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The history of the idea of allergy

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Abstract

About 100 years ago, a young paediatrician understood that the function of the immune system should be rationalized not in terms of exemption of disease but in terms of change of reactivity. He coined a new word to represent such an idea: 'allergy': the first contact of the immune system with an antigen changes the reactivity of the individual; on the second and subsequent contacts, this change (or allergy) can induce a spectrum of responses from protective (literally, immune) to hypersensitivity ones. The idea was at first hardly understood by the scientific community because it undermined the essentially protective nature of the immune response as it was defined. Nevertheless, in the next years, the growing clinical evidence led to the acceptance of this new point of view, but not of the new word, at least not unconditionally. The original significance of the neologism 'allergy' became perverted and limited to describe hypersensitivity conditions. Perhaps because of the corruption of the term, today 'allergy' does not have a well-delimited significance among health professionals. Furthermore, the word has long ago escaped from physicians and gone to the streets, where it is popularly used also as synonymous with antipathy and rejection. This vulgarization of the term 'allergy' has significantly increased its imprecision.

Both the idea of 'allergy' and the word itself are fundamental aspects of the medical discipline of clinical immunology. The term constitutes the prefix of other important medical words and has actually given its name to an entire medical specialty. But, despite the worthy efforts of eminent authors such as Samter (1), Silverstein (2), Simons (3), Kay (4), Jackson (5), Jamieson (6), and others in reviewing its history and meaning, few allergists and clinical immunologists know them. Perhaps it would be a good moment to ask ourselves, is it possible to know where we are going if we ignore where we come from?

Given the unconstructive impact of a negative answer, and in order to fill this gap in our knowledge, we propose to review in detail the origin and evolution of this important idea. We hope that this knowledge will provide all professionals interested in what now is known as 'allergic diseases' with the background necessary to advance in clinical and research work.

Inception

In the late nineteenth and early twentieth centuries, a notable group of scientists led by Louis Pasteur, Paul Erhlich, Elie Metchnikoff, Jules Bordet y Emil A. Von Behring described a novel system whose function was to defend the body from attacks by microorganisms. They called it the immune system (literally, a 'system that exempts' from the disease). The immunity provided by this system entailed an absolute protection against a noxious agent, or at least the occurrence of some process strictly advantageous to the host. Nobody could imagine then that it could harm the host it protects.

Meanwhile, the process of industrialization of Europe and North America and the new antitoxin parenteral treatments and vaccines caused new diseases and strange reactions that physicians could not explain. Few ones were able to suspect the implication of immune system in these new disorders, and the Viennese paediatrician Clemens von Pirquet Freiher (Fig. 1), more interested in his patients' clinical problems than in laboratory experiments, was one of the first to state clearly this possibility.

The idea first came to von Pirquet when he was a paediatric resident at the Universitäts KinderKlinic in Vienna. He thought that the immune system played a role in the pathophysiology of infectious diseases and determined the patent lesions of the disease, or at least a large part of them, apart from the evident role of microorganisms and their toxins. On 2 April 1903, and in collaboration with his co-worker Bela Schick, von Pirquet wrote a preliminary report of his theory

Figure 1 Clemens von Pirquet (1874–1929), creator of the idea of allergy. The photograph was taken in 1906, the same year that he published his seminal article explaining his idea of allergy and proposing a new terminology. Von Pirquet worked on his theory of allergy only between 1903 and 1911, although in 1927 he published a final review on the subject. Photograph from the Österreichische Gesellschaft für Allergologie und Immunologie.

entitled *Zur theorie der infektionskrankheiten* ('On the theory of infectious disease') and put it in a sealed envelope that was deposited in the Imperial Academy of Sciences in Vienna in order to establish priority. His caution advised him to delay its public reading to allow him to further develop his ideas.[1] The report contained a revolutionary idea: the cardinal signs of diseases caused by infections were not only the result of the action of microorganisms and their toxins, but also the body's response (antibody) against them (7). The strongest evidence supporting this theory was the resemblance between many spontaneous and experimental diseases of external origin in incubation time and disease manifestations. The incubation time was the time that elapses before the formation of antibody. The idea implied that immune system, a system essentially protective, could harm the host that housed it.

