# Chapter 4
# Experimental Allergic Encephalomyelitis as a Model of Multiple Sclerosis

## 4.1 Post-rabies Vaccination Allergic Encephalomyelitis

This complication of rabies vaccination was discovered almost by accident in 1880s, by Pasteur and his colleagues in Paris.

Louis Pasteur and Emile Roux developed the first rabies vaccine in France. This vaccine was first used on 6th July 1885 on a 9 year old boy Joseph Meister (1876–1940) who had been bitten by a rabid dog.

Pasteur was trying to immunise patients who had been bitten by rabid dogs and wolves. To produce anti-rabies immunity, he had available the brains of only two rabid animals, one from a dog and the other one from a rabid wolf. In an endeavor to increase the quantity of rabies material, he injected the brains of the two rabid animals into some 60 rabbits.

He then used the rabbit brain homogenates to immunize patients who had been bitten by rabid dogs or wolves, and injected them, vaccinated them with rabbit brain homogenates. Some patients developed, like young Joseph Meister as expected anti-rabies immunity and survived but a small number of injected subjects developed a neurological disease which was characterized by ataxia and in some cases led to a fatal outcome.

Pasteur's inoculum was prepared from desiccated rabbit spinal cord, injected with fixed rabies virus and would cause a "neuroparalytic accident" in approximately 1/1,000 of injected people.

An extensive literature is present in European medical journals describing these serious complications and by the 1940s, the "World Health Organisation" (WHO) in Geneva had reported between 200 and 300 cases of patients who had died from a disease known as "post-rabies vaccination allergic encephalomyelitis".



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## 4.2 Rabies as a Neurological Disease

Rabies still remains a serious problem in many parts of the world and about 20,000 people die from rabies every year in India (Santhoshkumar et al. 2012).

Rabies is a viral disease that causes acute encephalitis. The disease can be transmitted to humans from another species, commonly by a bite from an infected animal.

Most cases of human infection are due to dog bites, though bites of jackals, cats and wolves are occasionally responsible. Even bites from bats in Trinidad have been reported to cause rabies.

For a human, rabies is almost invariably fatal if post-exposure prophylaxis is not administered prior to the onset of severe symptoms. The rabies virus infects the central nervous system, ultimately causing severe disease in the brain and death.

The rabies virus travels to the brain by following the peripheral nerves. The incubation period of the disease is usually a few months in humans, depending on the distance the virus must travel, from the site of the bite to reach the central nervous system. Once the rabies virus reaches the central nervous system and symptoms begin to show, the infection is virtually untreatable and usually fatal within days to weeks.

Early-stage symptoms of rabies are malaise, headache and fever, progressing to acute, violent movements, uncontrolled excitement, depression and a characteristic hydrophobia due to pharyngeal spasm brought on by attempts to drink.

There is a progressive paralysis which affects first the lower extremities and then spreads upwards. Finally, the patient may experience periods of mania and lethargy, eventually leading to coma. The primary cause of death is usually respiratory insufficiency.

On post-mortem examination there are characteristic degenerative changes in the ganglion cells of cerebrospinal and sympathetic ganglia with clumps of inflammatory and glial cells known as Babes' nodes. Acidophil inclusions, known as Negri bodies are found in the cytoplasm of affected cells and are of diagnostic importance.

Rabies causes about 55,000 human deaths annually worldwide. Over 95 % of human deaths due to rabies occur in Asia and Africa. Roughly 97 % of human rabies cases result from dog bites.

In the United States, animal control and vaccination programs have effectively eliminated domestic dogs as reservoirs of rabies. In several countries, including Australia and Japan, rabies carried by terrestrial animals has been eliminated entirely. While classical rabies has been eradicated in the United Kingdom, bats infected with a related virus have been found in the country on rare occasions.

Rabies has a predilection for the gray matter whilst "acute disseminated encephalomyelitis" (ADEM) has a predilection for white matter. Magnetic resonance imaging helps to distinguish rabies from "acute disseminated encephalomyelitis" (Santhoshkumar et al. 2012).

The human diploid cell rabies vaccine was started in 1967 and produced from the attenuated Pitman-Moore strain of the virus. As the vaccine does not contain any brain antigens it does not lead to the complications initially discovered by Pasteur and colleagues.

The question arises as to the origin of the complications following rabies immunization with extracts containing brain antigens.

## 4.3 "Experimental Allergic Encephalomyelitis" as an Animal Model of Multiple Sclerosis

The disease complication occurring after rabies immunisation has to some extent been reproduced when injecting brain tissues into experimental animals.

Animals injected with brain homogenates were rabbits, guinea pigs, mice, rats and monkeys and in all these different species pathological brain lesions could be demonstrated.

The source of the normal brain homogenates came from a variety of animal sources; rabbits, sheep, ox, monkeys and even man but they all gave similar pathological and histological results on ante-mortem and post-mortem examinations. The disease is characterised by severe muscle wasting, producing predominantly hind quarters paralysis eventually leading to quadriplegia and finally death.

It has acquired the name of "Experimental allergic encephalomyelitis" (EAE) and is considered as an animal model of the demyelinating disease multiple sclerosis. It can also be transmitted by sensitised lymphocytes from animals who have developed "experimental allergic encephalomyelitis" following immunisation with various brain extracts (Paterson 1966).

This complication or disease was discovered in 1880s, by Pasteur and his colleagues in Paris as a result of anti-rabies therapy.

A great controversy followed about the rare but well documented cases of neuroparalytic accidents. Pasteur was trying to immunise patients who had been bitten by rabid dogs and wolves. The controversy involved claims that the injected vaccine had been contaminated by bacteria. Pasteur vigorously denied that such contaminations had occurred.

