressure ionization-tandem mass spectrometry. *Anal Chem* 2001;73:3828–3837.
32. Chen PH, Luo ML, Wong CK, Chen CJ. Polychlorinated biphenyls, dibenzofurans, and quaterphenyls in the toxic rice-bran oil and PCBs in the blood of patients with PCB poisoning in Taiwan. *Am J Ind Med* 1984;5:133–145.
33. Nagayama J, Masuda Y, Kuratsune M. Determination of polychlorinated dibenzofurans in tissues of patients with Yusho. *Food Cosmet Toxicol* 1977;15:195–198.
34. Lung S-C, Guo Y-L, Chang H-Y. Serum concentrations and profiles of polychlorinated biphenyls in Taiwan Yu-cheng victims twenty years after the incident. *Environ Pollut* 2005;136:71–79.
35. Ryan JJ, Levesque D, Panopio LG, Sun WF, Masuda Y, Kuroki H. Elimination of polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) from human blood in the yusho and yu-cheng rice oil poisonings. *Arch Environ Contam Toxicol* 1993;24:504–512.
36. Imamura T, Kanagawa Y, Matsumoto S, Tajima B, Uenotsuchi T, Shibata S, Furue M. Relationship between clinical features and blood levels of pentachlorodibenzofuran in patients with yusho. *Environ Toxicol* 2007;22:124–131.
37. Todaka T, Hirakawa H, Hori T, Tobiishi K, Iida T, Furue M. Concentrations of polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, and non-*ortho* and mono-*ortho* polychlorinated biphenyls in the blood of Yusho patients. *Chemosphere* 2007;66:1983–1989.
38. Masuda Y, Yoshimura H. Polychlorinated biphenyls and dibenzofurans in patients with yusho and their toxicological significance: a review. *Am J Ind Med* 1984;5:31–44.
39. Posada de la Paz M, Philen RM, Abaitua Borda I. Toxic oil syndrome: The perspective after 20 years. *Epidemiol Rev* 2001;23:231–247.
40. Posada de la Paz M, Philen RM, Abaitua Borda I, Bernert JT Jr, Gancedo JC, DuClos PJ, Kilbourne EM. Manufacturing processes at two French rapeseed oil companies: possible relationships to toxic oil syndrome in Spain. *Food Chem Toxicol* 1991;29:797–803.
41. Rigau-Perez JG, Perez-Alvarez L, Duenas-Castro S, Choi K, Thacker SB, Germain JL, et al. Epidemiologic investigation of an oil-associated pneumonic paralytic eosinophilic syndrome in Spain. *Am J Epidemiol* 1984;119:250–260.
42. Posada M, Castro M, Kilbourne EM, Diaz de Rojas F, Abaitua I, Tabuenca JM, et al. Toxic-oil syndrome: case reports associated with the ITH oil refinery in Seville. *Food Chem Toxicol* 1987;25:87–90.
43. Reig N, Calaf RE, Messeguer A, Morató A, Escabros J, Gelpi E, Abian J. LC-MS ion maps for the characterization of aniline derivatives of fatty acids and triglycerides in laboratory-denatured rapeseed oil. *J Mass Spectrom* 2007;42:527–541.
44. Hard GC. Short-term adverse effects in humans of ingested mineral oils, their additives and possible contaminants—a review. *Hum Exp Toxicol* 2000;19:158–172.
45. Closa D, Folch E, Calaf RE, Abian J, Rosello-Catafau J, Gelpi E. Absorption and effects of 3-(*N*-phenylamino)-1,2-propanediol esters in relation to toxic oil syndrome. *Lipids* 2001;36:1125–1133.
46. Guitart R, Norgaard L, Abaitua Borda I, Posada de la Paz M, Abian J, Gelpi E. Pentachlorophenol and pentachloroanisole in oil samples associated with the toxic oil syndrome. *Bull Environ Contam Toxicol* 1999;62:1–7.