But von Pirquet did not wait very long to publish his new theory. On June 25 in the same year, the French immunologist Nicolas Maurice Arthus published an eye-opening experiment (8): after the fourth subcutaneous injection of horse serum in rabbits, a local oedematous reaction occurred; after the fifth, it became purulent; and after the seventh gangrenous. In other words, an increased specific sensitivity followed repeated injections of a foreign protein that was primarily nontoxic. More importantly, Arthus recognized the relationship of the increased sensitivity with the anaphylaxis of Charles Richet, published the year before (see below) (9). This observation spurred von Pirquet and Schick to publish only 9 days later, on July 4, their preliminary note on infectious diseases (10).

Over the next 2 years, von Pirquet and Schick extended their work to a common systemic complication appearing 8–12 days after some children received a first dose of an antiserum which they named serum sickness (or 'disease caused by the serum'). Antitoxic sera were introduced in therapeutics in 1891 by von Behring and Kitasato and systemic complications quickly appeared that were interpreted as the results of several nonimmune causes. Von Pirquet and Schick reached another interpretation and concluded that serum sickness was due to a hypersensitivity reaction provoked by antibodies to the antitoxin. As in their earlier study of the incubation time of infectious diseases, they focused on the 'time factor', that is, the interval between the first injection and the onset of serum sickness or time necessary to produce the antibodies, which was accelerated after repetition of the injection. The serum sickness was induced 'by the collision of antigen and antibody'. All these ideas were discussed in depth in the book *Die Krankheit Serum* ('the serum sickness') published in 1905 (11).

Apart from the above-mentioned experiments performed by Arthus and Richet, other experimental observations helped to shape the new ideas of von Pirquet. In 1903, Hamburguer and Moro found precipitating antibodies in human blood following the administration of antisera. Theobald Smith noted in 1903 that guinea pigs used to standardize diphtheria toxin (injected with mixtures of toxin and horse serum) often died when injected several weeks later with normal horse serum; one year later, Paul Ehrlich put R. Otto to work in what he termed the 'Theobald Smith phenomenon' (12). In 1906, Milton Rossenau and John Anderson (13), in an attempt to understand the cause of the adverse reactions of some patients to diphtheria antitoxin, studied the effect of repeatedly injecting horse serum into guinea pigs.

At this point, it became clear to von Pirquet that the existing terminology was inadequate. The concept of immunity proceeded of a time when nothing was known about hypersensitivity and when the immune system was considered purely protective. It was necessary to start again from the beginning. So, von Pirquet further developed his theory and published it in 1906 in a now classic article of just two pages entitled *Allergie* (14). In it, he gave reasons to explain his theory and proposed the new terminology, the germinal theory of allergy (Fig. 2). He noted that the exposure of the body to a substance resulted in the production of antibodies that induced a change in subject-specific reactivity to the substance to which he called 'allergy' (from the Greek *allos*, meaning 'other or different', and *ergia*, meaning 'energy or action', in the sense of 'change in reactivity or capacity to react'). Such change could be protective, so that the subject does not manifest symptoms in response to that substance (i.e. a real immune response, in the etymological and original sense that such a term had at first, the exemption of the

[1]Five years later, on 13 February 1908, von Pirquet requested that the envelope be opened and the contents read. This was done at a meeting of the Academy's Division for Mathematics and Natural Sciences.

