Chapter 2
History of the Attempts to Find the Origin of Multiple Sclerosis

2.1 Introduction

Multiple sclerosis would appear to be a neurological disease which has been described in various patients throughout the ages. The cause of the disease is unknown and has stimulated numerous studies over the last 150 years.

A comprehensive study of the history of multiple sclerosis and of the various eminent contributors trying to elucidate this disabling neurological disorder has appeared in the literature (Murray 2005).

2.2 Multiple Sclerosis Before Charcot

The oldest report of a patient with possible multiple sclerosis is Saint Lidwina from Schiedam in the Netherlands. She was born in 1380 and in 1396, following a fall whilst skating, Lidwina developed headaches, walking difficulties and a muscular weakness of her face with a drooping lip. She continued to deteriorate, although at times she was free of any symptoms.

She was canonised in 1890 and has become the patron saint of skaters.

Another possible sufferer from multiple sclerosis was Augustus d'Este, a grandson of George III. His symptoms consisted of blurred vision which cleared up and then relapsed over the course of his lifetime.

He later developed weakness in his legs, numbness, episodes of double vision and bladder and bowel problems. The remissions and relapses were described in his diaries. In his last year he had persistent tremors, with spasms and was confined to bed.

The diagnosis of multiple sclerosis was made after his death by neurologists reading his diaries.

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2.3 Carswell in London

Robert Carswell (1793–1857) was a Professor of Pathological Anatomy at University College Hospital. He frequently carried out post-mortem examinations which were then published in 1838 in his "Atlas of Pathology". During a post-mortem examination in 1830, he found strange lesions in the spinal cord which were later considered to resemble sclerotic plaques. However Carswell did not describe the ante-mortem clinical features of the patient.

2.4 Cruveilhier in Paris

Jean Cruveilhier (1791–1874) was Professor of Pathological Anatomy in the University of Paris. In 1841, Cruveilhier described a woman who had neurological symptoms for 6 years. Her symptoms consisted of abnormal sensations in her lower limbs. Later on she developed trembling of arms and hands. Soon afterwards a trembling of the arms and clumsiness of the hands occurred. Later she could not use her upper limbs and often grasped objects would slip from her hands. She was handicapped by frequently stumbling, dragging her feet with occasional collapsing of knees and had to give up her job as a chambermaid. During the last weeks of her life she lost all sensory feelings in both her legs. The patient died aged 38 years. No post-mortem examination was carried out on the subject. Many of her symptoms were subsequently recognised to occur in other patients with the disease which eventually became known as "multiple sclerosis".

2.5 Charcot at the Salpetrière

Jean Martin CHARCOT (1825–1893) was Professor of Neurology in the University of Paris. He is also known as the "Father of neurology".

In 1868, Charcot examined a young woman at the Salpetrière Hospital who had a tremor that he had never seen before. He noted that she had three characteristic symptoms: intention tremor, slurred speech and abnormal eye movements or nystagmus. These three characteristic symptoms later became known as "Charcot's triad", but it occurs in only 20 % of multiple sclerosis patients.

He also noted that the patient had "cognitive changes" in that she had a weak memory and could not express her ideas clearly.

When she died, he carried out a post-mortem examination and found that her brain contained characteristic "plaques" of sclerosed tissue and labelled the disease as "sclérose en plaques", the name it has nowadays.

Although Charcot gave a complete description of the disease, he could not work out the cause of this condition and found that strychnine, gold or silver injections as well as electrical stimulation were of no help in treating such patients.

Charcot diagnosed several other patients in his hospital having a similar disease pattern. In total, he studied some 30 patients with multiple sclerosis and described most of the clinical features of the disease. He clearly can be credited in having discovered or identified a new neurological disease. For this alone he deserves to be called the "Father of Neurology".

Charcot had a bitter dispute over the causes of "hysteria" with his pupil Sigmund Freud. Charcot thought that there was a neurological explanation for this condition whilst Freud felt that it was a psychiatric problem which could be resolved by psycho-analysis.

2.6 Multiple Sclerosis in Other Countries

Multiple sclerosis was first recognised in the U.K. by Dr. Walter Moxon in 1873 and in the USA by Dr. Edward Seguin in 1878.

Wilhelm Uhthoff (1853–1927), a German ophthalmologist described optic neuritis patients who had visual problems which were made worse following physical exercise.

The Swiss pathologist Georg Eduard Rindfleisch (1836–1908) noted that the inflammation associated lesions were located around blood vessels.

In Sweden, a cluster of multiple sclerosis cases suggested that the condition arose some two centuries ago and acquired the name of the "Fenno-scandian focus" (Kurtzke 1968).

One of the problems in assessing multiple sclerosis in other countries is that there are in the community patients who have minor symptoms but have not been seen or diagnosed by a neurologist. There is thus an underestimate in the number of patients with the disease in the population which complicates attempts at studying the aetiology of this condition.

For instance, in a study from Catalonia in Spain, the whole population of a small town with 72,000 inhabitants was examined over a period 5 years and many of the subjects had not been seen previously by a neurologist. The prevalence rate of multiple sclerosis was found to be 58/100,000. This is 5–10 times higher than had previously been reported from Catalonia (Sempere et al 1995).

Since many subjects suffer from viral and bacterial infections in the upper respiratory tract, the presence of such common ailments would not be included in studying neurological problems.

