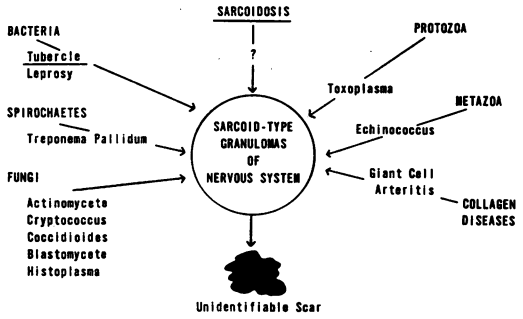

Fig 3 *Sarcoid type granulomas of the nervous system*

though bacteria may be seen they cannot be cultured or transmitted to laboratory animals and also caseation is often absent. The neural type of leprosy is almost confined to peripheral nerves. Schaumann and asteroid inclusion bodies, though not described in leprosy, on analogy with other diseases studied, might be expected, though absent in 4 cases personally studied.

Spirochætes: In tertiary syphilis, meningovascular and gummatous, sarcoid-like granulomas may occur. They are distinguished by extensive surrounding plasma cell and lymphocytic infiltration and coagulative necrosis which is absent in sarcoidosis. Endarteritis is also conspicuous.

Fungal diseases: Epithelioid cell granulomas, though rare, may occur in actinomycoses, cryptococcosis, coccidioidomycosis, blastomycosis and histoplasmosis. They are relatively easily distinguished by the presence of the causative parasite and the frequent presence of polymorphs and eosinophils.

Protozoa: Toxoplasmosis may cause miliary or large granulomas but these are distinguished from sarcoidosis by the causative parasite, *Toxoplasma gondii*, in epithelioid cells and frequently by necrotic centres.

Metazoa: It is possible that sarcoid-like granuloma may be found in relation to parasitic cysts as I have seen one example related to a ruptured hydatid cyst in the liver. The presence of chitinous cyst wall, hooklets and often eosinophils serve as distinguishing features.

Collagen disease: The only condition in which sarcoid-like granulomas may occur is giant cell arteritis. They are distinguished by being confined to vessels and the giant cells appear to be reacting to fragmented elastic tissue. Epithelioid cell granulomas are not a feature of polyarteritis.

In conclusion, the granulomas of sarcoidosis in the nervous system may be mimicked in a number of other diseases. In tuberculosis the granulomas may be completely indistinguishable. The diagnosis of sarcoidosis of the nervous system requires histological proof, and/or a positive Siltzbach-Kveim test and is assisted by other system involvement. The absence of any of these criteria makes the diagnosis extremely hazardous.

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The Natural History of Neurosarcoidosis

In 1909 Heerfordt's paper on uveo-parotid fever – 'Uber eine "Febris uveo-parotidea subchronica", an der Glandula parotis und der Uvea des Auges lokalisiert und haüfig mit Paresen cerebrospinaler Nerven kompliziert' – began the study of sarcoidosis of the nervous system. His patients, a man in his 20s and boys of 11 and 14, complained of lassitude and had the three cardinal signs of fever, parotid swelling and uveitis. Two had optic neuritis with papillœdema and facial palsy; one had paralysis of the vagus and scattered sensory signs suggestive of mononeuritis multiplex. Dysphagia was another transient symptom. The man had thirst and polyuria which gradually lessened and his spinal fluid showed a mild pleocytosis.

Heerfordt found that the prognosis was good, although at follow up 2 years later one of the boys had just developed an acute retrobulbar neuritis.

In the past 8 years in South Wales 28 patients referred to me because of neurological symptoms had sarcoidosis. In 26 cases with systemic signs of sarcoid the diagnosis was confirmed at autopsy in

3 and by positive Kveim test or biopsy in 18; in the remaining 5 it was made on clinical grounds alone. In 2 cases the neurological disorder was the only manifestation of sarcoidosis.

Four patients died. In 2, sarcoids were found within the central nervous system at autopsy; in another, an elderly man who had committed suicide, the nervous system was not examined; in the fourth, who died of motor neurone disease, active granulomas were present in the lungs, central lymph nodes and other organs 16 years after sarcoid had been diagnosed by biopsy. The neurological illness seemed in life to be coincidental and at autopsy no neurosarcoids were found.

Seventeen patients were women, 11 were men. Neurological symptoms like the symptoms of the systemic disorder began at all ages, mostly in the middle years.