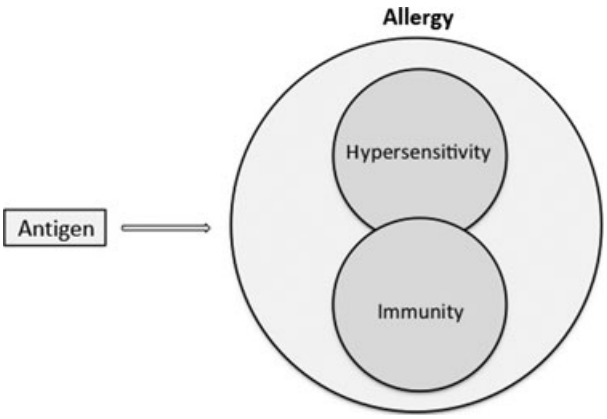

Figure 2 Diagram of the original idea of 'allergy' developed by von Pirquet. When the individual contacts with an antigen (germs, pollens, foods, etc.), a change in reactivity occurs. This change ('allergy' according to von Pirquet) can induce a protective or harmful response: the protective one renders the individual immune to the antigen, that is, he does not manifest any symptom or signs after exposure to that antigen, and the harmful one causes signs and symptoms after such a contact. The first response is known as 'immunity' and the second as 'hypersensitivity'. Both are the ends of the same physiological process and can overlap.

disease) or be harmful and cause symptoms and signs of the illness (in the sense of hypersensitivity). Then, immunity (protective) and hypersensitivity (harmful) were two ends of the same physiological process (the response of the host immune system or 'allergy') and not exclusive. In this second form of immune reaction, von Pirquet included cases hitherto considered idiosyncratic (asthma, hay fever and urticaria) and anomalous responses of some subjects to vaccines or antisera. According to this idea, in the first decades of the twentieth century, many immunologists interchangeably used 'allergy' and 'immune reaction'.

In 1911, in his final work about allergy,[2] von Pirquet wrote a monograph devoted to elaborating his theory (15), and accumulated an extensive amount of experimental data and clinical findings relating to changes in reactivity. Through this information, he showed that the 'allergic response' is capable of change through the time. Additionally, von Pirquet made it clear that he intended the term 'allergy' to be applied only to immunological reactions, something nor explicitly stated in his original definition.

Competition

The revolutionary idea of Pirquet was developed at a time when immunology was establishing its identity as science. In that historical moment, two principles were considered fundamental: the essentially protective and immutable characters of immune responsiveness. So, it is not surprising that Pirquet's hypothesis experienced a brief and unsuccessful reception from many of his contemporaries. We will only discuss a few early examples.

In 1908, Charles Bolduan, a German bacteriologist working in New York, indicated that von Pirquet's theory about the pathogenic role of antigens and antibodies in serum sickness was 'untenable' (16). When von Pirquet's monograph of allergy was revised in *The Lancet* in 1911, the reviewer considered the term 'not a happy combination' (17). Paul Ehrlich used an unkind pet metaphor when he referred to the terms 'allergy' and 'allergen': 'Pirquet was laying two research eggs which might with any luck hatch out into something later on' (cited by John Freeman in ref. 26). Richet rejected the new term and regarded it as unnecessary: 'Pirquet and Schick have termed the reaction of an organism to a foreign substance *allergy*; but it does not appear necessary to me to introduce this word in addition to the word anaphylaxis' (18). And many more criticisms were to follow in the next few decades.

Before we continue our discussion, it is worth analysing Richet's criticism. Some years before von Pirquet published his new idea of allergy, the French physiologist Charles Richet and his colleague Portier studied the pathological effects of the toxins of marine animals in dogs. In order to cut costs, they re-administered the toxin to dogs that had survived the first injection, and observed some sudden and impressive deaths. They evaluated them and found that they were not exceptional reactions, but obeyed a fixed pattern. They called them 'anaphylaxis' (or contrary to '*phylaxis*' or protection) (9). At first, Richet linked this phenomenon to the immune system, but soon he sought other explanations. He was obsessed with the nature of self, humoral personality, Darwinism and eugenics. Actually, Richet was not studying 'dogs' reactions' to toxin, but how individual dogs reacted to it (19). So, he finally saw anaphylaxis as a process that protected the chemical integrity of a species against potential corruption by exogenous agents. As we noted before, it was Arthus who really recognized the relationship of increased immune sensitivity with anaphylaxis. Von Pirquet and Richet's perspectives about the topic were very different, but the latter was initially easier to understand.

