2 Most Common Allergic Diseases: Historical Reflections in Understanding

Anaphylaxis

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Abstract

The term anaphylaxis was coined by Charles Richet and Paul Portier when they tried to immunize dogs with actinia extracts, but after a repeated injection of a small amount of the toxin the dog died within 25 min. The new term rapidly spread all over the world. The discovery of the phenomenon of anaphylaxis showed that by immunization not only protection but also harmful events could be induced. For this discovery Richet received the Nobel Prize in 1913, but he still believed the condition of anaphylaxis was a lack of protection to the poisonous effect of the substance. Already earlier similar clinical phenomena had been observed but not well described. A major breakthrough in understanding the pathophysiology came through the experiments of Dale and Laidlaw who showed that the newly discovered histamine was able to induce quite similar symptoms to anaphylaxis. For decades reactions mimicking anaphylaxis but without involvement of the immune systems were called ‘anaphylactoid’, ‘allergy-like’ or ‘pseudo-allergic’. Since the new definition of the World Allergy Organization (WAO) anaphylaxis is defined on the basis of clinical symptoms independent of pathomechanisms involved: one distinguishes be-

tween allergic and non-immune anaphylaxis. Epinephrine (Adrenalin) was soon recognized as treatment of choice of this dramatic condition.

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Although the term ‘allergy’ was coined in 1906 by Clemens von Pirquet [1], it was the short lecture given by Paul Portier and Charles Richet [2] on February 15, 1902, at the Société de Biologie in Paris that is regarded by many authors as representing the birth of modern allergology with the discovery of the phenomenon of anaphylaxis. The phenomenon itself was not totally new. We find descriptions of similar and sometimes dramatic and untoward reactions in ancient history [see the opening two chapters by Ring, this vol., pp. 2–20], especially with regard to the famous Pharaoh Menes, who supposedly died in 2641 BC after being stung by a wasp, hornet or honey bee [3, 4; see the chapter by Ring, this vol., pp. 2–14].

The first detailed description of an unusual reaction to the sting of a honey bee was found by Ulrich Müller [5] in an article written in Latin (‘De curiosis post apium ictus symptomatibus’) by Udalricus

Fig. 1. Charles Richet.

Fig. 2. Paul Portier.

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Staudigelius (Ulrich Staudigl), who was a monk at the Benedictine monastery of Andechs in Bavaria, situated south-west of Munich. In France in 1765, Dr. Desbrest described a 30-year-old man who was stung on his eyelid by a honey bee while he was working in the garden; a short time later he collapsed and died. Similar case reports from the 19th century of fatal insect stings have been reported in Europe and the USA [6]. A first experimental description of this phenomenon goes back to experiments done on rabbits with injections of ovalbumin by François Magendie, who noted that some rabbits died after the second or third injection [7]. These reactions were generally attributed to some poisonous substances or toxin given to the animals.

The Voyage on the Yacht *Princesse Alice II*

The French physiologist Charles Richet (1850–1935; fig. 1), son of Alfred Richet, professor of clinical surgery in Paris, became interested in the toxic effects of *Physalia* (Portuguese man o' war). He had studied medicine in Paris and received his doctoral degree in 1869 and his doctor in science in 1878. From 1887 he worked as a professor of physiology at the faculty of medicine in Paris and published a variety of papers on physiology, thermoregulation, se-

rotherapy of tuberculosis and the effect of injections of proteins on the chemical constitution of bodily fluids as well as electrolytes.

Together with Héricourt he described possible protective effects of the blood of animals infected with staphylococci [8]. This was 2 years before the finding made by Emil von Behring who, together with Shibasaburo Kitasato (1852–1931), observed this type of immunity with diphtheria toxin and the production of toxin-neutralizing 'antitoxin' in animals [9].

In 1898, Héricourt and Richet [10] studied the effect of eel serum in dogs, observing that a second or third injection made the dogs sicker, sometimes severely so. However, Richet later stated that he did not really recognize this phenomenon worthy of deeper investigation.

Paul Portier (1866–1962; fig. 2) was born in Bar-sur-Seine in France and began his career as a clerk in a country registry [11]. Through his interest in entomology and general natural science, he came to the faculty of science and medicine in Paris in 1889. In 1920, he was appointed professor of comparative physiology at the Sorbonne. Portier was a personal friend of Prince Albert I of Monaco, who was an enthusiastic oceanographer; thus, he was regularly invited to participate on cruises organized by the prince aboard the yacht 'Princesse

Fig. 3. The yacht 'Princesse Alice II' in front of Monaco.