2.7 Microscopy of Multiple Sclerosis Lesions in Edinburgh

Dr. James Dawson (1870–1927) of the University of Edinburgh, performed careful and detailed microscopic examinations of the brains of multiple sclerosis patients. He described that the inflammation was located around blood vessels, thereby indicating that the agent or toxin came from an extra-thecal space from the blood in the

vascular system and therefore was probably coming from an infectious source outside central nervous system.

Dr. Dawson further pointed out that the damage was primarily affecting the myelin sheaths of neurones and oligodendrocytes, the cells making myelin (Dawson 1916).

2.8 Clues from Therapy

Following the microbial discoveries of Louis Pasteur and Robert Koch the possibility of infection by microbes crept into many diseases. The clear implication being that if one could identify such external agents, the severe complications of the disease could be mitigated by immunization, as occurred in the case of rabies, smallpox and polio or eliminate the microbial agent by the use of antibiotics.

Since the cause of multiple sclerosis is not known, the main principle of treatment is to reduce the level of inflammation by steroids, azathioprine, interferons, glatiramer acetate, mitoxanthrone, intravenous immunoglobulins and a variety of biologicals (Pozzilli et al. 2002).

The clear clue provided by the variety of therapeutic agents is that reducing the level of inflammation somehow reduces the severity of symptoms and signs of the disease. This suggests that inflammation itself targeted at myelin and its related products is the probable cause of the disease. Agents that attack myelin would be auto-antibodies directed against that substance. Thus multiple sclerosis could be considered as an autoimmune disease where the main external antigen has sequences or shows "molecular mimicry" with myelin.

The question arises where is the external antigen which has sequences resembling myelin?

2.9 A "Eureka Moment" in London

"Molecular mimicry" has previously been shown to operate in rheumatic fever and many other auto-immune diseases. Work from the Immunology Unit at Queen Elizabeth College and later King's College showed that in the auto-immune disease ankylosing spondylitis there was "molecular mimicry" between HLA-B27 and the bowel microbe *Klebsiella.* Subsequent studies showed that there was "molecular mimicry" between the urinary microbe *Proteus mirabilis* and HLA-DR1/4, antigens which are prevalent in rheumatoid arthritis. The conclusions from these studies were that urinary tract infection by *Proteus mirabilis* was the probable cause of rheumatoid arthritis and bowel infection by *Klebsiella* microbes was the possible cause of ankylosing spondylitis.

These studies were carried out in the Immunology Unit which was located jointly within the Departments of Microbiology and the Department of Biochemistry. Professor John Pirt (1923–2000), who was the Head of the Department of

Microbiology strongly supported the work of the Immunology Unit with funds, laboratory space and SRC and MRC Ph.D studentships.

In the early 1980s Professor Pirt retired to Wales and came across an epidemic of a cattle disease known as “bovine spongiform encephalopathy”, which had been labelled by the lay press as “mad cow disease”. It was thought to belong to a group of conditions called collectively as “transmissible spongiform encephalopathies” and included the disease scrapie which occurs in sheep and goats and the human diseases Creutzfeldt-Jakob disease and kuru which occurs in New Guinea natives. Bovine spongiform encephalopathy was thought to have passed to humans by meat consumption where it was described as new-variant Creutzfeldt-Jakob disease (nvCJD).

The situation encountered by Professor Pirt was that several cattle graziers were reported to have committed suicide when they lost their livestock which they had nurtured for years. If only one cow showed symptoms of the condition, the whole stock was then culled and samples collected by the Ministry of Agriculture (MAFF) (Ministry of Agriculture, Fisheries and Food) for further investigations.

The possibility that the disease had been passed on to humans caused great concerns with the general public and the press. Parliament was inclined to support any studies on the cause of “bovine spongiform encephalopathy”.

Professor Pirt suggested that the Immunology Unit should investigate “bovine spongiform encephalopathy” using the methods that had been used to study ankylosing spondylitis and rheumatoid arthritis.

There was an initial reluctance to study a veterinary disease but on careful review in the press and on television, it showed a remarkable behaviour by the cows affected by “bovine spongiform encephalopathy”.

The television pictures showed affected cows being led by the farmer with a rope round their necks. The affected cows, were stumbling with ataxia and falling down, especially on their hind-quarters. The cows had difficulties in going round corners. There was clearly a hind-quarters ataxia and paralysis (Fig. 2.1).

Fig. 2.1 Cow affected by bovine spongiform encephalopathy has ataxia and paralysis of hind quarters but is able to stand on its fore-quarters (With permission from ITN)

The “eureka moment” occurred when hind-quarters ataxia and paralysis was found to resemble hind-quarters ataxia and paralysis in guinea pigs injected with brain homogenates, when they had developed “experimental allergic encephalomyelitis” (EAE) (Raine et al. 1974).

Furthermore, multiple sclerosis patients suffer from lower limb ataxia and paralysis 3–4 times more frequently compared to upper limbs involvement.

Clearly a clinical similarity present between “bovine spongiform encephalopathy”, “experimental allergic encephalomyelitis” (EAE) and multiple sclerosis, raised the issue of a possible aetiological similarity as to the origin of these disparate diseases.

It appeared that further studies were required to clarify these issues.

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