JACC Vol. 18, No. 5
November 1, 1991:1367–79

SEMINAR ON CARDIOVASCULAR MANIFESTATIONS OF THE TOXIC OIL SYNDROME AND RELATED CONDITIONS—III*

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Cardiac Abnormalities in the Toxic Oil Syndrome, With Comparative Observations on the Eosinophilia-Myalgia Syndrome

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Early in the course of studies of the Spanish toxic oil syndrome it was recognized that vascular lesions were a major problem, most logically attributable to endothelial damage by the toxic oil. However, most clinical attention has been directed to the pulmonary complications and the evolution into a scleroderma-like illness later.

In this study of 11 victims of the toxic oil syndrome careful postmortem studies of the coronary arteries and conduction system and neural structures of the heart demonstrated major injury to all those components of the heart. Obliterative fibrosis of the sinus node in four cases resembled findings in fatal scleroderma heart disease, and in eight the cardiac lesions resembled those of lupus erythematosus.

The more impressive pathologic features involved the coronary arteries and neural structures, which were abnormal in every heart. The arterial disease included widespread focal fibromuscular dysplasia, but there was also an unusual myointimal proliferative degeneration of both small and large coronary arteries in five patients, four of whom were young women. In two hearts, portions of the inner wall of the sinus node artery had actually detached and embolized downstream. Coronary arteritis was rarely found. Inflammatory and noninflammatory degeneration of cardiac nerves was widespread. Fatty infiltration, fibrosis and degeneration were present in the coronary chemoreceptor.

In most respects these cardiac abnormalities resemble those described in the eosinophilia-myalgia syndrome caused by an altered form of L-tryptophan. In both diseases there is good reason to anticipate more clinical cardiac difficulties than have so far been reported, and even more basis for future concern, especially relative to coronary disease and cardiac electrical instability.

(J Am Coll Cardiol 1991;18:1367–79)

Although rapeseed and the oil derived from it have been items of human consumption in some civilizations for several thousand years, the use of rapeseed oil as food has been familiar in the western world for less than half a century (1). During this recent period, increasing evidence of a cardiotoxic effect by rapeseed oil led to growing concern about its human use and the subject was reviewed in depth in Sweden in 1975 (2). That review and other reports (3–6) led one of us (T.N.J.) to call attention in 1980 (7) to rapeseed oil and its possible hazards at a time when extensive modifications of the American diet were being proposed, including the active recommendation of items such as rapeseed oil. In 1981 a devastating epidemic in and near Madrid, Spain was caused by the consumption of an adulterated form of rapeseed oil (8), killing several hundred people and poisoning many thousands. In fact, recurring epidemics of poisoning by various oils are an interesting footnote in the history of medicine (9).

Toxic rapeseed oil. Early examinations of the Spanish toxic oil demonstrated that a variety of adulterants and foreign substances were present in some samples, leading to

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Manuscript received April 9, 1991, accepted May 14, 1991.

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*Parts I and II of this Seminar appeared in the September and October issues of the Journal (J Am Coll Cardiol 1991;18:707–17, 1043–7). This review is based on a presentation and discussion at a symposium entitled "Cardiovascular Manifestations of the Toxic Oil Syndrome and Related Conditions" held November 2, 1990 in Geneva, Switzerland at the headquarters of the International Society and Federation of Cardiology, the sponsoring organization.

0735-1097/91/$3.50

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a few suggestions that the rapeseed oil could not be blamed for the catastrophe (10,11). However, the definitive analysis of representative aliquots of the toxic oil demonstrated that the *only* two substances consistently present in all the samples were rapeseed oil and a variety of oleoanilides, presumably the residue of aniline (traces were present), which had been intentionally added to denature the rapeseed oil and make it suitable only for the industrial purposes of machine lubrication for which it had been imported (more on this later). The adulteration was a legal requirement because the importation of rapeseed oil for human consumption was prohibited in Spain (8).

Cardiotoxic lesions have been produced experimentally by feeding rapeseed oil to a wide variety of animal species, including not only mice and rats (12) but also pigs (13,14), and monkeys (15). Most of those demonstrations were the result of using oil from native rapeseed, which contains >40% erucic acid, a cis-13 docosenoic acid (unsaturated fatty acid). Now a new genetically altered rape plant bears seeds containing oil with less erucic acid and with its use the experimental cardiotoxic lesions have been reduced, but even this new rapeseed oil still produces cardiotoxic effects, only less severely (at least initially) and less rapidly (16,17). Furthermore, there appears to be significant cardiotoxicity from rapeseed oil itself (18,19), independent of the effect of erucic acid, though what this other component of rapeseed oil may be has not yet been determined. Features of the cardiotoxicity prominently include lipid accumulation within myocardial cells and resultant cellular necrosis and later focal fibrosis (2), but rapeseed oil also produces degenerative lesions in the coronary arteries (20).

This review will examine findings from our eight previously investigated cases of the toxic oil syndrome (21), some of which have now been restudied and to which we add three new cases. Because of our findings in the newer cases and from restudy of the older ones, we will focus upon the probable importance of coronary artery injury in the toxic oil syndrome and its consequences in both the early and the late stages of the disease. There is also impressive evidence of a neurotoxic effect on the heart (21) and other organs (21–24) by the toxic oil in these cases. Neurotoxicity of rapeseed oil has regrettably not been the subject of experimental studies in animals, at least to our knowledge. Finally, the focal myocardial necrosis and later fibrosis that have been so prominent in the animal experiments find their counterpart in the human cases we report.

Because many of the clinical features of the toxic oil syndrome bear a surprising resemblance to those in victims of another modern epidemic, the eosinophilia-myalgia syndrome (25–27), it is useful to include discussion of that syndrome, particularly in relation to the cardiotoxic effects (28).

