Mortality among People Affected by Toxic Oil Syndrome

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The authors conducted a mailed questionnaire survey of a 5% sample of the cohort of 20643 people officially recognized by the Spanish government as having had toxic oil syndrome, a previously undescribed illness that was epidemic in Spain in 1981. After three mailings of a letter and questionnaire, responses for only 66% of the sample had been received. Nevertheless, responses were obtained from virtually all remaining patients (or surrogates for them in the cases of patients that had died) when they were sought by telephone. In 1981, there was clear-cut excess mortality in the cohort (standardized mortality ratio [SMR] 6.51; 95% confidence interval [CI] : 3.92-10.17). During the period January 1982 through 7 March 1988, there was no statistically significant overall mortality excess except during the period 1982-1983 among people aged <65 years (SMR 2.26; 95% CI : 1.03-4.29). Toxic oil syndrome substantially altered the patterns of mortality among affected people. Analysis of deaths by cause among the TOS cohort will be useful for further evaluation of the long-term impact of the TOS epidemic.

In 1981, an epidemic of a previously unrecognized illness occurred in central and northwestern Spain. Some 20000 people were affected, and the disease was severe enough to require hospitalization for more than 11000.1 The illness, now called toxic oil syndrome (TOS), apparently arose as the result of consumption of oil mixtures containing rapeseed oil denatured with aniline.17 The clinical features of TOS varied somewhat from patient to patient. Nevertheless, in the initial acute phase they generally included cough, dyspnoea, and pulmonary infiltrates. Findings of the acute phase resolved in surviving patients but were followed in as many as half of the cases by intermediate and chronic phases involving severe muscle pain, intense eosinophilia, ascending polyneuropathy, sclerodermiform skin changes, pulmonary hypertension, and other manifestations. The clinical features of TOS and their phasic appearance among affected people have been described elsewhere.1,2,8-11

The results of early studies of the TOS epidemic documented substantial mortality among those affected. The death-to-case ratio during the acute pulmonary phase, when patients died largely from respiratory failure, exceeded one per cent. By 1983, more than 300 deaths due to TOS had been reported.1 Nevertheless, our initial analyses of data on these deaths indicated substantial underascertainment, despite obligatory reporting of mortality among TOS patients. We therefore undertook the current study, the aims of which were (1) to study the long-term patterns of mortality among TOS patients and (2) to assess the feasibility of following the cohort over the long-term by means of mailed questionnaires and telephone calls.

METHODS

Sampling Frame
We chose to study the patients included in the official list of people affected by TOS (the 'census' or the 'TOS cohort'). This list was developed by the now-defunct Plan Nacional para el Sindrome Tóxico (PNST) for use in administering the Spanish government's programmes of financial compensation, social services, and special medical care for officially
recognized TOS patients and their families. Diagnostic criteria for TOS were developed and used to determine who should be included in the census, but these criteria were not applied with absolute consistency. In particular, clinical judgement sometimes entered into decisions regarding whether to include a specific patient, especially when reviewing appeals of patients excluded from the census.

In the course of previous work, we have encountered problems in using the census. Many data have not been updated since they were originally entered in 1981 or 1982. Errors in identifying information are frequent, and for many patients, important identifiers (e.g., address, month or day or birth) are missing. Thus, some additional work (for example, review of other data files or a phone call to the medical facility where a particular patient was treated) has frequently been required to contact censused patients.

Despite these problems and the absence of uniformly applied entry criteria, we have found, in the course of conducting several epidemiological studies on TOS, that review of the medical records of patients listed in the census generally shows their illnesses to meet a reasonably specific case definition of TOS. The sensitivity (completeness) of the census is more difficult to evaluate. Nevertheless, on the basis of (1) the powerful incentives for affected patients to register for the census (substantial financial benefits and special medical care), (2) the similarity between the number of people in the TOS census (20643) and the number of people in the TOS cohort. In order to choose a sample that was representative with regard to sex, age, and geographical location, we sorted the census on these variables, began at a randomly chosen starting point, and sampled every 20th record. In this manner we sampled 1032 of the 20643 patient records in the census.

Procedures for Data Collection

We developed a two-page questionnaire for patients to report health events in the previous year. In addition, the questionnaire contained items on identifying data, illness among family members, and children born to affected parents since the epidemic. A letter accompanying the questionnaire explained that the patient was being asked to participate in a study, the aim of which was to determine the extent to which TOS patients were suffering from illness and death to a different extent or from causes which differed from the rest of the Spanish population. A return-addressed postage-paid envelope was provided so that the patient could respond at no cost. The letter requested family members of patients who had died to reply to the questionnaire, giving the date and place of the patient's death.

