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Portier, Richet, and the discovery of anaphylaxis: A centennial

I must go down to the seas again, to the lonely sea and the sky,
And all I ask is a tall ship and a star to steer her by,
And the wheel's kick and the wind's song and the white sails shaking,
And a grey mist on the sea's face and a grey dawn breaking.
—John Masefield[1]

In a timetable of research and clinical advances in allergy, the year 2002 marks the 100th anniversary of Portier and Richet's[2] classic report on the experimental production of aberrant immunity. However seminal their contribution, it was not the first communication to note manifestations of untoward effects, systemic shock, and fatal outcomes in laboratory animals in response to repeat injections of initially well-tolerated doses of a foreign protein. Similar observations of the phenomenon were made in Magendie's[3] studies of nutrition with egg albumen in rabbits 63 years earlier, Behring's[4] studies with diphtheria toxin in guinea pigs in 1893, Flexner's[5] studies with dog serum in rabbits in 1894, and Richet's[6] own studies with toxic eel serum in dogs 5 years before his definitive studies with Portier. In 1896, 5 years after the successful introduction of therapeutic antitoxin to diphtheria, Gottstein[7] reported human fatalities to the administration of horse-derived antisera. Those observations, however, were treated as only incidental findings; the possibility of a newly revealed phenomenon had escaped their recognition and insights.

By contrast, Portier and Richet appreciated that the unanticipated outcome of experimental procedures to induce tolerance to a toxin could have pathologic consequences. Additionally pertinent, their work uncovered new knowledge of pathogenesis that proved to be a seminal step in the development of immunology beyond its base in bacteriology. Thus modern day understanding of hypersensitivity mechanisms and manifestations of anaphylaxis begins with an account of circumstances and events related to that milestone of 1902.

The team: Profiles and prelude

The path to the discovery of anaphylaxis can be retraced to 1901 in the principality of Monaco and to the common interest of 3 scientists in the mysteries of the sea and a fascination with its equally enigmatic populations.

Albert (Honoré Charles) Grimaldi[8] was born in 1848, the son of Charles III, Prince of Monaco. His growing up on the shores of the Mediterranean and, as a young man, his service in the Spanish and French navies engendered an early and perpetuating passion for the sea; it deepened further into a combined avocation and serious study of oceanography and marine biology. For that pursuit, he acquired progressively larger and specially equipped yachts manned with an on-board scientific staff and fitted with laboratory apparatuses and specimen-holding tanks. In 1885, he initiated a series of cruises accompanied by distinguished guest scientists who joined him in the conduct of innovative oceanographic surveys that would contribute to advancements in the field.

As his scientific pursuits deepened, so too did his royal responsibilities. In 1889, at age 41, he succeeded his father in governance of the principality. Having already established one of the earliest laboratories in marine biology, in 1899, Prince Albert founded and endowed the Oceanographic Museum of Monaco.

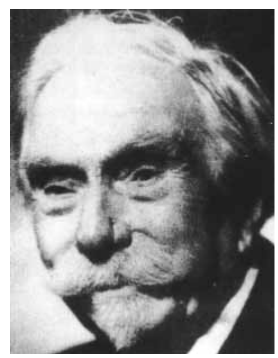

FIG 1. Paul Portier, 1866-1962. Courtesy of the National Library of Medicine.

Paul Portier[9] (Fig 1) was born in Bar-sur-Seine, France, in 1866. After the family tradition of pursuing careers in government, he entered national service as a clerk in the land registry. Although by his early twenties he had successfully competed for a position in the Finance Ministry, he declined the opportunity in favor of following an overriding interest in the natural sciences dating back to his childhood. Portier's parents supported his decision on the condition that he first study medicine. Accordingly, he complied and received a medical doctorate in 1897 and a subsequent doctorate in science from the respective faculties of the University of Paris.

After completing his studies, Portier became an assistant in the departmental chair's laboratory of physiology, through which he met Monaco's Albert I. With their evolving friendship and awareness of common scientific interests in marine biology, Portier was invited to sail with the Prince on his 1898 cruise and, by 1901, had become a regular member of the scientific staff for annual cruises.

