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Rabies, Anti-Rabic Vaccine and the Raj

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Abstract

Rabies is an acute encephalitis caused by a virus that affects hot- blooded animals, including humans. In 1881, Louis Pasteur discovered that the virus of rabies is localised in the central nervous system and by attenuating the diseased brain tissue of a rabid animal he prepared anti- rabic vaccine. In India, a chain of Pasteur Institutes were set- up at Kasauli (1901), Coonoor (1907), Shillong (1910), and Rangoon (1915) to treat cases of rabies. The Haffkine Institute, Bombay; School of Tropical Medicine, Calcutta and All India Institute of Hygiene and Public health, Calcutta also provided anti-rabic treatment. In 1911, David Semple developed a carbolized anti-rabic vaccine at Central Research Institute (CRI), Kasauli in which dead virus of rabies was used. Being a dead virus it had a little post -vaccinal complications and could be stored in and transported to distant places without affecting its potency and efficacy. So, the Government of India adopted the policy of decentralisation of anti- rabic treatment. Soon, the process of decentralisation was stopped as Lt. Col. J. Cunningham was experimenting with eitherized live vaccines. But the severe paralytic side–effects of etharised live vaccine made the First International Rabies Conference, Paris (1927), to pass a resolution in favour of dead vaccines. Decentralisation of anti – rabic treatment was again started. By 2005, the Semple vaccine remained the most widely used vaccine.

Key words: Anti-rabic vaccine, Decentralisation of anti - rabic treatment, Efficacy of live and dead vaccines, Pasteur Institutes, Rabies, Symptoms.

1. Introduction

Rabies, a latin word meaning 'madness', is an acute encephalitis caused by a virus that affects hot-blooded animals, including humans. The first ever written record of rabies is found in the Mesopotamian *Codex of Eshnunna* (c.1930) in which the owner of a dog with symptoms of rabies, was told to be careful against the bites of his dog. If another person was bitten by a rabid dog and later died, the owner was heavily fined. Earlier, it was thought that the virus of rabies existed in the saliva, because it is transmitted by the bite of rabid animal.

So, to prevent the transmission of disease cutting and removing the attachment of the tongue, i.e. the lingual frenulum, (a mucous membrane) was prevalent (Baer, 1991, p.25).

2. Louis Pasteur Work

In 1881, Louis Pasteur, one of the greatest scientists of the nineteenth century who founded the science of microbiology, began to work on a cure for rabies. He discovered that the virus of rabies is localised in the central nervous system - brain and spinal cord. After the bite of a rabid animal, the virus enters the peripheral nervous system. As the virus is neurotropic, it travels quickly along the neural pathways into the central nervous system and then to other organs. The salivary glands receive high concentration of the

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virus, thus allowing further transmission (Jackson & William, 2005, p.290). When the virus travels along the afferent nerves towards the central nervous system, it is always difficult to detect it within the host. When the virus reaches the brain, it rapidly causes encephalitis. This is the prodromal phase, i.e. the onset of symptoms. Once the patient becomes symptomatic, treatment almost proves ineffective and mortality is over 99%. Rabies may also inflame the spinal cord, producing transverse myelitis (Davis, King & Schultz, 2005, p.73) .

The period which elapse between the bite of a rabid animal and the onset of symptoms in the bitten animal is called incubation period. This time period is extremely variable and usually it varies from ten days to six months. However, it can vary from less than one week to more than a year. In fact, the extreme limits of the incubation period depend on the time taken by the virus to cover the distance to reach the central nervous system. Generally, the symptoms are not evident until the virus reaches the central nervous system to cause sufficient damage to its normal functioning. Once the virus reaches the central nervous system the infected dog passes through the following three stages--

Prodromal Stage: It lasts from one to three days. This period is characterized by behavioural changes. Restlessness, hallucinations, and disinclination for food by the dog is seen.

Exitative Stage: It lasts from three to four days. This stage is often known as "furious rabies" for the tendency of the affected animal to be hyper-reactive to external stimuli and bite at anything near.