Study Cases

A central registry in Madrid identifies and certifies Spanish cases that fit the criteria for a diagnosis of the toxic oil syndrome. In the first few weeks after the poisoning the major problems were a chemical pneumonia and marked peripheral eosinophilia, associated with muscle and joint pain; these were the principal factors in the early deaths (first few weeks). In the subsequent months and years many surviving victims have developed progressive pulmonary hypertension with severe cor pulmonale, especially those in the later fatal cases. Some of those who died later, as well as a number of chronically ill survivors, have exhibited muscular, cutaneous, esophageal and neurologic features of scleroderma. The scleroderma features and cor pulmonale were among the reasons why special studies of the 11 hearts in this report were undertaken.

Clinical features in the 11 cases are presented briefly in Table 1. There were four men and seven women whose ages ranged from 18 to 74 years; however, except for two men of 55 and 74 years, respectively, all nine other patients were <40 years old (range 18 to 39 years). At least 7 of the 11 had distinct clinical features of scleroderma. Although the time from ingestion of the toxic oil until death ranged from 11 months to 9 years, the cardiac histopathologic features (summarized in Table 2) were of the same nature, for all ages and either gender and any length of illness.

Histologic Examinations

The methods employed for histologic examinations included particular attention to the cardiac conduction system (sinus node, atrioventricular [AV] node and His bundle), the small coronary arteries and the neural structures of the heart. Details for examination of the human sinus node (29) and for the AV node and His bundle (30) have been published, as well as methods for study of neural structures of the heart (31,32). In brief, about 10 subserial slices (2 to 3 mm thick) were obtained from the regions of the sinus node and from the AV junction in each of the formalin-fixed hearts. After embedding in paraffin, at least 10 serial sections from each slice were routinely prepared with the Goldner trichrome stain. Special stains and additional serial sections were subsequently utilized, depending on the nature of findings in the initial serial section study. For studies of special intertruncal neural structures, a single block of proximal aorta and pulmonary artery was serially sectioned at 8 μm (32).

Gross Anatomic and Histopathologic Abnormalities of the Heart

The gross anatomic and histopathologic cardiac abnormalities are summarized in Table 2 and certain common features are apparent. In 10 of the 11 cases the right ventricle was hypertrophied, usually to a marked degree. Pulmonary

Table 1. Clinical Features of 11 Victims of the Toxic Oil Syndrome

Case	Age (yr)/ Gender	Time to Death After Eating Toxic Oil (yr)	ECG	Other Clinical Observations
1	18/M	1¼	Sinus tachy; RVH	Neuromuscular and cutaneous changes resembling scleroderma; pulmonary hypertension
2	24/F	4	RVH; terminal E-M dissoc	Neuromuscular and cutaneous abnormalities resembling scleroderma; pulmonary hypertension
3	19/F	3½	Sinus tachy; RAH; RVH	Neuromuscular abnormalities of scleroderma; pulmonary hypertension
4	55/M	4	1°AV block; RVH; RBBB; small Q wave in leads III, aVF	Old posterior myocardial infarct; generalized atherosclerosis; pulmonary hypertension; RVH
5	29/F	1½	None available	Atrophy of skeletal muscles, intercostals and diaphragm; pulmonary and renal infarctions; severe cerebral edema
6	26/F	5½	RAH; RVH	Pulmonary hypertension; chronic heart failure; neuromuscular and cutaneous abnormalities resembling scleroderma; terminal coagulopathy
7	18/F	5	Sinus tachy; RAH; RVH	Pulmonary hypertension; chronic heart failure; small interatrial septal defect; skeletal muscle atrophy; initial pneumonia, pulmonary infiltrates; eosinophilia
8	31/M	5½	Sinus tachy; RAH; RVH	Severe pulmonary hypertension; pulmonary artery thromboses; neuromuscular, cutaneous and esophageal features of scleroderma
9	25/F	8	Normal*	Severe pulmonary hypertension; left lower lobectomy for arteriovenous fistula; cardiorespiratory arrest and death; RVH
10	74/M	9	Sinus bradycardia	Adenocarcinoma with metastases; neuromuscular and cutaneous abnormalities resembling scleroderma; terminal bacteremia with multisystem emboli
11	39/F	9	Marked RVH; P pulmonale	Severe pulmonary hypertension (115/58 mm Hg); neuromuscular and cutaneous features resembling scleroderma

*The normal ECGs (several) in Case 9 are puzzling and unexplained, especially in view of severe pulmonary hypertension demonstrated during life and marked right ventricular hypertrophy found postmortem. AV = atrioventricular; E-M dissoc = electromechanical dissociation; F = female; M = male; RAH = right atrial hypertrophy; RBBB = right bundle branch block; RVH = right ventricular hypertrophy; tachy = tachycardia.

artery and parenchymal abnormalities have been reported previously (33) and are the subject of special review elsewhere in this Seminar (34).

Coronary arteries. These were abnormal in all 11 cases. The most frequent arterial histopathologic finding was focal fibromuscular dysplasia of small coronary arteries (Fig. 1 and 2), but in five hearts there was also an unusual foamy myointimal degeneration with sloughing of portions of the arterial wall and actual auto-embolization of arterial fragments downstream (Fig. 3 and 4). These unusual lesions were not associated with any arteritis; in fact, arteritis was a rare occurrence in all 11 hearts. It was notable that four of the five cases with sloughing arterial degeneration were young women aged 19, 24, 25 and 26 years. In one of these (Case 3) the foamy myointimal proliferative degeneration also involved the three major coronary trunks (left anterior descending, left circumflex and right coronary arteries) (Fig. 5 to 7) in a manner similar to that in the small coronary branches (Fig. 4).

This same arterial abnormality has been produced in experimental animals (20) fed rapeseed oil (Fig. 8). The arterial pathologic findings present in fatal cases of the toxic oil syndrome were recognized early (35) and are widespread, involving not only the heart but virtually every organ of the body. The general subject of vasculotoxic agents has been reviewed by Boor et al. (36), with particular reference to the toxic oil syndrome.

