Letters to the Editor

CYCLOSPORIN FOR PULMONARY SARCOIDOSIS

SIR,—A role for T lymphocytes in the pathogenesis of sarcoidosis is suggested by the fact that interleukin-2 increases the number of T cells in active disease.¹ The activated alveolar macrophage also plays a crucial role, not only in propagating the alveolitis associated with sarcoidosis, but also in initiating the progressive interstitial fibrosis that sometimes results.² Cyclosporin suppresses T helper lymphocytes³ and blocks the release of interleukin-2,⁴ preventing primary responses and terminating secondary T-dependent responses.⁵ Cyclosporin is widely used as an immunosuppressive agent in organ transplantation, but its use in juvenile diabetes,⁵ posterior uveitis,⁶ and Graves' ophthalmopathy⁷ suggests that it has a role in autoimmune disease too. We describe here three patients with active, biopsy-proven pulmonary sarcoidosis who were treated with cyclosporin.

Case 1.—This 28-year-old man presented with shortness of breath and cough of 6 months' duration. He had bilateral hilar adenopathy, partial collapse of the right upper lobe, and diffuse pulmonary infiltrates. His vital capacity was 54% of predicted. At bronchoscopy the mucosa of major airways was oedematous and friable, and the right upper lobe bronchus was 90% occluded by massive mucosal swelling. Biopsies revealed non-caseating granulomas. A gallium-67 scan was diffusely positive, and differential cell counts on bronchoalveolar washes (BAL) yielded 50% T lymphocytes, with a T4/T8 ratio of 1.2. In view of his obesity (160 kg) and hypertension, the patient was given the option of therapy with cyclosporin. The drug was administered, at a dose sufficient to maintain serum levels of 150–400 ng/ml, for 8 weeks. By the end of this course of therapy his vital capacity had increased (68% of predicted), a chest X-ray showed aeration of the right upper lobe, bronchoscopy was normal, and the negative gallium scan and BAL lymphocyte count 20% (T4/T8 ratio 0.76) confirmed suppression of the alveolitis. 3 weeks later the patient died at home after aspiration of gastric contents. Necropsy demonstrated persistence of multiple organ granulomas, but major bronchi were patent.

Case 2.—This 27-year-old woman had been treated unsuccessfully for biopsy-proven sarcoidosis for 2 years. She had active disease (positive gallium scan BAL lymphocyte counts above 40% T cells) but had not responded to prolonged therapy with prednisone at doses above 0.75 mg/kg. She was profoundly cushingoid. Dramatic relief of her cough and exertional dyspnoea was achieved with an 8 week course of cyclosporin (serum level 150–520 ng/ml) complicated only by mild, transient gingival hypertrophy. Radiographic improvement was accompanied by increased vital capacity and diffusion capacity (from 10.6 to 15.7 ml/min/mm Hg) and suppression of alveolitis (normal gallium scan, BAL T lymphocyte count 12%). During cyclosporin therapy, the prednisone dose was reduced to 0.18 mg/kg. For 3 months now she has remained symptom-free, with stable lung function.

Case 3.—This 39-year-old man had been treated for 12 months with up to 50 mg/day prednisone for biopsy-proven pulmonary

sarcoidosis. This was ineffective and treatment was stopped (positive gallium scan, BAL T lymphocyte counts above 65%). 12 months after steroids had been discontinued, cyclosporin was administered for 10 weeks (serum level 110–660 ng/ml), the only complication being a mild deterioration in renal function which was reversed once the drug was discontinued. The BAL T lymphocyte count decreased slightly to 55%, and both chest X-ray and gallium scintigram improved progressively. Lung function was more or less normal and the patient had no symptoms throughout the treatment period.

Cyclosporin inhibits the release of interleukin-2 from activated T lymphocytes³ and affects selected metabolic functions of alveolar macrophages.⁸ Since gallium-67 is taken up in the lung primarily by alveolar macrophages,⁹ the significant improvement in the scintigrams of all three patients strongly suggests that cyclosporin suppressed the macrophage-mediated component of the alveolitis, either directly or by way of T-cell lymphokine inhibition. This experience suggests the need for a controlled trial of cyclosporin in sarcoidosis.

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SPANISH TOXIC OIL SYNDROME IS A CHEMICALLY INDUCED GVHD-LIKE EPIDEMIC

SIR,—The hunt for the causative agent in Spanish toxic oil syndrome has concentrated unsuccessfully, on fatty acid anilides in adulterated rapeseed oil.¹⁰ We propose that, in the presence of aniline, heterocyclic compounds such as 1-phenyl-5-vinyl-2-imidazolidinethione (IZT) are formed from specific isothiocyanates present in unrefined rapeseed oil as degradation products of glucosinolates. Moreover, in commercial rapeseed products 5-vinyl-2-oxazolidinethione (OZT) is formed spontaneously from similar isothiocyanate precursors (figure).¹¹ Both IZT and OZT belong to the same chemical class as several anticonvulsant and antithyroidal drugs, known to induce allergic and autoimmune side-effects in susceptible patients. Here, we want to point to the strong clinical and pathological parallels between toxic oil syndrome, human graft-versus-host disease (GVHD), and chemically induced GVHD-like symptoms (table).