Paralytic Stage: In this stage motor neurons are damaged followed by paralysis of hind limbs, jaw and throat. Dropped jaw, continuously open mouth, hanging of sticky ropes of saliva from open jaws, difficulty in swallowing due to paralysis of facial and throat muscles is seen. Death occurs due to respiratory arrest.

In human beings, the symptoms of rabies are uneasiness, headache, insomnia, fever, confusion, agitation, abnormal behaviour, paranoia, terror, intolerance to bright light and sudden sounds, hallucinations, and delirium. The patient may suffer hydrophobia. Hydrophobia (fear of water) is the historic name for rabies. It refers to a set of symptoms in the later stage of the infection in which the victim has the difficulty in swallowing, shows panic when presented with liquids to drink, and can't quench his or her thirst. Saliva production is greatly increased and attempts to drink or even intention or suggestion of drinking may cause excruciatingly painful spasms of the muscles in the throat and larynx. Hydrophobia is entirely absent in the case of animals. Paralysis of diaphragm and bladder occurs within forty- eight hours of the onset of symptoms (Shortt, 1933, pp 2-5).

While Louis Pasteur had discovered that virus of rabies is localised in the central nervous system, H.E. Shortt, Director, Pasteur Institute of India, Kasauli further discovered in 1933 that in the brain, especially in a region called the *Hippocampus major*, certain bodies called *"Negri bodies"* existed in the large pyramidal cells which form a distinct zone or band in the tissue. Existence of such *"Negri bodies"* was 100% diagnostic for rabies infection (Shortt, 1933, pp. 19-20). In 1885, Pasteur conceived the idea of attenuating the diseased tissue of brain by repeated passages through rabbits. He inoculated an emulsion of brain substance prepared from the brain of a rabid dog under the brain membrane of a rabbit. The rabbit developed rabies. The brain of this rabbit was emulsified and similarly inoculated into the second rabbit, the later also developed rabies. This process of passing the virus from rabbit to rabbit was repeated for a number of times. Ultimately the 'street virus', i.e. the original virus obtained from a dog of streets, was weakened. Stripes of fresh brain material taken from rabbits which had died from rabies were exposed to dry in sterile air for various lengths of time. The tissue was then

ground up and suspended in a sterilized broth. This solution was used as a vaccine. Pasteur tried out this vaccine on Joseph Meister, a nine year old boy, who had been bitten by a rabid dog. The boy recovered from the disease. Pasteur's discovery of a vaccine for rabies made him a hero, and a movement began to collect funds for an institute that would honour him and carry on his scientific work. People from all over the world, including the Tsar of Russia and the Emperor of Brazil sent in contributions. The Pasteur Institute at Paris (France) was started in 1888 and Pasteur became its director. In 1895, Louis Pasteur died and was buried in the same institute (*Illustrated Family Encyclopedia,* 2007, p.645).

3. Development of Research Institutions

At that time there was no centralized agency for coordinated pathological research in India, although chemical examiners attached to some provincial governments were engaged in research work. Proper pathological research in India was started in 1869 with the appointment of Messers Lewis and Cunningham to investigate the causes of cholera. The German Cholera Commission under Robert Koch also arrived in India in 1883. In 1891, under the supervision of Dr E.H. Hankin, a small bacteriological laboratory was set-up at Agra to cater to the needs of practically the whole of North India (Cheema, 2013, p.11). On April 22, 1893, a meeting of some prominent citizens at Lahore passed a resolution to set-up a Pasteur Institute in the Punjab. In December 1894, the Indian Medical Congress at Calcutta accepted this resolution. Thereafter, Kasauli, an area in the Himalayas situated at 5000 feet above sea-level, was selected because of its salubrious climate for setting up this institute. In 1900, the Pasteur Institute of India at Kasauli was founded under the charge of David Semple (an officer of the Indian Medical Service, IMS). The institute was not a government institution. It was administered by Pasteur Institute Association and was supported by Governments grants and voluntary contributions. During the first year of its establishments the institute treated three hundred and twenty one patients of rabies. For the next seven years, the Pasteur Institute, Kasauli was the sole institution of its kind and it drew patients from all parts of the Indian sub –continent especially from the Punjab, United Provinces and other parts of North-Western India including Afghanistan and the North-West trans–frontier country (*Health Organisation in British India,* 1928, pp. 23-24,69). With the increasing demand for anti-rabic treatment, other Pasteur Institutes were set-up at Coonoor, Rangoon and Shilong, and departments at the Haffkine Institute, Bombay, the School of Tropical Medicine and Hygiene, Calcutta, and Prince of Wales Medical College, Patna were maintained for the manufacture and use of anti-rabic vaccine (Shortt, 1933, p. 11).

