

## MILESTONES IN NEUROLOGY IN THE LAST 50 YEARS ON MULTIPLE SCLEROSIS

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Progress in multiple sclerosis (MS), since the pioneering work of Charcot and his predecessors, has not occurred suddenly through dramatic scientific breakthroughs, but through the continued efforts of thousand of investigators. Advances in understanding of basic science, particularly immunology and pharmacology as well as developments in the investigation clinical disease, especially magnetic resonance imaging, ultimately contributed to the approval of the first drugs to impact the natural history of the disease. At the dawn of twenty-first century, the availability of interferons and glatiramer acetate has accentuated the hopes of those affected with MS and their families.

Multiple sclerosis is an autoimmune neurological disease characterized by dissemination of changes in the CNS white matter in both time and space.

Historical overview of the events provides insight into the understanding of the disease and in many medical trends during last two centuries.

The first description of the disease is in St Lidwine van Schiedam who lived in late XIV and early XV centuries. The history of her ailment was described by Medaer. She was born on April 18 1380 in Schiedam, the Netherlands. Dr Sonderdank, the physician who had treated her, said to his colleagues: "Believe me when I tell you that this disease has no cure; it comes straight from God. Neither Hippocrates, nor Galen would be able to help here. This woman was touched by the hand of God"<sup>1</sup>.

A well documented case, before the disease was recognized in medical circles, is the case of Augustus d'Este (1794-1848), George III's grandson. He had been writing a detailed journal since 1822 where he had described symptoms very graphically and followed the progression of his disease during several decades.

Another notable personality who is believed to have had multiple sclerosis was the poet Heinrich Heine (1797-1856).

Charles Prosper Olliveier d'Auders was the first to give an account of MS in a monograph published in Paris in 1824 in the work entitled "*Maladies de la moelle epinière*", where he described a twenty-year-old with relapsing-remitting neurological symptoms. Robert Carswell was the first to describe pathologic changes of MS in an atlas published in 1838. In France Jean Cruveilhier had described four cases in a text entitled "*Diseases of the spinal cord*". Charcot gives Cruveilhier the primacy as the first MS illustrator. Carswell's pictures appeared three years earlier. The first clinical diagnosis of MS in a living patient had been provided by Frerich Theodore von Frerich in 1849<sup>2</sup>.

Jean-Martin Charcot (1825-1893) is without doubt the physician who is historically most associated with the MS. He described tremor, nystagmus and dysarthria, which came to be known as Charcot's triad. Across the Atlantic JC Morris was the first to give an account of the disease in the USA in 1867. During the first half of the XX century there was little true progress in the understanding and therapy of MS. All therapeutic efforts were futile and non productive, following the fashion of the era. The medicaments were antispasmodic, antihistaminic, anticoagulant and a whole range of other agents. Therapy with strychnine, silver, gold injections and electric stimulation were unsuccessful.

In 1933 Rivers, Sprint and Berry gave very significant contribution to the understanding of the disease development in animals, experimental autoimmune encephalomyelitis (EAE), which has served as the model for MS ever since.

Therapy of MS has remained unsuccessful during the whole 1960s.

In 1960 JF Kurtzke published a scale for assessment of patients' affliction by multiple sclerosis<sup>3</sup>.

Augustus Rose carried out a study on ACTH in therapy of acute MS exacerbations. It was the first successful randomized, placebo controlled, multi-centric study of MS, as well as the predecessor of larger and more sophisticated studies of MS which have culminated in the development of new therapies in 1990s (4). In 1965 Schumacher offered diagnostic guidelines for the needs of clinical trials. The development of electrophysiological methods (evoked responses) and neuroimaging (MRI), introduced in MS diagnosis in 1981, as well as increased recognition of the use of CSF analysis, has provided new, so called, Poser's complex criteria for MS diagnosis<sup>3</sup>.

The results of many studies using different immunosuppressive medications have been published during 1980s. The majority of those medications have been shown to be successful in open, small, randomized studies, but provided only minimal effect in large, multi-centric, randomized, placebo controlled studies. Despite the failure of these studies to identify effective therapies, they served as a ground for training of many researchers who became extremely skillful in management of these very complex studies. The researchers in North America and Europe have carried out studies on interferons and glatiramer acetate in 1990s, which led to their approval in 1993 interferon beta-1b (Betaferon) became the first drug approved for MS by FDA. In 1996 interferon beta-1a (Avonex) was approved in the USA<sup>5</sup>. In 1997 glatiramer acetate (Copaxone) was approved in the USA<sup>6</sup>. In 2000 Mitoxantron (Novantrone) became the first drug approved for progressive MS in the USA.

