Chapter 1
Multiple Sclerosis as a Scientific Problem

1.1 Multiple Sclerosis: An Introduction

Multiple sclerosis is a neurological demyelinating disease which has numerous clinical manifestations involving the central nervous system.

There are over 10 million people in the world who suffer from this incapacitating disease but the number of affected individuals may be higher if early stages or "formes frustes" are included.

The disease is not only a health problem for the affected individual but is also a social burden to society in the costs involved in caring and treating such patients, as well as the attendant loss of economic activity by the patients.

Multiple sclerosis was first definitely described in 1868, by Jean Martin Charcot from the Pitié-Salpetrière Hospital in Paris who identified sclerotic plaques on post-mortem examination and gave it its modern name of "sclérose en plaques". However there were previous incomplete clinical descriptions by Cruveilhier (1845) and anatomical drawings of such plaques, especially by Robert Carswell (1838) Professor of Anatomical Pathology at University College Hospital in London.

The origin of this disease is unknown but extensive research studies have been carried out over the last 100 years to try and characterise the onset and cause of this disabling condition.

It is thought that the main pathological factor is the destruction by the immune system of myelin, the covering of neurones and myelin producing cells, the oligodendrocytes.

External agents that have been suggested as setting off this disease are Epstein-Barr virus infection, but other possible triggering conditions could be measles, mumps or rubella. These viral infections occasionally give rise to acute encephalomyelitis which in some features resemble multiple sclerosis.

Multiple sclerosis is usually diagnosed on the presenting symptoms and signs, together with supporting medical tests involving both examination of the cerebrospinal fluid for oligoclonal bands and radiological investigations.

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The multiple sclerosis plaques commonly affect the white matter of the optic nerve, brain stem, basal ganglia, spinal cord and areas near the lateral ventricles. There are widespread patches of demyelination followed by gliosis.

The study of this disease has had a close relationship with attempts at treating patients who had been bitten by rabid dogs or wolves. In the 1890s Pasteur and colleagues in Paris carried out attempts at immunising patients with rabbit brain homogenates which contained the rabies virus. Although the treatment was in the majority of cases successful, in some patients it led to the development of unusual neurological complications which in some cases had a fatal outcome.

It was not until the 1930s that it was discovered immunising animals with saline brain homogenates led to a condition labelled "experimental allergic encephalomyelitis" (EAE) which was a demyelinating condition resembling multiple sclerosis. This experimental condition came to be considered as an animal model of multiple sclerosis.

It is the theme of this book that the link between rabies, attempts to treat rabies patients with brain homogenates and the discovery of "experimental allergic encephalomyelitis" provides new ways of looking at the demyelinating disease multiple sclerosis.

1.2 Clinical Features of Multiple Sclerosis

The onset of the disease is often sudden but may be insidious and the patient may complain of transient muscular pains, stiffness, tiredness, malaise and fatigue with gait incoordination, slurred speech and eye problems.

The acute lesion causes temporary functional interruption but with the neuronal fibres not being permanently damaged, so the early symptoms tend to improve. The initial clinical feature develops fairly suddenly and disappears after a few days or weeks.

In young people, optic neuritis, involving blurring or temporary loss of vision is probably the commonest symptom, whilst in elderly subjects, weakness of one or both lower limbs is usually the presenting symptom.

In general, the lower limbs are three to four times more frequently affected than the upper limbs (Brain 1962).

Weakness, heaviness and stiffness of one or both lower limbs is due to corticospinal tract demyelination and may develop fairly suddenly. Often other symptoms are incoordination of arms with intention tremor, ataxia of gait and dysarthria presenting as slurred speech. Occasional unsteadiness of arm or leg may be due to impaired proprioception. Transient disturbances of bladder functions such as urgency, precipitancy or hesitancy of micturition, with impotence in men is occasionally reported by patients.

Nystagmus is present in at least 70 % of cases. It is usually absent on central fixation and appears on conjugate deviation both laterally and vertically.

Corticospinal tract signs such as extensor plantar responses, muscle weakness and increase in flexor tone are common.

Vibration sense is frequently diminished and impairment of the sense of passive movement may also be found.

Analgesia or loss of sensation of light touch may be found but rarely persists.

In many cases early manifestations are followed by remissions. However relapses are a striking feature of this disorder and are not predictable, occurring without warning (Compston and Coles 2002).