Alice II' (fig. 3). Charles Richet was also invited on one of these cruises, and they travelled via the Mediterranean Sea to the Canary Islands, Madeira and Cape Verde Islands (fig. 4). Due to his interest in oceanographic studies, Prince Albert founded the Oceanographic Institute in Monaco, which today hosts a multitude of objects attractive to visitors.

During this particular cruise the prince and G. Richard suggested to Charles Richet and Paul Portier that they study the toxic properties of certain *Physalia* species found in the South Seas, using a special laboratory on the boat (fig. 5, 6) [12]. Richet and Portier later decided to continue their studies in Paris, but could not obtain any *Physalia*. Thus, they continued with extracts of another species of *Actinia*:

On board the prince's yacht experiments were carried out proving that an aqueous glycerin extract of the filaments of *Physalia* is extremely toxic to ducks and rabbits. On returning to France I could not obtain any *Physalia* and decided to study comparatively the tentacles of actinaria, which resemble *Physalia* in certain respects and are easily procurable. Owing to the kindness of Y. Delage I was able to obtain a large quantity; the tentacles, cut close to the body, were placed in glycerin and thus we had in Paris several liters of an intensely toxic fluid, the glycerin dissolving and extracting the active principle. [13]

Fig. 4. Travel route of the 'Princesse Alice II' via the Mediterranean Sea to the Canary Islands, Madeira and Cape Verde Islands [12].

One fraction of these *Physalia* extracts contained a substance which was called 'hypnotoxin', which induced very painful urticarial reactions after contact with the skin, coupled with a drop in body tempera-

Fig. 5. The laboratory on board the yacht 'Princesse Alice II' of Prince Albert I of Monaco (1848–1922). Paul Portier is to the left side of the table, on his right is Dr. Richard [12].

ture and somnolence. The *Actinia* species was *Ane-
monia sulcata*. Richet described the toxic properties
of his extract:

One dog (Amphitryon) of 31 kg received 1.6 cc on 8 March 1902 of this liquid (corresponding to 0.8 cc of tentacles) and he died on the third day. If one admits that only 10% of the extract of the tentacles corresponds to solid material, 0.08 g are sufficient to poison the dog weighing 31 kg; therefore the minimal quantity per kg dog to produce fatal effects are 0.0025 g out of the total of extractable substances of the tentacle. [14]

Richet described the toxic effects of these extracts very precisely in several dog experiments and concluded that there were two different toxins, one which he called 'thalassine', which induced violent pruritus and urticaria but was not fatal. The other one he called 'congestine', which led to an intestinal and cardiovascular congestion with finally lethal outcome.

The aim of the studies was to immunize the dogs against the toxin. However, the opposite in fact occurred. They noted that dogs, having previously received small amounts earlier, reacted with more symptoms at the second or third injection. The critical illustrative experiment was performed on a dog called Neptune which Richet [15] described in his article from 1904:

Fig. 6. Handwritten notes from the protocol book used by Charles Richet and Paul Portier regarding the first experiments from January 15–19, 1902 [12].

Fig. 7. Sir Henry Hallett Dale. Photo taken at the Honorary Doctor Award in Graz, Austria, 1954.

Je prendrai notamment pour exemple le chien *Nep-tune*, gros matin à poil ras, très vigoureux, qui, après avoir reçu, 22 jours auparavant la dose de 0,10 qui ne l'avait presque pas rendu malade, reçoit du même liquide la même dose de 0,10. Alors aussitôt quelques secondes après que l'injection a été terminée, il est extrêmement malade: la respiration devient angoissée, haletante. Il peut à peine se trainer; se couche sur le flanc, est pris de diarrhée et de vomissements sanguinolents. La sensibilité est abolie, et il meurt en vingt-cinq minutes.

Or, chez des chiens non injectés antérieurement, des doses dix fois plus fortes, 1 cc par kilogramme, ne tuent pas les animaux avec cette même rapidité. [15]

Portier wrote about the experiment in the dog Neptune in which the phenomenon later called 'anaphylaxis' was first seen. This strong and healthy animal had received a low dose of actinium toxin on January 14 and 17, 1902 [16–18], which was tolerated with 'almost no reaction'. After 22 days, on February 10, he received the same dose when in excellent general condition. However, some seconds after the injections the dog began to gasp and to wheeze, the animal was agitated, was not able to stand and lay on his side, developed bloody vomiting and died within 25 min.