47. Morato A, Escabros J, Manich A, Reig N, Castano Y, Abian J, Messeguer A. On the generation and outcome of 3-(*N*-phenylamino)propane-1,2-diol derivatives in deodorized model oils related to toxic oil syndrome. *Chem Res Toxicol* 2005;18:665–674.
48. Ruiz-Mendez MV, Posada de la Paz M, Abian J, Calaf RE, Blount B, Castro-Molero N, et al. Storage time and deodorization temperature influence the formation of aniline-derived compounds in denatured rapeseed oils. *Food Chem Toxicol* 2001;39:91–96.

49. Posada de la Paz M, Abaitua Borda I, Kilbourne EM, Tabuenca Oliver JM, Diaz de Rojas F, Castro Garcia M. Late cases of toxic oil syndrome: evidence that the aetiological agent persisted in oil stored for up to one year. *Food Chem Toxicol* 1989;27:517–521.
50. Kilbourne EM, Bernert JT Jr, Posada de la Paz M, Hill RH Jr, Abaitua Borda I, Kilbourne BW, et al. Chemical correlates of pathogenicity of oils related to the toxic oil syndrome epidemic in Spain. *Am J Epidemiol* 1988;127:1210–1227.
51. Doll R. The aetiology of the Spanish Toxic Syndrome: interpretation of the epidemiological evidence. SPA/CEH 502. Copenhagen, Denmark: World Health Organization; 1985.
52. Tabuenca JM. Toxic-allergic syndrome caused by ingestion of rapeseed oil denatured with aniline. *Lancet* 1981;2:567–568.
53. Grandjean P, Tarkowsky S. Review of investigations and findings. In: World Health Organization: Toxic Oil Syndrome: Mass food poisoning in Spain. 1st ed. Copenhagen, Denmark: WHO, Regional Office for Europe; 1984:3–16.
54. World Health Organization. Report on the 21st Meeting of the WHO/FIS Scientific Committee for the Toxic Oil Syndrome. Copenhagen, Denmark: WHO; 1997.
55. Abaitua Borda I, Philen RM, Posada de la Paz M, Gomez de la Camara A, Diez Ruiz-Navarro M, Gimenez Ribota O, et al. Toxic oil syndrome mortality: the first 13 years. *Int J Epidemiol* 1998;27:1057–1063.
56. Diaz de Rojas F, Castro Garcia M, Abaitua Borda I, Alonso Gordo JM, Posada de la Paz M, Kilbourne EM, Tabuenca Oliver JM. The association of oil ingestion with toxic oil syndrome in two convents. *Am J Epidemiol* 1987;125:907–911.
57. Kaufman LD, Krupp LB. Eosinophilia-myalgia syndrome, toxic-oil syndrome, and diffuse fasciitis with eosinophilia. *Curr Opin Rheumatol* 1995;7:560–567.
58. Kilbourne EM, Rigau-Perez JG, Heath CW Jr, Zack MM, Falk H, Martin-Marcos M, et al. Clinical epidemiology of toxic-oil syndrome. Manifestations of a new illness. *N Engl J Med* 1983;309:1408–1414.
59. Martinez-Tello FJ, Navas-Palacios JJ, Ricoy JR, Gil-Martin R, Conde-Zurita JM, Colina-Ruiz Delgado F, et al. Pathology of a new toxic syndrome caused by ingestion of adulterated oil in Spain. *Virchows Arch A Pathol Anat Histol* 1982;397:261–285.
60. Alonso-Ruiz A, Zea-Mendoza AC, Salazar-Vallinas JM, Rocamora-Ripoll A, Beltran-Gutierrez J. Toxic oil syndrome: a syndrome with features overlapping those of various forms of scleroderma. *Semin Arthritis Rheum* 1986;15:200–212.
61. Escribano PM, Diaz de Atauri MJ, Gomez Sanchez MA. Persistence of respiratory abnormalities four years after the onset of toxic oil syndrome. *Chest* 1991;100:336–339.