The pathological lesion is a circumscribed patch of nervous tissue in which destruction of myelin occurs first, followed eventually by damage to the neurofilaments of the axis cylinders.

The most important method in making a diagnosis is a careful history and examination of the patient. In general, multiple sclerosis is defined as two or more neurological episodes or attacks separated in time and space. The diagnosis can be helped by examination of the cerebrospinal fluid and radiological examination of the central nervous system.

The McDonald criteria using clinical, laboratory and radiological evidence of lesions at different times and in separate areas, provide a comprehensive framework to arrive at a diagnosis (McDonald et al. 2001). Revisions of these criteria have been published emphasizing that extra information can be gleaned from radiological examinations.

Several patterns of progression of the disease have been described:

(a) relapsing-remitting,
(b) secondary progressive,
(c) primary progressive and
(d) progressive relapsing.

The primary-progressive is commoner in people in their 50s (Miller and Leary 2007). The most common length of time between disease onset and conversion from relapsing-remitting course to secondary progressive multiple sclerosis is 19 years (Rovaris et al. 2006).

The term “malignant multiple sclerosis” is sometimes used to describe multiple sclerosis patients who reach a significant level of disability in a short period of time.

1.3 Laboratory and Radiological Features

Abnormalities of the cerebrospinal fluid are found in well over half of multiple sclerosis patients. There is a mild lymphocytosis and an increased proportion of gamma globulin. On electrophoresis oligoclonal bands of IgG are found in 70–80 % of multiple sclerosis patients.

Elevated levels of autoantibodies to myelin are also found in the cerebrospinal fluid as well as in blood.

The blood-brain barrier of the capillary system prevents the entry of large molecules such as IgM or cells circulating in the vascular system to penetrate the central nervous system. However during inflammatory episodes, the blood-brain barrier may become permeable to cells or large molecules.

Gadolinium cannot cross a normal blood-brain barrier. However gadolinium enhanced magnetic resonance imaging (MRI) can show lesions and areas of increased blood-brain barrier permeability .

1.4 The Therapy of Multiple Sclerosis

The treatment of multiple sclerosis involves many parameters. One of the main aims is to reduce the frequency of neurological relapses and to prevent permanent disabilities. Some workers have also emphasized that reduction in disease progression is an important aim in the management of this condition (Compston and Coles 2002).

The therapy of multiple sclerosis involves not only the use of steroids, glatiramer acetate but also newer biological preparations which place an exorbitant financial strain on health providers and society in general. Many of these drugs have undesirable side-effects.

The general principle in such a therapy is to reduce the intensity of the inflammation once it has started in a patient.

Inflammation is the body's response to injury. The question arises "What has been responsible for the tissue injury?", in other words what is the primary cause which sets off multiple sclerosis.

A possible way as to how to answer such a question may be to look for previous successful solutions in finding the cause of a disease and no better example is provided than by rheumatic fever.

1.5 Molecular Mimicry and Rheumatic Fever

The prototype of an autoimmune disease evoked by an external agent and operating through the mechanism of "molecular mimicry" is rheumatic fever.

It usually occurs some 2–4 weeks after an upper respiratory tract infection by Lancefield group A *streptococci.* Some *streptococci* have been found to have antigens which crossreact with cardiac myosin and others resemble some molecular sequences found in the basal ganglia of the brain. When someone develops tonsillitis by this microbe the resultant antibodies will not only attack the *streptococcal* bacteria but also the heart and the brain. Thus anti-*streptococcal* antibodies produce rheumatic fever and Sydenham's chorea by acting as cytopathic autoantibodies. It would appear that rheumatic fever and Sydenham's chorea are autoimmune diseases caused by an infection.

Other diseases operate by a similar mechanism. Some 20–30 million individuals in South America, especially Brazil, are infected by the protozoan parasite *Trypanosoma cruzi.* Patients with Chaga's disease have antibodies which react with both antigens present on the surface of the parasite as well as with cardiac endothelium and myocardium giving rise to a myocarditis which pathologically resembles rheumatic fever. Thus it would appear that even parasites can be triggers or causative agents of an autoimmune disease (Ebringer et al. 2003).

Molecular mimicry has been demonstrated to operate in both ankylosing spondylitis and rheumatoid arthritis.

It is not inconceivable that a similar mechanism may operate in multiple sclerosis.

