Toxic Oil Syndrome: The Perspective after 20 Years

Manuel Posada de la Paz, 1 Rossanne M. Philen, 2 and Ignacio Abaitua Borda 1

INTRODUCTION

In 1981, a progressive multisystem disease, later called toxic oil syndrome, abruptly broke out in epidemic proportions in central and northwestern Spain (1). This previously unknown syndrome affected thousands of people, and several hundred deaths were attributed to toxic oil syndrome. As a result of this epidemic, the Spanish national health system was faced with one of the most critical public health problems of this century. Although certain clinical characteristics of toxic oil syndrome resembled those of other diseases such as scleroderma and graft-versus-host disease, a similar disease had never before been seen, and its effects on the public and the medical community were dramatic. Twenty years later many questions about this epidemic remain unresolved (2).

Toxic oil syndrome resulted from the consumption of rapeseed oil that had been denatured with 2 percent aniline for industrial use, subsequently refined, and then illicitly sold as pure olive oil (3). To date, the causal toxic agent remains unknown, as many substances which potentially could be the causative compound have been found in the implicated oils (4, 5).

Adulterated oils have contributed to serious epidemics in the past, such as one in Morocco in 1959 due to ortho-cresyl phosphate contamination of jet aircraft oil, which was fraudulently sold as food oil (6), and the one that occurred in Japan in 1968 from the accidental contamination of rice oil with polychlorinated biphenyls (6, 7). The toxic oil syndrome epidemic represents a unique episode of intoxication, however, since in this case the oil was known to have been used for human consumption because of denaturation with aniline.

The appearance of an epidemic that affected the population in terms of a large number of illnesses and deaths, the discovery of a specific food as the vehicle of the toxic exposure, the elucidation of the nature of a disease unknown in humans or animals, the response of the scientific community facing an unknown, acute phenomenon, and the attitude of the affected people and the society as a whole present issues and responses that are widely applicable to other situations. Epidemiologic research and the collaboration of epidemiologists with basic scientists have been fundamental to our present understanding of toxic oil syndrome. Twenty years after toxic oil syndrome first appeared in Spain, we propose to review and update the knowledge, potential causes, and past and present studies of toxic oil syndrome.

EARLY EVENTS

Hypothesis generation

On May 1, 1981, the index case of toxic oil syndrome, a boy aged 8 years, was pronounced dead on arrival at a Madrid hospital (8). Shortly afterward and over the next few days, five other members of his family were examined at the same hospital with signs and symptoms that included interstitial pulmonary infiltrate, headache, asthma, scalp itchiness, and slight fever. Initially diagnosed as an atypical pneumonia, within days the number of patients admitted to Madrid hospitals with the new disease increased dramatically.

Early in the epidemic the clinical picture supported the search for an infectious agent as the cause of the illness. Later, two findings lent support to this hypothesis: One was the isolation of Legionella gormany from a patient’s sputum, and the second, made by a group of pathologists, was of a morphologic structure compatible with Mycoplasma pneumoniae in the lung of a deceased patient. The medical, political, and social pressures to investigate the epidemic and the lack of a scientific authority to deal with the problem led the Spanish government to divert scarce epidemiologic resources to investigate a possible infectious cause. With an infectious hypothesis in mind, clinicians at a Madrid pediatric hospital compared children treated with erythromycin with groups who received other treatments, including antihistamines, other antibiotics, and placebo (9), but they found that the evolution of toxic oil syndrome was similar in all groups. A dietary study done early in the epidemic included many nonspecific questions about oil. The results, however, did not suggest oil as a possible cause.

Concurrently, Dr. Manuel Tabuenca, also a pediatrician, noted that children with toxic oil syndrome developed a clinical syndrome different from that of adults, with a rash...
suggestive of a reaction to an external agent (8). Although cases of illness had been frequent in children, babies under 6 months of age appeared to have been spared. Thus, when an infant aged less than 6 months was identified with toxic oil syndrome, Tabuenca focused on exposures the baby might have had in common with older children and adults. He learned that the infant's grandmother had added a variety of cooking oil, sold in an unlabeled 5-liter plastic container, to the baby's formula as a dietary supplement. To confirm this observation, mothers of children admitted to the hospital with toxic oil syndrome, trauma, or surgery were interviewed. This case-control study established that consumption of oil sold in unlabeled 5-liter plastic containers was a risk factor for developing toxic oil syndrome (10).

Following this discovery, oils were collected from some households and open air markets, analyzed by the official customs laboratory, and found to have come from rapeseed oil originally denatured with 2 percent aniline, but which now contained other aniline-derived compounds. Officials learned later that the customs laboratory had known of the importation of aniline-denatured rapeseed oil for several months (11). On June 10, 1981, 40 days after the epidemic started, in an attempt to prevent further cases, the Ministry of Health and Consumer Affairs alerted the population about the relation of toxic oil syndrome with the consumption of unlabeled adulterated oil.

Case definition

The intimate involvement of clinicians in the toxic oil syndrome investigation led to development of a clinically focused case definition, rather than one intended for epidemiologic research, 4 months after the epidemic began and after several thousand people had been diagnosed with toxic oil syndrome. The definition required two major, or one major and four minor, criteria (table 1) for inclusion in the patient registry, called the Official Census (12). The first Official Census was dated October 1981, 5 months after the epidemic began. One major criterion, consumption of an oil sold by itinerant salesmen, led to difficulties in many epidemiologic studies. In actual practice, however, case definition criteria were not rigorously applied to dubious cases to prevent further cases, the Ministry of Health and Consumer Affairs alerted the population about the relation of toxic oil syndrome with the consumption of unlabeled adulterated oil. Children less than 1 year of age (14). Middle-aged people were more likely to become ill; in particular, women between the ages of 20 and 50 years were affected more frequently than were men of that age (figure 1). Lower socioeconomic groups became ill most often, probably because they purchased this relatively cheaper oil. Socioeconomic status was deduced based on the geographic distribution of the epidemic cases; people in the most affected areas were primarily of lower socioeconomic status than those in other areas of Madrid and the surrounding province.

**Distribution of cases over time—the epidemic curve.** The epidemic curve shown in figure 2 is compatible with a short-term point source exposure (15). Interestingly, the curve begins to fall about 1 week before the announcement of the oil-disease relation on June 10, 1981. Although this could have resulted from several factors, most likely the etiologic oil had all been sold and further exposure was limited to households that already had the oil. The number of new cases decreased rapidly once the oil-disease relation was announced. However, some patients were readmitted who had been discharged in good condition, leading the Ministry of Health and Consumer Affairs to suspect that these patients may have been reexposed. Thus, an official oil recall program began on June 30, 1981. People concerned about their oil exchanged it for pure olive oil at government expense, and this program probably hastened the dramatic drop in the number of new cases of toxic oil syndrome seen in the epidemic curve.

The large number of cases identified in the first weeks of the epidemic led to problems in data collection, resulting in insufficient and sometimes erroneous data. The data included cases who were, both in place and in time, outside the Official Census (12). The first Official Census was dated October 1981, 5 months after the epidemic began. One major criterion, consumption of oil presumably toxic before onset of illness or occurrence of the illness in the nuclear family, 2. Pulmonary pathology with radiologic findings of diffuse interstitial or alveolar interstitial infiltrates, with or without pleural effusion, 3. Incapacitating myalgias with functional impairment, 4. Eosinophil count greater than 500 eosinophils per mm³.

