Toxic Oil Syndrome: A Current Clinical and Epidemiologic Summary, Including Comparisons With the Eosinophilia-Myalgia Syndrome

EDWIN M. KILBOURNE, MD. MANUEL POSADA DE LA PAZ, MD.*
IGNACIO ABAITUA BORDA, MD.* MERCEDES DIEZ RUIZ-NAVARRO,*
ROSSANNE M. PHILEN, MD, MSc. HENRY FALK. MD. MPH

Atlanta, Georgia and Madrid, Spain

In the spring and summer of 1981, an epidemic of a new illness now referred to as the toxic oil syndrome occurred in central and northwestern Spain, resulting in some 20,000 cases, 12,110 hospital admissions and >300 deaths in the 1st year of the epidemic. The initial onset of illness was usually acute, and patients presented primarily with a respiratory syndrome involving cough, fever, dyspnea, hypoxemia, pulmonary infiltrates and pleural effusions. While approximately 50% of patients recovered from this acute phase of the illness without apparent sequelae, the remaining patients developed an intermediate or chronic phase, or both, of illness involving severe myalgia, eosinophilia, peripheral nerve damage, sclerodermiform skin lesions, sicca syndrome, alopecia and joint contractures, among other findings.

The toxic oil syndrome epidemic occurred in Spain in the spring and summer of 1981 and was one of the largest epidemics of an intoxication ever recorded, resulting in some 20,000 cases, 12,110 hospital admissions and >300 deaths during the 1st 12 months after the epidemic began (1-4). Information regarding the epidemiology, clinical features and etiology of the toxic oil syndrome is summarized and reviewed here, both to provide an overall perspective of this unusual disease and to provide the background information necessary for a comprehensive understanding of the reports that will follow later in this Seminar on cardiovascular manifestations of the toxic oil syndrome and related diseases. In addition, information is presented regarding the eosinophilia-myalgia syndrome, an illness resembling the toxic oil syndrome that occurred in epidemic form in the United States in 1989. The implications of this syndrome for research on the toxic oil syndrome are discussed.

Epidemiologic and analytic chemical studies have clearly linked the toxic oil syndrome to the ingestion of oil mixtures containing rapeseed oil deaerated with aniline. However, the precise identity of the etiologic agent within this oil has never been determined. Aniline itself did not cause the illness, but the causal agent may be a reaction product of aniline with some oil component. Although many aspects of disease activity in the involved patients have lessened with time, the ultimate consequences of their disease are not clear and are the subject of ongoing study. The recently described eosinophilia-myalgia syndrome in the United States clinically resembles the toxic oil syndrome.

(J Am Coll Cardiol 1991;18:711-7)

Clinical Aspects of the Toxic Oil Syndrome

The Acute or Early Phase

The toxic oil syndrome epidemic is often reported to have started on May 1, 1981, the day on which a boy from the small town of Torrejon de Ardoz, Spain was admitted to a hospital in Madrid with fulminant respiratory failure that led rapidly to death (1). Over the next several weeks, this case was followed by others in rapidly increasing numbers. So many acutely ill patients with the toxic oil syndrome presented for medical attention as to threaten to overwhelm the capacity for treatment in existing inpatient and outpatient facilities in affected areas. During the peak of case occurrence in early June, the number of new cases reported each week approached 2,000 (1.4.5).

Pulmonary involvement. Initially, clinical findings referable to the respiratory system were particularly prominent. Typically, disease manifestations included fever (usually low grade), cough, hypoxemia, pulmonary infiltrates and pleural effusions. The pulmonary infiltrates were generally bilateral and showed an interstitial radiographic pattern. Nevertheless, many severely affected patients had alveolar and interstitial/alveolar infiltrates (2.3).

Other acute manifestations. Other disease manifestations during the acute phase seemed less important than the dramatic picture of respiratory compromise affecting most patients who were seen early in the course of their illness.
(within a week or so of onset). A common accompanying clinical finding was skin rash—frequently a maculopapular erythema. However, other dermatologic presentations included malar erythema or, less frequently, a frank petechial rash. Some patients had gastrointestinal symptoms, including nausea, vomiting or diarrhea. But while such symptoms were moderately frequent, they were not a particularly prominent part of the illness. Some patients also had hepatomegaly, splenomegaly or lymphadenopathy alone or in combination. Serum immunoglobulin E was often elevated. Biochemical evidence of liver involvement was frequent, and mild to moderate elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and gamma-glutamyl transpeptidase were common. Increases in serum bilirubin were seen somewhat less frequently (1,3,6,7).

