The toxic oil syndrome is a multisystemic disease caused by the ingestion of adulterated rapeseed oil. The basic lesion is a peculiar vasculitis that affects mainly the intima, showing the features of an endovasculitis. Vessels of every type and size are involved, affecting practically every organ.

The vascular lesion begins with endothelial damage that varies from cellular swelling to cellular necrosis. It then progresses by mixed cellular inflammatory infiltration of the intima and, in some cases, of the media and adventitia. In some cases the infiltrate is rich in eosinophils and a few show foamy histiocytes. Proliferation of myointimal cells and in advanced stages fibroblastic proliferation causes narrowing or obliteration of the vascular lumen. Thromboembolic complications perpetuate the vascular lesion and compound the ischemia and parenchymal atrophy of several organs.

The peripheral nerve lesions begin with an inflammatory neuropathy with lymphocytic perineuritis and progress to peripheral fibrosis with secondary axonal degeneration. Skeletal muscle lesions exhibit an interstitial inflammatory myopathy at first, followed by a neurogenic muscular atrophy.

A direct effect of unidentified toxic substances, possibly free radicals, may cause the endothelial lesion. Other factors, such as immunopathologic mechanisms of delayed hypersensitivity, may contribute to the progression of the vascular lesions.

The toxic oil syndrome caused by ingestion of adulterated rapeseed oil in Spain is a new disease of multisystemic character whose exact etiology and pathogenesis are unknown (1,2). It first appeared in May 1981 with an acute clinical picture characterized by pleuropneumopathy, headaches, exanthemas and eosinophilia (3). In this early period of the disease the main pathologic findings were observed in the lungs, where there was intense pulmonary interstitial edema with scanty inflammatory mononuclear infiltrates, and in the skin, which showed vascular lesions of the reticular dermis with perivascular inflammatory infiltrates and edema. The patients died of respiratory failure in this very early period (May 1981); later (June and July 1981) they died of thromboembolic complications (2). This stage in the evolution of the syndrome has been called the “first clinical phase” (1,2).

Later many patients followed a chronic clinical course, each of them manifesting a variety of symptoms. The most severely affected developed a neuromuscular syndrome (1,4), or sclerodermatous skin lesions (1,5), or both, but others developed a chronic pancreatitis (6) or sicca syndrome (7). About one fourth of the patients had mild clinical manifestations of hepatopathy due to a “cholestatic hepatitis” (8). The patients who died in this period (second clinical phase) developed severe weight loss and died predominantly of infectious complications and respiratory failure (2). A few patients with long-standing disease (after 1982) developed diffuse nodular regenerative hyperplasia of the liver (9-11) or pulmonary hypertension (12) due to a plexogenic pulmonary arteriopathy that led to death as a result of right heart failure (9,13).

Histologic abnormalities of the coronary arteries, neural structures and the conduction system have been found in the heart of persons dying of this disease (14).

**The Vascular Lesion**

Vascular lesions were found in all vessels (arteries, arterioles, capillaries, venules and veins), from practically every organ (2). These lesions showed a segmental distribution and exhibited primarily vasculitis or, more specifically, an “endovasculitis.” The damage then progressed from the intima more deeply into the tunica media, presenting a mixed
inflammatory infiltrate and eventually fibrosis but no fibrinoid necrosis. The sequence of changes was as follows:

1. The earliest vascular lesion. This consisted of intimal damage with cellular swelling, subendothelial edema, exposure of the endothelial space and cellular necrosis (Fig. 1) but no inflammatory cellular response or fibrinoid necrosis. Ultrastructurally, marked cytoplasmic hydropic degeneration and destruction of the cytoplasmic membranous organelles was observed (Fig. 2). These vascular changes, which were detected in the lungs of patients who died in the early days of the first clinical phase, were responsible for the interstitial pneumonopathy resembling acute respiratory distress syndrome. Histologically, the lungs showed, in addition to the vascular lesions, mainly lymphangiectasia and very intensive interstitial edema of the interlobular septa with almost no cellular inflammatory infiltrates.

2. The second stage: an inflammatory response. The intima of the affected segment of the vessel and eventually also the media showed edema and a mixed infiltration of lymphocytes, histocytes and, often, eosinophils (Fig. 3). Tests for antibodies by immunofluorescence technique were consistently negative (2). The lymphocytes present in the infiltrated vascular walls were demonstrated to be T lymphocytes (7). In a few cases xanthomatous histocytes were conspicuous and in three cases prominent giant cell granulomas in the intima were observed (15). In this stage the lesions showed characteristically a proliferation of myointimal cells presenting a concentric pattern, accompanied by edema and mixed inflammatory infiltrate. The inner elastic membrane and tunica media were well preserved. The described lesion corresponds to an endovasculitis (Fig. 4).

3. Obliterative fibroblastic lesions. A progressive evolution of this process led eventually to fibroblastic proliferation with deposition of collagen fibers, mainly at a subendothelial level. Immunocytochemically type IV collagen was demonstrated (16). Arteries were commonly more affected than veins. Eventually the affected vessels developed a partial or complete luminal occlusion. These advanced obliterative lesions were observed in most organs and in arteries such as the mesenteric arteries and coronary arteries. In medium size arteries the lesions showed features similar to the advanced lesions of atherosclerosis. In a few young patients this led to myocardial infarction. In four cases venoocclusive disease was observed in an acute phase, with almost complete obliteration of branches of the central lobular veins by scleroderma (15).
4. Thrombosis and thromboembolism. As a consequence of the endothelial lesion, vascular thrombosis and thromboembolism were observed in both clinical phases. In the early days of the epidemic, aggregates of fibrin and platelets were found in pulmonary capillaries. Later, thrombosis occurred in large veins (mesenteric and portal tree) and arteries (femoral, mesenteric, carotid and pulmonary). Pulmonary thromboembolism and intestinal hemorrhagic infarction were the cause of death in many patients during June and July 1981. Later, pulmonary thromboembolism was one of the main contributing factors in severe pulmonary hypertension (9,13).