Sampling Procedure

Because resources were limited, we confined our study to a systematically chosen 5% sample of the TOS cohort. In order to choose a sample that was representative with regard to sex, age, and geographical location, we sorted the census on these variables, began at a randomly chosen starting point, and sampled every 20th record. In this manner we sampled 1032 of the 20643 patient records in the census.

Data Collection Instrument

We attempted to telephone any patients who had not responded by 19 August 1988, or whose questionnaire had been returned as undeliverable and for whom no correct address could be found. We obtained patients' telephone numbers from directories or the telephone information service. In cases where no telephone number was available, we sought assistance over the telephone from neighbours, relatives, police, the Spanish Civil Guard (paramilitary police), municipal record keepers, physicians, health care institutions, and others, in an attempt to locate the patients.

When a patient was found through the telephone search, the questionnaire was administered over the phone. When someone other than the patient being sought responded for the patient and indicated that the patient had died, particulars of the death, including date, location, and attending physician or medical institution, were recorded.

We eventually found four of the 28 people for whom we initially lacked sufficient identifying data to send letters and questionnaires, and these patients were included in our analyses of mortality. Patients who did not return our calls, but whose vital status we were able to determine by means of phone conversations...
with their neighbors or family were also included in the mortality analysis.

We judged it impossible to find the remaining 24 patients, for whom we had only the name and no other identifying data, either from the census or from any other case listings or files to which we had access. This judgement was based, in part, on the extensive duplication of both first and last names among people in Spain. Such patients were included in neither the numerator nor the denominator of the proportions of people responding at each stage of the study, since there was never really any possibility of assessing their response to a questionnaire or determining their vital status. They were also excluded from the analysis of mortality.

Statistical Methods

The response rates to the first, second, and third mailed questionnaires and the subsequent telephone follow-up were calculated as simple proportions.

The numbers of deaths in the cohort were tabulated for the following periods: 1 May through 31 December 1981; each calendar year 1982 through 1987; and 1 January through 7 March 1988. 1 January through 30 April 1981 was not included in the evaluation of 1981 mortality because 1 May 1981 was the approximate date the epidemic began and was therefore considered the first date for any real risk of death due to TOS. Similarly, 8 March through 31 December 1988 was not included in the 1988 mortality evaluation, since we could not be certain of complete ascertainment of any deaths occurring after the study began.

We calculated standardized mortality ratios (SMR) for each time period mentioned above, using the set of age- and sex-specific death rates of the Spanish population as a whole in the year death occurred as the standard. Both SMR and directly adjusted rates were calculated on the basis of exact numbers of person-days at risk for each age and sex stratum. For each sex, age was stratified into a single-year category for the first year of life, a 4-year category for ages 1-4 years, 16 5-year age categories for ages 5-84 years, and a final category of ≥85 years. Thus, there were 19 age strata for each sex, a total of 38 age-sex strata.

To examine the differing effects of TOS on mortality among older and younger people, we calculated SMR and 95% confidence intervals (CI) separately for people aged 0-64 years and ≥65 years. These figures were calculated for the three time periods, 1 May 1981-31 December 1981; 1 January 1982-31 December 1983; and 1 January 1984-7 March 1988.

Exact Poisson 95% CI for SMR were calculated using a computer program we developed. A two-tailed $P$ value of ≤0.05 was considered statistically significant.

RESULTS

Representativeness of the 5% Sample

The distribution of ages of patients in the 5% sample of 1032 people was very similar to that of the cohort as a whole (Table 1). On 31 December 1982, the mean age in both groups (including the 19157 and 1010 for whom information on year of birth was available in the entire TOS cohort and 5% sample respectively) was 35.2 years. This figure takes into account the ages that dead cohort members would have reached had they survived through 1982.

The distribution by sex of the two groups were also extremely similar. Of the 20636 patients in the entire cohort for whom information on sex was available, 12530 (60.7%) were female, extremely close to the proportion of 60.8% (627) females among the 1032 patients in the 5% sample.

### Table 1: Distribution of ages in years at 31 December 1982 of patients in the toxic oil syndrome cohort and the 5% sample, Spain

<table>
<thead>
<tr>
<th>Group</th>
<th>Lowest value</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>90</th>
<th>95</th>
<th>99</th>
<th>Highest value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort (N = 19157)$^b$</td>
<td>0</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>18</td>
<td>35</td>
<td>50</td>
<td>61</td>
<td>68</td>
<td>78</td>
<td>94</td>
</tr>
<tr>
<td>5% sample (N = 1010)$^b$</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>18</td>
<td>35</td>
<td>50</td>
<td>61</td>
<td>68</td>
<td>78</td>
<td>87</td>
</tr>
</tbody>
</table>

$^a$ For patients that died before that date, the age they would have reached is included in the distribution.