When notified by Portier, Richet recognized immediately that this surprising phenomenon was new ('C'est un phénomène nouveau, il faut le baptiser!'). In trying to find a name he wanted to express 'lack of protection' and should have used the word 'aphylax-

is' (from the privative alpha in Ancient Greek grammar, meaning 'negation'). However, for euphonic and rhythmic reasons he preferred 'anaphylaxis' [15], and this term rapidly spread all over the world.

In the reminiscences of Paul Portier and Charles Richet there is a slight discrepancy with regard to the number and timely sequence of injections the dog Neptune actually received. According to Richet there were two injections within an interval of 22 days. However, Portier states that the dog received the first injection on January 14 followed 3 days later by another low dose, which was tolerated well, and only then, 22 days later on February 10 – on which there is total agreement – the dramatic reaction occurred.

The researchers had a similar experience with another dog called Galathee, who received 0.05 ml of the actinotoxin on January 14, and 0.1 ml on January 22, which was tolerated with 'almost no reaction'. He was in perfect health on February 10 when he received an injection of 0.12 ml/kg of actinotoxin and 'immediately produced vomiting of mucus and blood, some bloody defecation and very marked stupor'. These symptoms became worse in the following hours and he died in the night.

The small discrepancies concerning the details of the first experiment are obviously of no importance with regard to the discovery of the new phenomenon. The term anaphylaxis was – as always in medi-

cine – only accepted with some criticism. Especially Emil von Behring remarked in 1914 (note that it was the beginning of World War I) that Richet's report described nothing else than what he had previously called 'hypersensitivity' [19].

Untoward reactions to foreign, heterologous serum injection had been observed earlier. The most tragic event was probably published by Robert Langerhans (1859–1904), a pathologist in Berlin, who injected 1.2 ml of Behring's 'Heilserum' subcutaneously into his almost 2-year-old child on April 7, 1896. The child died within 7 min in the presence of the helpless father [20]. By 1910, 41 fatalities after injection of diphtheria serum had been described [21].

Regarding pathophysiology, Richet still believed that the dramatic symptoms elicited by the second or third injections represented an increased toxic effect. Interestingly, he obviously did not notice a difference in the quality of symptoms between the injection of a high dose of the toxin and the symptoms of 'anaphylaxis' after repeated low doses. This was correctly commented on by Paul Kallós and Kallós-Defner [22] in 1937.

In 1913, Richet was awarded the Nobel Prize. In his address on receiving the award, he humbly stated:

The discovery of anaphylaxis is not at all the result of thinking, but of simple observation, almost accidental. It had no other merit than that of not refusing to see the facts which presented themselves before me completely evident. [13, 23]

There is a movie clip of a very emotional address given by the aged Paul Portier at the World Congress in Paris on October 19, 1958 (online suppl. movie 1, see www.karger.com/chial100_movie1).

The story of the discovery of anaphylaxis also illustrates the importance of terminology. It remains an object of speculation whether the findings of Richet and Portier would have gained such rapid interest in the scientific community without the new name.

In the following decades anaphylaxis was regarded as an experimental phenomenon after the 'artificial' injection of proteins. The similarity to human disease was only slowly recognized. When they coined the term 'atopy', Coca and Cooke clearly distinguished this 'natural' occurring hypersensitivity

from the 'artificial' symptoms of anaphylaxis in animal experiments.

In his Nobel address, Richet clearly stated:

These two factors – (a) increased sensitivity to a poison after previous injection of the same poison and (b) an incubation period necessary for this state of increased sensitivity to develop – constitute the two essential and sufficient conditions for anaphylaxis. [13]

Earlier on, through the works of Louis Pasteur, Robert Koch, Emil von Behring and others, immunization was only connected with a positive and desired effect of protection against pathogenic organisms. The discovery of the phenomenon of anaphylaxis showed that by immunization harmful events and severe disease could also be induced. Similar observations regarding the example of serum sickness then led Clemens von Pirquet to coin the term 'allergy' in order to bring some clarity to these seemingly contradictory phenomena [1].