62. James TN, Posada de la Paz M, Abaitua Borda I, Gomez Sanchez A, Martinez Tello FJ, Soldevilla LB. Histologic abnormalities of large and small coronary arteries, neural structures, and the conduction system of the heart found in postmortem studies of individuals dying from the toxic oil syndrome. *Am Heart J* 1991;121:803–815.
63. Abaitua Borda I, Kilbourne EM, Posada de la Paz M, Diez Ruiz-Navarro M, Gabriel Sanchez R, Falk H. Mortality among people affected by toxic oil syndrome. *Int J Epidemiol* 1993;22:1077–1084.
64. Tello de Meneses R, Gomez de la Camara A, Nogales-Moran MA, Escribano-Subias P, Barainca-Oyague MT, Gomez-Sanchez MA, et al. Pulmonary hypertension during exercise in toxic oil syndrome. *Med Clin Barc* 2005;19:685–688.
65. Martin-Arribas MC, De Andres Copa P, De La Paz MP. Quality of life, disability and handicap in patients with toxic oil syndrome. *J Adv Nurs* 2005;50:595–604.
66. Gomez de la Camara A, Posada de la Paz M, Abaitua Borda I, Barainca Oyague MT, Abaira Santos V, Ruiz-Navarro MD, et al. Heath status measurement in toxic oil syndrome. *J Clin Epidemiol* 1998;51:867–873.
67. Cardaba B, Gallardo S, Del Pozo V, Ezendam J, Izquierdo M, Martin C, et al. DR2 antigens are associated with severity of disease in toxic oil syndrome (TOS). *Tissue Antigens* 2000;55:110–117.
68. ladona MG, Izquierdo-Martinez M, Posada de La Paz MP, De La Torre R, Ampurdanes C, Segura J, et al. Pharmacogenetic profile of xenobiotic enzyme metabolism in survivors of the Spanish toxic oil syndrome. *Environ Health Perspect* 2001;109:369–375.
69. Hill RH Jr, Schurz HH, Posada de la Paz M, Abaitua Borda I, Philen RM, Kilbourne EM, et al. Possible etiologic agents for toxic oil syndrome: fatty acid esters of 3-(*N*-phenylamino)-1,2-propanediol. *Arch Environ Contam Toxicol* 1995;28:259–264.
70. Posada de la Paz M, Philen RM, Abaitua Borda I, Diez Ruiz-Navarro M, Abaira Santos V, Pozo Rodriguez F, et al. Factors associated with pathogenicity of oils related to the toxic oil syndrome epidemic in Spain. *Epidemiology* 1994;5:404–409.
71. Posada de la Paz M, Philen RM, Schurz H, Hill RH Jr, Gimenez Ribota O, Gomez de la Camara A, et al. Epidemiologic evidence for a new class of compounds associated with toxic oil syndrome. *Epidemiology* 1999;10:130–134.
72. Martinez-Cabot A, Morato A, Messeguer A. Synthesis and stability studies of the glutathione and *N*-acetylcysteine adducts of an iminoquinone reactive intermediate generated in the biotransformation of 3-(*N*-phenylamino)propane-1,2-diol: implications for toxic oil syndrome. *Chem Res Toxicol* 2005;18:1721–1728.
73. Gallardo S, Cardaba B, del Pozo V, De Andres B, Cortegano I, Jurado A, et al. Study of apoptosis in human lymphocytes by toxic substances implicated in toxic oil syndrome. *Toxicol* 1997;118:71–82.
74. Gallardo S, Cardaba B, Posada M, del Pozo V, Messeguer A, David CS, et al. Toxic oil syndrome: genetic restriction

- and immunomodulatory effects due to adulterated oils in a model of HLA transgenic mice. *Toxicol Lett* 2005;159:173–181.
75. Hayashi T, James TN. Immunohistochemical analysis of lymphocytes in postmortem study of the heart from fatal cases of the eosinophilia myalgia syndrome and of the toxic oil syndrome. *Am Heart J* 1994;127:1298–1308.