$^b$ Year of birth was missing for 1486 patients (7.2%) of 20643 in the entire cohort and ultimately (after updating birthdate information from patient questionnaires) for only 22 patients (2.1%) of 1032 in the 5% sample.
Of the 504 patients, 118 responded (23.4% of those in the second mailing, 11.8% of the total). Letters and questionnaires to eight patients for whom we had no alternative source of address (1.6% of the second mailing, 0.8% of the total) were returned as undeliverable. We sent a third mailing to the remaining 387 patients (75.0% of the second mailing 37.6% of the total).

Of these 378 patients, 60 responded (15.9% of the third mailing, 6.0% of the total). Letters and questionnaires to nine patients for whom we had no alternative source of address (2.4% of the third mailing, 0.9% of the total) were returned as undeliverable. Although three presumably correctly addressed letters and questionnaires were sent to them, 309 patients failed to respond (81.7% of the third mailing, 30.8% of the total).

We then tried to telephone these 309 patients and the 33 patients (3.3%) for whom we had apparently lacked a correct address, a total of 342 patients (34.1%). Although numerous telephone calls to friends, family, neighbours, health institutions, physicians, police, and municipal records centres were sometimes required to locate a particular patient, we eventually succeeded in contacting and interviewing 339 patients by telephone, that is, all but three (99.1%) of those in the telephone phase of the study and 33.8% of the 1004 patients for whom we initially had some address. One patient could not be found. The two remaining patients were found, but they did not return our telephone calls. We were nonetheless able to ascertain the vital status (alive) of these last two patients from the people who had referred us to them.

We frequently found that patients had moved but that the letter-questionnaires still reached them. We specifically examined the responses in the subset of 560 patients for whom the names and addresses we used for our mailings were not substantially different from those on the returned questionnaires. A total of eight of these ‘correctly addressed’ letter-questionnaires corresponded to deceased patients and were ‘correctly’ sent to the patients’ residences at the time of their deaths. These letter-questionnaires were returned as undeliverable during one or another of the three mailings and were not discovered to have been correctly addressed until after telephone contact was made later with people who could explain the situation.

In this ‘correctly addressed’ subgroup, there were 302 (53.9%) responses received from the 560 patients to whom letters and questionnaires were sent in the first mailing, 51 (20.2%) responses from the 252 patients targeted in the second mailing, and 29 (14.6%) responses from the 199 patients involved in the third mailing. All but two of the remaining 178 patients responded to the telephone enquiry phase of the study. The proportion of patients responding in each phase of the study was not substantially better in this correctly addressed subgroup than in the study as a whole (Table 3).
LONG-TERM MORTALITY AFTER TOXIC OIL SYNDROME

TABLE 3 Responses to mailed and telephone questionnaires, 5% sample of cohort of people affected by toxic oil syndrome, Spain

<table>
<thead>
<tr>
<th>Point of response</th>
<th>Patients for whom there was address information (N = 1004)</th>
<th>Patients for whom address information was correct (N = 560)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. % of those remaining</td>
<td>% of total</td>
</tr>
<tr>
<td>First mailing</td>
<td>484 (48.2)</td>
<td>(48.2)</td>
</tr>
<tr>
<td>Second mailing</td>
<td>118 (23.4)</td>
<td>(11.8)</td>
</tr>
<tr>
<td>Third mailing</td>
<td>60 (15.9)</td>
<td>(6.0)</td>
</tr>
<tr>
<td>Telephone follow-up</td>
<td>339 (33.8)</td>
<td>(33.8)</td>
</tr>
<tr>
<td>Non-respondent</td>
<td>3 (0.3)</td>
<td>(0.3)</td>
</tr>
<tr>
<td>Total</td>
<td>1004 (100.1)</td>
<td>(100.1)</td>
</tr>
</tbody>
</table>

