

Pasteur and rabies: the British connection

J Théodoridès DSc PhD *Laboratoire d'Evolution, 105 Bd Raspail, 75006 Paris, France*

Keywords: Pasteur; rabies; hydrophobia; history of medicine

If one had to choose the most famous 19th century scientists from England, Germany and France, the names of Charles Darwin, Alexander von Humboldt and Louis Pasteur would immediately come to mind. In France, Pasteur's achievements have made him a national hero. His work on rabies was crowned in November 1888 by the foundation of the Pasteur Institute in Paris, the centenary of which was celebrated last year.

Pasteur's visits to Great Britain

Pasteur visited Great Britain on four occasions: in 1862, 1871, 1881 and 1884¹. The first visit, in 1862, occurred when he was working on fermentation and he hoped to meet the German chemist A W von Hofmann, who was living in London but happened to be away at the time.

The second visit took place in September 1871 when Pasteur was working on the production of beer. He visited Whitbread's brewery in Clerkenwell, London, and using his own microscope, he examined the yeast (*Saccharomyces cerevisiae*) used for the production of the porter and observed that it was contaminated by moulds. He therefore advised the brewers to change to another yeast².

The third visit was in August 1881 on the occasion of the 7th International Congress of Medicine held in London, when he led a delegation of 250 French medical scientists and delivered a lecture on the attenuation of microbes and on his method of vaccination against two animal diseases: fowl plague and anthrax. At the end of his lecture he explained that he had extended the use of the term vaccination (as used by Edward Jenner) to include other varieties of prophylactic inoculation. Pasteur's views produced a hostile reaction from the anti-vivisection and anti-vaccination lobbies but this did not prevent his lecture from being printed and distributed to all Members of Parliament. During his stay in London, he attended the garden party given by Baroness Burdett-Coutts at her Highgate home, which was recorded in A P Tilt's celebrated painting in which Pasteur appears³.

Pasteur's fourth and last visit was in 1884 when he represented the Académie des Sciences, Paris, at a commemoration of the University of Edinburgh. He spent also a few days in London where, on 21 April 1884, Sir James Paget gave a dinner in his honour and distinguished guests included John Tyndall, Sir Andrew Clark and Lord Avebury. At this meeting Pasteur spoke of his research on rabies which had begun three years previously.

The Royal Society honoured Pasteur with Fellowship in 1869 and he received the Rumford Medal in 1856 and the Copley Medal in 1874⁴.

Rabies: early knowledge

Rabies is an infectious encephalomyelitis caused by a rhabdovirus. The disease may be likened to a drama with three actors: the virus, a biting mammal (dog, cat, wolf, fox, bat) and man. It was previously known as hydrophobia because attempts at swallowing or even the sight of water produces painful spasms of the throat muscles. Once established, the disease is invariably fatal.

Since ancient times, the disease has been known to be transmitted by dogs but treatment was always totally inadequate. The cause was considered to be some form of poison and the old pharmacopoeias contained a medley of useless drugs of mineral, vegetable or animal origin which, it was hoped, would rid the body of the poison. Cauterization of the wound was advised from the time of Celsus (1st century AD).

In the 18th century rabies began to be classified among other human infectious diseases but it was not until the end of the 19th century that the prevention of rabies by means of a vaccine came to be considered. Although the eventual solution to this problem is usually credited solely to Pasteur and his collaborators, this would not have been realized without the previous fundamental work of Pierre-Victor Galtier (1846-1908), professor at the Veterinary School at Lyons. As early as 1879, Galtier demonstrated that a rabbit inoculated with rabies develops a paralytic form of the disease after an incubation period of around 18 days. The rabbit therefore provided a suitable experimental model for research.

