From Bretonneau to therapeutic antibodies, from specificity to specific remedies, Saint-Cyr-Sur-Loire, France, November 19, 2012

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Held on November 19, 2012 in Saint-Cyr-sur-Loire, France, the symposium “From Bretonneau to therapeutic antibodies, from specificity to specific remedies” focused on the historical development of antibodies as therapeutics, with an emphasis on the seminal work of the French physician Pierre-Fidèle Bretonneau (1778–1862). The morning session was devoted to discussion of the evolution of the concept of specificity in medicine, which started with an epistemological definition. The contributions of Bretonneau to the emergence of the concept of specificity, notably with his studies on diphtheria, and the subsequent development of antiphteritic serotherapy in Europe during the period 1894–1898 were then presented in detail. The afternoon session began with a presentation on the role of French physiologists during the years 1860–1890 in establishing the basic concepts of specific immunity and the principles of serotherapy. The history of antivenom serotherapy, particularly its discovery by Césaire Phisalix, and the development of antilymphocyte globulins as successful transplantation drugs were then discussed. The symposium ended with the inauguration of a stele representing Bretonneau, who lived in Saint-Cyr-sur-Loire and died 150 y ago.

The symposium “From Bretonneau to therapeutic antibodies, from specificity to specific remedies” was held on November 19, 2012 in Saint-Cyr-sur-Loire, on the riverside of Loire, in front of the city of Tours. Jean-Yves Couteau, deputy mayor of Saint-Cyr-sur-Loire, opened the symposium with a discussion of Pierre-Fidèle Bretonneau (1778–1862), who spent the second part of his life in this city, sharing his time between his medical activities and researches and other more epicurean occupations. Marc de Ferrière le Vayer (Université François-Rabelais de Tours, France) then explained that this symposium was co-organized by the Laboratory LEA (Université François-Rabelais de Tours)³ and the Laboratory of Excellence (LabEx) MAbImprove coordinated by Hervé Watier (Université François-Rabelais de Tours)² to close the celebrations commemorating the 150th anniversary of the death of Bretonneau.

This symposium also closed the ORHIBIO (Origin and History of Biotechnologies) research program, which started in 2007 with the objective of studying medical innovations, physicians and pharmacists of the 19th and early 20th centuries in Touraine.² Marc de Ferrière reminded the audience that at the beginning of the ORHIBIO program, study of Pierre-Fidèle Bretonneau was intentionally excluded because he dominated early work in this field and it seemed that other subjects must exist. It was quickly apparent, however, that many later critical achievements and advancement in Touraine, e.g., the Vaccine Institute of Edmond Chaumier (1853–1931) in Tours where the industrial production vaccinia virus (cowpox) occurred; the Bacteriological Institute of Tours, which was founded by Marcel Belin (1885–1950) to produce his vaccine against foot-and-mouth disease; the foundation of the Faculty of Medicine in 1962; the invention in 1976 of anti-hepatitis B vaccine by Philippe Maupas (1939–1981), could be traced directly or indirectly back to Bretonneau. He was indeed a central figure around whom medicine was built in Touraine, and it also appeared that many aspects of his life and its works remained unknown.

A public exhibition held in Saint-Cyr in May 2012² presented renewed aspects of his life and discoveries. The symposium described here was conceived to focus on Bretonneau's contributions to infectious diseases and immunology as a satellite meeting of the international congress “Therapeutic Antibodies and Infectious Diseases”³ held in Tours, November 20–22, 2012, a report of which is included in this issue of mAbs. It is of course anachronistic to combine Bretonneau, who died in 1862, and serotherapy, which was discovered in 1890; however, as a pioneer of specificity and of the germ theory, connections do exist between Bretonneau and serotherapy. Serotherapy was also developed as an active specific remedy, and now monoclonal antibodies, under the fashionable term “targeted therapy,” are indeed the most antigen-specific remedies currently available.

Bernardino Fantini (Université de Genève, Switzerland) brilliantly introduced the meeting, expounding the epistemology of the concept of specificity. This dimension of medical thought
is frequently neglected, although the term is commonly used in medical and biological texts. The notion of specificity evolved during the 19th and the 20th centuries due to the development of new medical disciplines like biochemistry, immunology and genetics. The definition of “specificity,” from an epistemological point of view, refers to the concept of evolution. Each disease has a particular nature, and simultaneously, “specificity” leads to a concept of individuality. As a result, “specificity” is a synonym of “identity.” The exact definition would have been “specific remedies” rather than “specificity,” but it was a definition that has evolved over time.

