Medicine in Stamps

Charles Robert Richet (1850–1935): discoverer of anaphylaxis

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Nineteenth-century France produced several eminent scientists such as Claude Bernard, who discovered liver glycogen, Armand Trousseau, a famous clinician-teacher, and renowned neurologist, Jean-Martin Charcot. To this list, we should add the name of Charles Richet, a true Renaissance man, both playwright and physiologist, who discovered anaphylaxis and won the Medicine Nobel Prize in 1913.

BACKGROUND Charles Robert Richet was born in 1850, the year Herman von Helmholtz of Germany invented the ophthalmoscope. Shaped by a father who was chairman of the Department of Surgery at the Paris Faculty of Medicine and a maternal grandfather who was a liberal journalist, Charles developed a lifelong love of learning – Latin, sailing, politics, literature and the arts. To please his surgeon father, he entered the Paris Faculty of Medicine in 1868, but continued his compositions during medical school in order to please his palate for the arts.

Notwithstanding his strong pacifist views due to the influence of his grandfather, Richet interrupted his medical studies to serve his country during the Franco-Prussian War of 1870. This experience deepened his appreciation for peace and heightened his disdain for violence. He then returned to the academic world and completed his medical studies, earning his Doctor of Medicine in 1877 and Doctor of Sciences a year later. He married Amelie Aubry, and fathered two daughters and five sons, one of whom, Charles Jr, independently gained prominence in the medical world.

DISCOVERY OF ANAPHYLAXIS Richet's internship was at the infamous Salpetriere, a gunpowder factory that was transformed into a hospital for poor Parisians. Here, under the tutelage of famed master neurologist, Jean-Martin Charcot, Richet treated patients with neurologic diseases and conducted experiments in sensory physiology. It would lead him to eventually study hypnosis, hysteria and psychic stimuli in health and disease.

At 37, Richet became Professor in Physiology at the Paris Faculty of Medicine. His call to fame came with the singular observation that dogs reacted strangely when injected with serum from eels. He noticed that the animals displayed aggravated symptoms when they received not just one, but a series of injections. Rather than offering protection, certain combinations of timed injections and repeat inoculations escalated injury. It was reverse immunity at work, and yet Richet was not the first to record this phenomenon. Earlier observations had been made in rabbits that received egg albumin or dog serum, and in guinea pigs and even humans who had received diphtheria toxin. But the significance and clinical relevance of re-challenge hypersensitivity had escaped earlier investigators. Richet himself spoke of serendipity in his 1913 Nobel speech, in which he confessed that his discovery was "*not at all the result of deep thinking, but of simple observation, almost accidental, so that I have had no other merit than that of not refusing to see the facts, which presented themselves before me, completely evident . . .*"

The actual discovery of anaphylaxis was readily traceable to a momentous sea voyage that involved three scientists: Charles Richet, the physiologist, a junior colleague, Paul Portier, who was a comparative physiologist and Albert Grimaldi, son of the Prince of Monaco and an avowed oceanographer. The two-and-a-half-month marine exploration aboard the steam-powered vessel, Princesse Alice II, set sail on July 5, 1901 from the French port of Toulon for the West African coast near

the Cape Verde Islands. Richet had this to say about the experimental model that started him on the path toward one of Medicine's most important discoveries: "*During a cruise on the yacht of Prince Albert of Monaco, the Prince advised me together with our friends Georges Richard and Paul Portier, to study the Physalia (Portugese man-o-war) toxin. We found that it easily dissolved in glycerol and that an injection of this glycerol solution reproduces the symptoms of Physalia poisoning.*"

Richet and Portier found that injections from the nematocysts of *Physalia* induced a violent reaction in dogs, including the death of "a fine big dog by the name of Neptunus." Remarkably, dogs experienced no apparent ill effects when they received only a single injection. These results harkened back to Richet's earlier observations of similar adverse symptoms with repeated injections of eel serum. Upon their return to France, the investigators settled for a comparative study using sea anemones (*Actinia sulcata*), which were obtainable in large quantities off the rocky shores of Europe. They were successful in replicating their *Physalia* results with an extract from the tentacles of *Actinia*. When injected into various experimental animals, actinotoxin, as the extract was termed, produced dramatic results especially in two dogs, which died when a repeat injection was given 14–23 days after the first "sensitising" dose. The animals experienced classical symptoms of shock: itching, dyspnoea, vomiting, hypotension, stupor and death in half an hour. In 1903, Richet published his findings: "*while a foreign substance might induce a mild reaction upon first exposure, it could produce severe hypersensitive symptoms and even death when re-introduced later.*" Instead of providing protection or phylaxis, Richet had discovered a new biological response he termed anaphylaxis, or anti-protection.

Additional studies followed. By 1903, Richet had established that numerous proteins could reproduce the same fatal effects if administered three to four weeks apart. He also showed that tiny doses given at periodic intervals could lead to gradual desensitisation. And in 1907, he demonstrated the passive transfer of hypersensitivity via serum from a sensitised to a normal animal.

FRENCH BOURGEOIS Richet was ultimately a product of his background and upbringing, and despite his democratic political convictions, his social tastes and behaviour were aristocratic. He promoted controversial views on eugenics and the means of constructing what he considered to be a strong and healthy society. This interest grew out of the work of Charles Darwin, although many French scientists at the time were skeptical of Darwin's book, *The Origin of Species*. Richet favoured limiting procreation by the deformed and intellectually challenged, but was in support of large families for those thought capable of "contributing to civilisation." Richet was also a pacifist and was active in the international peace movements of his day, joining the International Medical Association for the Suppression of War and the French Peace League.

On December 4, 1935, Richet died in his Parisian home, apparently of complications from congestive heart failure. He was 85, and left behind his wife Amelie, who lived for nearly twenty more years. Of all the accolades heaped upon this man of science, none said it better than neurophysiologist and fellow Nobelist, Sir Charles Sherrington: "*To honour Richet is to honour the spirit of physiology in its most graceful, most eloquent and inspiring presentment.*"

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