 76. Esteban A, Guerra L, Ruiz-Santana S, Fernandez A, Fernandez-Segoviano P. ARDS due to ingestion of denatured rapeseed oil. *Chest* 1983;84:166–169.
 77. Gelpi E, de la Paz MP, Terracini B, Abaitua I, De La Camara AG, Kilbourne EM, et al. WHO/CISAT Scientific Committee for the Toxic Oil Syndrome, Centro de Investigacion para el Sindrome del Aceite Toxico: The Spanish toxic oil syndrome 20 years after its onset: a multidisciplinary review of scientific knowledge. *Environ Health Perspect* 2002;110:457–464.
 78. Gomez-Sanchez MA, Mestre de Juan MJ, Gomez-Pajuelo C, Lopez JJ, Diaz de Atauri MJ, Martinez-Tello FJ. Pulmonary hypertension due to toxic oil syndrome. A clinicopathologic study. *Chest* 1989;95:325–331.
 79. Gomez de la Camara A, Gomez Mateos MA, Ferrando Vivas P, Barianca Oyague MT, Abaitua Borda I, Posada de la Paz M. Prevalence of cardiovascular risk factors in a cohort affected by the toxic oil syndrome. *Med Clin Barc* 2003;121:405–407. [Spanish]
 80. Plaza Cano MM, Garcia de Albeniz Martinez XA, De Andres Copa P, Braun Saro B, Suarez Alvarez C, Garcia De Aguinaga ML, et al. Diagnostic performance of echocardiography in the follow-up of patients with toxic oil syndrome. *Rev Esp Cardiol* 2003;56:1195–1201.
 81. Kaufman LD, Krupp LB. Eosinophilia-myalgia syndrome, toxic-oil syndrome, and diffuse fasciitis with eosinophilia. *Curr Opin Rheumatol* 1995;7:560–567.
 82. Sanchez-Porro Valades P, Posada de la Paz M, de Andres Copa P, Gimenez Ribota O, Abaitua Borda I. Toxic oil syndrome: survival in the whole cohort between 1981 and 1995. *J Clin Epidemiol* 2003;56:701–708.
 83. Lyon IB. Textbook of medical jurisprudence of India. 1st ed. Calcutta, India: Thacker, Spink & Company; 1889:214.
 84. Gomber S, Daral TS, Sharma PP, Faridi MM. Resurgence of epidemic dropsy. *Indian Pediatr* 1997;34:953–957.
 85. Khanna SK, Upreti KK, Singh GB. Trend of adulteration of mustard oil in rural markets of Uttar Pradesh. *Sci Cult* 1986;52:149–156.
 86. Verma SK, Dev G, Tyagi AK, Goomber S, Jain GV. Argemone mexicana poisoning: autopsy findings of two cases. *Forensic Sci Int* 2001;115:135–141.
 87. Newton SM, Lau C, Gurcha SS, Besra GS, Wright CW. The evaluation of forty-three plant species for *in vitro* antimycobacterial activities; isolation of active constituents from *Psoralea corylifolia* and *Sanguinaria canadensis*. *J Ethnopharmacol* 2002;79:57–67.
 88. Chakravarty NK, Chaudhuri RN, Werner G. Observations on vascular changes produced by *Argemone* alkaloids. *Indian J Med Res* 1955;43:107–112.
 89. Tandon S, Das M, Khanna SK. Biometabolic elimination and organ retention profile of *Argemone* alkaloid, sanguinarine, in rats and guinea pigs. *Drug Metab Disp* 1993;21:194–197.
 90. Pitts BJR, Meyerson LR. Inhibition of Na⁺-K⁺-ATPase activity and ouabain binding of sanguinarine. *Drug Dev Res* 1981;1:43–47.
 91. Upreti KK, Das M, Khanna SK. Biochemical toxicology of argemone oil: effect on hepatic cytochrome P-450 and xenobiotic metabolizing enzymes. *J Appl Toxicol* 1991;11:203–209.