Charles R(obert) Richet[10,11] (Fig 2) was born in 1850 in Paris into an affluent and socially prominent family. His distinguished father was chairman of the Department of Surgery at the Paris Faculty of Medicine and Chief of Surgery at Hôtel Dieu. His maternal grandfather, a liberal journalist and expert in admiralty law, exposed him to a variety of subjects and values that implanted in Charles a lifelong quest for knowledge in a disparate array of subjects: classical literature, Latin, love of the sea, sailing, philosophic views, democratic convictions, social consciousness, disdain of Napoleonic leadership, and hatred of war. While a student at the Paris Faculty of Medicine, Richet found diversion from anatomy and surgery, which he disliked, by writing plays, poetry, and fiction. Although a pacifist, Richet complied with the charge to serve in the military during the Franco-Prussian War of 1870. The experience heightened his distress over the casualties and unjustified loss of life as a price of war. On his return to academia, Richet successively completed medical studies, an internship at the Saltpêtrière, a residency in surgery, and research for doctoral theses.

FIG 2. Charles R. Richet, 1850-1935. Courtesy of the National Library of Medicine.

Before receipt of MD and ScD degrees in 1887 and 1888, he worked in the chemistry, anatomy, pathology, and physiology research laboratories of foremost faculty members. None of those experiences in experimental physiology or clinical medicine would ever equal the lasting influence of his internship at the Saltpêtrière where Jean Martin Charcot had established a teaching, diagnostic, and treatment center for nervous system diseases and functional disorders.

Richet chose to enter the field of experimental physiology and to undertake a broad range and staggering array of investigations on whatever happened to interest him at the time. These studies were as diverse as digestion, thermal regulation, respiratory control, diuresis, fever, pain, heart rate, toxicity of metal salts, "muscle plasma" (raw beef extract) for therapy of tuberculosis, and even aeronautics and construction and trial of a machine-powered, fixed, single-wing aircraft that predated the Wright brothers' flight. As a result of his introduction to the clinical application of hypnosis through work with Charcot, the majority of Richet's initiatives dealt with his perception of "physiologic psychology." Conceptually, it provided a base for his study of hypnosis, hysteria, sensory nerve perception, anorexia nervosa, memory, consciousness, and psychic stimuli in health and disease.

Amid that preoccupying pace of scientific activity, he continued to engage in endeavors in the humanities (ie, literature, philosophy, and history) and undertook editorships of 2 widely read journals. In 1887, at age 37, he was appointed to a professorship in physiology and in 1898 was honored by election to the Academy of Medicine.

Among his scientific pursuits, Richet had a record of long-standing interest in poisons, dating back to his early research on the toxic effects of heavy metal salts on bacteria. That sophistication, along with an interest in fish and other marine organisms, led to Prince Albert's welcome of the suggestion that Richet, who by then had been credited with 424 publications, join his 1901 scientific cruise. With the collaboration of Richet and Portier, Albert and his cruise scientific director, Jules Richard, sought to study the mechanism by which the grasping tentacles of the gelatinous invertebrae *Physalia*, Portuguese man-of-war, stunned prey and caused pain and central nervous system pathophysiologic effects in human subjects who unfortunately came within its reach.[12] Mediterranean sailors and fishermen were well acquainted with the discomfort and immobilizing effects of stings. Affected bathers, as ready targets, added to the adverse impact on French Riviera tourism and vacationing. There was reason to believe that isolation and characterization of the suspected toxic mediator could be expected to provide a likely productive first step for development of a biologic or pharmacologic attack on some of the problems.