**Eosinophilia.** One of the most striking findings in all phases of the toxic oil syndrome was intense peripheral eosinophilia. Virtually all patients had absolute eosinophil counts >500 cells/mm³ but counts of >2,000/mm³ were common. Eosinophilia was so frequent as to be considered a hallmark of the disease. However, it was occasionally absent very early in a patient’s clinical course, even in the presence of substantial pulmonary abnormalities (1,3). Very often the eosinophilia was accompanied by a more general leukocytosis with a left shift, but the increase in eosinophils was disproportionately to the increase in absolute numbers of leukocytes (1,3,5,8).

The respiratory manifestations of acute toxic oil syndrome were generally more intense than those of the eosinophilia-myalgia syndrome (see later) and were frequently life-threatening. Approximately 1% of patients with the toxic oil syndrome died in the acute phase of illness, principally from respiratory failure (1).

**Intermediate Phase**

Many patients with the toxic oil syndrome recovered from the early phase of illness, apparently without further clinical sequelae. However, a substantial proportion (perhaps 50%, the precise percentage varying with the case series cited) experienced an intermediate and subsequently a chronic or late phase of the illness (3,6,9).

**Severe myalgia, eosinophilia and thromboembolic complications.** There is disagreement among investigators regarding both the precise period of illness and the exact clinical manifestations that should be regarded as constituting the intermediate phase of the toxic oil syndrome (1,3). Nevertheless, there is consensus regarding the existence of a more or less definable period of illness occurring perhaps 1 to 3 months after the initial onset of symptoms, involving incomplete recovery from the acute phase of illness and heralding the onset of later disease. Extremely severe myalgia (including significant muscle tenderness to palpation) and particularly high eosinophil counts (higher even than in the acute phase) were characteristic of the intermediate phase, and many findings of the chronic phase (see later) began to make their appearance at this point. There was frequently nonpitting edema of the skin of the limbs and other parts of the body. Although infrequent, there were numerous serious thromboembolic complications among patients during the intermediate phase of the syndrome. For example, there were reports of strokes, mesenteric thromboses and even a report of hepatic vein thrombosis among patients during this phase of the illness (2,10). In many patients, liver function tests remained abnormal during the intermediate phase (3,7).

**Chronic or Late Phase**

**Neuromuscular complications.** The clinical manifestations of chronic toxic oil syndrome were numerous and varied. However, neuromuscular complications received particular attention because of the frequent development of severe weakness or paralysis. Many patients developed the findings of mononeuritis multiplex, with patchy sensory loss and associated muscular weakness. Nerve conduction and electromyographic studies typically showed peripheral nerve axonopathy along with some degree of primary muscle involvement. The extent of weakness associated with the neuromuscular lesion differed among patients, but in the most severe cases there was progression to essentially complete quadriplegia. In some patients ventilatory function was compromised and mechanically assisted ventilation was required. A number of patients eventually died of infectious complications of long-term mechanically assisted ventilation (1-3).

**Other manifestations of chronic toxic oil syndrome.** These included severe weight loss, muscle atrophy, chronic myalgia, muscle cramps, involuntary movements of the limbs, scleroderma-like hardening and thickening of the skin, joint contractures (independent of the limitation in movement caused by sclerosis of overlying skin), sicca syndrome, alopecia, pruritis, chronic hepatitis (both hepatic inflammation and fibrosis) and progressive pulmonary hypertension. Often, these components of the chronic illness worsened over a period of months to years (2,3,6,9). Nevertheless, recent informal reports of Spanish clinicians (9) suggest that many aspects of disease activity eventually seemed to lessen and, finally, to cease.

**After the disease stops progressing, some degree of remission of chronic manifestations of the syndrome occurs. Peripheral nerve function improves, but often the clinical gains are modest and come slowly. Hardened and thickened skin regains some of its lost elasticity, and other disease manifestations gradually become less evident.**

**Pathology**

**Vascular endothelial swelling and proliferation.** The pathologic lesion common to many tissues in the acute phase of this multisystemic disorder was swelling of the vascular endothelium. As the disease progressed through its early,
intermediate and chronic phases, intense endothelial proliferation occurred. In many tissues the growth of endothelial tissue was exuberant, with occlusion or near occlusion of vessel lumens (11-12).