The Pasteur Institute of Southern India was opened in 1907 at Coonoor, Nilgiris. The major portion of the necessary funds was provided through the munificence of Henry Phipps, an American philanthropist. In 1940, the institute became the property of the Pasteur Institute Association, a body registered under the Societies Registration Act of 1860. The institute was administered by Government of Madras and was supported by government grants and voluntary contributions (*Report of the Health Survey and Development Committee,* 1946, p.211).

The Pasteur institute of Burma at Rangoon was started in 1915. Its ground floor was used for anti-rabic treatment, while the upper storey had very well equipped laboratories. This institute was within easy reach of the Rangoon General Hospital, Contagious Diseases Hospital and the Military Police Hospital (*Health Organisation in British India,* 1928, p. 375).

The proposal to establish a Pasteur Institute in Assam was first put forward in 1906 by the Assam branch of the Indian Tea Association.

The continued effort of this association resulted in the allocation of the part of the King Edward VII Memorial Fund for the setting up of an institute in Shillong in 1910. Later on, this was supplemented by a grant of Rs. 40,000 from Indian Research Fund Association to establish a library and provide equipment for the institute. The buildings were completed and the institute was opened as an anti-rabic treatment centre in 1917 (*Report of the Health Survey and Development Committee*, 1946, p. 198).

At the Haffkine Institute, Bombay anti-rabic treatment was started on April 8, 1922. In 1909, it was proposed by Lieut- Colonel W.B. Bannerman, IMS, the then Director of Haffkine Institute that the branch of the Pasteur Institute, Kasauli should be opened at this laboratory. The proposal was approved by the Government of Bombay on December 10, 1909 but technical difficulties and financial constraints delayed the formation of a separate institute. Cases of rabies were fast increasing and it was difficult for a large number of people to get anti-rabic treatment from faraway places like Kasauli and Coonoor. Therefore, anti-rabic treatment was started at the Haffkine Institute itself by utilising the existing staff and buildings (*Health Organisation in British India*, 1928, p. 204).

A branch of the Pasteur Institute, Kasauli was started in the School of Tropical Medicine, Calcutta in 1922. The All India Institute of Hygiene and Public Health, Calcutta also started providing anti-rabic treatment in 1932. These two institutes in Bengal were primarily designed for teaching purposes, but later on research on a large scale was also started in them (*Report of the Health Survey and Development Committee,* 1946, p. 177).

4. Classification of Rabid Patients

The patients who came to these institutes for anti-rabic treatment were classified into four categories according to the degree of risk involved. Patients those who were not bitten but licked by a rabid animal on fresh cuts or abrasions were placed in the first category. Category second patients were those who were having superficial but not extensive bites on the trunk and extremities. Third category patients were those having superficial but extensive bites on all parts of the body, the head and neck. While, patients having maximum risks with deep extensive bites on all parts of the body, and bites and scratches on the head and neck were placed in the fourth category (Shortt, 1933, pp. 15-16). Average daily attendance of patients in the parent institute and its centres was over 300. Nearly 50 per cent of all cases getting treatment at Kasauli were severely bitten and 25 per cent of these were of maximum severity. Another important feature was that a large number of patients who came to these institutes were bitten by different animals. Dogs were responsible for 80 per cent and jackals for 17 per cent of cases, the remaining 3 per cent included human beings, wolves, horses, cats, donkeys, cows, monkeys, foxes, mongooses, camels, buffaloes, goats, mules, bears, hyenas, leopards, sheep and tigers (*Health Organisation in British India*,1928, pp. 23-24).