In 1879, Galtier wrote prophetically:

I have started experiments in order to look for an agent able to neutralise the rabies virus after its absorption and thus prevent the appearance of the disease because I am persuaded from my microscopical researches that rabies once it is declared, will remain incurable - due to the lesions it produces in the nervous system. I thus thought the discovery of a new effective preventive remedy would nearly be the equivalent of a curative one, chiefly if its action was really efficacious one or two days after the inoculation of the virus by the bite.⁵

By 1881, Galtier had succeeded in immunizing sheep and goats after inoculating them with rabid saliva. Only then did immunization become feasible in animals.

Rabies: Pasteur's researches

In 1881 Pasteur (together with Charles Chamberland and Emile Roux) published his first paper on rabies⁶.

Five months later (together with Louis Thuillier) they showed that rabies could be transmitted experimentally by inoculating fragments of infected brain or cerebrospinal fluid into a dog's brain.

Paper read to joint meeting of Sections of History of Medicine, Comparative Medicine and Epidemiology & Community Medicine, 5 October 1988

In 1884, Pasteur, Chamberland and Roux announced that they had developed a strain of *virus fixe*. Virus from a dog, when inoculated into monkeys, became more attenuated with each passage. Pasteur concluded that he would now be able to immunize a dog against rabies by inoculating it with attenuated virus. He asserted: 'Rabies is comparable by its relatively slow incubation to an omnibus train which has to be preceded by the vaccine comparable to an express train, thus preventing it from going further.'

Pasteur's anti-rabies inoculation in man

In 1885, Pasteur was sufficiently confident to apply his method to man.

His first case was a 9-year-old boy, Joseph Meister who had been bitten by a mad dog. On 6 July 1885, he was inoculated by Dr Jacques-Joseph Grancher, in the presence of Pasteur. The boy survived and was later employed as porter at the Pasteur Institute, Paris.

The second case was a 15-year-old boy, Jean-Baptiste Jupille, who was inoculated on 20 October 1885. He also survived but it was not proven that the biting dog was rabid.

The technique used (devised essentially by Emile Roux) consisted of making strips of infected spinal cord (containing the *virus fixe*) from a rabbit which had died from rabies 7 days previously, and suspending them in flasks kept dry by caustic potash. The strip was then mashed and suspended in sterile broth, which was then used to inoculate the patient. At first, a strip dried for two weeks was used, but later, strips which had been dried for a shorter period were used. The method proved successful in the great majority of cases, although we now appreciate that it was a potentially hazardous procedure because of the danger of inoculating 'live' vaccine which produced what Pasteur's opponents called 'Pasteur's Disease'!

British experience of Pasteur's method

Pasteur's technique of anti-rabies inoculation was investigated in Britain by a Committee of Enquiry set up in April 1886 under the chairmanship of Sir James Paget, with Victor Horsley as secretary, and including Sir Thomas Lauder Brunton, Sir Henry Roscoe, John Burdon Sanderson, Sir Joseph Lister and Sir Richard Quain. Its conclusions were reported in *Nature* in July 1887:

'From the evidence of all these facts, we think it certain that the inoculations practised by M. Pasteur on persons bitten by rabid animals have prevented the occurrence of hydrophobia in a large proportion of those who, if they had not been inoculated, would have died of the disease . . . M. Pasteur's may justly be deemed the first proved method of overtaking and suppressing by inoculation a process of specific infection'.

The report also raised the question whether Pasteur's treatment could induce rabies in inoculated persons. One such case was a British policeman, named Goffi, who was bitten by a rabid cat on 4 September 1886. He was sent to Paris for treatment by Pasteur the next day and was immediately subjected to intensive treatment. He returned to England at the beginning of October but soon became paralysed in the lower limbs and died. Victor Horsley inoculated rabbits and a dog with Goffi's spinal cord and they all died of paralytic rabies.

Another unsuccessful case was that of Lord Doneraile who was bitten on the hands by a rabid fox on 13 January 1887 and commenced a course of inoculations 11 days later. Four months later he died of rabies. Pasteur was impelled to write a letter to the *British Medical Journal* in which he explained that treatment had been too late and had not been an 'intensive' one⁸.

