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HISTORY OF ONCOLOGY

The Nobel Prize laureate - father of anaphylaxis Charles-Robert Richet (1850-1935) and his anticancerous serum

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Summary

Professor of Physiology Charles-Robert Richet, winner of the Nobel Prize in 1913, is best known for his work on anaphylaxis. However, with his collaborator Jules Héricourt studied the effects of antibody treatment and made the very first attempts to fight cancer with serotherapy. Being versatile, Richet contributed in neurology, psychology and was also a poet, playwrighter, pacifist and pioneer in aviation.

Key words: anaphylaxis, cancer, Charles Richet, physiology, psychology, serotherapy

Life-studies-career

Charles Richet, the most versatile figure in the history of medical sciences, was born in Paris on 26 august 1850 (Photo 1). Visiting regularly his maternal grandparents, he was influenced by the personality of his grandfather Charles Renouard (1794-1878), a liberal journalist and specialist in admiralty law, and developed a love for Latin, sailing, arts and literature. In 1861, he entered the prestigious Lycée Bonaparte. As a pupil, he had applied himself very little to his studies, spending much of his time writing poetry and plays. With his friend Paul Fournier wrote a book of verses entitled *Le livre d'or de la comtesse Diane* containing games and "bon mots" that were eventually published under the title *Maximes de la vie*. It was in that period that started to be interested in para-psychology and in 1866 he attempted to hypnotize a friend of his sister [1].

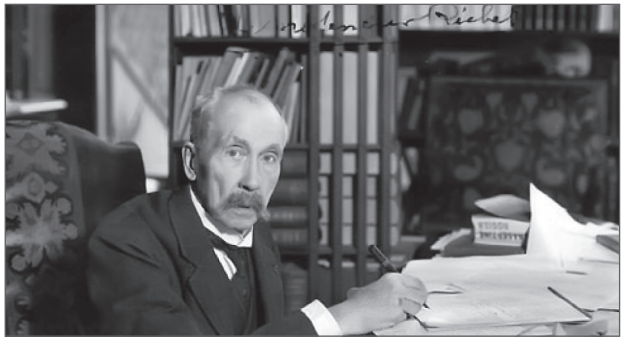

Photo 1. The Nobel laureate, Professor Charles Richet (1850-1935).

In 1867, he graduated from Lycée and passed the baccalaureate. He enrolled in the Faculty of Medicine in Paris as he wanted to please his father, the distinguished surgeon Alfred Richet (1816-1891), chairman of the Department of Surgery at the Hôtel-Dieu hospital in Paris.

When the Franco-Prussian war broke out in 1870, Richet interrupted his studies and served as Guard at Invalides. An experience that deepened his appreciation for peace and increased his dislike for violence [2,3].

In 1877, he received his MD thesis and one year later became Doctor of Sciences. The same year married Amélie Aubry. They had five sons and two daughters, among them Charles who became also Professor in the Faculty of Medicine in Paris and was in his turn succeeded by his son Gaston [4].

Richet, scientifically, was attached to the school of Etienne-Jules Marey (1830-1904), Claude Bernard (1813-1878) and Alfred Vulpian (1826-1887).

In 1881, he was appointed assistant professor of physiology and in 1887 chairman of physiology, replacing Jules-Auguste Béclard (1817-1887). He kept that position till his retirement in 1925.

In 1898, he was elected member of the Academy of Medicine; in 1913 received the Nobel Prize in Physiology or Medicine and in 1914 he was elected member of the Academy of Sciences and became Grand officer of the Legion of Honor [5].

Moreover, he was a pioneer in aviation, a pacifist and great thinker. His anti-war writings in the decades before World War I focused on the waste of war, including not only despairing populations but also the economic costs. Also, during the war he was active in medical corps, promoting battlefield first-aid methods [2,6].

Except medicine, Richet was also a pioneer in aviation. In 1888, he met Victor Tatin (1843-1913) while both were working in the laboratory of the physiologist Jules Marey; from 1888 they were experimenting with flying machines developing a helicopter (called gyroplane), and helping establish France's first air plane company [2,7].

Also, from 1889 he was editor of *Revue scientifique* and from 1917 co-editor of the *Journal de Pathologie et de Physiologie Générale.*

During his career he published more than 700 papers in scientific journals, and wrote novels (as *Possession*, 1887 and *Soeur Marthe,* 1890), plays (as *Socrate*, 1910) and poems (as *La Gloire de Pasteur*, 1913) under the pseudonym Charles Epheyre [8].

The culmination of Richet's career as dramatist was *Circé*, a play in verse that premiered on April 3, 1905 at the Theatre of Monte Carlo with the famous actress Sarah Bernhardt (1844-1923) playing the central role [1].

