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EDITORIAL

Sarcoidosis in the sunburnt country

The paper by Gillman and Steinfort, in this issue of the Journal, shines yet more light on antipodean sarcoidosis.[1] However, despite their claims to be the first, other investigators had charted its tortuous epidemiological estuarieslong before they were born.[2] A review of a potted history of sarcoidosis provides some salutary lessons about the difficulties in trying to paint a picture of it in any population.

The first description of what we now know as sarcoidosis was in 1877 by the London dermatologist, Jonathon 'Peg Teeth' Hutchison who described a man having 'a number of peculiar patches of dark purplish colour on his extremities'. He later described a Mrs Mortimer with sarcoidosis he called Mortimer's Malady. Across the Channel, Besnier in 1889 described '1upus pernio', a violaceous swelling of nose, ears and fingers the histology of which was described 3 years later by Tennyson as a 'predominance of epithelioid cells and a variety of giant cells'. In 1897 the Norwegian, Caesar Boeck described a policeman with 'multiple benign Sarkoid of the skin', which he thought was a new growth akin to a sarcoma (hence sarcoid), involving the epithelioid connective tissue cells. He later published 24 cases involving a variety of organs and was the first to realize it was a multisystem disease.[3]

Sarcoidosis was still not mentioned in the 10th edition of Osler's textbook of medicine in 1925. More papers followed, describing the plethora of organs affected by sarcoidosis. In 1946, the Swede, Sven Löfgren described erythema nodosum with bilateral hilar lymphadenopathy we now call the Löfgren's syndrome.[2] An unfortunate consequence of these radiographic abnormalities was a fixation with the lungs that has resulted in sarcoid patients being referred to respiratory specialists to this day. Sarcoidosis made its Australian début in 1940 when Lambie published a case of Besnier–Boeck's disease in the *Medical Journal of Australia*.[4] An important advance came in 1941 when Kveim modified a reagent that came to be known as the Kveim test; an injectable extract made from sarcoid spleen, which induced cutaneous granulomata in subjects with sarcoidosis. This was later used worldwide in the 1950s and the 1960s as a diagnostic tool and further refined by Siltzbach in 1961, although its mechanism of action has never been fully understood. Its main drawback was that it took 6 weeks for a result. In 1961 Hurley and Bartholomeusz produced an excellent Australian Kveim, which compared very favourably to foreign reagents.[5] Siltzbach tested his reagent in 37 countries and showed that it was the same disease worldwide.[6] In the 1970s, the fear that it could transmit diseases and the advent of transbronchial lung biopsy saw its decline.

The first to grapple with the incidence of Australian sarcoidosis was Dr Ray Marshman who worked in the Central Chest Clinic in Melbourne established to control tuberculosis (TB). Over the 4 years of the study (1959-1962) a mind-boggling 400 000 compliant people had a compulsory chest radiograph annually, making a total of 1 571 011 chest radiographs! They were white and were aged 15 years and more. The incidence was 9.2 per 100 000 (not 9.4 as stated by Gillman and Steinfort). The most common age was 30-34 years and the sex distribution roughly equal. Although of landmark significance, his paper was short on detail (one-and-a-half pages long).[7]

Anyone foolish enough to study sarcoidosis is soon confronted by some 'sarcoid facts of life'. Asymptomatic disease is probably more common that we think and cardiac manifestations can be particularly important. The disease often resolves after only 2 years or less, particularly when bilateral hilar lymphadenopathy (BHL) is the only manifestation. Extrathoracic disease is frequently

either misdiagnosed or results in referrals to non-thoracic specialists or not at all. Many patients have no lung involvement. Death from sarcoidosis, for example, sudden death from complete heart block or an arrhythmia may go unrecognized, particularly in a society averse to autopsies and where sarcoidosis is not considered. The incidence and manifestations of the disease are influenced by racial factors; this is important, given that our population is becoming increasingly heterogeneous. Why it seems so rare in our Aboriginal population may provide some clues to its pathogenesis.[8]

When a sarcoidosis clinic is established an immediate selection bias occurs as patients are referred from far and wide, some with chronic disease. It is important to distinguish between new cases, that is, incidence and all cases, that is, prevalence as sometimes these terms are incorrectly used interchangeably. Many large overseas studies have shown that approximately 50% of cases will be missed if the chest radiograph is relied on as a screening tool, that is, the tip of the iceberg phenomenon.[9] The diagnosis of sarcoidosis is essentially one of exclusion with no single diagnostic test of high specificity available; not even histology or serum angiotensin-converting enzyme.[10] Transbronchial biopsy is preferred to mediastinoscopy if a skin lesion is not available.

In the Geelong study, the patients had been referred to local thoracic physicians and the data were from their records. While retrospective studies are very valuable prospective studies are always likely to yield more valuable, information. In our prospective study of 112 patients, we found a striking increase in the incidence of neurological involvement compared with that found in our retrospective study of 313 patients.[11-14]

Dr Gordon Price from the Central Chest Clinic, Melbourne, studied sarcoidosis as well as TB patients from 1956 to 1975 by sequential chest radiographs. During that period 10,396,532 chest radiographs were obtained with 95% compliance by electoral roll. The radiographic incidence remained constant at 8.3 5 per 100 000 whereas the incidence of TB fell from 106 per 100 000 in 1956 to 11 per 100 000 in 1975.[15] A similar study was carried out by Dr Fred Heyworth in the Chest Clinic in Brisbane from 1965 to 1967, with 90% of the adult population surveyed for TB with 948 839 chest radiographs and a radiographic incidence of sarcoidosis of 10.1 per 100 000.[16]

The evidence suggests that the incidence is stable and is the same in Geelong, Melbourne and Brisbane. Of the 135 patients with sarcoidosis that I currently manage, every patient is examined by an ophthalmologist and 20 of these patients have cardiac involvement and many have pacemakers. Neurosarcoidosis, especially peripheral neuropathy is no rarity (approximately 5%) and some form of eye involvement common (approximately 15%). Although erythema nodosum is classically associated with sarcoidosis, it is surprisingly uncommon.

Positron emission tomography (PET) shows promise as a staging and diagnostic tool particularly for cardiac sarcoidosis.[17] In our prospective study of 10 patients with cardiac sarcoidosis in 1995, we found gated cardiac magnetic resonance imaging (MRI) had severe limitations with only two patients with a positive study.[18,19] Four had complete heart block (CHB), two had ventricular tachycardia (VT), one had VT with CHB and five had segmental left ventricular dysfunction. Notably, all had either a normal chest radiograph or stage 1 disease (BHL) with a mean age of 35 years and one required transplantation. There was one death. In the past 2 years we have used fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning in 33 sarcold patients, including 20 with cardiac involvement and have found it, combined with echocardiography, superior for day-to-day clinical management than MRI and now only occasionally use cardiac MRI. In addition, a significant number of sarcoidosis patients with heart block and malignant ventricular arrhythmias have pacemakers (usually defibrillating) inserted early,

thus precluding the use of MRI as a management tool.

The Geelong study had one unexpected finding; a high incidence of gastrointestinal involvement. It is gratifying to see that the word 'sarcoid' has been used in an Australian publication again and that there is another group of budding sarcoidologists. Collaborative research is likely to enhance our current knowledge of this condition. In such research it will be important to standardize our diagnostic measures and to examine changing epidemiological trends in different racial groups.

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