Pasteur was generally pleased with the British report and wrote to Victor Horsley on 9 July 1887 thanking and congratulating him.

Pasteur did not lack opponents, one of the most vociferous being Dr Lutaud, editor of the *Journal de Médecine de Paris*, who published a book criticising Pasteur's inoculation method⁹. On 22 July 1887, Dr Lutaud gave a lecture in London at Princes Hall, Piccadilly, in which he pointed out that, whereas Jenner's vaccination consisted of inoculating a benign disease to prevent a more serious one, in Pasteur's method, living rabies virus was used¹⁰.

Despite such criticism, by November 1886, around 2500 persons had been successfully treated by Pasteur's method; and by the time of Pasteur's death in 1895 around 20 000 persons had undergone the treatment, with a mortality of less than 0.5%.

Rabies in Great Britain: dog control

The British Committee of Enquiry (1886) not only considered Pasteur's inoculation treatment but also methods of containing rabies by quarantine and dog-muzzling. The dog population in Great Britain around 1867 amounted to 830 000 and by 1878 numbers had increased to 1 300 000. At the end of the 19th century, rabies constituted a problem with 82 fatal human cases in 1877 and 27 for London alone in 1882.

The Dogs Act of 1871 enforced muzzling of dogs in public places but this practice aroused the hostility of pet lovers, especially in the countryside. The Rabies Order of 1878 reinforced this measure and in 1889 the Board of Agriculture imposed muzzling in the London area and several northern counties where rabies was more rife¹¹.

By 1903, rabies had disappeared from the British Isles although it returned between 1918 and 1940 presumably because of violation of the quarantine regulations.

Since the occurrence of the European epizootic of fox rabies, now prevalent in Eastern Europe, draconian enforcement of quarantine Laws by Great Britain have ensured that this country is one of the few western European countries free of the disease. The proposed Channel tunnel, however, constitutes a new potential loophole!

The Lister Institute, London

When the Pasteur Institute of Paris was established in 1888 its function was intended to be the treatment of rabies. The Institute was visited by the Lord Mayor of London who was encouraged to raise funds in order to establish a similar institute in London.

In the summer of 1887, Pasteur had been invited by Sir James Paget to come to London and deliver a lecture on rabies but he declined this because of his poor health. In 1889, Pasteur was again invited to London, this time by the Royal Society, to deliver the Croonian Lecture on rabies. Again he had to refuse, and sent his collaborator Emile Roux, who gave the lecture on 23 May 1889¹².

On 1 July 1889, the Lord Mayor of London organized a meeting at the Mansion House and Pasteur's son Jean-Baptiste attended. On the following day, Pasteur received a telegram from Dr Marc Armand Ruffer, one of his former pupils:

'London: Meeting great success. All the resolutions have been unanimously voted with enthusiastic applause for M. Pasteur and his method. Have spoken: Lord Mayor, Paget, Roscoe, Lister, Lubbock, Foster, Brunton, Ray Lankester, Horsley, Stokes, Hart.'

On 16 August 1889, Armand Ruffer lectured on Pasteur's method at a meeting of the British Medical Association, held in Leeds.

Anti-rabies institutes were now being established all over the world. And so, in 1891, the Lister Institute of Preventive Medicine was established in London, with Armand Ruffer as its first Director.

Finale

In December 1892, the occasion of Pasteur's 70th birthday was celebrated with great solemnity in the great amphitheatre at the Sorbonne, Paris. Joseph Lister was present, representing the Royal Societies of London and Edinburgh. In his address to the hero of the day, Lister said (in French):

'You have lifted the veil which had covered, during the centuries, the infectious diseases, you have discovered and demonstrated their microbial nature.'

He then stepped towards Pasteur and embraced him, all the audience applauding. This moving, historic episode was a living demonstration of the cordiality

and admiration expressed by British physicians and British medicine for Pasteur's achievement.

Acknowledgment: The author thanks Dr Alex Sakula for his kind help with the preparation of the text for publication.

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(Accepted 4 January 1989)