The Neural Lesion

Peripheral inflammation and fibrosis. The earliest and most frequent findings in peripheral nerves were epineurial mixed inflammatory cell infiltrates around veins and capillaries as well as mononuclear cell infiltration of the perineurium. When the process progressed into a chronic stage, the perineural inflammation was followed by perineural fibrosis that varied in intensity among fascicles and was frequently severe. In such cases each fascicle within the nerve was encircled by an extremely fibrous thickened perineurium (Fig. 5). These chronic lesions showed degeneration of nerve fibers with destruction of axoplasm and myelin, macrophages removing debris and endoneural fibrosis (17).

Inflammatory myopathy and fibrous and neurogenic atrophy. The muscle lesion observed in the first clinical phase and at the beginning of the second was characterized by an inflammatory myopathy. The inflammatory infiltrates were built up by mononuclear cells and a few granulocytes including eosinophils in perimysial vessels and the perimysial space. Characteristically, the intramuscular nerve endings and muscle spindles had their fibrous capsules invaded by inflammatory cells very early. Later stages revealed a fibrous process and neurogenic atrophy of muscle fibers that advanced to include whole fascicles. In the second clinical phase, the neurogenic atrophy was quite devastating and there was peri- and endomysial fibrosis. The inflammation had practically disappeared at this stage, with a few cells around veins remaining (Fig. 6) (2,17).

Central nervous system involvement. In the central nervous system central chromatolysis was observed in the anterior horn cells of the spinal cord and neurons located in symmetric nuclei of the brain stem (locus coeruleus, nuclei of the basis pontis, reticular substance of the medulla and pons, gracilis and cuneate nuclei). The chromatolytic proc-
Figure 5. Transverse section of sural nerve biopsy specimen with perineuritis. Two nerve fascicles show mononuclear cell infiltration of a thickened perineurium. There is also mild epineural inflammation (hematoxylin-eosin ×200, reduced by 32%).

Figure 6. Cross section of muscle biopsy specimen from a patient with chronic neurovascular syndrome. There is severe atrophy of muscle fibers affecting whole fascicles, with an increase in collagen fibers in endomysial and perimysial spaces. Minimal inflammation around a small vessel is observed (hematoxylin-eosin ×80, reduced by 32%).

Pathogenesis

Role of anilides. In our opinion and in that of most investigators of this disease (1-3,7,13,16) the endothelial lesion is the first tissue damaged and thereafter the first pathologic step of this protean and variegated process. It is possible that the anilides detected in the toxic oil were the cause of this endothelial damage. However, although Kilbourne et al. (19) demonstrated in epidemiologic studies that there is an evident dose-response effect, no one has been able to reproduce experimentally all the lesions that have been observed in the toxic oil syndrome. Furthermore, the syndrome produced by anilides is different from the toxic oil syndrome (20).

Role of free peroxide radicals. It is possible that free radicals were responsible for the vascular changes since they have been implicated in lesions that show some similarities to those observed in the toxic oil syndrome, such as lesions produced by radiation or nitrofurantoin or after ingestion of a diet rich in polyunsaturated fatty acids (21-26). The release of free peroxide radicals induced by oleanilides could act on different cell membranes and provoke structural and enzymatic alterations leading to endothelial damage.

Coagulation abnormalities. In contrast, it is possible that on the other hand, the thrombotic phenomena observed in this syndrome were due to the interaction of the damaged endothelium and circulating clotting factors, and could have contributed to perpetuating the vascular injury in the advanced stages of the disease. Protective enzymes in lung endothelial cells, such as carboxypeptidase N, are able to interact with circulating substances within the pulmonary circulation, playing an important role in the acute respiratory distress syndrome at the experimental level (27). In patients with the toxic oil syndrome the toxic substances could have reached the pulmonary circulation and triggered this mech-
anism. Also the thrombocytes could have been directly activated by the action of free radicals (25). The thrombembolic complications could either have been caused by or have caused a disseminated intravascular coagulation, as detected in some patients.

Immunologic mechanisms. Some features of the toxic oil syndrome suggest that immunologic mechanisms may have been involved in the pathogenesis of certain lesions. The richness of lymphocytes or eosinophils, or both, in the inflammatory infiltrates seems to support this hypothesis; however, there is no evidence for humoral immunomechanism, because vascular or tissue immunocomplexes have not been found (2). Nevertheless, in the chronic phase, the toxic oil syndrome shows striking clinical and pathologic similarities to diseases in which immunopathologic mechanisms are well known to operate, such as progressive systemic sclerosis, Sjogren's syndrome and graft-versus-host disease (27). Furthermore, the lymphocytic infiltrates in lesions of the toxic oil syndrome have been demonstrated to be T lymphocytes (7), which may indicate that a cell-mediated immunopathogenetic mechanism is activated.

Conclusions. We believe that the first step in the evolution of the toxic oil syndrome is the endothelial lesion, probably a consequence of direct damage by the toxic substances contained in the oil or of another pathogenic mechanism such as free radicals, or both. Because a minority of patients showed progression of the vascular lesion and of the disease, other individual predisposing factors are probably also operative, such as immunopathologic mechanisms of delayed hypersensitivity.

References