The rabbit brain homogenates were used to immunize patients who had been bitten by rabid dogs or wolves.

Some patients developed, as expected anti-rabies immunity but a small number of injected subjects developed a neurological disease which was characterized by ataxia and in some cases led to a fatal outcome.

The cause for this unexpected and lethal response was not explained till the 1930s when it was shown that injection of foreign brain homogenates will evoke an immune response in the immunized individual or animal by the production of anti-brain autoantibodies which will damage the brain tissues of the host (Hurst 1932).

In the 1950s it became apparent that this was a general observation in immunology: immunization with any organ homogenate would produce an autoimmune disease in the target organ.

The classical work of Rose and Witebsky demonstrated that peripheral injection of homogenates of thyroid tissue produced an experimental disease in animals which was similar to the human autoimmune disease, Hashimoto's thyroiditis (Rose and Witebsky 1956).

It was only after the work of Medawar on allogeneic skin transplants when it was recognized that this phenomenon was an example of the homograft response by which the recipient recognizes foreign "transplantation antigens".

## 4.4 Features of Experimental Allergic Encephalomyelitis

Experimental allergic encephalomyelitis (EAE) is an inflammatory autoimmune condition following immunization with brain tissues.

Experimental animals can be immunised into various sites, such as foot-pads, intra-muscularly or subcutaneously and after several weeks will develop clinical symptoms of experimental allergic encephalomyelitis.

Rabbits were immunised with suspensions of white matter in isotonic saline intradermally into foot pads (Prineas et al. 1969) and monkeys were injected intramuscularly with brain homogenates but a similar pathological pattern of encephalomyelitis was obtained (Rivers and Schwentker 1935) in both sets of animals.

In animals killed within 3 weeks of injection large numbers of mononuclear cells were present in the gray matter, white matter and in the meninges. Some of the inflammatory cells were seen in tightly packed cuffs around blood vessels leading eventually to the formation of fibrotic plaques similar to those observed in multiple sclerosis patients. Most of the large diameter axons had lost their myelin sheaths.

In animals killed between 3 and 10 months, widely distended, apparently myelin sheaths were relatively common throughout the brain tissues with many areas showing remyelination.

These animal models have been used for studying demyelinating diseases, such as viral post infectious encephalomyelitis occurring in humans. The disease affects the central nervous system and leads to the formation of large plaques of demyelinated gliotic scar tissue traversed by axons which also eventually become destroyed.

The pathogenesis of EAE is mediated by immune responses mounted against self antigens present in the myelin tissues. A high proportion of circulating lymphocytes in multiple sclerosis exhibit lymphoblastic transformation on contact with myelin tissues (Behan et al. 1968).

Demyelination leads to the formation of plaques which coalesce to produce vacuoles with areas of remyelination (Prineas et al. 1969).

In "acute EAE" observed 1–3 weeks, following immunization with brain homogenates, there is perivascular infiltration with inflammatory cells leading eventually to the formation of fibrotic plaques resembling those observed in MS patients. This is one of

the main reasons why EAE is considered to be an animal model of MS. The anti-myelin antibodies are produced in an extra-thecal site as occurs in Sydenham's chorea.

In "chronic EAE" observed 3–6 months following immunization, characteristic "vacuolar changes" have been described, in rabbits (Prineas et al. 1969) and in guinea pigs (Raine et al. 1974).

The widespread vacuolation that develops in chronic EAE, at least in rabbits and guinea pigs gives rise to a spongiform appearance on histological examination. It would appear that "spongiform changes" occur in EAE.

One of the main components in the central nervous system responsible for the production of EAE is a basic protein present in the white matter of the brain. In 1970, a group from San Diego, identified a highly active peptide sequence from bovine myelin which when injected in microgram quantities into guinea pigs, would produce hind legs paralysis, tremors, weight loss and eventually death. Such a sequence could be used to study the molecular properties and biological consequences leading to the induction of experimental allergic encephalomyelitis.

The animal model of "experimental allergic encephalomyelitis" would appear to resemble multiple sclerosis and therefore could be used to study that disease.

However this concept is disputed by some workers (Sriram and Steiner 2005) who pointed out that it has failed to provide or propose a meaningful therapy or therapeutic approach for treatment of multiple sclerosis. The spectrum of agents and approaches that showed promising results in EAE ranges from turmeric to manipulation of the immune system with cytokines but the majority of these failed to provide a viable answer to the treatment of multiple sclerosis.

Glatiramer acetate represents the only drug currently in use whose application in a clinical setting was first useful in EAE (Lisak et al. 1983). It is modestly effective in reducing relapses but has not prevented the progression of multiple sclerosis.

## 4.5 Conclusions

The severe and fatal neurological disease of rabies, following a bite from a rabid animal, has been brought under control by immunisation with the vaccine developed by Pasteur and Roux over a century ago in France.

However an undesirable but rare complication of the immunisation with the vaccine led to the occurrence of a frequently fatal complication of post-vaccinial encephalomyelitis.

The original vaccine contained both xenogeneic brain tissues and viral antigens. Although the viral antigens stimulated anti-rabies immunity but the presence of foreign brain antigens led to the production of cells and anti-brain autoantibodies leading to brain pathology and allergic encephalomyelitis.

Some of the features of rabies post-vaccinial encephalomyelitis can be reproduced by injecting brain tissues into healthy animals and it is considered that this experimental allergic encephalomyelitis could be a model of the human disease multiple sclerosis.

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