Voyage and mission[11,13,14]

On July 5, 1901, the 2-masted, steam-powered Princesse Alice II departed from the nearby French port of Toulon to begin a 2½ month cruise. Although laboratory animals were aboard, scientific experimentation could not get underway until a supply of *Physalia* was obtained (Fig 3). Ultimately, a plentiful source was found and harvested from the waters of the central Atlantic, near the Cape Verde Islands, about 350 miles off the West African coast. To occupy the time not spent fishing and sailing during the first 4 to 5 weeks of the voyage, Richet added to his literary credits by writing a drama, *Circé*. The story so pleased the Prince that he supported its stage production at Monte Carlo in 1905 with the internationally acclaimed French actress, Sarah Bernhardt, in the starring role.

In a successful start, Richet and Portier were able to confirm the impression that the tentacles of the gelatinous creature were the source of a paralyzing poison. Because injections of glycerol extracts produced marked central nervous system depressant effects in ducks, pigeons, guinea pigs, and frogs, they gave it the name "hypnotoxin."

FIG 3. Postage stamp issued by Monaco in 1953 to commemorate the 50th anniversary of the discovery of anaphylaxis. Pictured are *Physalia (left)*, Prince Albert *(upper right)*, Richet and Portier *(lower right)*, the Prince's yacht Hirondelle II *(center)*, and the Oceanographic Institute of Monaco *(background)*. Gift of Charles May, 1985.

After completing the cruise in mid-August, Richet and Portier decided to continue collaboration to extend their findings. According to Jules Richard's scientific record of the voyage, they had pondered whether the experimental animals could develop tolerance to the toxin through repeated injections of increasing amounts at set intervals.[15] Because accomplishing the requisite long-term study while at sea was not feasible, they agreed to rejoin at Richet's laboratory in the physiology department of the University of Paris.

Richet and Portier set up the experiments with 2 modifications. First, they substituted the toxin from unavailable deep-water *Physalia* with extracts from a related coelenterate, a sea anemone abundant in coastal France. Second, they replaced the rabbits and other small experimental animals with dogs because canines were found to be less susceptible to the lethal action of the tentacle-derived "actinotoxin" (so named after the scientific classified designation of the source anemone *Actinia sulcata*). They were able to duplicate the same laboratory-induced, adverse, suppressive, central nervous system functional activity observed during the voyage. In a follow-up study, Richet and Portier isolated the toxin; demonstrated its toxic, physical, and chemical properties; and, by means of administration to 36 dogs, determined the lethal dose (>0.15 mL/kg).[16]

For the next investigative step, the knowledge Richet gained through his 1881 and 1888 deviations from research in pure animal physiology to the developing field of bacteriology proved useful. In 1881, he demonstrated the adaptive immunity of bacteria to poisonous salts of heavy metal engendered by exposure to repetitive doses given through successively cultured generations. In 1888, he and Héricourt performed an adaptation of Pasteur's pioneering introduction of bacterial vaccine production and effectively immunized dogs and rabbits with attenuated cultures of staphylococci and avian and human strains of tubercle bacilli. In a next step, transfusing blood from inoculated donors to infected recipients resulted in passive transfer of partial protection from infection. From that experimental lead, Portier and Richet hypothesized that protection against an animal (sea anemone) venom might be induced by means of injection procedures similar to those Kitasato and Behring[17] had accomplished with microbial (ie, diphtheria and tetanus) toxins 12 years previously.

Discovery

In experiments conducted in late 1901 and early 1902, Richet and Portier attempted to raise tolerance in guinea pigs and pigeons by administering incrementally larger doses of actinotoxin. The results proved ineffective or equivocal. Again they turned to dogs. Although initial trials with 4 dogs were inconclusive, the results suggested that reactions to some injections could produce an apparent increase rather than the anticipated decrease in sensitivity to actinotoxin. A retrial with pigeons and guinea pigs again was proven unsuccessful. Other test results enhanced the impression that some animals could become sensitized—even to a heat-attenuated toxin—after receiving an initial inoculation.