About 1910, hardly anyone had really understood the full scope of 'allergy', the new idea about the functioning of the immune system and its involvement in human disease, a point of view much broader than the initial purely experimental phenomenon of anaphylaxis. Instead, the scientific community only saw two terms related to the new idea of the potential detrimental effect of the immune system and with difficulty could distinguish between them. Von Pirquet himself, in his monograph of 1911, was aware that his idea of allergy had not been understood (15).

In this context, the notion of allergy remained marginal while, by contrast, interest in anaphylaxis increased. During the first 15 years of the twentieth century, and as a result of the simplicity of the phenomenon of anaphylaxis compared with the more complex idea of allergy, many more articles and books were published on the first subject than on the second. Some renowned authors such as J. Bordet, A. M.

[2]In 1927, he published a review on history of allergy at the request of the editor of the *Vienna Medical Journal*. But after 1911, von Pirquet's research interests changed and did not advance further in his theory of allergy.

Beshredka, A. Lumière or M. Blighse, for example, echoed the huge popularity that the term 'anaphylaxis' enjoyed at that time (5).

Misunderstanding and triumph

Paradoxically, in 1913 when Richet received the Nobel Prize for his work on anaphylaxis, the term 'allergy' began to make an impact and attracted the attention of clinicians and scientists, as reflected in its increasingly common appearance in different articles. Titles such as 'bacterial allergy' or 'allergic to tuberculin', faithful to the original idea of allergy, gained approval. The linguistic and scientific tides began to change and 'allergy' increased in popularity. But the increasing acceptance entailed paying a price: the original meaning of 'allergy' was misunderstood and, in consequence, perverted.

Perhaps the first important indication of this misunderstanding may date from 1912, when Ludwig Hektoen, an influential American pathologist, published a famous article in which he used the terms 'allergy' and 'anaphylaxis' in an almost interchangeable way (20). Three years later, B. P. Sormani, a Dutch serologist, used allergy as an abbreviation for hypersensitivity to pollen extract in an article published in *The Lancet* (21). And from the late 1910s, the word 'allergy' was already common in the titles of books and journals as a way of describing all those other adverse reactions of the immune system, and progressively exceeded 'anaphylaxis'. Furthermore, numerous allergic clinics appeared around Europe and North America. At that time, the perversion of its original meaning was complete: it stopped being the reactivity change and came to represent the dark side of immunity. Perhaps, the most important conclusion here is that the medical community finally seemed to understand the not-always protective character of the immune system, in spite of an incorrect use of the new terminology. English-written articles using the Pirquetian sense of the word 'allergy' completely disappeared in 1945, whereas from the 1920s there was a rapid emergence of articles using the new and perverted idea of 'allergy', a point of view that persisted over the time (Fig. 3).

As a consequence of this misunderstanding, the use and meaning of the word 'allergy' underwent many vicissitudes in the following decades. These can be easily summarized in the several attempts at classification of the new and diverse medical terms, besides allergy and anaphylaxis, which appeared in the first decades of the twentieth century in the context of clinical immunology: hypersensitivity, idiosyncrasy, contact dermatitis, hay fever, serum sickness and hypersensitivity to bacteria and their products.

The first attempt of classification was performed by the Hungarian bacteriologist Robert Doerr (22). He adopted the general term of 'allergy' to all of these pathological entities and classified allergic phenomena into those exhibited against antigenic substances and those against nonantigenic ones, for example drug idiosyncrasies. However, in a later version, Doerr went back to a more limited view of its meaning and excluded drug idiosyncrasies from the concept of allergy (23).