In 2004 the FDA approved a drug called natalizumab (Tysabri) for the treatment of MS. The drug has been pulled off the shelf a year later because of the brain infection in three patients, only to be re-approved for treatment of recurrent-relapsing form of MS in 2006<sup>7</sup>. Alemtuzumab (Campath 1H) is a monoclonal antibody which has been used for treatment of chronic lymphatic leukemia since 2001. In treatment of multiple sclerosis we use its activity on lymphocytes (T lymphocytes) in the patient's blood. The drug is given in infusions, which are repeated

after 12 and 24 months. There are reports about effectiveness of a drug rituximab (Rituxan), also monoclonal antibody, which binds to CD20 and is located on the precursors of B-cells and mature B-cells; it is recommended for the treatment of the non-Hodgkin lymphoma, rheumatoid arthritis and B-cells lymphoma. There are studies under way on the effect of daclizumab (Zenepax), a monoclonal antibody, which binds to CD25 on alpha chain of interleukin-2, thus influencing T-cells activity and proliferation. We are expecting soon two drugs for treatment of recurrent-relapsing multiple sclerosis: fingolimod (a sphingosine modulator) and Cladribine (a cytostatic with immunosuppressive action, used in leukemia treatment)<sup>8</sup>. Due to a series of adverse effects, the treatment with blood stem cells after previous chemotherapy requires additional research.

Recently, a vascular surgeon, Dr Paolo Zamboni, from the University of Ferrara in Northern Italy, has published very interesting data on obstructions in brain-spinal venous flow (circulation). The wife of Dr Zamboni suffers from MS, and that was the cause for him to dedicate so much attention of the disease. Using ultrasound and venography in examination of 65 patients, he was able to detect 4 different types (A, B, C and D) of obstruction in venous flow (circulation). The obstructions were in the form of stricture in neck venous system in different places. As a consequence of the stenosis, most frequently in neck blood vessels and in the spinal area, there is a reflux of the venous blood and the crash in the brain blood flow. Recurrent-relapsing MS and primary advancing type of the disease are connected with stenosis in different places in the venous flow. The expansion of those constricted places in the venous system and placement of stents managed to improve the blood flow. Treatment of the constrictions in venous system came to be known as "Liberation". The obstructions of the venous blood flow are connected with iron depositing in the brain. Iron takes part in creation of free radicals, which act toxically on nerve cells. Symptoms of the disease in Dr Zamboni's wife, who had difficulties with eyesight, balance and dramatic onset of the disease, have improved drastically. Treatment of more than 100 patients with acute relapse of the disease led to a fast improvement without the use of corticosteroids. After the treatment the patients cite smaller disease re-

lapses, a slight fatigue; there is less brain changes and the quality of life is improved. There is an ongoing study at the University of Buffalo, New York. Perhaps the removal of obstruction in venous blood flow can enable us to successfully treat a certain number of patients with multiple sclerosis<sup>9</sup>.

Another key development in the history of MS was the founding in the United States of the National MS Society, originally called the Association for the Advancement of Research in to MS in 1945. The establishment of this organization resulted from the tireless efforts of Sylvia Lawry. She had been frustrated by her inability to find help for her brother who was suffering with MS. This was followed by establishment of the MS Society of Canada and then similar organizations in other nations. This moment has been a mainstay of research funding for disease, in addition to promoting improved care and advocacy for MS patients. In 1986, seven prominent MS centers founded The Consortium of MS centers (CMSC) with the principal goal of improving the care of patients. This organization has since expanded to an international group with over 200 MS centers among its membership. An organization composed of a wide variety of professionals caring for MS patients, it has served as forum for the exchange of information and resource for the development of collegial relationships. The existence of the Consortium of MS centers has contributed greatly to the expansion of the number of committed individuals working in the field, as well as to their retention in a very stressful professional area<sup>2</sup>.

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