The trial with dogs that followed was as astonishing as it was unforeseen. All in the group of 8 dogs collapsed and died within a few minutes after repeat administration of even as small a dose as 0.1 mL/kg. After ruling out inadvertent protocol errors, confusion in identifications or differentiations within the vaccinated and control groups, and mistakes in copying notes, Richet and Portier identified 2 potentially productive factors. First, the dogs that had fatal reactions differed from normal animals in that they had been retained for follow-up study after survival from experiments designed to determine the toxic dose. Despite exposure to toxin and apparent complete recovery from nonlethal action, they were not rendered expectantly immune but exquisitely "sensitized." Second, development of a sensitive state seemed to correlate with having "received the first injection at a remote date" (14-23 days previously).

In a definitively designed protocol, 2 dogs were selected who previously had received 2 weak doses of actinotoxin but appeared in good health. They each were injected with "weaker doses" than they had received previously:

- Galathée: Day 1, 0.05 mL/kg produced itching and some dyspnea; day 8, 0.01 mL/kg did not produce a reaction; and day 27, 0.01 mL/kg immediately produced vomiting blood and mucus, bloody deification, marked stupor; death resulted several hours later.
- Neptune: Day 1, 0.05 mL/kg did not produce a reaction; day 4—0.1 ml/kg did not produce a reaction; and day 27, 0.12 mL/kg immediately followed by vomiting, deification, leg tremors, loss of consciousness, and death in ½ hour.

Their appreciation of uncovering a new phenomenon was described as the outcome of "administration of a substance insufficient to kill or even sicken a normal animal that produces fulminating symptoms and death in an animal previously inoculated with the same substance." For this "curious exception," Richet proposed the name "aphylaxis" (derived from the Greek: a, contrary to + phylaxis, protection), which was changed to "anaphylaxis" because "aphylaxis" lacked euphonic expression. Five days after completion of the experiment, Portier and Richet presented their findings to the Socíeté de Biologie.[2]

Portier and Richet's introduction implied the belief that the newly revealed pathophysiologic state occurred as a function of poisonous substances. According to their definition, anaphylaxis represented a lowered threshold of response to toxic effects as the outcome of critically timed reinjection. The concept, although erroneous, set the stage for further exploration by experimental pathologists and clinical scientists. One year later, Arthus[18] demonstrated that repeated injections of a substance universally accepted as being primarily nontoxic, horse serum, could produce an anaphylactic reaction. During subsequent years, further analysis of actinotoxin by laboratory scientists demonstrated a multicomponent character that explained its dual toxic and immunogenic-hypersensitivity effects. In addition to antigenic large-molecular-weight proteins, actinotoxin included recognized urticariogenic agents, and chemical mediators of inflammation (biogenic amines: histamine, serotonin, dopamine), prostaglandins, polypeptide neurotoxins and cardiotoxins, proteinase inhibitors, hemolytic, cardiotoxic, and enzymatic proteins.[12]

After the seminal 1902 report, Portier returned to his own university physiology laboratory, no longer associating with Richet in research. In 1903, Richet reported fractionating actinotoxin into 2 distinct active compounds: immunogenic and mildly toxic thalassin and its more toxic and anaphalactogenic counterpart congestin. The latter was so named because of its powerful action on the vasomotor system. Continuing to work on anaphylaxis with a variety of experimental techniques and procedures, in 1907, Richet demonstrated additional features of the phenomenon: (1) the anaphylactogenic property resided in serum taken from inoculated dogs and (2) after recovery from anaphylactic reactions, the dogs had become immune to the previous injurious dose of causative agent. Richet interpreted this finding to mean that the immunized and anaphylactic state or states resulted from factors produced by a challenged body system and not by the inoculated foreign agent per se. This realization provided further leads for evolving an understanding of hypersensitivity as an immune phenomenon. Defining its relevance to human disease followed.

Close to a decade later, Richet received recognition for the discovery of anaphylaxis with the award of the Nobel prize in Medicine or Physiology. Portier was not included as a recipient.