Neural lesions. Neural abnormalities have also been an important pathologic feature receiving early recognition in fatal cases of the toxic oil syndrome (22,23). Extracardiac neural and vascular abnormalities are reviewed by Martinez-Tello elsewhere in this Seminar (24). Every one of the 11

Table 2. Histologic Cardiac Abnormalities in 11 Victims of the Toxic Oil Syndrome

Case	Coronary Arteries	Neural Structures	Conduction System
1	FFMD sinus node artery, AV node artery	Focal hemorrhagic necrosis nerves, ganglia, chmx	Scirrhous fibrosis of sinus node
2	Sloughing degeneration sinus node artery and chmx artery; FFMD sinus node artery and AV node artery	Extensive degeneration chmx; cardioneuropathy in sinus node, IAS, IVS, chmx region	Sinus node similar to that in LE
3	Telescoping auto-emboli sinus node artery and 3 branches; foamy myointimal proliferation and degeneration LAD, RCA, LCx; FFMD many small arteries	Cardioneuropathy near sinus node, chmx, LAD	Sinus node similar to that in LE
4	Sloughing degeneration chmx artery; moderate coronary arteriosclerosis; FFMD many small arteries	Focal degeneration chmx; cardioneuropathy, sinus node	Sinus node similar to that in LE; focal fibrosis IVS
5	FFMD sinus node artery; AV node artery	Cardioneuropathy AV node, IVS	Scirrhous fibrosis of sinus node
6	Sloughing degeneration and auto-embolization sinus node artery; chmx artery; myointimal proliferation, degeneration sinus node artery, AV node artery, IVS arteries; FFMD AV node artery	Extensive degeneration chmx; grainy necrosis nerves near chmx	Sinus node similar to that in LE
7	FFMD chmx artery, small arteries LV and IVS	Caseous necrosis nerves near chmx; edematous degeneration of nerves near chmx; hemorrhagic necrosis chmx; perineural and intraneural hemorrhage sinus node	Sinus node similar to that in LE
8	FFMD sinus node artery	Inflammation, degeneration of chmx; cardioneuropathy near sinus node	Sinus node similar to that in LE
9	FFMD, sloughing degeneration, sinus node artery, with auto-embolization; FFMD, sloughing degeneration AV node artery	Ganglionitis sinus node; inflammation, degeneration in chmx, with fatty replacement	Fatty replacement in sinus node; focal fat in His bundle
10	FFMD AV node artery, with some degeneration; FFMD chmx artery	Perineural fibrosis; focal neuritis; widespread perineural, intraneural hemorrhage with focal degeneration; some epineural hematoma; focal inflammation, degeneration chmx	Focal fat, severe fibrosis sinus node; extensive fatty replacement at AV node-His bundle junction
11	FFMD sinus node artery, AV node artery	Focal neuritis, perineural fibrosis; focal inflammation, degeneration chmx	Fatty replacement, fibrosis in sinus node, AV node, His bundle; sinus node similar to that in LE; focal inflammation His bundle

AV = atrioventricular; chmx = coronary chemoreceptor; FFMD = focal fibromuscular dysplasia; IAS = interatrial septum; IVS = interventricular septum; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LE = disseminated lupus erythematosus; LV = left ventricle; RCA = right coronary artery.

hearts in the present study exhibited a variety of significant neural lesions. Focal inflammation of both nerves and ganglia was present in the vicinity of all parts of the conduction system, which is normally so richly innervated, but cardioneuropathy was also present elsewhere in the heart. One structure that received special attention in each of the 11 hearts is the coronary chemoreceptor (32), composed of several small masses of glomoid tissue with associated large nerves and ganglia lying in the region between the origin of the aorta and pulmonary artery. Abnormalities of the coronary chemoreceptor were present in 10 of the 11 hearts and included focal degeneration (Fig. 9) with and without hemorrhage as well as fatty replacement and focal fibrosis (Fig. 10) of the glomoid tissue. In Cases 1, 7 and 10 there were extensive perineural and intraneural hemorrhage and degeneration of nerves in the intertruncal region (Fig. 11) and the conduction system as well as the coronary chemoreceptor.

Cardiac conduction system. Given the high prevalence of clinical features resembling scleroderma (7 of our 11 cases) and related collagen diseases in late survivors of the toxic oil syndrome, we were not surprised to find cardiac abnormalities, especially in the *cardiac conduction system*, characteristic of both scleroderma (37) and lupus erythematosus (38) in 10 of the 11 hearts. In 4 of the 10, the major histopathologic features (Fig. 12) were of scleroderma (37) and in 6 they were of lupus (38), but Cases 10 and 11 shared cardiac features of both diseases. In addition, the pathologic changes in the sinus node, AV node and His bundle also included the previously described arterial and neural abnormalities.

Focal myocardial degeneration and fibrosis. Examples of these lesions were present in all 11 hearts, but it is not clear whether these were best attributed to ischemia because of the numerous narrowed arteries or were the result of old previous focal inflammation or were due to focal intracellular

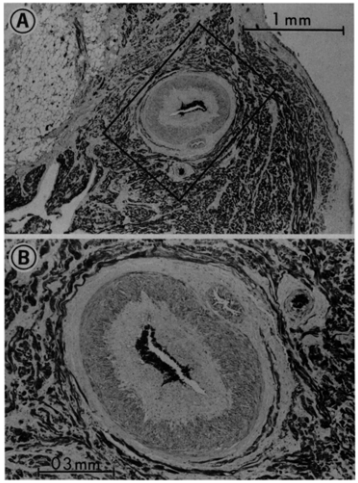

Figure 1. Case 1. Focal fibromuscular dysplasia markedly narrows the sinus node artery of an 18-year old man. The area boxed in A is shown at higher magnification in B. All magnifications are indicated with reference bars; the stain routinely utilized is the Goldner trichrome stain, unless indicated otherwise.

