EDITORIAL

The limits of epidemiology and the Spanish Toxic Oil Syndrome

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The outbreak of the condition eventually called Toxic Oil Syndrome (TOS) in Madrid and north-western Spain in May 1981 was unique because of its size (20 000 affected, over 300 dying within a few months, a few thousand invalids), the novelty of the clinical condition, and the complexity of its aetiology. The illness is currently thought to be a multisystem disease initiated by a non-necrotizing endothelial injury, with a likely immune mechanism in its inception and/or evolution.1 Clinically, it started as a varying combination of fever, rash, lung and pleural effusions, myalgias, paresthesias, and eosinophilia: in a sizeable proportion of survivors it evolved to lung hypertension, cachexia, contractures, and scleroderma.

Shortly after the episode, a collaboration started between the Spanish Government and the European Office of the World Health Organization, leading to the creation of a Joint Scientific Committee (of which I have been a member since the mid-1980s), which identifies priorities for research, and reviews applications for funding scientific projects. It has published an update of present knowledge.1

The mention of ‘oil’ in the syndrome’s name reflects the prevailing aetiological hypothesis, based on a complex chain of events. Twenty years ago, in order to protect its own edible oil industry, Spain allowed the import of rapeseed oil, but only for industrial uses: the oil had to be made inedible through the addition of aniline (usually 2%). Legal import of denatured rapeseed oil, particularly from France, was common: much of it was subsequently illicitly refined in order to remove the colour, and sold as olive oil. Several plants throughout Spain were involved in the process of illicit refining, on behalf of several oil distributors. A number of studies indicated that there was a single source of TOS-related oils.2 This was a shipment of denatured rapeseed oil entering Spain in March 1981, promptly sent to the ITH (Industria Tranera de Hidrogenacion) refinery in Seville, mixed with other oils by the distributor RAELCA in Madrid and finally (after mid-April) marketed in typical plastic containers through street vendors in Madrid and in the north-western provinces of Spain. An ‘accident’ is postulated to have occurred on the occasion of the processing of that particular batch of denatured rapeseed oil.

A recent review3 narrated how the unforeseeable hypothesis of the fraudulent oil was generated in the hectic days of May–June 1981, when hundreds of new cases of the ‘obscure disease’ were reported as occurring daily. Underlying the hypothesis were the results of an extemporaneous intra-hospital case-control study, a few surveys of cases, and the detection of aniline derivatives in oil samples reported as being consumed in families where cases had occurred. On this basis, on 10 June, the Spanish government officially announced that the source of the outbreak had been identified in a batch of alleged edible oil and that guaranteed olive oil was to be given to anybody returning any oil thought to be toxic. (This led to the creation of a repository of oils relevant or possibly relevant to the new disease which turned out to be a precious tool for later studies.) Additional evidence included several case-control studies carried out in 1981–1982 (most of which were affected by recall bias), investigation of clusters of cases in convents in the Madrid area, identification and interpretation of a handful of TOS cases occurring outside the original area or after the outbreak had subsided. Finally, comparing oils preserved in the repository between those returned by families in which cases of TOS had and had not been reported showed a clear-cut correlation between the concentration of aniline derivatives and the odds ratio for disease. There were two independent, such ‘toxi-epi’ studies. Chemical analyses in the second study used more sophisticated methods and identified the esters of 3-[(N-phenylamino)-1,2-propanediol as the most specific markers of case oils. These compounds were also present in a sample of oil produced in April 1981 at ITH and in oils produced in the laboratory during attempts to mimic what may have happened in ITH when the single batch of lethal oil was produced.3

In 1987, the available epidemiological findings indicated causality to the point where it was accepted (also through a deposition by Sir Richard Doll) by the Spanish Court, which condemned and sent to jail a number of people involved in the oil circuit. Nowadays, searching Medline with the keyword ‘Toxic Oil Syndrome’ leads to over 300 entries, covering epidemiology, aetiology, clinical evolution, pathogenesis, immunology, and oil reconstitution.

This concise, schematic and incomplete account of TOS puts into perspective the content of books and articles in the media, addressed to the general public3–8 which deny a role for the fraudulently processed rapeseed oil in the aetiology of the ‘obscure disease’ (a ‘theory palpably bogus’ according to Woffinden). Moreover, these publications suggest that, over 20 years, through subterfuge and reticence, scientists investigating TOS together with Spanish and international health authorities have artfully and surreptitiously covered up a different truth. Proposed hidden truths range from accidental massive pesticide contamination of agricultural products to chemical warfare disaster. Allusion is made to other episodes in which (according to the authors of the reports) the public was given a distorted version of facts and responsibilities, often with the connivance of scientists. The examples range from the alleged effects of organophosphorus

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(OP) pesticides on farmers in the UK\(^8\) to bovine spongiform encephalopathy (BSE).\(^6\) Therefore, undoubtedly, this was also the case of the TOS episode.