Experiments were conducted on rabid animals and data of untreated cases in which the percentage of infection varied was collected. Both experimental and statistical evidences indicated that the degree of virulence possessed by different strains of rabies virus differed considerably in different geographically areas. For instance, the virus of United Province was more virulent than that of the Punjab and the viruses of Eastern Provinces of India and of Burma were less virulent than those of the North-West and centre of India (Shortt, 1933, p.3).

The anti- rabic vaccine developed by Louis Pasteur was in vogue. In 1911, David Semple developed a carbolized anti-rabic vaccine at the Central Research Institute at Kasauli. It was widely accepted and was the most commonly used anti-rabic vaccine throughout the world up to

2000. Pasteur asserted that diseases caused by living organisms could be treated by the same living organism in an attenuated form. Attenuation of living organisms was fundamental to the Pasteurian method. Pasteur and his disciples' preferred live vaccines as they believed that they produced higher immunity. David Semple adopted the technique of his tutor Almroh Wright and used carbolized dead virus for anti-rabic vaccine. Almroh Wright was a professor of pathology at the Army Medical School at Netely, Hampshire. He established a highly successful and productive research group from 1892 to 1902, and worked on opsonins and vaccine therapy. Wright discarded Pasteurian technique of using attenuated vaccines as he discovered that killed vaccines were more useful for inducing the formation of antibodies and stressed that such vaccines could be used to stimulate the natural resistance of the individual body and not just as a prophylactic agent. Apart from it, the killed vaccines were easier to standardize than attenuated live vaccines because they carried fewer risks. Wright used acid to kill the viruses for his vaccine but Semple used an antiseptic called carbolic acid derived from coal. First, he developed carbolized dead vaccine for typhoid (Chakrabarti, Fall: 387-423). Then he developed carbolized anti-rabic vaccine at the Central Research Institute (CRI) from the brains of rabbits deliberately infected and then killed (Semple, pp.27-28). Semple's vaccine was prepared by mixing 2 per cent emulsion of fixed virus in normal saline containing 1 per cent carbolic acid. After being kept at 37°C for twenty –four hours, the vaccine was diluted with equal volumes of normal saline, and after testing its sterility it was bottled in single dose ampoules of 5cc. It was stored at 4°C for at least 21 days before issue (*Annual Report of the Public Health Commissioner with the Government of India,* 1932, p. 205).

Cases of categories II, III, IV were given one injection daily for 14 days; those of category I were given one injection daily for 7 days.

The scheme of doses and duration of treatment were as follows:

Category IV: Adults – face: 10cc daily for 14 days; extremity: 7cc daily for 14 days; Children – face: 7cc daily for 14 days; extremity: 5cc daily for 14 days

Category III: Adults – 5cc daily for 14 days; Children – 3.5cc daily for 14 days

Category II: Adults and children – 2cc daily for 14 days

Category I: Adults and children – 2cc daily for 7 days

(*Annual Report of the Public Health Commissioner with the Government of India,* 1933, pp 202-203).

In Bengal, where strains of rabies virus were less virulent than those in other parts of India, 1 per cent carbolized brain emulsion was used for anti- rabic vaccine (*Report of the Health Survey and Development Committee,* 1946, pp. 193-194).