In the middle of the 17th century, the definition of disease was particularly vague and the notion of antique humors still prevailed. The English physician Thomas Sydenham (1624–1689) provided another perspective by asserting that each animal, plant and disease species had a particular nature. He initiated the taxonomist movement, which developed until the 18th century. The anatomo-clinical method founded by the Italian physician Giovanni Battista Morgagni (1682–1771) defined disease by both symptoms and lesions, and their interactions. The anatomo-clinical revolution drastically changed nosology and semiology throughout the 19th century. At this time however, the word “specificity” referred to pharmaceutical products, i.e., “specific remedies.” Each drug was associated with a disease. In this traditional vision of specificity, the French physician Pierre-Fidèle Bretonneau (1778–1862) understood that each disease had a specific nature when he treated rickets with cod-liver oil.

During the 19th century, the definition of the cause of diseases itself also evolved. One disease could have several causes and etiologies, sometimes combined with external factors such as miasmas. Laboratory medicine soon allowed physicians to search for specific causes of diseases, working under the assumption that a determining cause explains a disease. The birth of microbiology involved a new paradigm: the definition of diseases by germs. Robert Koch’s (1843–1910) postulate expounded the series of conditions to establish a germ as causative agent of a disease, i.e., an infectious disease is defined by the presence of a germ and this germ is necessary to induce the disease. The researcher should be able to isolate, cultivate, and inoculate it. The disease was then defined by three specific aspects belonging to the domains of nosology, semiology and etiology.

Even so, physicians wondered about the nature of specificity. Was it the product of a biological phenomenon or was it the cause? In his works, Claude Bernard (1813–1878) focused on the opposition between the atavistic factor (control of the molecular phenomena) and the physico-chemical factor (production of phenomena). The physiologic regulation was the critical point of his work, but the concept did not evolve until the appearance of genetics. With the work of James D. Watson and Francis Crick, the concept of specificity was transferred to genetics. The information became a criterion for determining specificity, and thus the notion of specificity was then established in molecular biology.

Françoise Tauty (Université de Tours, France) talked about the concept of specificity in the works of the famous physician of Tours, Pierre-Fidèle Bretonneau (1778–1862). Son of a surgeon practicing in a small village of Touraine, Bretonneau was 17 when he came to Paris during the French Revolution to start medical studies. He returned to Touraine in 1802, to the small village of Chenonceaux, as a country practitioner. He observed smallpox disease and introduced inoculation in the district. He finally defended his doctoral thesis in 1815 to be appointed medical doctor in chief at the hospital of Tours, an office he kept until 1838, where he contended with the epidemic diseases occurring in Tours at the time.

Bretonneau practiced observation at a high level, applied the anatomo-clinical method and described the symptoms and evolution of diphtheria. His major work on the “diphterite” was published in 1826. In characterizing diphtheria, and a few years later typhoid fever, as specific diseases, he actually demolished the dominating theory of spontaneous generation held by François Broussais (1772–1838). Bretonneau described a disease not as an inflammation of the tissue, but with specific symptoms and the possibility of transmission. For him, the causes of the disease were not endogenous, but the results of “invisible organisms” from the outside. Bretonneau is therefore considered to be a pioneer of the germ theory, the concept of specificity allowing the advent of the Pasteurian era.

Pierre-Fidèle Bretonneau was a famous doctor who was always in search of therapeutic novelty, and he was also a charismatic teacher. His students, including Alfred Velpeau (1795–1867), Armand Trousseau (1801–1867) and Moreau de Tours (1804–1884), spread the master’s thoughts in their own publications. Details of Bretonneau’s work, research and experimentation are known today thanks to his substantial volume of correspondence, which was first published at the end of the nineteenth century and recently revised.

To close the morning session and transition to the topics of serotherapy and antibodies, Gabriel Gachelin (Université Denis-Diderot, Paris, France) presented the development of serotherapy against diphtheria in Europe from 1894 to 1898, through the examples of Germany, France and Denmark. Following the initial description of diphtheria by Bretonneau in 1826, Armand Trousseau quickly popularized the practice of tracheotomy as the best technique to alleviate the obstruction of the upper respiratory tract. In his own cumulative experience on 216 patients, tracheotomy allowed the survival of 46. His good reputation in pediatrics, and the fact that it was one of the few available methods able to “cure” laryngeal diphtheria at that time, allowed this practice to become known as a great success and to spread rapidly in France. It was, however, challenged by intubation in most other countries.