Vasculitis. There were primarily mononuclear inflammatory infiltrates associated with blood vessels. In some tissue sections only perivascular collections of inflammatory cells were seen; in others, there was evidence of a nonnecrotizing vasculitis (11).

Perineurial inflammatory infiltrates and fibrosis. Inflammatory infiltrates involved the perineurium of peripheral nerves. In later stages of the diseases there was perineural fibrosis. The muscular lesion involved inflammation primarily of the perimysium and epimysium, with relative sparing of the endomysium. In the late stages of the toxic oil syndrome, however, there was endomysial fibrosis. A peculiar finding was inflammation specifically involving muscle spindles and intramuscular nerves (12).

Examination of the bone marrow of patients with eosinophilia revealed a marked increase in numbers of eosinophil precursors.

Epidemiology

There have been three major areas of epidemiologic research into the toxic oil syndrome: 1) development of descriptive data, including information about the demographics of affected persons, the extent to which different geographic areas were affected and the occurrence of cases over time; 2) etiologic epidemiologic studies aimed at identifying the etiologic agent and its mode of transmission; and 3) studies of the specific clinical findings in affected persons, their frequency and the extent to which they vary over time.

Descriptive Epidemiology

Although the epidemic has long been said to have begun on May 1, 1981, painstaking and detailed review of computerized patient listings and clinical records has shown that cases occurred at least as early as April 23, 1981 (15).印刷 versions of medical reports were found that showed cases of toxic oil syndrome were diagnosed in early May 1981. In mid-June 1981, the incidence began to decrease. This decrease in the epidemic curve coincided approximately with the public announcement of the association of the toxic oil syndrome with the consumption of a contaminated oil being sold for food use (1,4).

Location. The toxic oil syndrome epidemic affected primarily central and northwestern Spain. Over 99% of the cases officially registered with the Spanish government occurred in the following 14 provinces (in rank order according to the number of cases that occurred there): Madrid, Valladolid, Leon, Palencia, Segovia, Avila, Zamora, Burgos, Guadalajara, Salamanca, Soria, Toledo, Santander and Orense. Cases were tremendously concentrated in Madrid Province, located in central Spain, where almost 75% of the total number occurred. The incidence rate, however, was not highest in Madrid, because of its relatively large total population. Other populous cities in Spain (Barcelona, for example) were essentially unaffected (1).

Gender distribution. Many more women than men were affected. At the national level, >60% of persons with the toxic oil syndrome were female. Moreover, the disease seemed to be more severe for women. There were approximately twice as many deaths due to the toxic oil syndrome among women as among men (1).

Socioeconomic status. The disease had a particularly high incidence among persons with a low to low-middle socioeconomic status. There was relative sparing of persons with higher socioeconomic status, but the disease was also infrequent among the very poorest persons in affected areas (1).

Etiologic Epidemiology

Suspect oil. As has frequently been the case in the solution of complex epidemiologic problems, the astute observations of a clinician led to studies that eventually yielded data firmly implicating the vehicle of the etiologic agent. Dr. Juan Manuel Tabuenca-Oliver noticed that, although cases tended to cluster in families, children in affected families who were younger than approximately 6 months remained well. Because the nutritional sources of these infants (generally breast milk) differed substantially from those of the rest of the family, Tabuenca wondered whether the vehicle of the toxic oil syndrome agent might be an ingested item to which most family members (with the exception of breast-fed babies) were exposed. By questioning his patients, he found that, essentially without exception, all of those affected by the syndrome had consumed an unlabeled food oil, marketed as pure olive oil and sold by traveling salesmen either door to door or in the weekly open air markets (mercadillos) typical of Spain (5-13). Oil fitting this profile in most respects will be referred to as "suspect oil" in the remainder of this review.

The oil hypothesis. A number of studies comparing affected and unaffected persons or families (case-referent studies) and other etiologic work have now established the validity of the oil hypothesis. The food exposures of 62 children with the toxic oil syndrome were compared with those of 62 children with other diseases at the Nino Jesus Hospital in Madrid. All of the children with the syndrome had consumed suspect oil compared with only 6% of the children being treated for other problems (13). In the town of Las Navas del Marques (Avila Province), all of 27 case families had consumed suspect oil compared with only 13 (24%) of 54 size-matched and 17 (31%) of 54 randomly chosen control families (4). In a door to door questionnaire study conducted in 1981 in the working-class neighborhood of Ocreus in Madrid, participants were asked about the types and sources of oils they consumed. Suspect oil had been consumed in all five houses surveyed in which cases of
the toxic oil syndrome had occurred but in only 71 (34%) of 207 unaffected families (14).