The standardized carbolized anti-rabic vaccine had additional advantages. In hermetically sealed ampoules, the vaccine could be transported to and stored in distant places without affecting its potency and efficacy especially in tropical climates. Apart from it, being a dead vaccine it had witnessed a little post- vaccine complications. As a result, the Government of India adopted the policy of decentralization of anti-rabic treatment. Assistant Director of Bombay Bacteriological Laboratory announced that the objective of the Government was to "bring anti- rabic treatment nearer to home of those who need it" (Lt. dt. May 8, 1923, Morrison to Director, Bombay Bacteriological Laboratory, *General Dept. File No.*, 476(1), pp.5-7). First out centre was opened at Allahabad. By 1924, some more out centres were opened at Lahore, Rawalpindi, Karachi, Ahmedabad, Poona Belgaun, Ahmednagar and Karwar. New centers were proposed at Hyderabad, Sindh, Sukkur, Surat, Jalgaon, Sholapur, Nasik and Ratnagiri. Questions were raised at Bombay

Legislative Council about the expenses of these centres, to which the government gave assurance that there would be no expense and vaccines would be sent by post from laboratory of the Haffkine Institute, Parel, Bombay to the hospitals where patients would be treated locally (*Bombay Legislative Council,* 1924, p.765, *Health Organisation in British India,* Office of Public Health Commissioner with Govt. of India, Simla, Oct. 1928, p. 23). When the process of decentralisation of anti- rabic treatment was going on, almost at the same time Lt. Col. J. Cunningham, who was the director of the Pasteur Institute of India, Kasauli, was experimenting with etherized live vaccines. Through influential medical personnel's of the Government of India, Cunningham persuaded the government to take decision to stop the ongoing decentralization of rabies treatment and to send all patients to Kasauli to facilitate his experiments (*Annual Report of the Public Health Commissioner with the Government of India, 1925,* Vol. I, pp61-62). The government stopped decentralisation. This decision of the government alarmed the medical fraternity, both at national and international levels, because attenuated live vaccines had the potential to paralyse the patients of rabies. John Morrison, director of the Shillong Institute, condemned the decision of the government. It was not judicious as it ignored the 'human side' of the question. He also argued that the lack of treatment in the remote areas would lead to high mortality (*Extract from Official Report of the Assam Legislative Council Debate,* April 9, 1928, p. 482).

In January 1927, at Kasauli, a case of severe paralysis after being treated by etherized live vaccine was reported. It gave set back to Cunningham's experiments. In April 1927, First International Rabies Conference was held at Paris. John Taylor, the director of the Pasteur Institute in Rangoon, Burma, represented India. Through statistical data, which he had collected from all over the world, he argued that the maximum and severest cases of rabies occurred in India. He further stressed that carbolised dead vaccine was very effective and post-vaccinal paralytic incidents hardly occurred with it. As a result at the end of the Conference, a resolution was passed in favour of dead vaccines, either carbolized or etherized. Thereafter, in December 1928, a Rabies Conference was held in Calcutta to discuss the future of anti-rabic policy in India. The Conference was attended by directors of all the Indian Pasteur Institutes. All of them decided unanimously that geographical and human factors should be given preference to laboratory requirements. They also stressed the immediate need for decentralisation of anti-rabic treatment in India. At the Conference, it was also decided that it would be better to give a "stable" vaccine to millions of Indians affected by rabies than a "freshly prepared non- stable vaccine containing a living virus"(Chakrabarti, 2010, Fall: 387-423). Initially, anti-rabic vaccine was prepared from rabbit brain but later on, sheep brain emulsion also began to be used. The original Semple vaccine which was introduced in 1911 was 1 percent carbolised rabbit brain. From 1923 this was replaced by the experimental vaccines ranging from 1 per cent to 5 per cent. From 1930 onwards the standardized Semple vaccine which was exclusively used in India consisted of 5 per cent carblosied sheep brain (*Report of the Health Survey and Development Committee,* 1946, pp. 193-194).