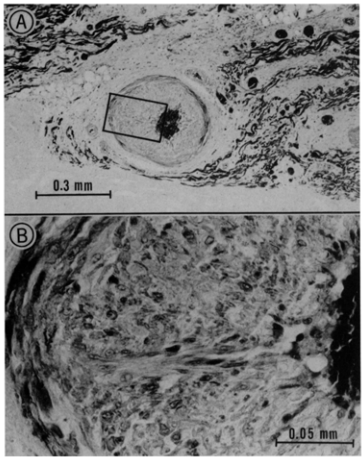

Figure 2. Case 1. The atrioventricular node artery is similarly narrowed by focal fibromuscular dysplasia.

deposit of abnormal lipids. In 6 of the 11 hearts (Cases 1, 2, 4, 5, 7 and 11) there were many foci of myocardial cells (more in the atria than in the ventricles) containing small fatty intracellular globules, still demonstrable with both oil red O and sudan black stains (Fig. 13) even though the tissue had been preserved in aqueous fixative (formalin). Although deposits of intracellular fat are nonspecific and can be caused by many forms of injury to the myocardium, we report these observations here because of their similarity to one of the most extensively studied features of the cardiotoxicity of rapeseed oil: intracellular lipid deposits with subsequent degeneration of the cells. Because it seems unlikely that such intracellular lipid deposits would have persisted without destroying the cells over such a long period of time after the ingestion of the toxic oil, the intracellular lipids we saw may be the result of continued very slow mobilization of toxic oil from depots of storage in the body, the normal turnover of human fat deposits known to be very slow (39).

Comparison with eosinophilia-myalgia syndrome. In three hearts studied post mortem from men who died of the eosinophilia-myalgia syndrome (28), cardiac abnormalities were generally similar to those in fatal cases of the toxic oil syndrome, with some exceptions. In the eosinophilia-myalgia cases there was conspicuous focal fibromuscular dysplasia of small coronary arteries (Fig. 14) but we also found more arteritis (28), possibly because these deaths and autopsies happened early in the course of illness. An important difference was the absence of any myointimal foamy degeneration of coronary arteries in three eosinophilia-myalgia syndrome cases, perhaps because all of the victims were older men. However, this unusual arterial degeneration was present in the toxic oil syndrome not only in four young women, but also in one older man of an age similar to that of the three men in the eosinophilia-myalgia cases. Cardioneuropathy (Fig. 15) was more prevalent and more severe in the eosinophilia-myalgia cases, but neural structures of the heart were certainly also found to be abnormal in all the toxic oil cases.

Cardiac features of scleroderma heart disease (37) were present, especially dense fibrosis of the sinus node, in all 3 cases of eosinophilia-myalgia syndrome and in 4 of the 11 toxic oil cases. Thus, there were more similarities than differences among cardiac findings in the two syndromes, and the relatively small number of total cases as well as some variations in duration of illness may account for much of the differences.

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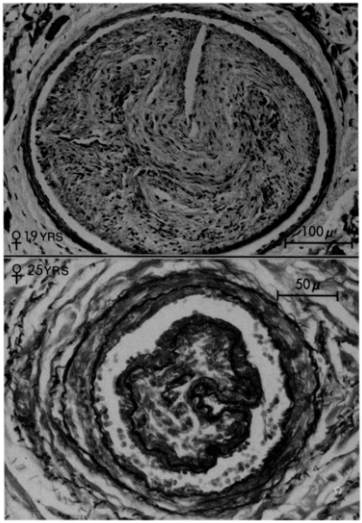

Figure 3. Cases 3 (top) and 9 (bottom). Autoembolization of the sinus node artery from two different patients, both young women. The embolus in the 19-year old has markedly distended the artery, less so in the 25-year old. Verhoeff-van Gieson stain in **B**. See also Figure 4.

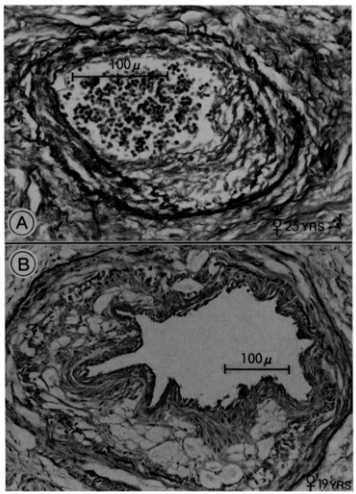

Figure 4. Cases 9 (top) and 3 (bottom). These two photomicrographs of sinus node arteries are from sections made a few millimeters upstream from the same sinus node arteries with autoemboli downstream seen in Figure 3. In both cases there is extensive myointimal proliferative degeneration of the sinus node artery. Verhoeff-van Gieson elastic stain in **A** and **B**.

Discussion

Characteristics of damage to the heart in the toxic oil syndrome. There are two ways in which the heart is damaged in the toxic oil syndrome. One is secondary to the influence of chronic pulmonary hypertension, leading to cor pulmonale and in some cases to both pulmonary and tricuspid valve regurgitation. In association with this stress on the right side of the heart, there have unsurprisingly been several cases of bacterial endocarditis (34) that led to a vicious cycle of pulmonary embolizations (both bland and septic) with further aggravation of the pulmonary hypertension and consequently still additional stress on the pulmonary and tricuspid valves.