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
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<tbody>
<tr>
<td>1. Consumption of oil presumed toxic before onset of illness or occurrence of the illness in the nuclear family</td>
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<td>2. Pulmonary pathology with radiologic findings of diffuse interstitial or alveolar interstitial infiltrates, with or without pleural effusion</td>
<td>2. Severe skin itching</td>
</tr>
<tr>
<td>3. Incapacitating myalgias with functional impairment</td>
<td>3. Rash or localized edema of skin</td>
</tr>
<tr>
<td>4. Eosinophil count greater than 500 eosinophils per mm³</td>
<td>4. Severe and persistent mouth dryness</td>
</tr>
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<td></td>
<td>5. Minimal or moderate myalgias</td>
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<tr>
<td></td>
<td>6. Neurologic pathology</td>
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<tr>
<td></td>
<td>7. Abdominal pain</td>
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<tr>
<td></td>
<td>8. Clinical or analytical signs of hepatic involvement</td>
</tr>
<tr>
<td></td>
<td>9. Recent onset of exertional dyspnea</td>
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<tr>
<td></td>
<td>10. Recent onset of hypoxemia</td>
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<tr>
<td></td>
<td>11. Pulmonary hypertension</td>
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<td></td>
<td>12. Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>13. Vascular thrombosis</td>
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</tbody>
</table>

* Two major or one major and four minor criteria were required for clinical case definition.

**EPIDEMIOLOGIC STUDIES**

**Descriptive epidemiology.**

**Person.** The 19,904 records in the census represent 11,897 (60.8 percent) females and 8,007 (39.2 percent) males of all ages; only 38 records (0.2 percent) represent

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**TABLE 1. Case definition of toxic oil syndrome proposed by the Spanish Clinical Commission, August 3, 1981***

<table>
<thead>
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* Two major or one major and four minor criteria were required for clinical case definition.
the scope of the epidemic and led some investigators to disregard oil as the causal agent. Ultimately, different studies were done on early cases (prior to the date of the index case), late cases (cases who presented symptoms later than expected), and peripheral cases (those from other geographic areas).

Using the Official Census and a case definition that did not include exposure to the oil, a review of all available epidemiologic information showed that 63 persons developed toxic oil syndrome before May 1 and that the first of these 63 became ill on April 21. Of the 63 early cases, 58 (92 percent) were from the province of Madrid (unpublished data, Centro de Investigación sobre el Síndrome del Aceite Tóxico, 1994).

A few cases of illness were diagnosed from 6 months to 1 year after the epidemic began. These cases were found to have bought oil during the epidemic period, but they had stored the oil and consumed it only a few days before becoming ill. In one instance, a family had their oil analyzed and were told that it was not contaminated. However, they became ill after consuming the oil because the laboratory that did the analysis did not use the appropriate methods to detect the contaminants (16).

A presumed latency period has been determined based on information from certain cohorts. One was a convent of nuns who took all their food, including oil, to a retreat. Thus, the date of their oil consumption and the time elapsed between consumption and illness were known (17). We also know the date of first oil consumption for cases who moved into the epidemic area from geographic zones outside the epidemic area. From these data the latency period was determined to be in general no more than 10 days, and more likely between 4 and 7 days, although in some people this period may have been longer because of the dose ingested or the concentration of the toxic agent (18).
Geographic distribution of cases. Cases were first reported 20 km northwest of the city of Madrid. Later, the geographic distribution of the epidemic was linked to the secondary road network in Spain's central and northwestern areas used by itinerant salesmen who sold oil in unlabeled 5-liter plastic containers door-to-door and in local open air markets (19). Fourteen of Spain's 52 provinces reported cases of toxic oil syndrome (figure 3). The province of Madrid reported 14,445 cases (72.6 percent of all cases), while Segovia and Palencia had the highest incidence rates of over 300 cases per 100,000 population (20).

A review of the Official Census found only 40 cases of toxic oil syndrome who lived outside the epidemic area. All 40 cases had in one way or another consumed oil from the epidemic area, either because they had obtained oil from the epidemic area via friends or relatives, they had traveled briefly to the epidemic area at the time the oil was in use, or they worked at the refinery implicated in the production of the toxic oil and had used oil from the implicated lot (21).

Risk factors

Investigation of the risk factors for the development of toxic oil syndrome has been problematic. The variety of foods prepared with oil and the number of ways in which food can be prepared with oil have made it extremely difficult to quantify consumption. Moreover, identification of which oils among all the oils collected in the government oil exchange program were potentially toxic has added to the difficulty of identifying the exposed population (15).

Cases clustered in families, doubtless as a result of family oil consumption patterns; school students, military personnel, and others typically at high risk of infectious diseases were not disproportionately affected, substantiating a pattern of exposure related to household life.

Although more women than men were affected (18), we do not know if age or sex was a risk factor. We believe that more women than men of all age groups may have been exposed, because women in the families which were studied prepared the foods, tended to stay home, and likely consumed more meals at home. We believe it is likely that given sufficient exposure to the toxic agent all exposed persons would have become ill regardless of age, sex, or other factors. However, this has never been systematically evaluated, and because it is not clear who all the exposed were, attack rates cannot be calculated.

The date of each patient's diagnosis is also associated with the severity of the illness. People diagnosed with toxic oil syndrome during the first month of the epidemic were more severely affected than were people diagnosed later in the epidemic (22). Although no explanation has been established for this, oil sold early in the epidemic may have contained more of the toxic agent than that sold later on, and we have found that concentrations of contaminants vary substantially from one bottle of oil to another (15). Evidence from toxicoepidemiologic studies (described below) has shown that the risk of developing toxic oil syndrome was related to the concentration of certain contaminants in the oil in a dose-response fashion (23, 24).
The etiologic role of aniline-denatured rapeseed oil

For years before the epidemic, Spanish laws designed to protect the olive oil market made the importation of rapeseed oil into Spain for human consumption illegal. Imported rapeseed oil was required by law to be denatured, typically with castor oil, methylene blue, or aniline, to ensure that it was unsuitable for human consumption and went to industrial use. Nevertheless, the sale of rapeseed oil for human consumption was a lucrative business in Spain. As a result, large segments of the population purchased oil mixtures sold as pure olive oil or other vegetable oils that were marketed as pure olive oil. This type of fraudulent oil sales had been marked by a proliferation of itinerant salesmen and open air markets.

Two French oil companies, which sold rapeseed oil for human consumption in France, also sold 2 percent aniline-denatured rapeseed oil to Spanish intermediaries (25). In late 1980 and early 1981, importation of aniline-denatured rapeseed oil, presumably for industry, increased. Much of this oil was later found to have been diverted for human consumption through Catalonia, and this became known as the Catalan circuit (figure 4).