The distribution of systemic sarcoids followed the usual pattern, involving the lungs in 23, the uveal tract in 13, and the skin and lymphoid tissues each in 11. The salivary or lacrimal glands were swollen in 7, joints also were affected in 7, and in 3 there was clinical and electrical evidence of myocardial disorder. Two patients had sarcoid lesions of the mouth and one had myxœdema.

Synopsis of the neurological symptoms and signs showed that in 12 cases cranial nerves were involved; in 10, peripheral nerves; and in 2, muscles. In 11 cases evidence of intracranial disease was found and in 4 paraplegia or sensory ataxia was due to spinal involvement. (The patient with motor neurone disease was allocated to this group.) 4 cases had meningeal symptoms, one presenting with acute sarcoid meningitis. In 6, headache was a new and clamant symptom at the onset of the illness; 5 patients had past or present symptoms of psychiatric disorder.

The Acute Sarcoid Relapse

One of the puzzling facets of sarcoidosis is the generalized relapse which flares up after years of local, seemingly benign, disease.

Case 1 A middle-aged man had had a rash over his calves, attributed to varicose eczema, for twenty years; for eight years he had had a similar papular rash on his forearms and about his face.

He became excessively tired, had a cough and complained that he was short of breath. Chest X-ray showed pulmonary infiltration with enlarged hilar nodes. Within a few weeks he developed Heerfordt's syndrome: conjunctivitis and parotid swelling were soon followed by facial palsy, loss of taste on the opposite side of his tongue, ptosis and signs of peripheral neuritis. The spinal fluid protein was increased.

With prednisone his skin lesions cleared rapidly, his facial palsy improved but did not recover, taste returned, the ptosis persisted. Symptoms and signs of peripheral neuritis disappeared and nerve conduction studies were normal.

Within six months of stopping his prednisone he relapsed with new skin lesions and further changes in the lung fields. No fresh neurological signs were found but his wife noticed a return of indecision and havering – Micawber-like behaviour in an eminently practical man – which had marked his previous illness. Remission followed further therapy with corticosteroids.

Symptoms of an acute relapse may be confined to the nervous system and sarcoidosis may then be missed if the systemic signs are slight. Sometimes recovery from the acute episode is followed by a chronic complaint, hinting that the origins of chronic neurosarcoidosis can be lost in some forgotten ailment of the past.

Of 2 patients with persistent diabetes insipidus, one had had an attack of pleurisy at the age of 17, sarcoid being diagnosed almost by chance, 15 months before she developed thirst and polyuria; the other barely survived overwhelming sarcoid invasion of the hypothalamus from which he recovered fully except for the loss of water control.

Case 2 Following an epileptic fit at home a dental student was admitted with meningitis. He was conscious but in a state of collapse, dehydrated and with signs of peripheral circulatory failure. The electrocardiogram showed a changing pattern of nodal tachycardia, bundle branch block and atrial fibrillation. The spinal fluid was abnormal, its sugar content ominously low.

In the spring of 1962 he had had an indolent whitlow of his left ring finger. After a summer of strenuous out-of-door life his finger became swollen and painful and tuberculous dactylitis was eventually diagnosed. During the winter months he became thirsty and started to pass large volumes of urine. His studies began to suffer.

He had chipped a tooth in his fit. Subungual nodules of his toes had characteristic histology; his swollen finger had typical bone changes on X-ray and sarcoid granulomas were seen in the synovial biopsy from the interphalangeal joint. His chest X-ray was normal.

He responded at once to adrenocorticotrophin and prednisone, making an excellent recovery except for persistent diabetes insipidus which is controlled with vasopressin. He is now a practising dental surgeon.

Chronic Neurosarcoidosis

Epilepsy should be remembered as a lone sign of chronic intracranial sarcoidosis. A patient now aged 29 had her first focal fit at 17, two years after sarcoid eruptions appeared at the scalp margin.

Sarcoid penetrates the nervous system along meningovascular pathways and local proliferation may give rise to signs of tumour. This happened, for example, in a man of 37 nine years after his first symptom of diplopia. Chronic meningitis leads eventually to obstructive hydrocephalus which was a further complication in this case. Such dramatic episodes, in the evolution of chronic

neurosarcoidosis should be distinguished from the new symptoms of a generalized sarcoid relapse.