The other damage to the heart is of a primary nature and most notably affects the coronary arteries and cardiac neural structures. Some of the cardiac abnormalities we found resembling those of the heart in scleroderma or lupus erythematosus can be logically classified as either primary or secondary in nature. For example, the abnormal fibroplasia now considered characteristic of scleroderma as it affects the skin or esophagus is undoubtedly active in the heart as well, as seen by the scirrhous fibrotic destruction of the sinus node disproportionate to any other explanation such as focal ischemia. If this same abnormal fibroplasia involves the tunica media of both small and large coronary arteries, one logical consequence could be focal fibromuscular dysplasia, which is one characteristic of scleroderma heart disease (37) even in persons who have not ingested toxic oil.

Coronary artery abnormalities. From the standpoint of both immediate consequences and longer-range problems, an ominous finding in our cases was the myointimal proliferative degeneration of both small (Fig. 4) and large coronary arteries (Fig. 5 to 7), particularly since it occurred primarily in young women aged 19 to 26 years. This unusual degenerative abnormality in those four women and one older man was additionally accompanied in each by widespread occurrence of focal fibromuscular dysplasia significantly narrowing small coronary arteries.

Because of these coronary artery abnormalities, which

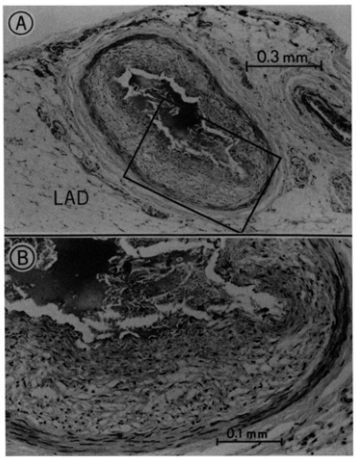

Figure 5. Case 3. The left anterior descending coronary artery (LAD) shows myointimal proliferative degeneration similar to that in the sinus node artery of this 19-year old woman.

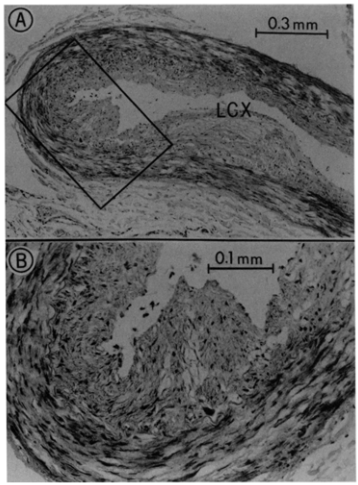

Figure 6. Case 3. The left circumflex artery (LCX) also shows degeneration similar to that in the sinus node artery. There were multiple sites of such focal degeneration in all major coronary branches in this case.

included the blood supply to the conduction system, it may be anticipated that some future deaths among currently surviving victims of the toxic oil syndrome will be sudden and unexpected, that there will be examples of progressive heart failure (with or without cardiac electrical instability) due to "cardiomyopathy" and, on the basis of previous demonstrations of similar arterial lesions in other organs of the body (24,35), that functional abnormalities of those other organs may likewise be due in part or entirely to recurring and progressive focal ischemia there. If body stores of toxic oil in long-term survivors continue to be slowly mobilized, their putative vasculotoxic effect could continue to cause recurring episodes of acute arterial injury intermittently for several years. We cannot yet know how many examples of either chronic or acute coronary artery disease will be found in future years among surviving victims of the toxic oil syndrome, but in light of our present experience we recommend that coronary artery disease particularly be kept in mind concerning the future care of such persons, and that consideration of the possibility may especially be appropriate for young women.

Cardioneuropathy. There are so many powerful influences on the heart by its neural structures (40), including not only chronotropic, inotropic and dromotropic effects but also effects acting on myocardial repolarization and arterial reactivity, that the extensive cardioneuropathy present in victims of the toxic oil syndrome must be an additional source of future concern to those caring for currently surviving victims of the toxic oil syndrome. Actually, the cardioneuropathy probably has a synergistic effect, with the focal arterial lesions as well as the special focal fibrosis and focal inflammation attributable to components of the collagen disease effect of the toxic oil, all serving to destabilize both mechanical and electrical activity of the heart.

Delayed mortality in the toxic oil syndrome. Why was death due to the toxic oil so delayed in most of these cases, ranging in time from 11 months to 9 years? In fact, is it logical to attribute the deaths to the toxic oil so long after its ingestion? In answer to the second question one important point is the similarity of the abnormalities in all our 11 cases. As for the long duration of the illness, one notable feature of fat deposits in the body is their remarkably slow turnover rate (39). Thus, if there is some antigenicity of the toxic oil, as some present evidence suggests, there is ample time for the antigenic stimulus to become maximally effective because of slowly continuing mobilization from body stores of the toxic oil. A scleroderma-like illness has been described as occurring well over a decade after silicon breast implants

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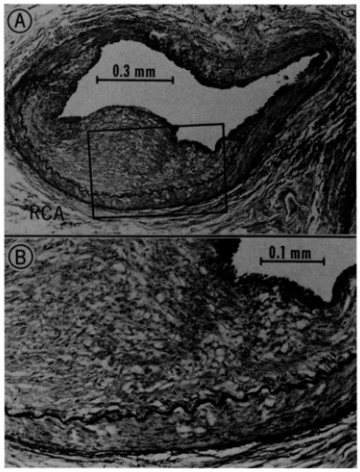

Figure 7. Case 3. The right coronary artery (RCA) is involved with the same process seen in Figures 4 to 6. Verhoeff-van Gieson elastic stain.

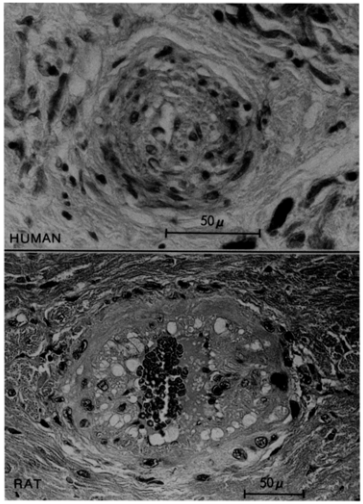

Figure 8. Case 11. A small branch of the sinus node artery of this 39-year old woman **(top)** is narrowed by a process similar to that seen in Figures 4 to 7, and resembles the abnormal small coronary artery of a rat **(bottom)** that had been fed rapeseed oil. The latter photomicrograph is printed from original negatives kindly furnished to us by Umemura et al. (20).