Catalonian circuit. In the Catalan circuit, a variety of types of oil, denatured or not, were brought into Spain and taken to various refineries. Denatured oil was usually diluted with other oils that had not been denatured, including rapeseed oil. Then, the oil was refined and resold through a network of distributors and itinerant salesmen. Although this oil contained aniline prior to refining, the consumption of oil from the Catalan circuit was never associated with toxic oil syndrome (5). During the last quarter of 1980, RAELCA, an oil distributor in the center of Madrid now recognized as the principal company involved in the outbreak, entered the illicit oil sales market and bought refined rapeseed oil from the Catalan circuit for resale. From March 1981 onward, however, RAELCA imported the oil directly from France and used its own commercial networks to refine the oil (25).

When oil was first implicated as the cause of the epidemic, RAELCA had been handling several types of oils, including olive oil, marc oil, denatured and non-denatured rapeseed oil, sunflower seed oil, grapeseed oil, and oils from animal fat. RAELCA mixed the denatured rapeseed oil with these other oils after the refining had taken place, in contrast to the process in the Catalan circuit, where the oils were first mixed with non-denatured oils and then refined. Thus, investigators have speculated that the order of dilution first and then refining could be one reason that the Catalan oils were not toxic.

Oil traceback. Traceback of the oil implicated as the cause of toxic oil syndrome is shown in figure 5. In March 1981, RAELCA bought five lots of aniline-denatured rapeseed oil from two French food oil companies (25). Three lots were shipped to the ITH oil refinery in Seville, and two went to the Danesa Bau refinery in Madrid. The first of the three lots shipped to ITH was received on March 23 (5). The three lots were refined together at ITH and then shipped to RAELCA in two batches on the 14th and 23rd of April. The two lots of oil sent to Danesa Bau were refined and sent to RAELCA on May 19 and 20. Thus, the Danesa Bau oil could not have been sold earlier than 3 weeks after the epidemic began and after the epidemic curve had peaked (26, 27) (figure 6).

**ANALYTICAL EPIDEMIOLOGY**

The large number of toxic oil syndrome cases identified in the first few weeks of the epidemic led to data collection problems, resulting in insufficient and sometimes erroneous
information. Although many studies had established the oil-disease association, hypotheses that tried to link the disease with causes other than oil were proposed to explain cases in which oil consumption as the causative agent did not seem justified. Some researchers focused on these hypotheses, in particular consumption of organophosphate pesticide-contaminated vegetables, a hypothesis which was vigorously pursued. These alternative theories were primarily limited to unpublished anecdotes and lacked supporting data. Other theories, such as poisoning from cadmium, thallium, or other heavy metals, were easy to dismiss after comparing the clinical picture of toxic oil syndrome patients with descriptions in the literature or after looking for biologic markers of intoxication (18).

Early studies

The first case-control study of pediatric patients (study 1, table 2; table 3) performed during the first 40 days after the epidemic began examined the hypothesis of a toxic ingestion via food (10) and was the first to suggest a relation between unlabeled oil sold by itinerant salesmen and toxic
TABLE 2. Case-control studies of toxic oil syndrome, done early in the epidemic, Spain, 1981

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Selection of subjects</th>
<th>Cases</th>
<th>Controls</th>
<th>OR*</th>
<th>95% CI*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Madrid (10)†</td>
<td>Hospital cases</td>
<td>62/62</td>
<td>4/62</td>
<td>1,652</td>
<td>85.6, infinity</td>
</tr>
<tr>
<td>2</td>
<td>Navas del Marqués (Avila) (28)</td>
<td>27/27 affected families in town</td>
<td>27/27</td>
<td>30/108</td>
<td>195.6</td>
<td>11.6, infinity</td>
</tr>
<tr>
<td>3</td>
<td>Pozuelo de Alarcón (Madrid) (29)</td>
<td>Families of patients from Pozuelo admitted to Clínica Puerta de Hierro</td>
<td>42/48</td>
<td>32/96</td>
<td>14.0</td>
<td>5.4, 36.4</td>
</tr>
<tr>
<td>4</td>
<td>Chozas de Abajo (León) (29)</td>
<td>All affected families</td>
<td>19/19</td>
<td>15/19</td>
<td>11.3</td>
<td>0.6, 226.7</td>
</tr>
<tr>
<td>5</td>
<td>Cerezo de Arriba (Segovia) (29)</td>
<td>All affected families</td>
<td>13/13</td>
<td>25/44</td>
<td>20.6</td>
<td>1.2, 369.1</td>
</tr>
<tr>
<td>6</td>
<td>San Cristobal de Entrevías (Zamora) (29)</td>
<td>All affected families</td>
<td>10/10</td>
<td>8/19</td>
<td>28.4</td>
<td>1.5, 555.1</td>
</tr>
<tr>
<td>7</td>
<td>Bocigas de Perales (Soria) (29)</td>
<td>All affected families</td>
<td>11/11</td>
<td>22/33</td>
<td>11.8</td>
<td>0.6, 217.8</td>
</tr>
<tr>
<td>8</td>
<td>Arconada (Palencia) (29)</td>
<td>All affected persons</td>
<td>18/18</td>
<td>9/21</td>
<td>48.7</td>
<td>2.6, 914.4</td>
</tr>
<tr>
<td>9</td>
<td>Colmenar Viejo (Madrid) (29)</td>
<td>Patients from Colmenar admitted to specific hospital</td>
<td>16/20</td>
<td>6/20</td>
<td>9.3</td>
<td>2.2, 40.0</td>
</tr>
<tr>
<td>10</td>
<td>Madrid (29)</td>
<td>No detailed information</td>
<td>52/58</td>
<td>615/1,725</td>
<td>15.6</td>
<td>6.7, 37.0</td>
</tr>
<tr>
<td>11</td>
<td>Madrid (17)</td>
<td>Convent 1 (nuns)</td>
<td>14/36</td>
<td>0/56</td>
<td>72.8</td>
<td>4.2, infinity</td>
</tr>
<tr>
<td>12</td>
<td>Madrid (17)</td>
<td>Convent 2 (laywomen)</td>
<td>42/43</td>
<td>0/70</td>
<td>3,995</td>
<td>159.1, infinity</td>
</tr>
<tr>
<td>13</td>
<td>Madrid-Orcasur neighborhood (19)</td>
<td>Door-to-door neighborhood survey</td>
<td>8/8</td>
<td>72/204</td>
<td>31.1</td>
<td>1.8, 546.1</td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval. † All data have been recalculated using SAS for Windows, version 6.12. Every cell has been corrected with 0.5 in those tables that contained zero. The upper confidence limit has been marked with infinity for values over 1,000.
‡ Numbers in parentheses, reference number.

The first of these four studies examined various hypotheses including respiratory transmission, but it did not ask about oil consumption and found no potential risk factors for illness. When the oil-disease relation described above was made public, a second study was done in the same town, which asked about the use of oil from unlabeled 5-liter containers and which confirmed Tabuenca’s results. This study showed not only an association between the oil and illness but also an association between a specific vendor of unlabeled oil and toxic oil syndrome (tables 4 and 5). Another of the four studies suggested a dose-response effect, but this was never replicated.