Chronic sensory neuropathy may be the only symptom of sarcoidosis – in a 57-year-old pharmacist the positive Kveim test was the first clue to the diagnosis – or it may be a worrying feature of a case of obscure chest disease.

Case 3 A man aged 69 had been troubled by pins and needles of his hands and feet for three years. He had signs in his chest which at first suggested carcinoma but his pulmonary symptoms had not changed over many years and he had also a story of recurrent joint pains. Atrial fibrillation and bundle branch block were thought to be due to cardiomyopathy.

Before the clinical suspicion of sarcoidosis was confirmed the patient had taken an overdose of sleeping pills, driven to suicide by his tormenting dysæsthesiæ. No lung cancer was found at the coroner's autopsy but the nervous system was not examined. Histological section of the enlarged hilar lymph nodes showed the changes of sarcoid.

Is there a local tissue reaction within the nervous system which mimics sarcoid without having the systemic multifocal features of true sarcoidosis (Anderson *et al.* 1962)?

One of the cases suggested this possibility in life but at autopsy disseminated lung sarcoids were found. The patient was a physical weakling with congenital ptosis and abnormalities of the heart and gut; his elder sister was an imbecile with micrognathos and spastic legs.

Case 4 As a child he was too clumsy to play games. Constipation and, later, encopresis were attributed to megacolon. Despite these handicaps he grew to better health and served for two years in the Royal Air Force as a storeman. He was graded to a low medical category.

Deterioration began at 25 with an attack of acute iritis. Within a year he had become so unsteady that he fell frequently and was no longer able to help his parents in their shop. Increasing constipation and finally retention of urine brought him into hospital.

Inactive pupils, ptosis, absent knee-jerks and rombergism, together with signs of aortic incompetence (due in fact to a bicuspid valve), suggested syphilis. Diabetes insipidus, an abnormal spinal fluid but with low sugar content and negative serology, muscle biopsy and a positive Kveim test established the true diagnosis.

He lived for four years, dying of peritonitis after an operation for transplantation of the ureters. Histological study of the central nervous system showed long-standing sarcoidosis, the older lesions occurring in the cord and nerve roots (*see* Figs 1 and 2 of Dr Jones Williams's paper, p 1170).

Biochemical Hypotheses

Apart from direct invasion of the nervous system sarcoid may have remote effects on neural and glial elements, although proof of this is lacking. The extreme languor and complaint of heaviness of the limbs at the time of relapse may be a result of hypercalcæmia. Little support for this was found from my cases as only 4 had a raised serum calcium whereas lassitude was an almost constant symptom. Despite this, the diffuse slow-wave changes often seen in electroencephalograms strengthened my suspicion that some symptoms of an acute relapse were due to a metabolic disturbance.

Areas of exceptional vascularity, such as the hypothalamus or the optic nerve-head, and the sites of cerebrospinal fluid secretion are particularly prone to sarcoid invasion. As a small increase in the serum concentration of any substance would have a maximum effect at these places, granulomas might form in response to sensitization or preselection by a chemical agent. The frequency of facial palsy might be the result of the nerve sharing a common vascular bed with the parotid gland and of high exposure to the hypothetical toxin.

Slowing of nerve conduction in some cases of sarcoid neuritis is of a severity usually ascribed to segmental demyelination. Such slowing has been found both in facial and limb nerves of some of my cases. It adds to the idea of a remotely acting chemical agent but needs further elaboration and confirmation by nerve biopsy.

Transient attacks, akin to episodes of arterial insufficiency or of migraine, may be the only symptom of an acute sarcoid relapse. Anoxic infarction and demyelination distal to arteries strangled by sarcoid tissue are well-known histological findings: these transient attacks may therefore have a similar pathogenesis in life. Alternatively, their cause may be biochemical.

One young man at the time of acute pulmonary sarcoid with mild hypercalcæmia had repeated episodes of this kind which subsided soon after starting prednisone. The following case is thought to be another example of this unusual syndrome:

Case 5 Within the space of a month a woman aged 48 had two short-lived episodes of diplopia and loss of the temporal fields of vision, followed by throbbing vertical headache. She had a cough and was unaccountably tired and breathless.

Neurological examination was normal but the Lange curve was paretic. Chest X-ray showed enlarged hilar nodes. Mantoux tests at several dilutions were negative but the Kveim reaction was positive.

She had no treatment and a year later was well and without symptoms.

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