(41), and the scleroderma-like illness now rather characteristic among survivors of the toxic oil ingestion may have a similarly prolonged pathogenesis.

Cardiotoxic components of rapeseed oil. Now to the more substantial question of whether the cardiac abnormalities we found are best attributed to the toxic oil and, if so, which component of the toxic oil? To understand the factors involved it is essential to keep in mind that the toxic oil was rapeseed oil. Although it had been legally adulterated with aniline to prevent its sale as food in Spain, criminal vendors tried to elute the aniline without realizing (or perhaps caring) that the oleoanilides that had formed could not be eluted. None of the features of the toxic oil syndrome resembled in any way the known toxic effects of either aniline or oleoanilides. There were also both legal and illegal additives to the toxic oil, including other oils, but in a definitive study conducted on a large number of samples of the known toxic oil, it was convincingly demonstrated that the only two common denominators were rapeseed oil and oleoanilides, with some traces of aniline (42).

This brings us back to the question of the rapeseed oil itself. Some (43) have stated that despite repeated efforts there has as yet been no suitable experimental model for the toxic oil syndrome. However, for the cardiac effects at least there may have been many such models utilizing the experimental feeding of rapeseed oil to a wide variety of animals (2–6,12–20). Early investigations of this type led to the regular use of the term "cardiotoxicity" in reference to rapeseed oil. Although these toxic effects include an initial intracellular lipid accumulation in cardiocytes, followed by cellular degeneration and foci of myocardial inflammation leading eventually to widespread focal myocardial fibrosis, it has generally been forgotten (or perhaps ignored) that these effects also include (20) the production of myointimal proliferative degeneration of coronary arteries (Fig. 8). Thus, in a real sense there have already been many experimental models of at least portions of the cardiac abnormalities found in the toxic oil syndrome.

Critics of these previous experimental studies point out that the cardiotoxicity, which they do not deny, is attributable primarily to the high erucic acid content of older natural strains of the plant bearing rapeseed (44,45), because of which a new genetically altered rape plant has been developed that produces seeds with low erucic acid content in

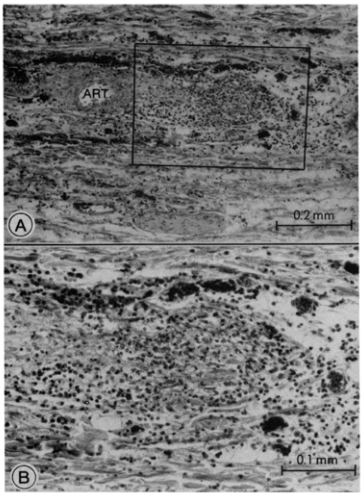

Figure 9. Case 9. The coronary chemoreceptor exhibits degeneration associated with infiltration by numerous leukocytes. All the tissue in **A** and that seen at higher magnification in **B** is chemoreceptor that extends to both sides of its nutrient artery (ART).

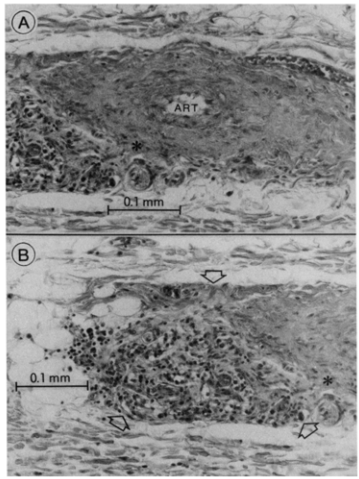

Figure 10. Case 9. There are several glomera normally in each coronary chemoreceptor, and the one here was located about 9 mm away from the one shown in Figure 9. Here most of the chemoreceptor tissue near the artery has been replaced by fibrous tissue, whereas the remaining glomus tissue (three arrows in B) is infiltrated with leukocytes. These two photomicrographs are of adjacent areas, and the asterisks in **A** and **B** mark a reference point for viewing.

their oil (46). This new genetically altered strain of the rape plant is the source of Canola oil, now widely marketed throughout the world but particularly in the United States, where Canola oil bears the endorsement and recommendation of the National Cholesterol Education Program (47) led by the American Heart Association, the National Heart, Lung, and Blood Institute and the American Medical Association. But how safe is Canola oil in comparison with its indisputably cardiotoxic ancestor?

There is no question that the speed of onset of cardiotoxicity is much slower with low erucic acid rapeseed oil (Canola), and that the eventual damage to the heart seems to be less. However, there is probably no safe level of erucic acid, small concentrations simply taking longer to be toxic. Furthermore, it should be kept in mind that the Spanish toxic oil was itself *low* erucic acid rapeseed oil (42). It has also recently been suggested that the rat, an animal in which even low erucic acid rapeseed oil is cardiotoxic, is for a variety of reasons thought not to be a suitable model for studies of cardiotoxicity as it may relate to humans (48). This interpretation regarding principles of comparative pathology is eminently arguable. But there is the more worrisome assumption that all of the new rapeseed plants will always run true to genetic form, in all climates and all soils with every imaginable different agricultural practice. Put simply, if an original natural form of rapeseed is admittedly toxic, how reliable can a genetically altered progeny be as to the possible reversion to original form? Or, what is known of all the possible other consequences (in addition to changing the erucic acid content) that may have been produced by genetic alteration of the rape plant?