In retrospect

The independent recountings by Richet and Portier of the experimental circumstances that led to the discovery of anaphylaxis evolve into a scenario reminiscent of the tale of Rashomon. In that Japanese classic, the 3 principals in a rape and murder crime, perpetrator and victims alike, relate different versions of the same incident according to their individual perceptions.[19]

In 2 publications, Richet's monograph *L'Anaphylaxie*[20] and his Nobel laureate address,[21] he offered the impression that the attempt at desensitization was neither designed nor planned but serendipitous.

> … (the discovery) 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.

In a differing tenor, Portier's account cast the sequential events as purposeful rather then developed by chance.

> We considered our work (determination of toxic dose) almost finished when I proposed to Richet to proceed with some trials of immunization. My proposition did not arouse much enthusiasm in him, and I considered it more or less as a routine completion of our work. Was it not in effect, evident that we would repeat the classic phenomenon, commonplace, since the work of Pasteur and the school?[22]

In a similar vein, biographers examining the same source records, laboratory notebooks, manuscripts, and publications arrive at different interpretations of the relative roles and contributions of Richet and Portier. During his Nobel laureate address, Richet made only the 2 following passing references to Portier's role, "During a cruise made on the yacht of Prince Albert of Monaco, the Prince advised me and our friends, Georges Richard and Paul Portier, to study the poison of *Physalia*," and, "I was searching then, with Portier, to specify the exact toxic dose."[21]

That Portier did not share the Nobel prize nor receive more definitive recognition by Richet seemed understable to May in noting the academic tradition of the "older, distinguished scholar allowed to overshadow a relatively unknown younger junior assistant."[13]

In a congratulatory letter on Richet's election to the Académie des Sciences, Portier addressed his former coinvestigator and coauthor as "Mon cher Maitre," The term "Maitre" denotes Portier's evident respect for seniority, rank, and stature taking precedence over informally shared experiences and personal associations in scientific undertakings.

Nevertheless, in his evaluation, May posed the question of inequity in that Portier's name on their journal papers appeared as first and thus principal author. In addressing that point, Gabriel Richet pointed out that his grandfather (as verified in his complete list of 743 publications[10]) always respected the listing of authors in alphabetical order. Furthermore, although Portier's handwriting is also found in the experimental notebook records, such practice "usually was the youngest's responsibility."[14]

In a similar context, Portier's dedication to exploring research questions has been the subject of doubt. Contrary to May's championing recognition of Portier's initiative and insights, Wolf viewed Portier as "having little interest in the work." In relating to another critique that Portier "did not grasp the significance (of the Neptune dog experience),"[23] Wolf offered, as an explanation, their different interests in biology. Richet's was that of a medical scientist. Portier (although a medical school graduate) was primarily a marine biologist and entomologist having perhaps "less curiosity about anaphylaxis and less understanding of its medical significance".[11]

According to May, such perceptions and presumptions ignore Portier's own words clarifying his reason for withdrawing from collaboration before completion of the extending studies.

> I was perfectly aware of the importance of the discovery… but I was simply an assistant in physiology at the Sorbonne. I was obliged… to direct the practical work of numerous students. Besides some coworkers at the Sorbonne were claiming my presence in the laboratory (because of prolonged absence)… Our studies on digestion had led us to study the mechanism of secretion from glands which control intestinal digestion… a discovery of first importance… Were we, because of my fault, to lose the fruit of lengthy research? I was obliged to return to work regularly at the Sorbonne….[24]

Although Richet's Nobel laureate address made only token mention of Portier's role, subsequently in his memoirs, Richet praised him for "giving up all claim to the honor of the discovery."[11] Portier, for his part, never expressed resentment, envy, or bitterness, and in collegial fashion, they remained friendly for the rest of their lives.

Epilogue

By the time of Richet's last recorded work on anaphylaxis in 1907, a flow of immunologic-related studies, derived from the original Portier and Richet milestone, were beginning to expand the scope and understanding of causative factors and pathogenetic mechanisms of the phenomenon. At the same time, dissemination of their report within the clinical community created an awareness of anaphylactic manifestations, particularly relevant to human disease. Meanwhile, the 3 members of the since-disbursed original team had returned to their home bases to resume endeavors and undertake new challenges.