Research then focused on “false membranes” developed by the patient. The diphtheria bacillus was discovered by Theodor Klebs (1834–1913) in 1883 and cultivated by Friedrich Löffler (1852–1915) in Berlin in 1884. In 1888, the French Pasteurian physicians Emile Roux (1853–1933) and Alexandre Yersin (1863–1943) succeeded in isolating the toxin produced by the bacillus and demonstrating that it was responsible for the clinical signs of the disease. Two years later, the German physician Emil von Behring (1854–1917) and the Japanese microbiologist...
Shibasaburo Kitasato (1852–1931) succeeded, in the Koch’s laboratory in Berlin, in immunizing animals against diphtheria toxin and transfusing this acquired immunity to another animal by injection of the serum of immunized animals.11 In December 1891, they administered their serum for the first time to a child. After those first trials, serotherapy developed rapidly. Emile Roux with Louis Martin (1864–1946) at the Pasteur Institute in France, and Behring in Germany started immunization of horses and thus large-scale serum production began.

In collaboration with the young physician Auguste Chaillou (1866–1915), Roux and Martin performed a large clinical trial on 300 children from the Trousseau and Enfants-Malades hospitals and proved that serum was efficacious.12 The method was criticized because the placebo had been administered to children from lower class while the serum was injected to patients from middle and upper classes in a different hospital. There was, however, a clear decrease in death rate among treated patients, and identical results were obtained in Germany and publicized at the same time. The French and German series of successes prompted the worldwide use of anti-diphtheria serum as soon as 1895, leading in two years to a two- to 3-fold decrease in children mortality due to diphtheria. A rigorous randomized trial was only performed in 1898 by the Danish researcher Johannes Fibiger (1867–1928).13

To start the afternoon session, Hervé Watier (Université de Tours, France) presented a personal view of the history of immunology and succeeded in establishing other connections between Bretonneau and serotherapy. During his talk, he highlighted the main role of the French school of physiology in formulating the basic concepts of immunity. Bretonneau recognized Claude Bernard (1813–1878), founder of the experimental method, as a “prince of physiology.” Bernard was also a close friend to Alfred Richet (1816–1891), a surgeon who was the pupil of Velpeau (1795–1867), himself the pupil of Bretonneau. Another close relative to Bernard, Casimir Davaine (1812–1882), discovered the microbial nature of anthrax in 1863. Auguste Chauveau (1827–1891), a talented physiologist who followed Claude Bernard’s precepts, then discovered the virulent nature of cowpox in 1868. As early as 1866, Chauveau stated that virulent diseases always proceed from a special agent, the virus, and that the experimental method would soon discover it.

The studies by these physiologists preceded those by Louis Pasteur, which took place in the late 1870s. Not being a physiologist, Pasteur thought that the immunity conferred by attenuated living vaccines resulted from nutrient exhaustion in the organism, preventing the secondary growth of virulent germs. On the contrary, by studying the materno-fetal transmission of anti-anthrax immunity, Chauveau concluded in 1880 that the preventive inoculations had an effect on the humors and hypothesized that something nocive to the microbe was “added” during the course of immunization. On the same year, he also observed that natural immunity toward anthrax depended on the ovine breed, highlighting the role of the host rather than the microbe.

Elie Metchnikoff (1845–1916) then discovered phagocytosis in 1882 and others in Germany and Hungary discovered the “chemical potency” of blood serum (1884–1888). The next major advance occurred in 1888 when Charles Richet (1850–1835) and Jules Héricourt (1850–1835) discovered the passive transfer of immunity.14 Charles Richet, son of Alfred Richet, was trained in Claude Bernard’s lab and became professor of Physiology in the Faculty of Medicine of Paris in 1887. His friend Jules Héricourt, former military physician, was vice head of his laboratory. Inspired by the observations from Chauveau in sheep and applying the experimental method, they transferred blood from animals resistant to staphylococci (dogs) to susceptible animals (rabbits), and showed that blood from dogs already inoculated with Staphylococcus was particularly capable of protecting rabbits. They deployed immense efforts to transfer this therapeutic principle they called “hematotherapy” (despite the fact they used serum) to humans, for the treatment of tuberculosis. It was, however, the wrong choice, which left Emil von Behring and Shibasaburo Kitosato the great honor of discovering in 1890 the method of treating diphtheria by the transfer of immune serum, and the privilege to launch their own term, “Serumtherapie” (or serotherapy). Charles Richet remains known now for the discovery of anaphylaxis, for which he received the Nobel Prize in 1913, exactly one century ago.