None of these reports is scientific or has the structure of a scientific document. Several investigations are alluded to as providing evidence for hypotheses alternative to the fraudulent oil one, but none is described in terms of design and methods (incidentally, none of these studies are traceable in the conventional scientific literature). Doubts about the rapeseed oil hypothesis expressed in the laypress by Spanish and international health officers are reported, but no indications of the criteria for retrieving such statements and the underlying scientific basis are given. The distinction between evidence-based and other pieces of information seems to be light years away from the authors’ minds. Apparent contradictions within the ‘fraudulent’ rapeseed oil theory are highlighted as proof of its unsoundness, with no consideration of alternative explanations. For instance, the fact that the decline of the epidemic curve began before the government’s announcement of 10 June 1981 does not necessarily invalidate the oil hypothesis (indeed, RAELCA’s marketing strategies are largely unknown). Similarly, the observation that in the toxi-epi studies approximately one-third of the cases of TOS-related sacking occurred in the fragile democracy that was Spain in May 1981 (3 months after Colonel Antonio Tejero stormed the Spanish parliament). The first and most reputable person to be sacked was Dr Antonio Muro y Fernandez-Cavada, director of the Hospital del Rey and head of the unit where Granero Moré was working. Muro, a passionate character, realized early that the lethal ‘obscure disease’ was not a respiratory infection but a massive foodborne intoxication, which he attributed to the ingestion of tomatoes containing OP residues. After publicly reporting his interpretation, on 15 May he was relieved of his duties as hospital director, ‘because of a nervous breakdown’. Muro’s focus on tomatoes and OP was wrong. Not only does OP toxicity differ from the clinical picture of TOS, but Muro’s team’s rationale for sustaining their hypothesis is untenable. Granero Moré and Pérez insist on the irrelevant parallelism between the systemic nature of the disease and the fact that Nemacur is a systemic pesticide. In their book, they also indirectly allude to chemical determinations of OP compounds in case-related oils the results of which are not reported (nevertheless, page 75 depicts structural formulæ of some OP, handwritten by Muro). Mention is also made of an enquiry into over a thousand patients and as many controls carried out until Muro’s death in 1985, however, the design and results remain unknown to the reader (neither is this study traceable through the conventional databanks of the scientific literature).

All of these reports fail in providing an insight to the vital point of how the complexities and uncertainties of causal inference should be shared between experts and the general public. The reader is bluntly told that the oil hypothesis is untenable and fraudulent: since no specific chemical cause of the disease has been found and since the clinical condition has not been reproduced in laboratory animals, results of the epidemiological studies can be discarded.

In fact, the puzzle of TOS aetiology deserves more elaborate consideration, in terms of both causal inference and communication with the public. The fraudulent oil hypothesis is supported by the very high strength of the association and by the consistency of results between independent epidemiological studies. The association is specific in the sense that only one type of exposure is related to the outcome.\(^9\) Admittedly, the fact that the exposure cannot be described as a chemically defined agent is unsatisfactory. What is missing is biological plausibility (i.e. consistency with knowledge on the mechanisms of toxicity and pathogenesis), as well as the demonstration that either experimentally reconstituted oils, case-related oils or aniline derivatives found in the latter reproduce a condition comparable to TOS (or to some of its clinical components) in laboratory animals. How much weight should be given to these missing pieces of the puzzle, when there is no biological model for TOS? As a matter of fact, no disease comparable to TOS has been reported to occur spontaneously or under experimental conditions in any animal species, including man. Only the condition known as Eosinophilia Myalgia Syndrome in humans shares some (but not all) features with TOS. This condition also has, as yet, only occurred as a unique outbreak in the history of medicine.\(^10\)

Helping the layman to ponder about causality is a healthy exercise: familiarity with Bradford Hill’s criteria is an important step towards a proper partnership between experts and laymen in the management of environmental risks. It is a pity that none of the reports under review bring such principles to the attention of the layman (who is entitled to his/her autonomous causal inference). Perhaps there was some embarrassment about Bradford Hill’s emphasis on the fundamental question: is there any other way of explaining the set of facts before us? Is there any other answer that is more likely than cause and effect?

References