Leading Article

Silk Route disease

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In 1979, we reported (James, 1979) the findings of an international symposium on Behçet's disease, a multi-system disorder of unknown aetiology principally affecting young adults in various parts of the world (Behçet, 1937). Yet another international conference was held in London in September 1985, on this occasion at the Royal College of Physicians. One hundred papers were shared by nearly 200 participants from 20 countries. Not only was it truly international but also truly multidisciplinary for ophthalmologists, chest physicians, dermatologists and internists shared the programme with immunologists, pathologists, epidemiologists and other disciplines.

S. Ohno (Sapporo, Japan) mapped out the world-wide incidence of Behçet's disease, which is commonly recognized in Japan, China and Turkey. It is most frequent in a belt lying latitude 30° to 45° North, precisely the distribution of the old Silk Route from Japan and the Far East across the Mediterranean countries and to Europe. Hence his suggestion that if Behçet's disease was renamed Silk Route disease, then it would at least convey epidemiological significance. All his remarks and those of his fellow nationals had a ring of authority for 15,000 Japanese are afflicted with a prevalence rate of 15 per 100,000 population. The male:female ratio was 1.2:1 in 1972 but it is now nearer 0.95:1. By comparison, it is estimated that there are 600 patients with Behçet's disease in China, about 250 in Korea and Iran, and 1,000 in Turkey.

Its worldwide distribution may be associated with the prevalence of certain HLA antigens, particularly HLA-B51 and HLA-DRW52. There was a significant association not only in patients but also in mothers and siblings but not in fathers. Antigens HLA-DR1 and HLA-DQw1 are significantly decreased. Ohno announced that this was the first recognition of disease resistance genes in Behçet's disease.

It is difficult to explain its rarity in the USA even amongst Japanese-Americans, perhaps because this essentially clinical bedside diagnosis is not supported by any significant laboratory test. Or is it just because

the United States does not figure in the Silk Route and its HLA affinities and possible endemic viruses or other allergens?

Oro-genital ulceration is so constant that it is a cornerstone of the diagnosis, which becomes more confident if the patient also suffers ocular inflammation, polyarthritis, erythema nodosum and other well-recognized major and minor criteria. W.J. Dinning (London) recognizes three ocular presentations, namely pain and photophobia of anterior uveitis, blurring of vision due to floating vitreous opacities, and visual failure due to severe retinal vasculitis. There may be vitreous and retinal haemorrhage and exudates, retinal vein and artery occlusion, retinal and optic atrophy, and the ophthalmologist is also alert to perivascular sheathing and capillary closure due to the disease. Fluorescein angiography has added a fresh dimension to the recognition of the retinal vasculitis, which is one of the most troublesome causes of morbidity (Page *et al.*, 1982). H. Pazarli (Istanbul) noted eye involvement in 253 of 540 (47%) patients with Behçet's disease; it was three times more frequent in men. Hypopion occurred in 10% of his ophthalmic series and it seemed to herald optic atrophy, which ensued within a few months in one-half of the patients with hypopion. The other clinical features are not quite so devastating as the threat of blindness, but troublesome neurological and cardiovascular disease, polyarthritis and perforating intestinal ulceration may be crippling (James, 1982; Mori *et al.*, 1983). A.V. Muftuoglu (Istanbul) and M. Vella (London) stressed the frequency of vascular involvement. In the Turkish series of 129 patients, 122 were male and only seven females had vascular disease. The most frequent involvement was deep and superficial thrombophlebitis. Vascular involvement was closely associated with erythema nodosum, which was observed in 101 of the 129 vascular patients. If a man presents with phlebitis and erythema nodosum, one should enquire immediately whether he suffers from recurrent orogenital ulceration.

Y. Fukuda (Tokyo) reported the necropsy findings in 193, including 75 with neurological disease, 37 with vascular involvement and 21 with intestinal Behçet's

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disease. The predominant histology is vasculitis, thrombosis, aneurysms and perivascular fibrosis. Intestinal involvement resembles chronic inflammatory bowel disease, particularly Crohn's, with an admixture of necrotic and granulomatous ulceration, which may perforate.