**Mortality**

Although we had sufficient address information to attempt to contact only 1004 of the 1032 patients in the sample by mail, we located five of the remaining 28 patients in the course of the telephone search and ascertained their vital status. These five patients were considered together with the 1003 patients to whom questionnaires were mailed and whose vital status was eventually ascertained, either by mail or by telephone. Thus, a total of 1008 patients were included in the analysis of mortality.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Deaths</th>
<th>Age- and sex-adjusted rate per 1000 person-years in the 5% sample of the TOS cohort*</th>
<th>Age- and sex-adjusted rate per 1000 person-years in the Spanish population*</th>
<th>Standardized mortality ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 May 1981-31 December 1981</td>
<td>19</td>
<td>30.65</td>
<td>7.77</td>
<td>6.51 (3.92-10.17)</td>
</tr>
<tr>
<td>1 January 1982-31 December 1982</td>
<td>5</td>
<td>4.88</td>
<td>7.41</td>
<td>1.15 (0.37-2.69)</td>
</tr>
<tr>
<td>1 January 1983-31 December 1983</td>
<td>6</td>
<td>9.22</td>
<td>7.62</td>
<td>1.29 (0.47-2.81)</td>
</tr>
<tr>
<td>1 January 1984-31 December 1984</td>
<td>2</td>
<td>2.74</td>
<td>7.35</td>
<td>0.41 (0.05-1.48)</td>
</tr>
<tr>
<td>1 January 1985-31 December 1985</td>
<td>4</td>
<td>10.44</td>
<td>7.47</td>
<td>0.77 (0.21-1.96)</td>
</tr>
<tr>
<td>1 January 1986-31 December 1986</td>
<td>4</td>
<td>4.32</td>
<td>7.26</td>
<td>0.74 (0.20-1.89)</td>
</tr>
<tr>
<td>1 January 1987-31 December 1987</td>
<td>6</td>
<td>6.73</td>
<td>7.04</td>
<td>1.04 (0.38-2.27)</td>
</tr>
<tr>
<td>1 January 1988-7 March 1988</td>
<td>1</td>
<td>5.39</td>
<td>7.07</td>
<td>0.90 (0.02-5.02)</td>
</tr>
</tbody>
</table>

* Values standardized to the age and sex structure of the 1981 Spanish national population.
patients. Spain, 1981-1988

specifically requested that research be conducted on health are unknown. In fact, representatives of

no statistically significant excess mortality in our sample after 1981. There were 28 deaths during this period, a figure not substantially different from the 31.4 deaths expected. During the years 1982-1988, the age-and sex-adjusted mortality rate in our sample oscillated around that of the country as a whole in 1981. The lowest SMR (0.41) occurred in 1984 but was immediately preceded by the year for which the highest SMR (1.29) was recorded (1983). None of the SMR calculated for the years subsequent to 1981 showed a statistically significant deviation from unity. Nevertheless, the number of deaths during the period 1982-1983 among people <65 years old was significantly higher than expected (SMR = 2.26; 95% CI: 1.03-4.29) (Table 5).

When all ages were considered together, there was no statistically significant excess mortality in our sample after 1981. There were 28 deaths during this period, a figure not substantially different from the 31.4 deaths expected. During the years 1982-1988, the age-and sex-adjusted mortality rate in our sample oscillated around that of the country as a whole in 1981. The lowest SMR (0.41) occurred in 1984 but was immediately preceded by the year for which the highest SMR (1.29) was recorded (1983). None of the SMR calculated for the years subsequent to 1981 showed a statistically significant deviation from unity. Nevertheless, the number of deaths during the period 1982-1983 among people <65 years old was significantly higher than expected (SMR = 2.26; 95% CI: 1.03-4.29) (Table 5).

DISCUSSION
The relatively low cumulative response rate (66%) to three mailed health questionnaires was surprising because TOS patients are generally quite aware that they have suffered from a life-threatening and previously undescribed illness that is still symptomatc for many patients and for which the long-term effects on health are unknown. In fact, representatives of some of the associations of affected people have specifically requested that research be conducted on the possible long-term adverse effects of the causal agent of TOS. Nevertheless, the response rate in this pilot study was substantially below that reported for a number of other health studies conducted elsewhere and involving mailed questionnaires. These results suggest that this method of data collection may not be particularly effective in Spain. Interestingly, whether or not we sent the questionnaire to an up-to-date address had little effect on the probability of eliciting a response. Many incorrectly mailed questionnaires apparently found their way eventually to the person for whom they were intended.

One factor that may have contributed to the low response rate was that our questionnaires were mailed during the widely publicized trial of people accused of having been involved in the distribution and sale of the oil that contained the causal agent. We were told by some patients that they had been reluctant to answer the questionnaire because they were afraid that their responses might in some way support the defendants' case in the trial. Distrust in this regard was so great that one patients' organization told us that it would urge its members not to respond to the survey. Unfortunately, we are unable to quantify the effect of this temporary factor in reducing the response rate.