Each patient with toxic oil syndrome presents a different combination of symptoms,^{12,13} as in GVHD.^{14–17} Most recipients of allogeneic bone-marrow acquire a variable degree of acute GVHD, which only in a minority of cases evolves into chronic GVHD. This biphasic evolution corresponds well with the early and late phase of toxic oil syndrome (table). Death from interstitial pneumonitis is common in bone-marrow transplantation, and respiratory failure

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Structural analogues of OZT and IZT.

Left to right: OZT, IZT, phenytoin, nitrofurantoin, trimethadione, ethosuximide, propylthiouracil.

from interstitial pneumonitis is a major cause of death in toxic oil syndrome too. Vascular lesions and thromboembolism are characteristic of both diseases. Eosinophilia, increased IgE levels, and thrombocytopenia, which are prominent features of the early phase of toxic oil syndrome, are common in acute GVHD. Scleroderma-like lesions, sicca syndrome, Raynaud's phenomenon, inflammatory myopathy, peripheral neuropathy, polyarthralgia, weight loss, and alopecia are characteristic of both chronic GVHD and toxic oil syndrome. During the late phase of toxic oil syndrome the most common cause of death was sepsis, as in chronic GVHD.

A variety of drugs can induce autoimmune and allergic disorders¹⁸—notably, in this context, hydantoins, succinimides, oxazolidines, and thiouracils, drugs closely related structurally to IZT and OZT (figure). Phenytoin¹⁹ and related drugs induce most of the clinical and pathological abnormalities of true GVHD (table). The lesions are usually drug dependent since they rapidly disappear when the drug is withdrawn. However, autoimmunity sometimes persists after discontinuation of the agent. This pattern closely matches that of toxic oil syndrome. Phenytoin, nitrofurantoin, and

propylthiouracil induce many of the features of toxic oil syndrome, ranging from exanthema, hyperpigmentation, alopecia, and eosinophilia to interstitial pneumonitis, lymphadenopathy, thrombocytopenia, vasculitis, and weight loss (table). Trimethadione, an oxazolidine derivative, induces some of these features too.¹⁸ Phenytoin and mephenytoin have been reported to induce immunologically mediated inflammatory neuromuscular disorders²⁰ and hydantoins and ethosuximide have been associated with scleroderma-like lesions.¹⁸

The parallels between GVHD and Spanish toxic oil syndrome; the similarity between the severe side-effects of certain drugs and the symptoms of the two diseases; and the probable presence in adulterated rapeseed oil of isothiocyanate-derived imidazolidinethione compounds, closely related to the aforementioned drugs suggest that toxic oil syndrome should be considered as a chemically induced GVHD-like syndrome.

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MAJOR SYMPTOMS OF TOXIC OIL SYNDROME (TOS),^{12,13} GVHD,¹⁴⁻¹⁸
AND CHEMICALLY INDUCED GVHD-LIKE DISORDERS¹⁸⁻²¹

Early phase of TOS (1-3 mo)	Acute GVHD	Chemically induced disease*		
		DPH	NF	PTU
Maculopapular exanthema	+	+	+	+
Pruritus		+	+	+
Purpura	+	+		+
Hyperpigmentation	+	+	+	+
Oedema of face and limbs	+	+		+
Fever	+	+	+	+
Cough	+		+	
Dyspnoea	+		+	
Interstitial pneumonia	+	+	+	+
Hepatomegaly	+	+	+	+
Raised liver enzymes	+	+	+	+
Myalgia	+	+		+
Polyarthralgia	+	+	+	+
Vasculitis	+	+		+
Lymphadenopathy	+	+	+	+
Eosinophilia	+	+	+	
Thrombocytopenia	+	+		+
High IgE (non-specific)	+	+	+	
Late phase of TOS	Chronic GVHD	Chemically induced disease		
		DPH	NF	PTU
Scleroderma-like lesion	+	+		
Sicca syndrome	+			
Raynaud's phenomenon	+			
Dysphagia	+			
Inflammatory myopathy	+	+		
Peripheral neuropathy	+	+	+	
Muscular atrophy	+			
Weight loss	+	+	+	
Alopecia	+	+	+	+
Hypertrichosis	+	+		

*DPH = phenytoin; NF = nitrofurantoin; PTU = propylthiouracil.

HFRS OUTBREAK ASSOCIATED WITH LABORATORY
RATS IN UK

SIR,—Earlier publications in *The Lancet*^{1,2} have described cases of haemorrhagic fever with renal syndrome (HFRS) in laboratory staff exposed to laboratory rats infected with Hantaan-like viruses, and workers in France³ have also described Hantaan antibodies in laboratory rats. We now have evidence for a Hantaan virus-type infection being the cause of nephropathy in staff at a research institute in the UK. The source of infection appears to have been imported Louvain (Lou/WSL/M) rats during the period March, 1975, to November, 1979. The presence of Hantaan virus had not been suspected in the UK but this institutional outbreak parallels the experience reported in Belgium⁴ and is further confirmation of HFRS due to rats outside the Far East.

Between January and June, 1977, four staff members of a research unit (Institute of Cancer Research, Sutton) were admitted to hospital with similar symptoms described as spiking fever, abdominal and back pain, varying degrees of respiratory problems, proteinuria, oliguria, and renal failure. Final diagnoses varied from pyelonephritis to viral disease of unknown origin. All patients received treatment for 2-3 weeks, followed by a convalescent period of 4-11 weeks. While investigating Hantaan virus in the UK we felt that these patients might have been cases of HFRS, especially since

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