Possible harm from naturally occurring foods. As recently emphasized by Morgan and Fenwick (49), food is the most chemically complex substance commonly encountered by the public. There are probably over half a million naturally occurring compounds in fresh plant foods, and still more are formed during food preparation either domestically or commercially. Morgan and Fenwick (49) describe four reasons to be concerned about possible harm from some of these naturally occurring compounds, or at least to recognize our dangerous ignorance about their long-term effects. *First*, dietary advice today emphasizes green vegetables, vegetable protein and fiber, each of which will assuredly lead to

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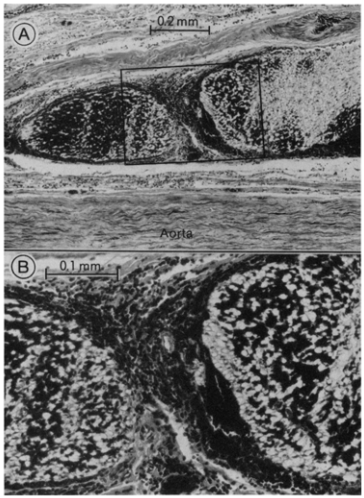

Figure 11. Case 10. Two myelinated nerves adjacent to the aorta in the intertruncal space exhibit perineural and intraneural hemorrhage and degeneration. Similar lesions were extensive in the heart of this 74-year old man, as well as in Cases 1 and 7.

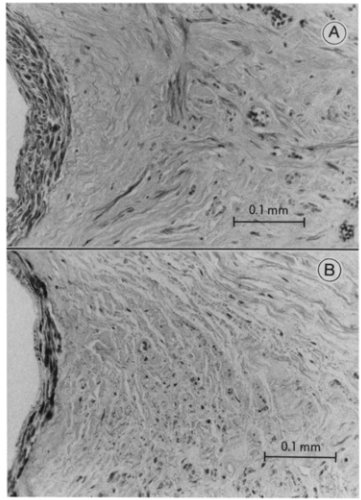

Figure 12. Case 10. Two photomicrographs from the sinus node; the two sections were made about 6 mm apart with **A** anterior to **B**. In **A**, a few remaining sinus node fibers can be seen, but at the midpoint of the sinus node, shown in **B**, virtually all the sinus node fibers have been replaced by fibrosis similar to that seen in scleroderma heart disease.

exposure to various natural chemicals with unknown long-term effects. *Second*, there are fashionable trends to vegetarianism and the consumption of exotic or ethnic foods, any or all of which may be adopted by those obsessed with avoiding cholesterol or fat. *Third*, a corollary fashion includes increased public interest in "health foods" and herbal remedies, a predictable consequence of continued bombarding of the public by an enormous assortment of health advice with the admirable but unrealistic intention of preventing virtually all diseases. *Fourth*, current agricultural practices designed to decrease the use of herbicides, fertilizers and other chemicals have led plant pathologists and genetic engineers to develop new plant varieties with enhanced natural stamina and disease resistance, but disease resistance by plants is complex and an increase in this trait can be associated with increased concentrations of natural toxicants. Every one of these caveats has direct applicability to new products such as canola oil. For matters related to the entire cholesterol hypothesis it is essential to recognize that dietary advice intended to be simple may actually be simplistic.

Is rapeseed oil the sole culprit in cardiotoxicity? Still, it is true that rapeseed oil has been consumed in the western world for several decades and in other parts of the world for several millennia without the recognized occurrence of anything resembling the epidemic of the toxic oil syndrome. However, that is not to say that more insidious toxicity does not exist, perhaps in the form of chronic arterial or neural disease or "idiopathic" cardiomyopathy. Such a possibility would be difficult to prove, but the postmortem evidence in our 11 cases suggests that it merits some concern. However, it seems more probable that the rapeseed oil is not the sole culprit and that either the aniline or oleoanilides acted as an adjuvant for the rapeseed oil to produce an antigenic response and then both an acute and later chronic illness, with some cardiac effects resembling components of the cardiotoxicity produced experimentally by feeding rapeseed oil alone to animals.

Then, if there is an adjuvant effect by aniline (or oleoanilides), which is not normally encountered by most persons, what would happen to the heart (and its vessels and nerves) of persons who do work one way or another with aniline or a close analog to aniline and who then eat Canola

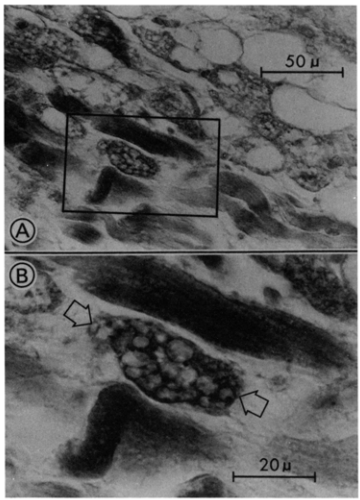

Figure 13. Case 2. Myocytes in the interatrial septum above the atrioventricular node from a 24-year old woman. There is foamy degeneration with small intracellular globules that have stained positively for fat with Sudan black. A typical example is indicated by the two arrows in **B**.

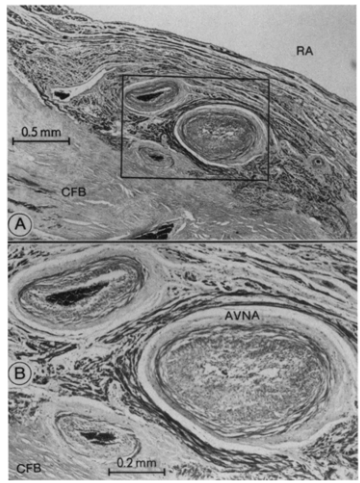

Figure 14. *Focal fibromuscular dysplasia narrows the atrioventricular node artery of an older man who died of the eosinophilia-myalgia syndrome.* There is some endarteritis, seen well in this artery (AVNA) in **B**. CFB = central fibrous body; RA = right atrium.

oil? Furthermore, many medicinal and pharmaceutical compounds are closely related to aniline: what would happen if someone took one of these medicines regularly and then consumed canola oil? These hypothetical combinations of circumstances will be an unwelcome suggestion for the National Cholesterol Education Program and its adherents, but it will be anathema to growers of plants producing rapeseeds, now a multibillion dollar international agricultural enterprise, and to manufacturers and purveyors of canola oil and its related products such as oleomargarines. But for the sake of public health it does not seem prudent to ignore them.