The pattern of occurrence of cases of the toxic oil syndrome among the residents of two convents of the same order located side by side in the city of Madrid was of particular interest. The residents of the convents included nuns, novices, and laywomen. All residents at each convent ate the same foods, with the exception that nuns and novices were permitted to use olive oil as a condiment, whereas laywomen were not. (The "olive oil" used in each convent at the time of the epidemic was bought from stores and came in 5-liter plastic containers.) In one convent, 23 (66%) of the 35 nuns and novices but none of 36 laywomen had symptoms of the toxic oil syndrome. In the other convent, 42 (98%) of 43 nuns became ill while all of approximately 70 laywomen living there stayed well (15).

Sources of suspect oil. Work done toward tracing the sources of suspect oil and chemical analyses of such oils had shown the oils to be complex mixtures of low quality olive oil, various seed oils and rapeseed oil. The rapeseed oil component drew attention because it was not produced in Spain and could only be imported after being mixed with one of several denaturants (most commonly aniline) designed to make it unfit for human consumption. The specific oil vehicle of the etiologic agent was thus thought to be aniline-denatured rapeseed oil, but doubts arose regarding this conclusion when such oils failed to produce illness resembling the toxic oil syndrome in experimental toxicologic animals (1). Because the clinical findings of the toxic oil syndrome are quite distinct from those of aniline toxicity, the idea arose that perhaps another component of the oil mixtures carried the etiologic agent. Some even speculated that some food exposure other than suspect oil was the true cause of the syndrome.

Aniline-denatured rapeseed oil. A study of oils turned in to the government by affected and unaffected families and meeting the general description of suspect oils helped to resolve these questions. Measurements of specific chemical analytes in oils turned in by affected families (case oils) were compared with similar measurements in oils turned in by unaffected families (control oils). The results showed a clear association of illness in a family with the presence of aniline and fatty acid anilides (reaction products of oil constituents and the aniline denaturant) in that family's oil. Moreover, there was a clear-cut dose-response effect: the greater the extent of contamination, the more likely it was that an oil had come from an affected family. Consistent with these findings was the fact that fatty acids and sterols occurring in particularly high concentrations in rapeseed oil were significantly higher in case than in control oils. Conversely, the specific fatty acid and sterol components in which rapeseed oil is relatively poor were found in reduced concentrations in case oils. These findings provided strong evidence to support the hypothesis that aniline-denatured rapeseed oil (and not some other component of oil mixtures) was the vehicle of the toxic oil syndrome etiologic agent (16).

Long-Term Evolution of the Toxic Oil Syndrome

Mortality. Data developed to date regarding the long-term evolution of the toxic oil syndrome are relatively few. Recent unpublished information (Fondo de Investigacion Sanitaria) strongly suggests that the current age-adjusted death rate among affected persons does not differ substantially from that of the Spanish population as a whole. Although there was a clear-cut and statistically significant increase in mortality during the 1st year of the epidemic, subsequent mortality in a sample of 5% of patients with the toxic oil syndrome has not differed significantly from that expected. However, there may have been a tendency for patients with the syndrome to die at a relatively young age, and this finding requires further investigation. In general, these epidemiologic data are consistent with the informal clinical observation that disease activity diminishes and disease manifestations tend to regress some months to years after the onset of illness. Spanish health authorities are currently implementing further epidemiologic and clinicopathologic studies that should address more fully the question of whether excess morbidity or mortality, or both, is already occurring or may be expected to occur among persons with the toxic oil syndrome.

Risk of cancer and cardiovascular disease. Patients with the toxic oil syndrome are particularly concerned about the possibility that their long-term risk for cancer may have been increased by their exposure to the toxic oil syndrome agent. However, given the fact that endothelium and blood vessels were prime target tissues for the initial insult, the possible development of cardiovascular disease, cerebrovascular disease or other vascular diseases is also a concern that should be addressed in future studies.