The Navas del Marqués studies identified patients with toxic oil syndrome from reports of the two physicians and

TABLE 4. Use of oil from unlabeled 5-liter containers, by family units, Las Navas del Marqués, Spain, 1981

<table>
<thead>
<tr>
<th>Exposed (no.)</th>
<th>Unexposed (no.)</th>
<th>Total (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Not III</td>
<td>30</td>
<td>108</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>108</td>
</tr>
</tbody>
</table>

The use of oil from unlabeled 5-liter containers was investigated in a case-control study of hospitalized children in Las Navas del Marqués, Spain, 1981. The study compared 62 hospitalized children diagnosed with toxic oil syndrome with 62 children who were either admitted to the same hospital with other diagnoses or who were treated in a surgical outpatient clinic of that hospital. Each child responded to a detailed questionnaire with specific questions about 42 items of food and drink, including the use of oil purchased in unlabeled 5-liter plastic containers. All children with toxic oil syndrome had been exposed to the illicit oil, whereas only four of 62 children who did not have toxic oil syndrome were exposed.

Another investigator performed four population-based, case-control studies in the town of Las Navas del Marqués, 47 miles (75.64 km) northeast of Madrid (study 2, table 2) (28).
one hospital that served the town. Families of patients with toxic oil syndrome were matched to control families either by family size or randomly from the 1981 town census. Families rather than persons were selected as the unit of study, as oil was typically purchased by one family member (not necessarily the family member who was ill in the case families), but use of oil in family meals meant that persons were usually unaware of the quantity or type of oil they consumed. The study also assumed that all family members consumed similar amounts of the same oil, and this was estimated by family size or randomly from the 1981 town census.

A potential problem with most of the studies was the common knowledge of the proposed relation between consumption of oil from unlabeled 5-liter plastic containers and toxic oil syndrome. This knowledge could have introduced a recall bias into the studies in table 2. However, the short time between the possible exposure and most of the studies, the use of only one case per affected household, and the frequent need to interview someone other than the ill person to determine the type of oil used by the household likely kept recall bias to a minimum.

### Studies after the acute epidemic period

Although outbreaks of disease in other close-knit groups had not been seen, two convents were identified that reported several cases of toxic oil syndrome each. Because convents are closed communities and residents there share virtually all their meals, a study was done to examine the use of food oil in the convents in detail. Both convents housed a group of laywomen in addition to nuns. Meals for the laywomen and nuns in each convent were prepared in the same kitchen, and with the exception of the oil used for cooking and salads, all the other food that was prepared and served was the same for all the residents in each convent. In each convent, a number of the nuns who were served the oil from unlabeled 5-liter containers developed toxic oil syndrome, while none of the laywomen, who were served soybean oil, became ill. These two case-control studies (studies 11 and 12, table 2) (17) confirmed that the vehicle of the etiologic agent was a rapeseed oil denatured with 2 percent aniline.

A study done in Orcasur (study 13, table 2) (19) showed that, of all the ways in which people purchased unlabeled 5-liter bottles of oil, such as grocery stores, supermarkets, oil-pressing facilities at olive farms, warehouses, itinerant salesmen, open air markets with 5-liter plastic containers, or some other manner, only the oil sold by itinerant salesmen or in open air markets was associated with illness. This is consistent with information obtained through the Ministry of Health (which regulates oil sales) that the system used by RAELCA, the most implicated oil distributor, was distribution through itinerant salesmen rather than through the usual outlets for food products (19).

### Toxicoepidemiologic studies

**New definition of exposure—the RAELCA bottling method.** In all the analytical studies, exposure was defined as consumption of oil sold by itinerant salesmen in unlabeled 5-liter containers without a sanitary registry number. Investigators who performed the first case-control studies were unaware that this definition might include oil from more than one source or from nonadulterated sources that were potentially not toxic. Despite this, most of the studies produced statistically significant estimators of risk. Studies of RAELCA's bottling methods and the company's use of a network of itinerant salesmen for oil distribution, as well as chemical studies of the oil contents of differently shaped containers, have clarified the role of RAELCA in the epidemic (15). The plastic bottles found at RAELCA were clearly made using raw material and a plastic injection mold found onsite. This resulted in identical bottles that often contained oils with different chemical compositions as a result of their bottling methods. Unfortunately, the many oil mixtures sold by RAELCA also led to problems in the choice of oil specimens for toxicology research.

When the oil recall took place, attempts were made to place identifying information on each oil specimen. Not all specimens were clearly labeled. Thus, many of the over 100,000 containers of oil collected during the recall were unsuitable for use in epidemiologic or chemical studies. Nevertheless, in two case-control studies, toxic oil syndrome investigators systematically looked for oil containers stored in the official warehouses by the Ministry of Health and Consumer Affairs and identified those containers potentially useful for research from the thousands in storage. The two studies in which chemical analyses of epidemiologically selected oils were performed have become known as the toxicoepidemiologic studies.

Toxicoepidemiologic study I (23) was conducted in two locations in the province of Madrid, Alcorcón and Leganés, and involved examination of thousands of bottles of oil to select those most likely to be associated with illness from...
among the oils in the official warehouses. Selection was based on the container that appeared to be the original 5-liter plastic container that had an easily recognizable shape termed "atypical" (determined from observation of the general characteristics of bottles found at the RAELCA warehouse) and the degree of fullness of the container (if it was full, no oil had been consumed and therefore it was not associated with disease). The identifying information was then noted and used to attempt to contact the family who had originally turned in the oil. Sixteen other criteria were then applied to the containers of oil initially selected, to arrive at the case oils and the control oils. These criteria included sufficient identifying information to locate the family, fulfillment of the case definition for toxic oil syndrome by at least one family member, and a red top on the oil container. Specimens of the oil were chemically analyzed for 21 oil constituents and two measures of oil rancidity, and these results were statistically analyzed. Three fatty acid anilides, oleyl, linoleyl, and palmityl anilide, were highly statistically associated with the oil's having come from a family with a member who was ill with toxic oil syndrome. Of these three fatty acid anilides, oleyl was present in the highest concentrations and was used to assess the dose-response relation of oils and the risk of toxic oil syndrome (table 6).

A subsequent study, called toxicoepidemiologic study II, used a similar design in the choice of case oils and noncase oils, but it covered all the geographic areas affected by the epidemic (24). The dose-response relation was similar to that found in toxicoepidemiologic study I (table 7). The overall results of both these studies were the same: a clear relation between the concentration of an aniline-derived chemical marker, the fatty acid anilide oleyl anilide, and the risk of becoming ill. These studies support the finding that the consumption of contaminated oil was important but that there was a definite dose-response relation of the chemical compounds found in the oil to the risk of developing toxic oil syndrome, and thus, this oil most likely came from only one source.

These two toxicoepidemiologic studies (23, 24) have demonstrated a clear relation between the concentration of the fatty acid anilide oleyl anilide (tables 6 and 7) and the risk of illness. These studies allowed a more precise and specific identification of possible toxic oils and, thus, more accurate toxicologic studies.