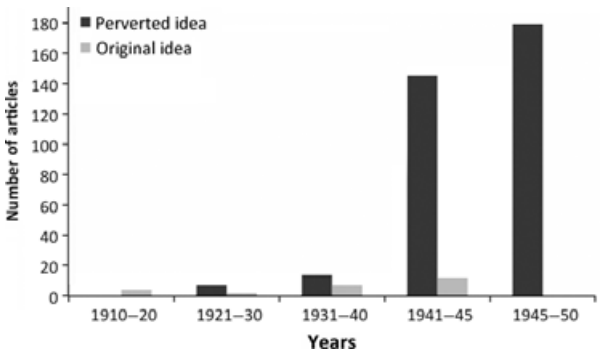

Figure 3 Number of medical articles published in English with the original (von Pirquet's) and perverted ideas of 'allergy' during the period 1910–1950. In *y*-axis is shown the number of articles using the word 'allergy' as a key term. The *x*-axis shows the period studied. In 1941–1945, there is a very significant increase in articles using the perverted idea of 'allergy'. In contrast, from 1945, no articles using the original idea of allergy were published in English (Source: PubMed, 2012).

From America came the answer to this first classification in form of several articles published between 1923 and 1926 by Arthur F. Coca and Robert A. Cooke (24, 25). They preferred to employ the word 'hypersensitiveness' as a general term for all these phenomena and advised the abandonment of the term 'allergy' on the basis of its then abundant and conflicting uses. They suggested subdividing hypersensitiveness into normal (contact dermatitis and serum sickness) and abnormal (anaphylaxis, hypersensitiveness of infections and atopy[3]). The normal type appeared in a high percentage of normal individuals, never in animals, and their development in one or another individual depended on quantitative differences. The abnormal type only appeared in certain individuals, both in human beings and in animals, and their presence in a one or another individual depended on qualitative differences.

In spite of the enormous influence of Coca and Cooke, the word 'allergy' was not forgotten. On the contrary, the word was used increasingly and more and more articles were published in the Western world using the term 'allergy' as synonymous with hypersensitiveness reactions. But the classification of these American investigators had a notorious effect on the interpretation of allergy. Because of their clear distinction between abnormal and normal hypersensitiveness (which included anaphylaxis) and because anaphylaxis had

[3]Within this group of 'atopy' (literally, 'strange disease', coined by Professor Edward Perry at request of Coca), they placed hay fever and asthma. This was mainly because of the usual absence of demonstrable precipitins in the blood, the strongly familiar character of atopy, their possible appearance in response to nonantigenic substances (like pollens), the impossibility of achieving a complete desensitization (unlike anaphylaxis) and the nonexistence of conclusive evidence of the possibility of it being transferred passively. All the reasons were a consequence of the scarce technical means available in 1920s. Later, in 1947, when emerging evidences convinced Coca of the anaphylactic nature of hay fever, asthma and allied conditions, he publically abandoned the term 'atopy'.

been defined and studied only in experimental animal models, the medical community began to use 'allergy' as equivalent to hypersensitivity diseases of humans and 'anaphylaxis' as equivalent to hypersensitivity diseases in experimental animals. This segregation was responsible in part for the consideration of anaphylaxis as an animal phenomenon with doubtful implications in humans until well into the 1940s. Investigations performed during the 1930s and 1940s made it clear that 'human allergy' and 'animal anaphylaxis' shared the same basic immune mechanisms, but the use of the term 'allergy' remained for decades restricted mostly to human diseases.

From the beginning of the 1930s, the new word coined by von Pirquet was completely introduced in the medical terminology. To this success also contributed its appeal. John Freeman compared the word 'allergy' with a beautiful woman (26); in fact, he attributed its success more to its attractiveness than to its intrinsic value as scientific term. This evident beauty and appeal of the word captivated not only physicians but also the general public. Soon, allergy escaped from scientific and clinical arenas and went on the streets, where people began to use it to express any apparent adverse reaction to anything. Furthermore, people used the word to express antipathy, rejection or aversion. 'Allergy' appeared in newspapers, novels and songs with both medical and nonmedical significances. Even kings and queens suffered allergic diseases (27). 'Allergy' became a fashionable word.