Etiology and Pathogenesis

The precise identity of the etiologic agent of the toxic oil syndrome has yet to be determined. Toxico-epidemiologic data strongly implicate aniline-denatured rapeseed oil as the vehicle of the etiologic agent (16). However, the clinical manifestations of the syndrome are not those of aniline toxicity. The estimated doses of aniline ingested by patients were not toxicologically significant and typical manifestations of aniline poisoning (methemoglobinemia, for example) were absent (5,13). Thus, unmodified aniline could not have caused the disease.

Fatty acid anilides. These reaction products, involving an amide linkage between aniline and fatty acids (the principal chemical components of edible oils), have been proposed as the etiologic agents of the syndrome. However, attempts to reproduce toxic oil syndrome-like biologic phenomena in in vitro and in vivo systems to which fatty acid anilides have been added have not, so far, met with unequivocally positive results (17). Of course, the absence of positive findings in these experiments is difficult to interpret, because whole-
implicated oils have failed to produce toxic oil syndrome-like findings in experimental animals (4). Thus, the question of whether the ingestion of fatty acid anilides caused the toxic oil syndrome remains unanswered.

Chemical contaminants. Other chemical substances derived from the reaction of aniline with other constituents of rapeseed oil have been proposed as potential etiologic agents of the toxic oil syndrome (17,18). However, no convincing evidence has yet been developed that any particular one of these compounds was the cause. Thus, all of these hypotheses remain highly speculative.

It is possible that the etiologic agent of the toxic oil syndrome has nothing to do with aniline. An investigation sponsored by the Fondo de Investigacion Sanitaria (unpublished data) involved a visit to the two French oil companies from which rapeseed oil implicated in the toxic oil syndrome epidemic originated. Apparently, rapeseed oil sent to Spain was taken from undenatured stock that was refined and distributed as edible oil on the domestic French market without any known adverse health consequences. The companies added aniline to denature their product before sending it to Spain. However, because that denatured product was theoretically to be employed in industrial processes and not for use as a food, the usual precautions involved in the handling and transportation of a food product were not necessarily taken. The French company exporting the largest quantity of denatured rapeseed oil to Spain hired trucks that usually carried industrial chemicals. The mixing of denatured rapeseed oil with some still unknown chemical contaminant during the process of transport cannot be ruled out.

Pathogenesis: role of eosinophilia. Data on the pathogenesis of the toxic oil syndrome are almost as sketchy as those on the identity of the etiologic agent. It seems, however, that eosinophilia may play an important role in the tissue damage caused by the illness. In many histologic sections, whole eosinophils are rare among the inflammatory cells. Nevertheless, eosinophils degranulate in target tissues and therefore may not appear in histologic sections as intact cells. In fact, special tests for eosinophil-derived proteins are positive in tissue sections (12,19). Thus, tissue damage caused by eosinophil-derived products may at least partly explain many of the pathogenetic features of the toxic oil syndrome.

Treatment

Early in the course of the toxic oil syndrome epidemic, it was widely believed that the illness was caused by one of the microorganisms that commonly produce the syndrome of atypical pneumonia (4). Consequently, erythromycin and tetracycline were widely prescribed, although they had no apparent effect on the illness (13). As the hypothesis of an infectious cause seemed less tenable, glucocorticoids began to be employed in therapy. Data regarding their efficacy in acute toxic oil syndrome are few, but there is a consensus that they ameliorated pulmonary aspects of the acute phase of the illness (20). Glucocorticoids were very effective in suppressing eosinophilia, but there are no firm data documenting an overall beneficial effect on the course of intermediate and chronic toxic oil syndrome.

Relation to Other Illness

Apparent Uniqueness of the Toxic Oil Syndrome

Individual clinical findings of the toxic oil syndrome are seen in other diseases and syndromes. For example, interstitial pulmonary infiltrates can be seen in the hypersensitivity pneumonitides, a variety of infectious conditions produced by toxicants that affect the lung (paraquat, for example), and many other disease states. The rashes described in patients with the toxic oil syndrome are by no means specific. Eosinophilia is commonly associated with many parasitic infections, the hypereosinophilic syndrome, eosinophilic fasciitis, polyarteritis nodosa and hypersensitivity reactions to drugs and chemicals, among other conditions. Axonal neuropathy resembling that seen with the toxic oil syndrome can be produced by conditions that affect the vascular supply of peripheral nerves, such as diabetes mellitus and polyarteritis nodosa. Some of the skin findings in chronic toxic oil syndrome resemble those of progressive systemic sclerosis.