5. Out Centers for treating anti-rabic cases

In 1933, some out-centres for treating anti-rabic cases of northern and central India were opened at military centres like Allahabad, Bannu, Bareilly, Dhera Dun, Fort Sandeman, Jhansi, Karachi B.M.H., Karachi I.M.H., Lansdowne, Lucknow, Meerut, Mhow, Murree, Peshawar, Quetta B.M.H., Quetta I.M.H., Rawalpindi, Ranikhet, Razmak, and at civil centers like Abu Road (Sirohi State), Agra, Ajmer, Allahabad, Bhawalpur, Benares, Bikaner, Chamba, Dheradun,

Delhi, Gwalior, Jammu, Jind, Jodhpur, Kota, Kapurthala, Lahore, Lacknow, Mussorie, Nanital, Rampur, Srinagar, Udaipur. This process of decentralisation of anti-rabic treatment proceeded rapidly. By 1938, about 200 out-centres were getting supply of anti-rabic vaccine from Kasauli alone. The Pasteur Institute of Southern India, Coonoor had also decentralised anti- rabic treatment to a very large extent. The treatment was available at all Government Headquarter hospitals, in selected hospitals of Native States, Railways, Mission Hospitals, Cantonments, District and Central Jails. About 115 out-centres were authorised to provide anti-rabic treatment in Southern India. The King Edward VII Memorial Pasteur Research Institute, Shillong provided anti-rabic vaccine to15 public centres and 33 private centres. Haffkine Institute, Parel, Bombay started its out -centres at 44 places. The treatment charges were Rs. 5 per patient. Concessions at all out-centres similar to those sanctioned for Kasauli were also given to patients by the concerned local governments (Shortt, 1933, pp. 22-23, 38-40, 44-45).

During the 1960, suckling mouse brain anti- rabic vaccine was tried. But the most widely used vaccine was Semple vaccine. In 2005, WHO Committee on Rabies discovered that Semple vaccine was widespread yet it had severe and long term side effects. Less expensive purified chicken embryo cell vaccine and purified Vero cell rabies vaccines are now available.

BIBLOGRAPHY

1. Primary Sources

Annual Report of the Public Health Commissioner with the Government of India, 1925, Vol. I.

Annual Report of the Public Health Commissioner with the Government of India, 1929, Vol. I. Govt. of India, Calcutta, 1932.

Annual Report of the Public Health Commissioner with the Government of India, 1933, Vol. I. Govt. of India Press, 1935.

Bombay Legislative Council, 1924.

Extract from Official Report of the Assam Legislative Council Debate, April 9, 1928.

General Dept. File No., 476(1)

Health Organisation in British India. Office of Public Health Commissioner with Govt. of India, Simla, Oct. 1928.

Report of the Health Survey and Development Committee, Vol. I. Govt. of India Press, Calcutta, 1946.

Semple, David. *The Preparation of a Safe and Efficient Antirabic Vaccine: Scientific memories by the Office of the Medical and Sanitary Departments of the Govt. of India.* Superintendent Govt. Printing.

Shortt, H.E. *Rabies and Anti- Rabic Treatment in India, Information and Instructions for Anti-Rabic Treatment.* Govt. Printers, Delhi, 1933.

2. Secondary Sources

Baer, George. *The Natural History of Rabies.* CRC Press, 1991.

Cheema, Gagandip. *Western Medicine and Colonial Punjab, A Socio- cultural Perspective*, 1849-1901, Unistar Books Pvt. Ltd., Chandigarh, 2013.

Chakrabarti, Praktit. 'Living verses dead', The Pasteurian Paradigm and Imperial Vaccine Research. *Bulletin of History of Medicine*, 2010, Fall:387-423. *http:// www.ncbi. nlm.nich.>Journal list>Bull. Hist. Med*

Davis, Larry Ernest, King, Molly K. Schult Jessica L. *Fundamentals of Neurologic disease.* Demos Medical Publishing, 2005.

Illustrated Family Encyclopedia, Dorling Kindersley Ltd. London, 1997, reprinted, 2007.

Jackson, Alan C., William, H. *Rabies.* Academic Press, 2005.