A study of the shapes of unlabeled 5-liter plastic containers has recently shown that including the consumption of oil from a 5-liter plastic container that did not have a sanitary registry number as part of the case definition was not enough to establish exposure to a genuinely toxic oil (15). This study involved chemical analysis of over 1,000 oils from bottles of 10 different, but very similar, shapes. Bottles that were made at the RAELCA bottling plant were considered as one specific

<table>
<thead>
<tr>
<th>TABLE 6. Dose-response relation between the amount of an aniline-derived chemical compound (oleyl anilide) in oil and the risk of becoming ill, toxicoepidemiologic study I, toxic oil syndrome, Spain, 1981</th>
</tr>
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<tbody>
<tr>
<td><strong>No. of oils at each concentration of oleyl anilide</strong></td>
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<td></td>
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<tr>
<td>0 μg/g</td>
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<tr>
<td><strong>Case oils</strong></td>
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<tr>
<td>11</td>
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<tr>
<td>1–100 μg/g</td>
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<tr>
<td><strong>Total</strong></td>
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<td>59</td>
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<tr>
<td><strong>Odds ratio</strong></td>
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<td>1.00</td>
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*A "case oil" is an oil specimen selected from those turned in to the Spanish government during the oil recall, which had one or more ill persons associated with it.
† A "control oil" is one that was turned in to the Spanish government during the oil recall, which had no ill family members associated with it.

<table>
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<tr>
<th>TABLE 7. Dose-response relation between the amount of an aniline-derived chemical compound (oleyl anilide) in oil and the risk of becoming ill, toxicoepidemiologic study II, toxic oil syndrome, Spain, 1981</th>
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<tr>
<td><strong>No. of oils at each concentration of oleyl anilide</strong></td>
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<td>---------------------------------------------------------------</td>
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<tr>
<td><strong>Case oils</strong></td>
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<tr>
<td>29</td>
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<td>1–300 μg/g</td>
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<tr>
<td><strong>Total</strong></td>
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<tr>
<td>89</td>
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<tr>
<td><strong>Odds ratio</strong></td>
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bottle type, and bottles with even very small variations in the shape were classified into other groups. Not all 5-liter bottles studied were found to have the same oil composition or the same contents in terms of contaminants.

The bottles most associated with contaminants were made at RAELCA. However, not all bottles of oil from RAELCA contained contaminants, and very few non-RAELCA bottles contained any contaminants (15). Of 849 bottles from RAELCA, 319 (37.6 percent) contained oleyl anilides, whereas extremely few of the other bottle shapes studied contained oleyl anilides in any quantity. The finding of uncontaminated oil from the implicated distributor would have tended to bias the toxicoclinicoepidemiologic and other case-control studies to the null, because many people who did report consumption of implicated oil did not become ill. In 1981 this detailed knowledge about the specific contents of similar oil bottles was unavailable and, although lack of this knowledge probably affected all the case-control studies, it also serves to further strengthen the oil-illness association that was found.

New toxicoclinicoepidemiologic findings

Chemical compounds, unrelated to fatty acid anilides and described years before (30), have been studied recently (5, 27, 31). Analyses using laboratory techniques not available in 1981 of oil samples from the case-control studies mentioned above, as well as analysis of oils from implicated refineries, have established that 3-(N-phenylamino)-1,2-propanediol (DEPAP) is a better marker of case oils than is oleyl anilide. These analyses also show that the presence of DEPAP and related compounds in oil is an equally sensitive but more specific correlate of case relatedness of an oil than is the presence of fatty acid anilides (26). Furthermore, DEPAP has been found in samples from the ITH refinery in Seville, some of whose workers became ill from consuming oil from the same lots implicated in the epidemic (21) and the only refinery whose oil was clearly associated with illness; DEPAP has not been found in anilide-containing oils sold in other parts of Spain that did not cause illness. These relations are shown in figure 4. These findings suggest that DEPAP or related compounds may be the causal agent of toxic oil syndrome. A causal association, however, has not been unequivocally established.

Researchers are working to duplicate the original toxic oil and to further study the changes that might occur to aniline-denatured rapeseed oil. Although all the original conditions under which the oil was produced will never be known and duplication presents a variety of difficulties, researchers have made substantial progress. While the possibility remains that other contaminants were introduced by the tank trucks that transported the oil, attempts to duplicate the original toxic oil may supply some solutions to the toxic oil syndrome puzzle and will be useful for toxicologic studies.

CLINICAL ASPECTS

Acute phase

Toxic oil syndrome developed in three clinically distinct phases (22, 32) now referred to as acute, intermediate, and chronic. The acute phase was characterized by noncardiogenic pulmonary edema with dyspnea. Chest roentgenograms showed alveolar-interstitial infiltration often accompanied by pleural effusion (32, 33). The most characteristic acute histologic lesion was a vascular lesion involving all organs except for the central nervous system (34). During the acute phase the lesion was at the level of the endothelium (35–37). Myalgia occurred in 80 percent of patients, peripheral eosinophilia in 78 percent, and rash in 39 percent. Acute encephalopathy was seen in 1.2 percent of patients during this phase. Other features of the acute phase were fever and scalp itch. Severe myalgias and muscle cramps marked the end of the acute phase. Approximately 70 percent of all patients with toxic oil syndrome had pulmonary findings with a combination of the symptoms listed above during the first 2 months of the epidemic (38). More than 10,000 patients were admitted to the hospital with this phase of the illness, and most deaths due to toxic oil syndrome in this phase resulted from respiratory insufficiency.

Intermediate phase

After the first 2 months of illness patients typically entered an intermediate phase lasting about 2 months. This phase was characterized by frequent changes in signs and symptoms. Clinical features frequently observed included sensory neuropathy in 55 percent, intense myalgia in 47.4 percent, dysphagia in 6.5 percent, pulmonary hypertension in 4.6 percent (38), thromboembolic phenomena of the large vessels in 1.8 percent (39), marked weight loss (40), hepatic cholestasis, and induration of the skin followed by skin infiltration. High levels of peripheral blood eosinophils, hyperglycemia, and elevated triglycerides and cholesterol were also seen. The platelet count often decreased, and some patients developed a disseminated intravascular coagulopathy leading to death (39), although pulmonary hypertension and vascular thrombosis more frequently caused death in the intermediate phase. In severe cases histologic examination showed a proliferation of the vessel intima with fibrosis and thrombosis (41).

Chronic phase

Later, about 59 percent of affected persons developed the chronic phase, characterized by hepatopathy in 7.3 percent (42, 43), peripheral motor neuropathy in 32 percent (44), contractures (45), scleroderma in 21.3 percent (46), pulmonary hypertension in 8.2 percent (38, 47), and involuntary muscular activity such as cramps, myoclonus, and tremor in 60 percent (48). Interstitial fibrosis is the most characteristic histologic finding in the chronic phase of the disease, particularly in the skin, peripheral nervous system, and gastrointestinal tract. However, this fibrosis was never observed in the lungs. Death was typically a result of infectious complications of respiratory insufficiency secondary to neuromuscular weakness, pulmonary edema, thromboembolic events, or pulmonary hypertension in the chronic phase (32, 49). More than 300 people died as a direct result of these causes during the first few years (49, 50). A variety
of treatments were tried to control the course of the illness without success. High doses of steroids were administered in the acute phase to control respiratory distress, but no long-term beneficial effects were clearly demonstrated. Physical rehabilitation has proven to be very beneficial in the chronic phase, in particular with patients with contracts and severe neuropathy (44).