In marked contrast to the poor response to the mailed letters and questionnaires, the response to our attempts to contact patients by telephone met with success far exceeding our initial expectations. Once located by telephone, only two patients persistently refused to return our calls, and once on the telephone with one of our interviewers, none refused to give the requested information. Many people unconnected with the epidemic or its investigation helped us locate those who had moved or who did not have their own telephones. Information operators patiently reviewed lists of names and numbers looking for possible matches with the people for whom we were searching. The operators were often willing to give us the number of a neighbour or someone with similar last names—two last names is the norm in Spain—so that we could call them for any information they might have regarding the person being sought. Patients' relatives and neighbours, or even the local police or officers of the Spanish Civil Guard, upon learning that we were working in the Ministry of Health and Consumer Affairs and were engaged in a study of TOS, sometimes made special visits to houses without telephones to ask the occupants to call us. Municipal departments of vital statistics were frequently willing to tell us whether a patient had moved and, if so, to give us the new address. Using these techniques with some persistence, we were eventually able to locate all but one of the 1004 patients for whom we were able to find an apparently complete mailing address when the study began.

We do not know the precise reasons for the substantial success of telephone interviewing despite the unimpressive response to mailed questionnaires. We speculate, however, that one reason may be the relative rarity of telephone enquiries in Spain. Although they are becoming increasingly frequent they have not yet reached the point of becoming annoying. Another factor favouring our success may have been the well-known devastating consequences of the TOS epidemic and many people's consequent desire to aid the investigation. Finally, experience showed that upon

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<tbody>
<tr>
<td>0-64</td>
<td>11.27 (6.31-18.58)</td>
<td>2.26 (1.03-4.29)</td>
<td>0.45 (0.12-1.15)</td>
<td></td>
</tr>
<tr>
<td>65+</td>
<td>2.52 (0.69-6.46)</td>
<td>0.40 (0.05-1.44)</td>
<td>0.96 (0.51-1.65)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 5: Standardized mortality ratios (95% confidence intervals) by time period and age group in a 5% sample of toxic oil syndrome patients, Spain, 1981-1988.
reaching the patient by telephone and presenting the purpose of the interview verbally, respondents' distrust of the interviewers' motives generally disappeared.

During 1981, the year in which the epidemic first arose and a number of disease manifestations reached maximum intensity, there was clearcut excess mortality among the affected cohort. There was continued statistically significant excess mortality among people <65 years during 1982–1983, but otherwise our study showed no obvious or statistically significant mortality excess in the years subsequent to 1981. In fact, after 1983, the numbers of deaths in all but one year was less than expected (Table 4). This trend was not statistically significant in any given year, but because of our relatively small sample size, confidence limits around the SMR were wide. The trend might prove statistically significant in a similar study involving either a larger sample or the entire TOS cohort.

Despite the absence of any clearcut overall mortality excess after 1981, the trend toward death at a relatively young age in 1982–1983 was both substantial and statistically significant. Thus, premature mortality continued to occur in the cohort after 1981, most likely as a result of the late effects of TOS. The trend toward premature death among TOS patients appeared to diminish with time.

The fact that overall SMR were not significantly elevated immediately following 1981 despite the cohort's shift toward younger ages at death implies that fewer than expected deaths were occurring among older cohort members. It is possible that this finding represents a 'healthy survivor' effect; elderly cohort members (perhaps those with chronic illnesses) who might otherwise have died in years subsequent to the epidemic may have succumbed to TOS in 1981. It is also possible that survival of elderly patients after 1981 was improved as a result of better-than-average medical care in the special clinics set up for TOS patients after the epidemic. Alternatively, the crippling effects of chronic TOS may have limited some older cohort members' activities to such an extent that they no longer faced many hazards of everyday life (e.g., death from motor vehicle collisions).

This pilot study did not include an analysis of death by cause. Epidemiological investigations involving ascertainment of the official cause of death are difficult to conduct in Spain, because no centralized mechanism for obtaining death certificates of a study population exists. Nevertheless, a quantitative comparison of causes of death among TOS patients with those in the general population of Spain would be extremely useful, and such a study is underway. The results of this study may shed light on the reasons for the patterns of increase and decrease in death rates in the TOS cohort and may also highlight conditions particularly likely to cause death in this group. Physicians' awareness of such conditions could aid in their early diagnosis and treatment and might improve the life expectancy of TOS patients.

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