EPILEPSY

Protease inhibitor implicated

James O. McNamara and Ram S. Puranam

THE culprit responsible for a rare form of inherited epilepsy, known as progressive myoclonic epilepsy of the Unverricht–Lundborg type (EPM1), has been collared. Writing in *Science*[1], Pennacchio *et al.* describe how they have exposed the identity of the mutant gene that is carried unbeknown by both parents and can manifest as EPM1 epilepsy in their offspring. The culprit, surprisingly, had not even been a suspect — of all the aberrant proteins that might have been expected to be encoded by this gene, which include ones affecting neuronal excitability or synaptic transmission, this turns out to be a cysteine protease inhibitor, whose normal function is to prevent the destruction of key proteins.

The epilepsies comprise a common collection of disorders that affect at least one per cent of the population worldwide and which consist of more than 40 distinct types, all sharing the common feature of an enduring increase of neuronal excitability that causes a periodic and unpredictable occurrence of seizures. EPM1 is an exceedingly rare form. Children afflicted with it start to suffer seizures between the ages of 8 and 13 (ref. 2). There follows a gradual decline in neurological function and the intellect deteriorates slowly, with a loss of roughly ten IQ points per decade. Survival into adulthood is common and some individuals reach the sixth decade. Autopsy discloses widespread neuronal degeneration.

The past decade has witnessed enormous progress in our understanding of the mechanisms that underlie a number of these disorders. But the restraint imposed by the daunting complexity of the mammalian nervous system makes the power of genetics especially appealing. Many of the epilepsies recognized to have genetic determinants (about one-third of cases) appear to be complex genetic disorders where several genes are probably at fault,

MEDICAL HISTORY

Country doctor and speckled monster

As the world knows, Edward Jenner (1749–1823) was the man who, through his observation of the immunity of milkmaids in his native Gloucestershire to the 'speckled monster', as smallpox was then known, established the means in 1796 by which the disease was eventually to be eradicated. A statue to commemorate him has long stood in Kensington Gardens, London; but it had become forgotten, and last week a ceremony was held there as a feature of the bicentennial celebrations of the advent of vaccination.

Jenner has sat there reflectively, chin in hand, for nearly 150 years. The sculptor, William Calder Marshall, gave a clue by inscribing a head of a cow on the chair on which his model sat. But only the name — Jenner — was inscribed on the pedestal and so, over time, the memorial became virtually forgotten. The Friends of Hyde Park and Kensington Gardens 'rediscovered' the memorial in their effort to foster recognition of the unique Victorian statues in Kensington Gardens. They were then joined by the Jenner Educational Trust and St George's Hospital Medical School, and together they have now placed a commemorative plaque at the memorial — at last giving full recognition to Jenner.

It is difficult to imagine the horror that smallpox brought in its train. No one was safe. In Jenner's time, it caused ten per cent of the total deaths and a third of those of children in London. It was the cruellest of the emissaries of the Grim Reaper.

On 14 May 1796, lymph from a pustule of dairymaid Sarah Nelmes was vaccinated by Jenner into James Phipps. Later, when the boy was inoculated with smallpox, the feared symptoms — high fever, followed by spots and, often, death — failed to appear. Vaccination was shown to give protection. It then took nearly 200 years before the World Health Organization, on completing an international eradication programme, declared in 1980 that the world was rid of the disease.

A number of statues of Jenner have been erected. The first was placed in 1825 in Gloucester Cathedral. Another, erected in 1865, stands in Bologne-sur-Mer, where the first vaccinations in France were carried out. Later, a memorial was placed in 1904 in Tokyo in the gardens of the National Museum. Perhaps the best known, with a cast in the Wellcome Building in London, is in the Museum of Fine Art in Genoa. It was by a leading Italian sculptor, Giulio Monteverde, and was commissioned in 1873 by Maria Brignole Sale, Duchess of Galliera, in recognition of the protection that vaccination gave her family.

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

Dan Atkin

Jenner reflects in Kensington Gardens.

But Jenner's statue in Kensington Gardens is his main memorial. Calder Marshall was a competent artist of the Victorian era and it was he, in fact, who first conceived the idea of the memorial. The necessary funds were slow in coming until an appeal was launched internationally. The United States headed the donations; Russia, despite the intervention of the Crimean War, came second; and Britain only third.

With the permission of Queen Victoria, a site in Trafalgar Square was secured and Prince Albert, the Prince Consort, presided over an inaugural occasion in 1858. Everybody who was anybody attended. But, soon afterwards, Jenner was banished. A non-military character was thought inappropriate in an area devoted to British success at arms. *The Times* spoke up for his removal, and it was demanded in Parliament. *Punch* took an ironic view:

England's ingratitude still blots
The escutcheon of the brave and free;
I saved you many million spots,
And now you grudge one spot for me.

And so, in 1862, Jenner was moved to become the first statue in Kensington Gardens. St George's Hospital, originally at Hyde Park Corner, put in a bid for the statue on the centennial anniversary of his discoveries. It had good grounds: the illustrious John Hunter, a surgeon at the hospital, was Jenner's mentor. But the attempt failed.

And so, today, his memorial still stands in Kensington Gardens. But now with acknowledgement of his place in medical history. John Empson

John Empson is at 26 Pembroke Place, Kensington, London W8 6EU, UK.

■See also page 18.