However, one of the most controversial of Richet's interests was eugenics. He was vice-president of the French Eugenics Society and in his book entitled *Sélection humaine* (Human selection), published in 1919, Richet mentioned: "The weak are crushed, the individual is nothing, the species are everything…. one will no longer simply be content to perfect rabbits and pigeons but will try to perfect humans"[9].

Richet died in Paris on 3 December 1935.

His scientific work

Throughout his career, Richet conducted interesting studies in physiology. He discovered the phenomena of refractory period and summation in nerves and demonstrated summation in vision with his colleague Antoine Breguet (1851-1882) [1]. Also, he conducted studies on the nervous control of the heart beat; he discovered the diuretic effects of sugar; he claimed first that hydrochloric acid was the basis of gastric fluid; he studied the liver function and the mechanism of digestion in fish. In 1883 he began his studies on the mechanism of thermoregulation; he discovered the heat loss in dogs by panting; he built a siphon calorimeter; in 1887, he discovered the brain's role in the regulation of body temperature and performed several metabolic experiments with Hanriot studying among other the starvation effect on body [10].

Richet saw also the need for a more effective anesthetics than the chloroform which was typically used. Together with his assistants, he devised a new compound of the old chloroform base and sucrose which they called *chloralose*. Its effect was that of a hypnotic sleep but with all of the animals' reflexes intact [11]. During World War I Richet demonstrated the usefulness of *chloralose* as a general anesthetic and also recommended it for childbirth in place of ether [2].

His interest in psychology, especially hypnosis, began when he was a youth and continued through his life. As he considered psychology to be a part of physiology, the central nervous system played a prominent part in most of his physiological research [2]. He was following the lessons of Jean-Martin Charcot (1825-1893) in Salpêtrière hospital and he treated hysteria with hypnosis. Also, he published a work on somnambulism based on experiments that he continued while an intern in the 1870s and in his manuscript *Essai de psychologie générale* (Essay of general psychology, 1887) he considered psychology as a neural science [12]. In 1896, he presented one of the first studies of anorexia nervosa. However, most of his psychology was focused on neuroscience, including studies of pain, epilepsy, and the electrophysiological processes of the cerebral cortex, and in 1910, he predicted neurotransmitters. At the 1892 International Congress of Experimental Psychology in London, Richet argued that "without brain, or rather without nerve cell, there is no intelligence. The first problem of psychology is therefore a most complete physiology of the brain: relations of ideation to cerebral circulation, with chemical changes in nerve-cells, with electric phenomena; localization of psychical acts in this or that part of the brain; in other words a physiological résumé of the brain" [13,14].

Moreover, he was interested on the metaphysical phenomena. He became even more deeply involved in the subject after a visit to Paris in 1884 by the Russian psychologist Alexandr Nikolayevich Aksakov (1832-1903) who told him of an Italian medium named Eusapia Palladino (1854-1918) whom Richet not only visited but invited to his island *the Grand Ribaud* for three months. There, she was studied by such visitors as the English writer Frederic Myers (1843-1901), Richet's fellow physiologist Arsène d'Arsonval (1851-1840) and other scientists with an interest in psychism such as the astronomer Camille Flammarion (1842-1925) and the Curies [2] (Photo 2). The following year Richet, Sir William Crookes (1832-1919) and others founded the Society for Psychical Research with Richet as the first president. He kept an active interest in the subject for the next thirty years, founding also a journal *Les Annales des Sciences Psychiques* (Annals of Psychic Sciences) where he published further experiments in hypnotic lucidity or clairvoyance [15,16].

His most important work in physiology began

Photo 2. Charles Richet on the left during a séance.

Photo 3. Charles Richet and his collaborator Paul Portier in the laboratory of *Princesse Alice II.*

in 1901. Richet joined a marine exploration with Paul Portier (1866-1962), a professor of comparative physiology at the University of Paris. The exploration was led by the Prince Albert I of Monaco (1848-1922), deeply interested in oceanography (Photo 3). Albert's ship, *Princesse Alice II*, was equipped with a laboratory and they aimed to study the toxic effects of the fluid from the nematocysts of *Physalia* and the tentacles of the sea anemone *Actinia*, attempting an immunization to the toxin. Instead of providing prophylaxis, they induced a fatal hypersensitivity reaction to Richet's dog Neptune. Returning to their laboratory in Paris they repeated the experiment. A single injection of the toxin produced no symptom in the dogs; however a second injection in an interval of 14-22 days provoked classical symptoms of shock and death in less than 30 minutes [1,17].