 92. Upreti KK, Das M, Kumar A, Singh GB, Khanna SK. Biochemical toxicology of argemone oil. IV. Short-term oral feeding response in rats. *Toxicol* 1989;58:285–298.
 93. Tandon S, Das M, Khanna SK. Effect of sanguinarine on the transport of essential nutrients in an everted gut sac model: role of Na⁺-K⁺-ATPase. *Nat Toxins* 1993;1:235–240.
 94. Das M, Babu K, Reddy NP, Srivastava LM. Oxidative damage of plasma proteins and lipids in epidemic dropsy patients: alterations in antioxidant status. *Biochim Biophys Acta* 2005;1722:209–217.
 95. Lal RB, Dasgupta AC. Investigation into epidemiology of epidemic dropsy X: a note on an outbreak of epidemic dropsy associated with the use of mustard oil pressed from adulterated seed. *Indian J Med Res* 1941;29:157–163.
 96. Das M, Khanna SK. Clinicoepidemiological, toxicological, and safety evaluation studies on argemone oil. *Crit Rev Toxicol* 1997;27:273–297.
 97. Kar HK, Jain RK, Sharma PK, Gautam RK, Kumar P, Bhardwaj M. Epidemic dropsy: a study of cutaneous manifestations with histopathological correlation. *Indian J Venereol Leprol* 2001;67:178–179.
 98. Sood NN, Sachdev MS, Verma LK. Pressure dynamics and treatment modalities of epidemic dropsy glaucoma. *Glaucoma* 1990;12:20–27.
 99. Sachdev HP, Sachdev MS, Verma L, Sood NN, Moonis M. Electrophysiological studies of the eye, peripheral nerves and muscles in epidemic dropsy. *J Trop Med Hyg* 1989;92:412–415.
 100. Sharma BD, Bhatia V, Rahtee M, Kumar R, Mukharjee A. Epidemic dropsy: observations on pathophysiology and clinical features during the Delhi epidemic of 1998. *Trop Doct* 2002;32:70–75.
 101. Singh K, Singh MJ, Das JC. Visual field defects in epidemic dropsy. *Clin Toxicol* 2006;44:159–163.
 102. Singh NP, Anuradha S, Dhanwal DK, Singh K, Prakash A, Madan K, Agarwal SK. Epidemic dropsy—a clinical study of the Delhi outbreak. *J Assoc Physicians India* 2000;48:877–880.
 103. Sachdev MS, Sood NN, Verma LK, Gupta SK, Jaffery NF. Pathogenesis of epidemic dropsy glaucoma. *Arch Ophthalmol* 1988;106:1221–1223.
 104. Malik KP, Dadeya S, Gupta VS, Sharan P, Guliani, Dhawan M. Pattern of intraocular pressure in epidemic dropsy in India. *Trop Doct* 2004;34:161–162.

105. Prakash J. Acute renal failure in epidemic dropsy. *Renal Failure* 1999;21:707–711.
106. Tandon RK, Tandon HD, Nayak NC, Tandon BN. Liver in epidemic dropsy. *Ind J Med Res* 1976;64:1064–1069.
107. Senegupta PC, Napier LE. Haematological changes in epidemic dropsy. *Ind J Med Res* 1940;28:197–203.
108. Chopra RN, Basu VP. Cardiovascular manifestations of epidemic dropsy and their treatment. *Ind Med Gaz* 1980;65:546–550.
109. Singh GB, Khanna SK. Argemone mexicana strikes again. *Sci Rep* 1983;20:108–110.
110. Husain S, Narsimha R, Rao RN. Separation, identification and determination of sanguinarine in argemone and other adulterated edible oils by reversed-phase high-performance liquid chromatography. *J Chromatogr Anal* 1999;863:123–126.
111. Tandon RK, Singh DS, Arora RR, Lal P, Tandon BN. Epidemic dropsy in New Delhi. *Am J Clin Nutr* 1975;28:883–887.
112. Das M, Babu K, Reddy NP, Srivastava LM. Oxidative damage of plasma proteins and lipids in epidemic dropsy patients: alterations in antioxidant status. *Biochim Biophys Acta* 2005;1722:209–217.