Max Goyffon (emeritus professor, Museum d’Histoire Naturelle, Paris, France) has devoted himself to rehabilitation of the works by Césaire Phisalix (1852–1906) in the field of antivenomous serotherapy at the Museum. Phisalix was an army medical officer and a physiologist, and was recruited at the Museum on the suggestion of Auguste Chauveau to study whether the principle of serotherapy discovered by von Behring and Kitasato could be applied to toxic secretions (venoms). Together with Gabriel Bertrand (1867–1962), he was the first to discover in 1894 the antitoxic properties of blood serum from animals vaccinated with heated viper venom.15 Soon after, Albert Calmette (1863–1933) obtained the same kind of results, working on the venom of Naja (Cobra) at the Pasteur Institute in Saigon. Beyond the anteriority argument which followed, there was a clear divergence between the two groups in terms of serum specificity. Phisalix, working with his wife Marie (1861–1946), who was a physician and a zoologist specialized in venomous animals and venoms, was convinced of the specificity of the serum for a given snake venom.16 In contrast, Calmette thought his serum could be universal and his opinion benefited from the Pasteur Institute renown. The debate was eventually settled by a Brazilian physician, Vital Brazil (1865–1950), who demonstrated the non-universality of the serum, and thus the correctness of Phisalix’s theory.17 The antivenomous sera, which are still in use today, are distributed under a “polyvalent formula,” created by the mixture of specific antivenoms sera or the vaccination of animals with different venoms.

To close the meeting, Yvon Lebranchu (Université de Tours, France) presented the history of organ transplantation and discussed the role played by anti-lymphocyte serum in the development of allogeneic transplantation. First, he recognized in Elie Metchnikoff and Alexis Carrel (1873–1944) two pioneers of transplantation because, besides the discovery of phagocytosis, Metchnikoff initiated research on cellular immunity and antilymphocyte serum and Carrel developed programs about
transplant surgery and cell culture. Despite these pioneering studies, transplantation only started after the World War II. Initially, transplantation of organs was only possible between members of the same family, but the discovery of immunosuppressive drugs in 1963 allowed the first successes of transplantations between unrelated individuals. In 1967, subsequent studies concerning allogeneic recognition by T cells provided a rationale for the use of anti-lymphocyte globulins and the characterization of human leukocyte antigen (HLA), allowed additional progress. In theory, monoclonal antibodies such as murononab OKT3 (Orthoclone®) and modern immunosuppressive drugs have progressively taken the place of the anti-lymphocyte serum. Paradoxically, anti-lymphocyte globulins have never been withdrawn, and are currently widely used and one of the most important factors for transplantation success. This polyclonal serum is far from being specific, as it is directed against a wide array of lymphocyte antigens, and its mode of action is not entirely known. Its production reflects the glory days of serotherapy: human thymus extracts are injected to rabbits and the serum is drawn, and are currently widely used and one of the most important factors for transplantation success. This polyclonal serum is far from being specific, as it is directed against a wide array of lymphocyte antigens, and its mode of action is not entirely known. Its production reflects the glory days of serotherapy: human thymus extracts are injected to rabbits and the serum is collected, pasteurized and packaged (Fig. 1).

The symposium ended with the inauguration of a stele of Pierre-Fidèle Bretonneau, created by the artist and sculptor Michel Audiard, in the square “La Perraudière” at Saint-Cyr-sur-Loire. This inauguration took place in the presence of Jean-Yves Couteau, Dr Christophe Leisner, current owner of Palluau, Bretonneau’s house and president of the association “Saint-Cyr-sur-Loire, Hommes et Patrimoine,” Prof. Daniel Alison, Vice-Dean of the Faculty of Medicine of Tours, Prof. Marc de Ferrière le Vayer and Prof. Hervé Wavier.

In the evening, a public lecture was given by Patrice Debré (Université Pierre-et-Marie-Curie, Paris, France) to detail the main historical steps of infectious diseases, microbiology and immunology, which placed Bretonneau and the specificity of typhoid fever and diphtheria in perspective. He spoke of the work of Ignace Semmelweis (1818–1865) and Joseph Lister (1827–1912) in asepsis, Louis Pasteur’s (1822–1895) establishment of the basis of the molecular microbiology, Elie Metchnikoff’s work in cellular immunity, and von Behring and Kitasato’s contributions to serotherapy. The second part of the conference was dedicated to the co-evolution between man and microbe, and the conflict between the immune system and the constantly evolving microbial environment. In the 1970s, these conclusions led Leigh van Valen (1935–2010) to develop his theory of the Red Queen, a reference to the character in Lewis Carroll’s book Alice’s Adventures in Wonderland. In this eternal conflict, specificity plays a major role, requiring the adaptation of each to the specificity of the other.  

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Figure 1. Stele of Pierre-Fidèle Bretonneau created by Michel Audiard, Square “La Perraudière” at Saint-Cyr-sur-Loire.
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