**FOLLOW-UP STUDIES**

**Mortality of the cohort**

A 1993 pilot study examined the usefulness of a mail and telephone survey of the toxic oil syndrome cohort to assess overall mortality (49), and this technique has since been applied to the entire cohort. Of the 19,904 persons in the Official Census, 1,663 persons died from May 1, 1981, through December 31, 1994, for a crude mortality rate of 8.4 percent. All standardized mortality ratios reported here have been adjusted for age and sex. An excess of deaths occurred in 1981, corresponding to a standardized mortality ratio of approximately 500, with an absolute difference between the observed and expected number of deaths of approximately 250. The standardized mortality ratio for total mortality in 1982 was about 100, whereas a consistent deficit of deaths was seen from 1983 onward, corresponding to statistically significant standardized mortality ratios of approximately 70–80 for most calendar years (50).

The highest standardized mortality ratio of 20.4 (95 percent confidence interval: 16.0, 25.7) was seen among women aged 20–39 years during the period from May 1, 1981, through December 31, 1982. A statistically significant excess mortality persisted in these women for several years after the epidemic; up to 1994, 62 deaths occurred in this subcohort versus 32 expected (51). In contrast, up to 1991, in women aged 40–59 years, standardized mortality ratios were close to unity and, in very young men, the number of observed deaths was too small for any inference. In all other categories (i.e., women aged 60 years or over and men aged 20 years or over), during 1983–1991 standardized mortality ratios were consistently lower than unity, and most differences were statistically significant (50). Over the entire follow-up period in this study, from May 1, 1981, through December 31, 1994, the mortality of the toxic oil syndrome cohort was less than expected when compared with either the mortality of the general Spanish population or with the mortality of the population of the 14 provinces where the epidemic occurred (50).

**Mortality by cause**

Age- and sex-adjusted standardized mortality ratios have also been estimated on the basis of mortality rates in the Spanish population, for large categories of causes of death. Of the 409 deaths from external agents (*International Classification of Diseases*, Ninth Revision, codes 800–999), the death certificates for 350 indicated toxic oil syndrome as the underlying cause of death. The most frequent causes of death in the toxic oil syndrome cohort in order of importance are external agents (including toxic oil syndrome), 350 (21.1 percent); cardiovascular and pulmonary diseases, 536 (32.3 percent); and malignancies, 310 (18.7 percent). Pulmonary hypertension (*International Classification of Diseases*, Ninth Revision, code 416.0) was the cause of death for three people in the toxic oil syndrome cohort during the study period, with a standardized mortality ratio of 18.15 (95 percent confidence interval: 3.65, 53.02) (50, 52). Except for deaths attributed to external causes including toxic oil syndrome and deaths due to pulmonary hypertension, all causes of death were decreased in patients with toxic oil syndrome compared with the Spanish population.

**Clinical follow-up study**

In 1994 a transverse follow-up study examined approximately 4,000 members of the toxic oil syndrome cohort in detail, including the collection of complete histories and physical examinations, as well as laboratory and other special studies. Results of a pilot of this study available for a stratified random sample of patients with toxic oil syndrome (53) show that the self-perceived health status of toxic oil syndrome patients, as measured by the Nottingham Health Profile Questionnaire, was substantially poorer than that of a comparison group taken from the general Spanish population. Patients with toxic oil syndrome scored at approximately the same level as those comparison respondents who rated their health as poor or very poor. This study also found that women were more affected than men in terms of neuropathy, scleroderma-like skin changes, and contractures. Future plans include a complete follow-up of the entire cohort in terms of clinical outcomes and non-toxic oil syndrome health problems.

**World Health Organization Regional Office for Europe**

**Centro de Investigación sobre el Sindrome del Aceite Tóxico: current research and new findings**

Since 1987, experts from the Spanish research agency CISAT, in cooperation with WHO, have collaborated to guide toxic oil syndrome research. This WHO-CISAT committee has studied existing research, identified gaps in knowledge, recruited investigators to perform studies, and contracted out research projects. Research has focused on areas that committee members believe have the most potential to address the issue of what the etiologic agent was and how it produced toxic oil syndrome. WHO-CISAT continues to support and encourage research efforts worldwide.

Of the new research being conducted on toxic oil syndrome, some of the most important progress has been *made in* the field of the chemistry of the oils, the potentially toxic compounds in the oils, the kinetics of formation and degradation of contaminants in the oils, and, above all, the possibility of reproducing toxic oil in the laboratory through the modification of one or more of the refining variables (54). Reproduction of the toxic oil will greatly enhance the performance of toxicologic studies in animal models by providing oil of the same standardized composition to all researchers, allowing for more comparability among different studies.

Until recently, however, experimental animal studies have used oils selected using specific epidemiologic criteria,
chemical composition analyses, and bottle shape. Notwithstanding, only a few studies have been performed following these guidelines because of concerns that since 1981 chemical decomposition of the oil samples may have occurred, making an accurate evaluation of the effect on animals difficult. Thus, many studies have used specific chemical compounds identified in the oils and synthesized for this purpose, since these are believed to have a high likelihood of a relation to disease. Using the specific chemical compounds in a blind-coded manner, collaborative studies among immunologists, chemists, biologists, and epidemiologists have yielded important information (55, 56).

Among the most recent important work in toxic oil syndrome, a number of findings of most note have been made in the area of immunology. The implications of the immunologic system in this disease have been tested in many studies from the beginning of the outbreak. The presence of high levels of soluble interleukin-2 receptor factor in the serum of patients from the acute phase of toxic oil syndrome has been established (57). Investigators have discovered the predominance of TH2 lymphocytes in lesions from the acute phase of toxic oil syndrome (58). The effects of free fatty acids on endothelial, platelet, and macrophage cell lines have been determined (59, 60). Deposits of major basic protein in tissues from the acute phase of toxic oil syndrome and an increase in granulocyte stimulating factor in the sera of patients have also been documented by investigators (61). Additionally, the presence of some human lymphocyte antigen (62) markers as risk factors clearly suggests the participation of the immune system in this disease. This human lymphocyte antigen finding in conjunction with metabolic risk factors, such as the presence of a major prevalence of mutations in the gene that codes N-acetyl transferase 2 (63, 64), will help to explain more about the variability of the expression of toxic oil syndrome among people with a supposedly similar exposure.

Toxic oil syndrome research continues in several other areas. A thorough revision of the registry of patients, referred to as the REVCEN (65), has been completed and has led to as complete as possible a listing of all toxic oil syndrome patients. The REVCEN also contains a wealth of information about each patient with toxic oil syndrome, and these data will be further analyzed. The REVCEN has also been a key factor in the success of the long-term mortality study.

**Eosinophilia-myalgia syndrome**

In the fall of 1989, a new epidemic, referred to as eosinophilia-myalgia syndrome, associated with ingestion of L-tryptophan, manufactured by Showa Denko, K.K., Tokyo, Japan, occurred in the United States. Because eosinophilia-myalgia syndrome was clinically similar to toxic oil syndrome, American researchers with a wide knowledge of toxic oil syndrome were able to identify this as a new illness and to direct epidemiologic and clinical research appropriately. The pathogenesis of eosinophilia-myalgia syndrome appears to have much in common with toxic oil syndrome, although its complete evolution remains unknown. The clinical features of eosinophilia-myalgia syndrome (66, 67) have been described in detail elsewhere, and the epidemiology has been the subject of an extensive review (68).