Pathophysiology

During the search for an active substance to induce the symptoms of anaphylaxis it soon became clear that it was not the effect of the toxin itself, but rather some principle in the organism. The credit for the elucidation goes to Sir Henry Dale (1875–1968; fig. 7), born in London, who studied at Trinity College in Cambridge and began his career in neuroanatomy together with J.N. Langley. He had been working since 1903 in the laboratory with E.H. Starling at the University College in London, from where he visited Paul Ehrlich in his laboratory in Germany. In 1904, he became director of the Wellcome Physiological Research Laboratories. His studies covered many fields of pharmacology, physiology and biochemistry. In 1910, he studied the physiological action of histamine together with his coworker, P.P. Laidlaw, and developed the concept of histamine shock as a basis of anaphylaxis [24]. They clearly described the effect upon the smooth muscle of different organs, as well as an effect (mildly stimulating) on cardiac muscle, but the absence of an effect on skeletal muscle. They noted the similarity to the effect of Witte's peptone after several injections:

This symptom complex has recently acquired interest in another direction. Biedl and Kraus drew attention to the identity of the symptoms of anaphylactic shock with those produced by intravenous injection of 'peptone' which, as we have seen, are again very largely identical with those of β -iminazolyethylamine. The correspondence cannot yet be regarded as sufficient for theoretical speculations, and we content ourselves with recording, as a point of interest and possible significance, the fact that the immediate symptoms with which an animal responds to an injection of a normally inert protein, to which it has been sensitized, are to a large extent those of poisoning by β -iminazolyethylamine. [24]

In later works Dale also noticed that anaphylactic antibodies had to attach themselves to cells before reacting with antigen. This was more clearly established by Prausnitz and Küstner [25] in 1921 when they were able to transfer individual hypersensitivity to fish via serum from one allergic individual to another non-allergic individual.

The French physiologist Nicolas-Maurice Arthus (1862–1945) reported that after repeated injection of sterile horse serum into the skin increased inflammatory reactions with redness, edema, bleeding and necrosis could be observed. He called this 'local anaphylaxis' and it later became known as 'Arthus phenomenon' [26].

In the USA, M.J. Rosenau (1869–1946) and John F. Anderson (1873–1958) established animal experiments, particularly in the guinea pig [27]. Laboratory notes of the American pathologist Theobald Smith (1859–1934) were given to Paul Ehrlich (1854–1915) when he was visiting America. Recognizing the value of these experiments, Ehrlich gave the notebooks to Richard Ernst Wilhelm Otto (1872–1950) and asked him to continue the experimental work. Otto finally published his and Theobald Smith's results and coined the term 'Theobald Smith's phenomenon' for anaphylactic shock in guinea pigs [28].

In the years following the discovery of anaphylaxis some researchers noticed that similar symptoms can also be elicited in animals that had not been previously immunized, as well as through the direct injection of histamine. The term 'anaphylactoid reaction' was used for this non-immunological type of induction of symptoms [29–31; see also the chapter by Ring, this vol., pp. 46–52]. A direct histamine re-

lease evoked by several substances (e.g. codeine, dextran) in certain rat strains or gelatin blood substitutes led to the development of the concept of pseudo-allergic reactions by Paul Kallós [22, 32, 33].

Only at the beginning of the 21st century did the nomenclature task forces of both the European Academy of Allergy and Clinical Immunology (EAACI) and the World Allergy Organization (WAO) come to a new terminology and define 'anaphylaxis' on the basis of clinical symptoms independent of the pathomechanism evolved in elicitation [34]. Thus, one now distinguishes between an allergic and a non-immune anaphylaxis, formerly called a 'pseudo-allergic reaction'.

Today, anaphylaxis seems to be increasing in prevalence all over the world, maybe due to the pollen-associated food allergies which follow the rising prevalence of atopic diseases. Since anaphylaxis describes a syndrome of clinical symptoms involving several organ systems with varying intensity, attempts have been made to classify the severity of this reaction using so-called severity scales, as proposed by Mueller [35] or Ring and Messmer [36], which are the most commonly used.

While we know a lot about the events in IgE-induced sensitization and IgE-induced mast cell activation and degranulation, there is still only limited knowledge on the final pathophysiological events at the smooth muscle and microcirculatory level which finally lead to the fatal symptoms.

Epinephrine (Adrenalin) as a treatment of choice has been known for more than a hundred years. There is no new therapeutic substance on the horizon with a less dangerous or narrow therapeutic profile between beneficial effect and pharmacological side reaction [28, 37; see also the chapter by Starke, this vol., pp. 288–301].

Guidelines for acute treatment of anaphylaxis have been developed at the national [38] and international level [39]. The complex interactions between elicitors, pathophysiology, pharmacotherapy and general measures have to be explained to the patient together with prescribing emergency medication, including the epinephrine autoinjector. It has been shown that educational programs ('anaphylaxis school') may be helpful in this context [40].

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