113. Khilnani GC, Trikha I, Malhotra OP, Prabhakaran D, Pande JN. Pulmonary functions in patients with epidemic dropsy. *Indian J Chest Dis Allied Sci* 2003;45:25–29.
114. Upreti KK, Das M, Khanna SK. Role of antioxidants and scavengers on argemone oil induced toxicity. *Arch Environ Contam Toxicol* 1991;20:531–537.
115. Singh K, Singh MJ, Das JC. Visual field defects in epidemic dropsy. *Clin Toxicol* 2006;44:159–163.
116. Sainani GS Epidemic dropsy. In: Ahuja MM, ed: *Progress in clinical medicine in India*. New Delhi, India: Arnold Heinemann Publishers, 1976:92–104.
117. Sternberg EM, Van Woert MH, Young SN, Magnussen I, Baker H, Gauthier S, Osterland CK. Development of a scleroderma-like illness during therapy with L-5-hydroxytryptophan and carbidopa. *N Engl J Med* 1980;303:782–787.
118. Swygert LA, Maes EF, Sewell LE, Miller L, Falk H, Kilbourne EM. Eosinophilia-myalgia syndrome. Results of national surveillance. *JAMA* 1990;264:1698–1703.
119. Hertzman PA, Blevins WL, Mayer J, Greenfield B, Ting M, Gleich GJ. Association of the eosinophilia-myalgia syndrome with the ingestion of tryptophan. *N Engl J Med* 1990;322:869–873.
120. Kilbourne EM, Philen RM, Kamb ML, Falk H. Tryptophan produced by Showa Denko and epidemic eosinophilia-myalgia syndrome. *J Rheumatol* 1996; 23(suppl 46):81–88.
121. McKeon P, Swanwick G, Manley P. L-Tryptophan and the eosinophilia-myalgia syndrome: a clinical and laboratory study. *Acta Psychiatr Scand* 1993;90:451–454.
122. Sullivan EA, Staehling N, Philen RM. Eosinophilia-myalgia syndrome among the non-L-tryptophan users and pre-epidemic cases. *J Rheumatol* 1996;23: 1784–1787.
123. Naylor S, Williamson BL, Johnson KL, Gleich GJ. Structural characterization of case-associated contaminants peak C and FF in L-tryptophan implicated in eosinophilia-myalgia syndrome. *Adv Exp Med Biol* 1999;467:453–460.
124. Hill RH Jr, Caudill SP, Philen RM, Bailey SL, Flanders WD, Driskell WJ. Contaminants in L-tryptophan associated with eosinophilia myalgia syndrome. *Arch Environ Contam Toxicol* 1993;25:134–142.
125. Philen RM, Posada M. Toxic oil syndrome and eosinophilia-myalgia syndrome: May 8–10, 1991, World Health Organization Meeting Report. *Semin Arthritis Rheum* 1993;23:104–124.
126. Philen RM, Hill RH Jr, Flanders WD, Caudill SP, Needham L, Sewell L, et al. Tryptophan contaminants associated with eosinophilia-myalgia syndrome. *Am J Epidemiol* 1993;138:154–159.
127. Mayeno AN, Benson LM, Naylor S, Colberg-Beers M, Puchalski JT, Gleich GJ. Biotransformation of 3-(phenylamino)-1,2-propanediol to 3-(phenylamino)alanine: a chemical link between toxic oil syndrome and eosinophilia-myalgia syndrome. *Chem Res Toxicol* 1995; 8:911–916.
128. Martinez-Cabot A, Messegue A. Generation of quino-neimine intermediates in the bioactivation of 3-(N-phenylamino)alanine (PAA) by human liver microsomes: a potential link between eosinophilia-myalgia syndrome and toxic oil syndrome. *Chem Res Toxicol* 2007; 20:1556–1562.