Early in the epidemic many patients with eosinophilia-myalgia syndrome had unremarkable physical examinations with relatively few abnormal findings. As their illnesses progressed, however, patients with eosinophilia-myalgia syndrome developed signs and symptoms similar to those seen in patients with toxic oil syndrome. Fewer patients with eosinophilia-myalgia syndrome demonstrated serious pulmonary findings than in toxic oil syndrome, although when present these findings included pulmonary hypertension with marked hypoxia, at times severe enough to require hospitalization. Chest roentgenograms were as likely to show infiltrates or pleural effusions as to be normal, even in the presence of pulmonary symptoms. Some patients developed hepatomegaly and abdominal tenderness, although these were rarely severe. Liver function tests were often mildly elevated, although no characteristic pattern of liver function abnormalities was identified. Edema of the face or extremities could be present initially. However, extremity edema in particular was a more common late finding and was typically accompanied by scleroderma-like skin changes. Cardiac manifestations, such as mild arrhythmias or heart failure with pulmonary edema (apart from the pulmonary hypertension), were found in a few patients. Patients developed a wide range of neurologic symptoms that included both minor paresthesias and a life-threatening ascending polyneuropathy. Clinical depression in patients with eosinophilia-myalgia syndrome is also thought to be part of the disease process.

The principal laboratory finding was typically a striking eosinophilia, although the eosinophilia would often abate spontaneously while the patient remained symptomatic. Thus, a lack of eosinophilia at the time of a physician's examination did not preclude a diagnosis of eosinophilia-myalgia syndrome. Albumin was frequently found to be low and aldolase was often elevated. In spite of the severity of the muscle symptoms, the level of creatine phosphokinase was usually normal.

Eosinophilia-myalgia syndrome was most often seen in women and was not limited to a specific ethnic or social group, although the pattern of people affected was similar to the pattern of people who used supplement products in general. Eventually approximately over 1,500 patients were reported, and data on their disease were collected into one large surveillance database.

Unlike the toxic oil syndrome epidemic, patient identifying information was not collected at the national level, and since patients with eosinophilia-myalgia syndrome were not limited to a certain area of the country, this made the long-term follow-up of any substantial number of patients quite challenging (1, 69). Because of this limitation, eosinophilia-myalgia syndrome does not have a national registry of cases established, and any follow-up that has been done has been on either an individual basis or with a small group of cases. Thus, long-term follow-up in toxic oil syndrome is of great importance, because, in addition to documenting the clinical outcomes of patients with toxic oil syndrome, follow-up will
assist investigators in the United States who continue to study eosinophilia-myalgia syndrome.

Because the clinical resemblance of these two disorders is remarkable, they could be similar etiologically (70, 71). Investigators have suggested that the 3-(phenylamino)alanine, found in L-tryptophan, and the 3-phenylamino-1,2-propanediol, found in some samples of toxic oil syndrome oils, may be interconverted biologically, and that one or both of these compounds, or their metabolites, could be the etiologic agent of both toxic oil syndrome and eosinophilia-myalgia syndrome. While this line of research has not progressed as much as hoped, another more plausible theory is that, if either compound is found to be the etiologic agent of either disease, that compound may be one of a group of related compounds, all capable of causing diseases similar to toxic oil syndrome and eosinophilia-myalgia syndrome.

Certain features of eosinophilia-myalgia syndrome and of toxic oil syndrome, especially in its chronic phase, are similar to those of other immunologic diseases. Recent work in drug-induced lupus (72) suggests that different environmental exposures can provoke connective tissue diseases and that an immunologic similarity may exist among these diseases. Continuing investigation of chemical compounds in toxic oil syndrome oils or in eosinophilia-myalgia syndrome-associated L-tryptophan may one day establish the identity of the etiologic agent in these diseases and help explain the etiology of connective tissue diseases whose causes are as yet unknown, including scleroderma, systemic lupus erythematosus, and rheumatoid arthritis.

Social aspects and communication

A variety of books and guides on risk communication in public health crises are available (73). Nevertheless, consistently following one key rule is essential to avoid increased stress and anxiety in the population: Only one channel of communication should be used to provide information that is clear, understandable, and truthful. Reassuring, but incorrect, messages issued at the beginning of the toxic oil syndrome epidemic, while the number of deaths and the clinical severity of the disease increased, only led to increased distrust and fear among patients, their relatives, and the general public (74).

Most toxic oil syndrome-affected people came from medium to low socioeconomic areas of Madrid, because the causative oil was most commonly sold in the outskirts of town primarily to people in these socioeconomic groups. The overall educational level of this population was also low (75), leading to increased difficulty in transmitting detailed and important disease information. Additionally, from the beginning of the epidemic, personal tragedies were frequent, such as the loss of more than one family member, the loss of the primary breadwinner, and the development of severe handicaps or prolonged hospitalizations that led to loss of employment for many toxic oil syndrome patients. Young people who had not yet entered the workforce faced serious difficulties obtaining any form of employment, and homemakers could no longer care for their families and perform their usual activities of daily living. In short, many families suffered tremendous economic and emotional impacts in the midst of an epidemic of a severe disease whose long-term effects were unknown. Once these social problems became evident, the government implemented a series of interventions in an attempt to mitigate social and economic hardships among those affected by toxic oil syndrome (76).

In time, the oil companies and involved employees who had caused this catastrophe, as well as a number of government officials who knowingly allowed the fraudulent oil importation by failing to enforce restrictions on food and oil imports already in place, were punished by the legal system. As a result, the Spanish government has paid economic reparations of over 250 million dollars.

Physician-patient relationships suffered as a result of the economic reparations. Physicians not only were caregivers to people with a serious disease whose long-term prognosis was unknown, but they also were put in the untenable position of determining the patient’s economic rights. Compensation neurosis also appeared in some cases, and physicians were poorly prepared to handle this situation (74).

Various factors played a role in the social and political repercussions of the toxic oil syndrome epidemic (77). The beginning of the epidemic was acute and massive: Within the first month and a half after the epidemic began 80 people had died and over 12,000 had become ill. Toxic oil syndrome was a new systemic disease without any known treatment that affected primarily people of middle to low socioeconomic status. The immediate cause of toxic oil syndrome was unknown for at least a month and a half after the epidemic began, and rumors surrounding possible causes were rampant. Toxic oil syndrome was also a toxic illness associated with illegal trade in a fraudulent food product. As the epidemic progressed, serious deficiencies in the control of the food oil market by regulatory authorities were documented.

Taken together, these factors caused a societal upheaval, first based on fear and anxiety about an unknown, and potentially deadly, illness, and later based on compassion for affected citizens. In the end, the government provided economic and social assistance to mitigate needs that toxic oil syndrome had created in families, and the judicial process sentenced those who were held legally responsible.

These social attitudes made the work of the investigators and physicians difficult. On the one hand, the media exerted pressure regarding what should be investigated at any particular time, increasing public anxiety and unease, and on the other hand, the association of possible economic benefits with a person’s health caused confusion for physicians regarding the authenticity of the complex symptomatology of this disease, an attitude which persists even today.

Toxic oil syndrome: lessons learned

The toxic oil syndrome epidemic shares many important features with other public health crises. Thus, we can refer to the way this epidemic transpired to apply the lessons learned from toxic oil syndrome to other mass illness situations in the future.