Comparison with the eosinophilia-myalgia syndrome: rapeseed oil versus L-tryptophan. *A serendipitous opportunity* for fuller understanding of the pathogenesis and pathophysiology of the toxic oil syndrome may lie in recent investigations of the eosinophilia-myalgia syndrome (25–28,50–52). Both syndromes have followed the ingestion of a substance previously thought by the public to be innocuous, rapeseed oil in the toxic oil syndrome and L-tryptophan in the eosinophilia-myalgia syndrome. Both syndromes are characterized by an initial profound eosinophilia in the peripheral blood, both have early pulmonary complications, both cause pains in muscles and joints and both later lead to scleroderma-like findings. In fatal cases of the eosinophilia-myalgia syndrome there are abnormalities of the small arteries, neural structures and conduction system of the heart; these differ slightly from abnormalities in the toxic oil syndrome but share more similarities than differences. However, how do two substances as dissimilar as rapeseed oil (from genetically altered plants) adulterated with aniline, and a new form of L-tryptophan (a dimer: the di-tryptophan aminal of acetaldehyde) produced by a genetically altered bacillus, cause so many similar pathologic changes, including these in the heart?

There are several possible explanations. It may be that the genetically altered L-tryptophan and the genetically altered rapeseed oil both act in some antigenically similar fashion in susceptible (but not resistant) persons, and the late appearance of scleroderma in both syndromes would support this hypothesis. Attention has recently been drawn also to the facts that anthranilic acid is used in the manufacture of L-tryptophan (53) and that aniline adulterated the

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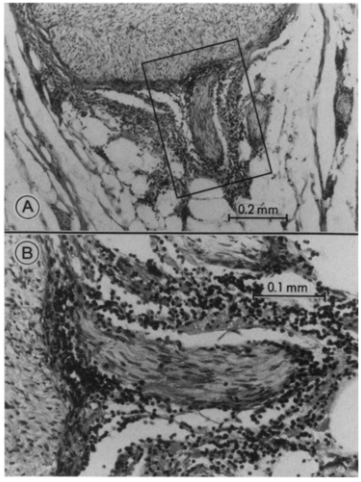

Figure 15. Typical neuritis involving a large myelinated nerve near the coronary chemoreceptor of a man who died of the eosinophilia-myalgia syndrome is illustrated here at two magnifications. See text for discussion.

rapeseed oil, posing a common link through one form or another of aniline. Another intriguing report (54) has suggested that the altered L-tryptophan acted to damage the intestinal barrier, permitting the abnormal absorption of powerful antigens normally excluded, and an analogous event could be associated with eating toxic oil. Finally, some have suggested that a major participant in the pathogenesis of the eosinophilia-myalgia syndrome (and possibly the toxic oil syndrome) may be the eosinophils themselves, since they bear distinct neurotoxic and other noxious chemical substances (25,55).

But there are also important differences between the two syndromes that must be accounted for. People who took the bad L-tryptophan rarely became ill quickly and most victims had continued to use this substance daily for weeks or months after becoming ill. Those eating the toxic oil became acutely ill almost immediately or at least within a few days. Furthermore, there were an unknown but possibly large number of persons who took either bad L-tryptophan or the toxic oil and did not become ill at all. Whether this represents difference in individual susceptibility or a difference in contemporaneous eating habits or some other factor is completely unknown but exceptionally intriguing. These "well" survivors merit careful evaluation, both for possible subclinical illness and for possible explanations of their "resistance." Although the total number of persons made ill with the toxic oil (>25,000) is far greater than those for L-tryptophan (<2,000), the percentage of deaths is about 2% for both syndromes. However, follow-up of the eosinophilia-myalgia group is as yet much shorter. The unusual myointimal proliferative degeneration found in the toxic oil syndrome (Fig. 4) has not been observed yet in the eosinophilia-myalgia syndrome.

Clinical cardiac events in the two syndromes. In view of the extent of cardiac abnormalities present in fatal cases of both syndromes, why has there been no wider recognition of clinical cardiac events related to the disease in the coronary arteries, the conduction system and the neural structures of the heart? In fact, the examinations in persons who died of the eosinophilia-myalgia syndrome *were* conducted because of several documented examples of electrical instability of the heart and sudden death (28). Similar events have also been recognized in the toxic oil syndrome. However, in the toxic oil syndrome the severe pulmonary hypertension and related clinical problems may simply have overshadowed primary cardiac manifestations. Furthermore, it seems likely that at least some of the cardioneuropathy may have involved afferent pathways that would normally mediate cardiac pain or other symptoms in both syndromes. The coronary chemoreceptor, found damaged in both syndromes (21,28), has been suggested to be one important afferent pathway for mediation of angina pectoris (32,56).

Implications. There is obviously much yet to be learned about how either syndrome is produced, and what their long-term consequences will be. Equally obviously, obtaining such knowledge will be valuable in understanding more than these two syndromes alone. One example is scleroderma, which has emerged in later stages of each syndrome. But a better understanding of the body's response to odd antigenic assaults can be usefully applicable to the fuller explanation of a wide variety of other diseases such as primary pulmonary hypertension, the various eosinophilic syndromes and graft-versus-host responses. What must not be lost in the various hypothetical considerations, however, is that the fundamental component in the pathogenesis of each syndrome is well established: adulterated rapeseed oil in the one and a genetically altered production of L-tryptophan in the other.

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