Leading Article

Sarcoidosis around the world

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The 11th World Congress on Sarcoidosis and Other Granulomatous Disorders was held in the University of Milan in September 1987. It attracted 400 participants from 30 countries who enjoyed 96 communications and 148 poster presentations – proof that research in these fascinating disorders is very much alive and kicking.

The sarcoid granuloma is a battlefield between invading antigen and the cellular and humoral defences of the body. Such new techniques as immunofluorescence, histochemistry, monoclonal antibodies and ELISA have provided new insights in this immunologic battlefield for it is now possible to identify the uniforms of the participating warriors. The activated T helper lymphocyte releases interleukin-2 (IL-2) in abundance. The initiating signal for this exaggerated response has not yet been recognized but it seems that local stimuli in the battlefield maintain this exaggerated state of alert. The IL-2 gene is activated and soluble interleukin-2 receptors have elevated levels in serum and bronchoalveolar lavage fluid in active sarcoidosis.¹ But if IL-2 is present in abundance, why is there no dramatic response to treatment with cyclosporin?

In about 10% of sarcoidosis patients the granuloma persists with the development of extensive patchy fibrosis, mainly affecting the upper and middle lobes. What are the steps from granuloma to fibrosis? The alveolar macrophage hastens fibrogenesis via fibronectin and a progression growth factor, both of which influence fibroblasts to cause recruitment-attachment and to produce collagen type 1 fibrosis. Chemical mediators maintain a continuous cascade to fan on this process. The monocyte-macrophage lineage possesses calcitriol receptors, promoting the metamorphosis of macrophages into multinucleate giant cells and to granuloma formation.²

What are the best markers of this ongoing

fibrosis? Is it electron microscopy, histochemistry, humoral mediators, monoclonal antibodies, magnetic resonance, or a combination of all of them and why the predominance of fibrosis in the lungs whereas it is inconspicuous and infrequent in the liver and other organs? Is it possible that a foreign-body giant cell reaction is the inciting nidus? Under certain circumstances this initial foreign body reaction progresses inexorably to granuloma formation and fibrosis but in the absence of co-factors fizzles out harmlessly. This theory is dictated by the like behaviour of the Kveim-Siltzbach test.³

The Kveim-Siltzbach skin test is no longer used as frequently for three reasons. It is not commercially available so it is difficult to obtain the antigen. Secondly, it takes a month for a result, and a month in which systemic steroids must be avoided for this would suppress the test. But most important is that fiberoptic bronchoscopy provides histological confirmation within a day or so. Nonetheless, it remains most helpful in delineating sarcoidosis as a cause of uveitis, erythema nodosum, hepatic granulomas, hilar adenopathy and hypercalciuria.

What remains of considerable academic interest is the way in which it expresses granuloma formation so vividly. Serial biopsies of the developing Kveim papule at two weeks display a dense perivascular infiltration of T4 and T8 lymphocytes and HLA DR+ dendritic cells. The latter are RFD+ indicating their macrophage lineage. There is progressive serial development to acid-phosphatase-positive epithelioid cells and to true sarcoid granuloma formation.³

The question surrounding this test is its longterm future. Many of us are dedicated to its value in diagnosis and monitoring progress of the disease. But for many it has an even greater academic future, for it expresses the natural history of an evolving granuloma and of sarcoidosis itself. What new techniques are there to study this phenomenon? Is it just an exaggerated foreign-body reaction in a favourable terrain of co-factors?

Y.P. Kataria (North Carolina) has provided an exciting new twist to the Kveim-Siltzbach (KS) story. His study shows that bronchoalveolar lavage cells of sarcoid patients harbour a granulomagenic principle. Autologous bronchoalveolar lavage cells were prepared, processed and injected, just like the conventional KS antigen, into the same sarcoid patient with positive results. This elegant study demonstrates that an immunologic type of granulomatous inflammation can be induced by autologous bronchoalveolar lavage cell preparations. It is not yet clear whether the granulomagenic principle is associated with alveolar macrophages or lymphocytes.

Jacques Chretien (Paris) classified markers of activity into clinical, biochemical, isotopic and immunological – the latter being related to macrophage or lymphocyte activity. Macrophage markers include angiotensin-converting enzyme, serum lysozyme, carboxypeptidase and thermolysin-like neutral serum metalloendopeptidase. Lymphocyte markers include B2 microglobulin, adenosine deaminase, transcobalamine 11, and serum and urinary neopterin. Laudably, he hopes that workers will harness these and other new markers in the future for predictive criteria and therapeutic guidelines. For instance, neopterin levels bear a close relationship to lymphocytic alveolitis in active sarcoidosis. Activated T lymphocytes produce gamma interferon which stimulates alveolar macrophages to release neopterin. Thus it reflects activated cellular immunity. It may not be specific for sarcoidosis but rather a reflection of a whole group of pulmonary granulomatoses.