An adequate initial hypothesis is fundamental to abort an epidemic quickly. Although symptoms seen early in the epi-
Epidemic may be limited to only one organ system, such as the lung in toxic oil syndrome, it is important to keep an open mind with regard to possible routes of exposure. This was a prominent contributing factor to the direction followed by the first case-control study carried out in Spain in 1981 (28). Few questions were asked about foods or other items that might have been ingested, as the focus was primarily on respiratory and infectious agents. Thus, while a new disease or outbreak may initially appear to result from a specific cause (such as infectious, as was believed initially in toxic oil syndrome), the possibility of another etiologic agent (such as environmental) should not be excluded without thoughtful consideration. Failure to carefully weigh all possible causes when studying a disease of unknown origin can lead to delays in implementing preventive measures and treatment (78).

In a crisis situation such as the toxic oil syndrome epidemic, a case-control study design is the best method to assess the likely cause of the epidemic, because of the relatively short length of time required to perform one compared with other study designs, and because of the ease with which several hypotheses can be explored in the same study (79). Another important consideration when conducting a case-control study in this type of situation is to anticipate more than the usual amount of recall bias. Publicity was heightened during the toxic oil syndrome episode, and the public was bombarded with correct and incorrect information about the new disease, thus making it difficult in the long run for epidemiologists to recruit study subjects who were not somehow already biased. In the cases of both toxic oil syndrome and eosinophilia-myalgia syndrome, however, the strength of the association was so high that we do not believe even a larger than usual recall bias would have changed the final result. In view of this, epidemiologists should do whatever possible to test their hypotheses before official announcements regarding a cause are made, thus avoiding this kind of bias as much as possible.

Another major problem in an epidemic such as toxic oil syndrome is to accurately determine the exposed population. As was the case with the toxic oil, some exposures may be very widespread, or their extent may not be determined before investigators identify the source or vehicle of exposure. Thus, when public authorities attempt to intervene, important epidemiologic information or evidence may be destroyed or damaged, leading to problems for subsequent investigators.

The crisis atmosphere that surrounds episodes such as toxic oil syndrome may also affect the quality of information collected during and after the acute phase of the epidemic. For a variety of reasons people who should be included in the cohort or patient registry may not be. Our experience with toxic oil syndrome suggests that the best solution to this problem is the establishment of only one centralized case register. Nevertheless, some misclassification is unavoidable. The total spectrum of the disease may not yet be evident, thus excluding legitimate cases, while in other instances some persons may be tempted to take advantage of a situation that they believe will be profitable by feigning subjective symptoms (80). To mitigate this effect, all possible patients should initially be registered, and enough information should be collected so that future attempts to categorize these patients have a better chance for success.

Collaboration across multidisciplinary lines is also an important issue when dealing with an outbreak of an unknown disease. Decisions regarding follow-up of sick or exposed people should be made contemporaneously with the epidemic, as this may prove one of the most crucial considerations for future research and treatment. In most cases, however, decisions that could affect future studies are not made in a systematic manner and, since the long-term evolution of the disease is not known, long-term follow-up of the cohort may not be an initial consideration unless a specific group of researchers takes on this responsibility independently.

Epidemiologists play a fundamental role throughout an epidemic. Teamed with clinicians, toxicologists, and specialists in other areas such as infectious disease, epidemiologists should take a lead in the development of a working hypothesis and in the design of the initial epidemic studies. The epidemiologist's role also includes defining both the possible exposures and the exposed population in detail, as well as providing advice on biologic and environmental sample collection. Later, continued collaboration between epidemiologists and scientists from other disciplines is central for development of additional study designs, assessment of biologic and environmental sample validity, selection of study subjects, and data analysis (79).

A little recognized role of epidemiologists in crises such as toxic oil syndrome, in addition to assisting public health authorities and advising in all phases of the investigation, is to make every effort to ensure the accuracy of data and other pertinent information, as situations of this type often have legal repercussions lasting well beyond the near term public health issues. Additionally, in spite of the complexity of crises such as toxic oil syndrome and the participation of scientists and others from many disciplines, comprehensive responsibility for the epidemic must be handled by only one group, typically the pertinent public health officials, including epidemiologists. Finally, while decisions to fund long-term research and follow-up activities may fall to political authorities, input from epidemiologists is essential to provide accurate information on which to base critical future health care decisions, including estimates of future health care system needs.

SUMMARY

Toxic oil syndrome burst upon the scene in Spain in May of 1981, draining the resources of a newly evolving political and social medicine system. The vehicle of the causative toxic agent was identified as an illicit oil that had been diverted from industrial use and refined in order to remove the aniline denaturant, and that was sold in unlabeled 5-liter containers by itinerant salesmen. Over 20,000 people were ultimately affected, and over 1,200 deaths from all causes have been recorded in the affected cohort.

The epidemiologic investigation of toxic oil syndrome involved all facets of investigative and analytical work, from visits to factories and interviewing workers, to sophis-
ticated chemical and statistical analytical techniques. This investigation serves as a further illustration that data and information of all types, and from a wide range of fields, need to be systematically collected and evaluated in order to best resolve an epidemiologic mystery. Astute clinical observation of the patients, however, led to the hypothesis that toxic oil syndrome was a result of a toxic exposure. In this and other epidemics of unknown etiology, clinical observation and the intense scrutiny of patients’ histories, signs, and symptoms by treating clinicians have often led to hypotheses that could be tested epidemiologically. When there are medical unknowns, the role of the astute clinician continues to be crucial.

The toxic oil syndrome epidemic is an example of how even a developed country can be affected by a massive epidemic of environmental origin if failures occur in the systems that control and regulate the food supply or other consumer products. However, such failures could occur anywhere that large commercial networks operate on the regulatory edge, and if these businesses lack an in depth knowledge of the consequences of alterations in manufacturing conditions. Such was the case with eosinophilia-myalgia syndrome as well, when apparently minor alterations in manufacturing conditions of L-tryptophan led to an increase in impurities in the product that were later associated with the illness. These risks are even greater in countries with few or inconsistent control systems, making the food and drug supply potential portals of entry for serious health hazards, as is further exemplified by the tragic episode of pediatric renal failure in Haiti associated with a legitimate consumer product, paracetamol elixir, that had been manufactured using a fraudulently supplied toxic ingredient, diethylene glycol (81).

The potential toxicants in the adulterated rapeseed oil were present in extremely small amounts. If fatty acid anilides or related compounds are indeed the etiologic agents in toxic oil syndrome, then these compounds must be extremely toxic at the parts per million concentrations at which they were found. Further, the roles of causative agents in the development of disorders such as scleroderma, eosinophilic fasciitis, eosinophilic perimyositis, and other similar diseases are unknown, but scientists can speculate that some sort of low level environmental agent may play a role if such extremely small quantities of contaminants are indeed capable of causing disease.

Although the exact identity of the etiologic agent in toxic oil syndrome remains unknown, work on toxic oil syndrome continues. Follow-up clinical studies and long-term mortality studies are under way. Investigation of the mechanisms involved in toxic oil syndrome continues. The identification of suspect chemical compounds, their characterization, and effects will hopefully one day contribute to the prevention of other similar diseases.

REFERENCES