He called this effect anaphylaxis from the Greek *an* meaning without and *phylaxis* meaning protection. Later, he demonstrated the facts of passive anaphylaxis and anaphylaxis *in vitro* [18].

In recognition of his work on anaphylaxis, Richet was awarded the 1913 Nobel Prize in Physiology [19].

Richet's anticancerous serum and its impact in nascent oncology

After the studies of Louis Pasteur (1822-1895), Pierre-Émile Roux (1853-1933), Alexandre Yersin (1863-1943), Emil von Behring (1854-1917) and Shibasaburo Kitasato (1852-1931) on the curative effects of antidiphtheric serum on children suffering from the disease, serotherapy became the center of attraction of all scientists. Charrin, Roger and Marmoreck, developed the antistreptococcal serum, Calmette the antivenomous serum and Chantemesse the antityphoid one [20].

In this ambiance, it seemed natural in the partisans of parasitic theory of cancer (the parasitic theory held that cancer was caused by some infectious agent, and this infectious theory implied that cancer was contagious), to take enthusiastically this promising. Several were the anticancerous serums that appeared.

In 1895, Richet and his collaborator Jules Héricourt (1850-1938) announced the development of a serum whose hypothetical virtues would generate the enthusiasm of medical societies and cancer patients [21].

It was during a session of the Academy of Medicine that Richet informed his colleagues of his discovery: "The February 9, 1895 Paul Reclus removed a leg from a patient with osteosarcoma. The tumour was crushed, and then mixed with a little water. The obtained liquid was then filtered and injected in 3 animals (a donkey and two dogs). The injection did not provoke any reaction and 15 days later we took a blood sample from the animals to obtain serum. Then, we injected the serum in two cancer patients". According to Richet this experiment was successful.

The first patient was a woman suffering from fibrosarcoma that was hospitalized in the surgical department of Professor Louis-Félix Terrier (1837-1908). A daily injection was administrated to her for 13 days. On day 14, the tumour began to shrink gradually and the general condition of the patient improved.

The second observation concerned an inoperable tumour in the epigastric region in a 44 year-old man who was hospitalized in the department of Professor of Surgery Paul Reclus (1847-1914). After 15 days of treatment the patient started gaining weight while the palpation of the epigastric region revealed an almost total disappearance of the tumor.

As a true scientist Richet, judging these results too good to be significant, kept a cautious optimism and he declared: "In the second case, as in the first, the improvement was fast, brilliant and undeniable. Could we think,

because of this extraordinary success, the possibility of a misdiagnosis? The observation of Professor Terrier nevertheless persisted in all its strength: the anticancer serum treated a case of cancer" [22].

This communication diffused by the press and commented enthusiastically, raised hopes in an amazed public by the recent progress of medicine and convinced that the anticancer serum had nothing to envy the antidiphtheric and antitetanic ones.

A great number of cancer patients were referring to Richet and his collaborators. Much more reserved, physicians multiplied their experiments. Dozens of inoperable cancer patients were receiving Richet's serum and in October 1895 it was finally possible to have a better idea of its therapeutic value. In 80% of the treated cases, the intensity of the pain diminished, the ulcerations improved, the volume of tumors and ganglia diminished, the vascular and neural compressions were attenuated and the patients' physical condition improved [20].

But it was in fact a Pyrrhic victory that inspired in *Revue scientifique* a cruel euphemism: "This improvement occurs in end-stage cancer patients that they have only few days of life and the serum can give to them 2-3 months of life". In other words, "this improvement does not extend to the healing... after a period of 1 or 2 months cancer returns to its original virulence" concluding " however there is no treatment known till now that can give such good results that are so close to the cure of cancer" [23]. Probably, for this reason, Richet's serum had some supporters 10 years after its discovery [20].

In 1906, Ernest von Leyden (1832-1910) accorded to the serum his confidence and considered the absence of metastasis a proof of its efficacy [20]. But, one year later Ménétrier wrote in his manual on cancer: "We have to believe that, despite everything, the results were not very encouraging and the majority of scientists did not persist in this way of treatment" [24].

Conclusion

The reputation of Professor Richet opened the way and encouraged other initiatives in serotherapy.

As example we mention the serum of Bra and Mongour, named "nectriamine"; the serum of Wlaeff named "anticellulaire", the "erysipelas curator" of William Coley and Neisser, the serum of Doyen and many others [25].

While serotherapy was at its peak by giving illusions and promises, cancer surgery was in a considerable progress. However, even the word surgery frightened the patients who were still hesitant to be subjected to this kind of treatment.

Nevertheless, in this period newer surgical procedures had been developed that remain even today the supreme recourse for cancer patients.

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