G. Dilsen (Istanbul) has studied the autonomic nervous system and its activity by 1:1000 adrenaline and histamine skin tests. A sterile hypodermic needle punctures the drop of solution at the centre intracutaneously and readings are charted at frequent intervals from 1 to 60 minutes. There is a white spot at the adrenaline site and a red spot at the histamine site, compared with a normal parallelism between sympathetic and parasympathetic hyperactivity. S. Tabuch (Kitasato, Japan) has carried out infrared electric pupillometry, which revealed smaller pupils with shortened latency times suggesting a cholinergic pupil abnormality.

L.W. Poulter (London) has made an immunohistological investigation of oral ulcers in Behçet's disease and in idiopathic recurrent oral ulceration; they both show similar features of a cell-mediated immune response with conversion of Ia- to Ia+ state of epithelium adjacent to the ulcers, a rich influx of T4 helper cells, T6 Langerhans cells, and a few B cells, mainly in the lamina propria.

The immunological abnormalities are numerous but none is specific. H. Hamza (Tunis) reported a decrease in the OKT4:T8 ratio and an increase in NK cells. The impaired NK activity seems to be due to the lack of some factor which normally activates NK cells, possibly interleukin 2 or IFN γ ; when the latter is added to culture media of Behçet's peripheral blood lymphocytes there is some improvement in NK cell activity. About one-third of patients have circulating immune complexes (CIC) and Elizabeth Graham (London) noted an interesting clinical correlation. Severe retinal disease was associated with the absence of CIC whereas raised CIC occurred with less severe ocular inflammation and with remissions. E. Kansu (Ankara) pointed out another clinico-immunological correlation, namely that spinal fluid-IgG and serum immune complexes are significantly increased in neuro-Behçet's disease.

Behçet's disease is a vasculitis predisposing to venous and arterial thrombosis probably because of abnormalities in platelet function. The degree of platelet aggregation may be correlated with clinically detectable inflammatory activity of the disease. W. Kirch (Essen, Germany) and T. Matsuda (Kawasaki, Japan) independently showed that there is increased

platelet aggregation in those with active inflammatory disease, and both suggested that anti-thrombotic drugs preventing platelet aggregation were helpful. N. Hizli (Ankara) showed that prostaglandin E and F2 levels were significantly raised in plasma and in rectal tissue in 44 patients with active Behçet's disease. P. Souza-Ramalho (Lisbon) noted increased plasma viscosity in active disease and that this could be reduced by treatment. Fibrinolytic activity is significantly but not constantly decreased according to J. Conard (Paris). A serum factor enhances the migration of polymorphonuclear leucocytes and may be responsible for pustular vasculitis, which is commonly recognized by dermatologists (Jorizzo *et al.*, 1984).

There are several different treatments suggesting that none is really satisfactory. Corticosteroid therapy is the universal sheet anchor, accompanied by either azathioprine, chlorambucil, cyclophosphamide, cyclosporin A, colchicine, levamisole, thalidomide, radiotherapy, plasmapheresis, fibrinolytic therapy with stanazolol and drugs to prevent platelet aggregation. J.D. O'Duffy (Mayo Clinic) gave a balanced review of the value of colchicine (Rogers & Duffy, 1981) and Elizabeth Graham (London) outlined the value and dangers of cyclosporin A (Graham *et al.*, 1984). R.B. Nussenblatt (Bethesda), a pioneer of cyclosporin A therapy, is starting a trial of cyclosporin G, which should hopefully be less toxic (Nussenblatt *et al.*, 1983a,b). The most compelling indication for treatment is to prevent visual failure, and in this respect cyclosporin is effective but at the price of troublesome nephrotoxicity. Colchicine, levamisole and thalidomide overcome orogenital ulceration, but nobody needs to be reminded of the 1961 thalidomide disaster.

It remains to identify the cause(s) which may amount to a constellation of co-factors triggered off by an inciting infective agent or some non-infectious irritant. Contributory background factors would include such diverse features as ethnic group, HLA affinities, T cell and autonomic imbalance, circulating immune complexes, blood viscosity and fibrinolytic activity, sex hormones, zinc deficiency and polymorphonuclear leucocyte chemotaxis.

Pugh and Lehner (London) provided evidence that herpes simplex might be the trigger factor for there is hyperactivity of a T8 suppressor-cytotoxic subset of cells to HSV1 and possibly other microbial antigens.

Copies of the proceedings of this International Conference, to be published in early 1986, may be ordered from Liz Graham, Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, UK.

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