Prince Albert continued pioneering oceanographic studies. By 1914, he had completed 21 scientific cruises, each with documented accounts. Before his death at age 72 in 1920, he had founded a second Oceanographic Institute in Paris and had been honored by election to the French Académie des Sciences and to the Académie Nationale de Médecine.

Richet's amazing displays of versatility, imagination, enterprise, intellect, and creativity continued to feed an ascending career in scientific, cultural, literary, sociologic, and psychic arenas. In the image of a renaissance man, Richet pursued an array of interests and activities that included pacifism, philosophic works, eugenics, societal concerns, mysticism, and studies in the history of medicine, science, and civilization. He wrote several monographs, a large treatise on metaphysics, and 10 volumes of literature (ie, poetry, novels, fables, and plays); edited and published an 8-volume encyclopedia of physiology; and promoted adoption of the international language Esperanto. Although he remained a fervent pacifist, Richet volunteered his medical skills to saving life and relieving suffering at the battlefronts of World War I. He collaborated in the development of a device for detecting the poisonous gas chlorine and in the invention of a combination life vest and wet suit for protection against both cold exposure and drowning. Independently, he pioneered the development of innovative methods for treating soldiers with tuberculosis and the use of plasma for transfusion therapy. He was elected to the Académie des Sciences in the seat that was reserved for surgeons and had been occupied by his father.

Charles R. Richet died in 1935 at age 85. The Richet line of professorships of medical science would continue through his son Charles and his grandson Gabriel. For activities with the French underground, Charles fils was taken captive and held for 2 years (1943-1945) in the Nazi concentration camp at Buchenwald.[25] With a background of specialization in nutrition, he recorded especially perceptive observations on the effects of malnutrition on himself and others confined to the camp during World War II. Following and applying his father's initiatives in hypersensitivity research to his own clinical field, Charles fils (1882-1966) contributed to the development of a knowledge base on "alimentary anaphylaxis" (gastrointestinal and food allergy).[26] Gabriel (1916–), a pioneering nephrologist at the clinical and investigative forefront of the specialty, in

1958 was appointed to one of Paris' first professorships of nephrology[27] and served as a unit scientific director of INSERM (France's National Institute of Health and Research Medicine).

Three centuries earlier, Ben Jonson (1573-1637) penned the thought, "Greatness of name in the father oft-times overwhelms the son; they stand too near one another. The shadow kills the growth…."[28] Had he been endowed with the gift of clairvoyance to foresee the continuity of accomplishments, attainments, and eminence of 4 generations of the Drs Richet, Johnson might well have considered adding a qualifier to his maxim.

Portier's continuing contributions to biologic science also demonstrated considerable versatility. His published studies covered physiology of aquatic insects and animals, marine birds, and fish; symbiosis; nutrition; human artificial respiration; and carbon dioxide in biochemical tissue processes, and, in his 80s, he wrote a large treatise on butterflies. In 1906, he was appointed professor and first director of the Institut Oceanographique in Paris founded by Prince Albert of Monaco. In 1923, he became professor of comparative physiology in a chair especially established for him at the Faculté des Sciences in Paris. Ultimately, Portier was duly honored and recognized by election to the Académie de Medicine and by election to the Académie des Sciences in the seat formerly held by 2 generations of Richets. At the 50th anniversary celebration of anaphylaxis, he received international acclaim. Whereas Richet's colorful reputation was that of flamboyance, Portier was spoken of as humble and gentle. Portier died in 1962 at age 95.

Whether the series of experiments that led to the discovery of anaphylaxis were initiated by reasoned intent or chance or evolved through a combination of both elements, in later years, Portier reminisced about the likely determinant factor:

> We discovered anaphylaxis without looking for it, and almost in spite of ourselves. But it was necessary to have the eyes and mind of a physiologist to understand the interest.[29]

Reflected therein is the essence of the axiom by Louis Pasteur, "In the fields of observation, chance favors only the minds that are prepared."[30]

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