These similarities notwithstanding, the toxic oil syndrome was considered a new and distinct clinical entity because none of the conditions or toxicants just mentioned produce the sequential evolution of clinical findings seen among patients with the syndrome: initial respiratory difficulty that resolves over a period of days to weeks only to lead to severe myalgias, persistent eosinophilia, thromboembolic phenomena and late progression to a chronic syndrome involving neuromuscular compromise, sclerodermiform skin changes, joint contractures, chronic hepatitis and the other manifestations of chronic toxic oil syndrome.

The Eosinophilia-Myalgia Syndrome

The uniqueness of the toxic oil syndrome has now been challenged by the appearance of the eosinophilia-myalgia syndrome, which occurred in the United States in epidemic form in 1989 and involved >1,500 cases (21,22). The disease was apparently caused by contaminated preparations of L-tryptophan taken as a food supplement (23–25). Clinical manifestations of the eosinophilia-myalgia syndrome. These are strikingly similar to those of the intermediate and chronic stages of the toxic oil syndrome. Patients with the eosinophilia-myalgia syndrome typically come to medical attention because of persistent and severe myalgia, much like that associated with intermediate and chronic—and to some extent in acute—-toxic oil syndrome. The eosinophil count is dramatically increased, usually >2,000 cells/μL. There is concomitant leukocytosis, and the bone marrow
shows hyperplasia of eosinophil precursors. As in the toxic oil syndrome, there are mild to moderate elevations in liver enzyme levels, and aldolase is frequently increased despite a normal or minimally elevated creatine kinase level. Muscle inflammation tends to spare the endomysium and, as in the toxic oil syndrome, there is selective inflammation of intramuscular nerves and muscle spindles (21, 22, 26, 27).

**Skin lesions and neuropathy.** Many patients with the eosinophilia-myalgia syndrome have skin lesions typical of eosinophilic fasciitis, and these reports may reflect a lesion similar to the nonpitting edema described clinically in patients with the toxic oil syndrome. Sclerodermiform hardening and thickening of the skin occurs in the eosinophilia-myalgia syndrome. Alopecia, joint contractures and pulmonary hypertension have also been reported. Axonal neuropathy levocorticotis multiplex similar to that seen in patients with chronic toxic oil syndrome occurs with the eosinophilia-myalgia syndrome and is severe among some patients, with some becoming quadriplegic and ventilator dependent. As in the toxic oil syndrome, glucocorticoids are effective in reducing the eosinophil count, but their overall effect on disease progression, while probably positive, is less clear-cut (26, 27).

**Respiratory syndrome.** Many patients with the eosinophilia-myalgia syndrome have a respiratory syndrome, particularly early in their illness, typically involving cough and dyspnea. Interstitial pulmonary infiltrates and pleural effusions have been seen, but less frequently than in acute toxic oil syndrome. Overall, the respiratory manifestations of the eosinophilia-myalgia syndrome tend to be either nonexistent or substantially milder than the typical acute pulmonary findings of the toxic oil syndrome. This difference in the degree of respiratory manifestations is perhaps the most significant factor distinguishing the eosinophilia-myalgia syndrome from the toxic oil syndrome (22, 26, 27).

**Implications.** Continuing epidemiologic and laboratory work on the eosinophilia-myalgia syndrome appears likely to lead soon to the discovery of the specific etiologic agent (28). Such a discovery would have substantial implications for toxic oil syndrome research. Chemical analytic work directed toward examining the possibility that a compound similar or identical to the eosinophilia-myalgia syndrome agent existed in case-related toxic oil syndrome oil specimens would become particularly important.

The recent report of a possible animal model of the eosinophilia-myalgia syndrome is also of interest (28). Attempts to develop a similar animal model of the toxic oil syndrome should continue. Development of a toxic oil syndrome animal model, if applied in conjunction with careful chemical work with oils selected by appropriate epidemiologic techniques, could lead to more precise identification of the toxic oil syndrome agent even if it bears little or no chemical similarity to the compound responsible for the eosinophilia-myalgia syndrome.

---

**References**


We thank Dr. Lain Saldoveira for his assiduous work in facilitating many of the studies on which this review is based.