1.6 The Properties of the Multiple Sclerosis Problem

A "scientific problem" involves defining the properties of the puzzle which interests the scientist and in tackling the relevant question. It is these properties that provide possible answers for the scientific enquiry.

The philosopher of science Karl Popper has always emphasised that in trying to solve a scientific problem one must generate hypotheses which can then be tested experimentally. For such hypotheses to be labelled as scientific they must prohibit certain results. If such prohibited results are obtained then the theory is found to be invalid or has failed in explaining the "scientific problem".

We then must produce new hypotheses to tackle the problem under investigation. So scientific research proceeds by a succession of conjectures or guesses and refutations.

The properties of the multiple sclerosis problem would appear to be the following:

1. **Sex ratio:** Multiple sclerosis is found 2–3 times more frequently in women than men.
2. **Early age of onset:** The age of onset in multiple sclerosis is between the ages of 20 and 30 years. In some patients it starts even in their teens. This clearly distinguishes this autoimmune disease from rheumatoid arthritis where the age of onset is in the 40s and 50s although again occurring more frequently in women.
3. **Family studies:** It has been known for a long time that there is a familial aggregation of multiple sclerosis and this suggests somehow that there is a genetic link associated with the development of the disease.

   The probability of getting multiple sclerosis is higher in relatives of an affected person. If both parents are affected, the risk in their children is almost ten times compared to that found in the general population (Milo and Kahana 2010).
4. **Genetic links:** The most consistent finding is an association between multiple sclerosis and HLA-DR15 and HLA-DQ6. Overall it has been estimated that

HLA accounts for about 30 % of the genetic predisposition in this disease (Baranzini 2011).

5. **Geography, latitude and sunlight:** There is a striking North-to-South prevalence of the disease. It is commonly found in the northern countries of Europe. It is found frequently in Norway, Sweden and Finland compared to Italy or Spain. Multiple sclerosis is commoner in Scotland compared to England. This latitude gradient is also found in the USA (Kurtzke 1993).

   It appears that multiple sclerosis is associated with the latitude, in that it is commoner the further one goes from the equator.

   In the southern hemisphere, the reverse occurs, multiple sclerosis is seven times commoner in the southern island of New Zealand and Tasmania, compared to Queensland in populations having the same ethnic origin.

   This has led to the suggestion that the relative lack of sunlight may reduce the level of vitamin D.

   The lack of this vitamin may affect the functioning of the immune system. However in other autoimmune diseases, such as rheumatoid arthritis or ankylosing spondylitis, the possible lack of vitamin D has so far not been noticed.
6. **Upper respiratory tract infections and sinusitis:** Several studies over the last 30 years have indicated that there is an association between upper respiratory tract infections including sinusitis and the presence of multiple sclerosis. Whether this indicates some viral or bacterial trigger factor involved in this disease is not clear but requires further consideration.

   It is proposed to use these properties of the multiple sclerosis problem to investigate the possible cause of this disease by research workers associated with the King's College Immunology Unit in London.

1.7 King's College Immunology Unit[1]

The Women's Department of King's College London opened in 1885 and in 1915 moved to Campden Hill road, Kensington.

In 1953, it received a Royal Charter and was named Queen Elizabeth College after the Queen Mother.

The college distinguished itself in teaching and research in microbiology, biochemistry, physiology and nutrition. In 1972 an Immunology Unit was set up within the departments of biochemistry and microbiology with an interest in research into genetic and environmental factors in rheumatic diseases, especially ankylosing spondylitis and rheumatoid arthritis and later in Crohn's disease, as well as bovine spongiform encephalopathy and multiple sclerosis.

[1] This section appeared in an abbreviated form in *Rheumatoid Arthritis and Proteus*. Alan Ebringer. Springer, London 2012.

Many students and doctoral candidates passed through the Unit and two stayed for over 12 years, Dr. Clyde Wilson Ph.D, FRCPath and Dr. Taha Rashid MBChB, M.Phil.

In 1985 Queen Elizabeth College remerged with King's College and moved to the Waterloo Campus in Stamford street on the South Bank.

It is the aim of this book to try to answer some of the questions posed by the properties of the scientific problem and to try to examine whether current difficulties involving cattle diseases may be associated with "experimental allergic encephalomyelitis" and thereby suggest some novel approaches to the study of this disease.

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