H. Fleming (Cambridge) reported on a series of 300 patients, with sarcoidosis of the heart, including 161 males aged 25 to 65 years, with 138 deaths. He drew particular attention to a frightening group of 77 young men with sudden deaths. Sarcoidosis had not been suspected in life and was only disclosed at necropsy. They included athletes who played regular football, cricket and skittles. They had died of cardiac arrhythmias, heart block and cardiomyopathy. It is difficult to know how to recognize the disease amongst these otherwise fit and seemingly healthy young athletes. They could quite easily have been airline pilots or in other special occupations responsible for public safety. There was another group of 39 older patients, mainly men, who died of congestive cardiac failure, following arrhythmias, pulmonary fibrosis and pulmonary hypertension. Within this large series of 300 patients there was also a group of 77 patients with complete heart block progressing to congestive cardiac failure. It is hoped that earlier diagnosis by electrocardiogram, Holter monitoring, radioactive tracers, magnetic resonance and even selective

myocardial biopsy may lead to earlier treatment and a decline in the present woeful mortality statistics.

Dr C. Voisin (Lille) presented his fascinating data on bronchoalveolar lavage in 15 patients with primary biliary cirrhosis (PBC) and 21 patients with Crohn's regional enteritis. These are chronic granulomatous disorders which have similar histology to sarcoidosis but are unrelated from the clinical standpoint. Nonetheless they share similar evidence of a subclinical alveolitis with macrophages and a T helper preponderance. Whereas the bronchoalveolar T4:T8 ratio is about 6:1 in sarcoidosis, it is about 4:1 in PBC and 3:1 in Crohn's disease. We should regard them as overlap syndromes, and it is important to seek evidence of all three in family histories of any one of these disorders.⁴

Each succeeding World Congress brings to the fore yet another country which has achieved manhood by joining in the world recognition of sarcoidosis. India was already beginning to assert itself in the Johns Hopkins Congress (1984) through the pioneer studies of Dr Samir Gupta (Calcutta). The Voice of India was loud and authoritative in Milan for Samir Gupta's contributions were also joined by the painstaking studies of Dr P. Bambery (Chandigarh). India has suffered from tuberculosis to such an extent over the years that latent silent sarcoidosis has been in an eclipse, perhaps even unimportant and unnoticed. Sarcoidosis has now emerged with such distressing symptoms that Gupta has had to treat 124 patients with steroids or chloroquine or oxyphenbutazone. Ten years ago vigorous steroid therapy would have been avoided because of endemic tuberculosis. It is now being used to advantage to overcome symptoms, prevent blindness, and hopefully to prevent respiratory failure in the future. Dr Bambery has described a series of 40 patients with essentially the same pattern as that seen in Europe. Sarcoidosis has emerged from behind a veil of obscurity in India.⁵

Likewise in China where Dr Yu Ren Jiang (Shenyang) has noted 64 patients in a survey of 17 hospitals. He was unable to be present at the Congress but his report indicates that the clinico-radiographic pattern, histology and serum angiotensin-converting enzyme levels are similar to European observations.⁶

1987 was the 80th birthday of Professor Frederick Wegener (Lubeck) who was the Guest-of-honour at this Congress. He first described three patients in 1936 in a Breslau seminar of the German Society of Pathology. He defined it as a necrotizing and ulcerative granulomatous vasculitis involving the upper respiratory tract, kidneys and

eyes. This report was published in 1937, so we not only celebrated his birthday but also the 50th anniversary of this seminal article. For 30 years this condition was incurable but cytotoxic chemotherapy has now made recovery possible. It is splendid to feel that the natural history and course of this fatal disorder has changed for the better during Wegener's lifetime. The *Postgraduate Medical Journal* congratulates Professor Wegener and wishes him a happy birthday year.

The World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG) was born in Milan on Monday 7 September 1987 and it will take over the old duties of the International Committee on Sarcoidosis. Its first Secretary-General is Professor Gianfranco Rizzato, Via

Juvara 9, Milan 20129. Write to him so that you can become a member of WASOG. This will entitle you to free issues of the Journal, *Sarcoidosis*, and a substantial reduction in registration fees for the future conferences. There will be a 2-day regional workshop in Lisbon during October 1989, and a 5-day World Congress in September 1991 in Kyoto, Japan. Further information on both meetings will be announced in future issues of this *Journal*.

The transactions of this Congress are being edited by Gianfranco Rizzato and will be published by Elsevier Science Publishers, PO Box 211, 100 A.E. Amsterdam, in March 1988.

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