129. Sato F, Hagiwara Y, Kawase Y. Subchronic toxicity of 3-phenylamino alanine, an impurity in L-tryptophan reported to be associated with eosinophilia-myalgia syndrome. *Arch Toxicol* 1995;69:444–449.
130. Patmas MA. Eosinophilia-myalgia syndrome not associated with L-tryptophan. *N J Med* 1992;89:285–286.
131. Michelson D, Page SW, Casey R, Trucksess MW, Love LA, Milstien S, et al. An eosinophilia-myalgia syndrome related disorder associated with exposure to L-5-hydroxytryptophan. *J Rheumatol* 1994;21:2261–2265.
132. Martin RW, Duffy J, Engel AG, Lie JT, Bowles CA, Moyer TP, Gleich GJ. The clinical spectrum of the eosinophilia-myalgia syndrome associated with L-tryptophan ingestion. Clinical features in 20 patients and aspects of pathophysiology. *Ann Intern Med* 1990;113:124–134.
133. Smith MJ, Garrett RH. A heretofore undisclosed crux of eosinophilia-myalgia syndrome: compromised histamine degradation. *Inflamm Res* 2005;54:435–450.
134. Slutsker L, Hoesly FC, Miller L, Williams LP, Watson JC, Fleming DW. Eosinophilia-myalgia syndrome associated with exposure to tryptophan from a single manufacturer. *JAMA* 1990;264:213–217.
135. Belongia EA, Hedberg CW, Gleich GJ, White KE, Mayeno AN, Loegering DA. An investigation of the

- cause of the eosinophilia-myalgia syndrome associated with tryptophan use. *N Engl J Med* 1990;323:357–365.
136. Kamb ML, Murphy JJ, Jones JL, Caston JC, Nederlof K, Horney LF. Eosinophilia-myalgia syndrome in L-tryptophan-exposed patients. *JAMA* 1992;267:77–82.
 137. Centers for Disease Control. Eosinophilia-myalgia syndrome and L-tryptophan-containing products—New Mexico, Minnesota, Oregon, New York, 1989. *MMWR Morb Mortal Wkly Rep* 1989;38:785–788.
 138. Eidson M, Philen RM, Sewell CM, Voorhees R, Kilbourne EM. L-Tryptophan and eosinophilia-myalgia syndrome in New Mexico. *Lancet* 1990;335:645–648.
 139. Shapiro S. Epidemiologic studies of the association of L-tryptophan with the eosinophilia-myalgia syndrome: a critique. *J Rheumatol* 1996;23(suppl 46):44–59.
 140. Horwitz RI, Daniels SR. Bias or biology: evaluating the epidemiologic studies of L-tryptophan and the eosinophilia-myalgia syndrome. *J Rheumatol* 1996;23(suppl 46):60–72.
 141. Sullivan EA, Kamb ML, Jones JL, Meyer P, Philen RM, Falk H, Sinks T. The natural history of eosinophilia-myalgia syndrome in a tryptophan-exposed cohort in South Carolina. *Arch Intern Med* 1996;156:973–979.
 142. Pincus T. Eosinophilia-myalgia syndrome: patient status 2–4 years after onset. *J Rheumatol Suppl* 1996;46:19–24.
 143. Meyer K, Moller A, Karg C, Steinhart H. Formation and determination of aldehyde-addition products of tryptophan. *Adv Exp Med Biol* 1996;398:711–717.
 144. Trucksess MW, Thomas FS, Page SW. High-performance liquid chromatographic determination of 1,1'-ethyldenebis(L-tryptophan) in L-tryptophan preparations. *J Pharm Sci* 1994;83:720–722.
 145. Williamson BL, Tomlinson AJ, Hurth KM, Posada de la Paz M, Gleich GJ, Naylor S. Rapid HPLC screening method for contaminants found in implicated L-tryptophan associated with eosinophilia myalgia syndrome and adulterated rapeseed oil associated with toxic oil syndrome. *Biomed Chromatogr* 1998;12:255–261.