Also from the 1930s, the definitive settlement of the idea of allergy in medicine translated into the formation of professional organizations. A new medical subspecialty called allergology became established. It was made up of physicians diagnosing and treating hay fever, asthma, contact dermatitis, drug reactions, adverse reactions to food, serum sickness and many other emerging pathologies. Terms such as 'allergic', 'allergological', 'allergopathy', 'allergist' and so on became integrated in the clinical practice of these professionals. Soon, working groups of allergists began to appear first in USA and then in UK.

In the USA, physicians and patients had already established hay fever clinics and associations in the late nineteenth century. In 1923 and 1924, the Western Society for the Study of Hay Fever, Asthma and Allergic Diseases in San Francisco (28) and the Society for the Study of Asthma and Allied Conditions in New York were founded (29). They merged in 1943 to form the first national allergic society and established a specialty board for recognizing and certifying allergists (30). These institutions fostered the foundation of numerous academic centres focusing on research and training in allergy and immunology and under their auspices flourished important researchers like R. Cooke, A. F. Coca, S. Feinberg, M. Loveless, F. Lowell, W. Frank, H. Sampson, R. Patterson and an ever-ending list of names. A sure evidence of the triumph of the 'allergy' word was the creation in USA in 1929 of an important journal with this term embedded in its name: the *Journal of Allergy*. The use of the word was then controversial, but the editorial of the first issue clearly stated it (31): 'We believe that (allergy) does not have an established meaning in the scientific use. However, the term is very generally employed by clinicians, who apply it to conditions of specific hypersensitivity exclusive of anaphylaxis in lower animals. […] It is sufficient to state that its sense in the title of this journal corresponds with its current medical usage'. Surprisingly, among the first editors of the journal was Coca, initially so reluctant to use the word allergy.

In UK, the development of clinical allergy was more gradual. The nucleus of this advance was the Inoculation Department at St. Mary's Hospital in London founded by Almroth Wright (1861–1947)[4]. Afterwards, in the 1920s and 1930s, other clinics were established throughout the country, particularly after the founding of the Asthma Research Council in 1927, which rose and distributed funds for the 'investigation into the cause and treatment of asthma and allied disorders' (32). This attracted key researchers who made substantial contributions to the development of allergy during the middle decades of twentieth century, such as J. Pepys, H. Hughes, R. Augustin, J. Brostoff and A. W. Frankland.

There were no significant modifications either in understanding of idea of 'allergy' or in its use until the early 1960s. Specifically in 1963, Philip Gell and Robin Coombs made a new and seminal classification of hypersensitivity diseases in their book *Clinical aspects of immunology* (33), which is still in use today with minor changes (34). The classification summarized for the first time the shift in immunology from the earlier immunochemical point of view to one more concerned with clinical and biological issues. In their book, Gell and Coombs showed themselves very scrupulous with the terminology and expressed their concern about the contemporary inaccuracy of the use of the word 'allergy'. So, they tried to restore the word 'allergy' to its original sense because, in their own words, its meaning 'was expressed with the greatest precision in the [Pirquet] paper published in 1906'. Instead of 'hypersensitivity', deemed too ambiguous, they used the term 'allergic reactions producing tissue damage' to collectively name all of these reactions. The classification divided these adverse allergic reactions into the types I to IV, based on initiating immune mechanisms. Therefore, all types were allergy. The type I ones were called anaphylactic or reagin dependent due to the yet unknown nature of the reagin antibody, although the antibody-mediated mechanism of this type of reactions was universally acknowledged.

In the late 1960s, the independent discovery of the real nature of the reaginic antibody by Teruko and Kimishige Ishizaka (35) and Gunnar Johansson (with Hans Bennich) (36) ushered in a new era of research into allergic disease. This elusive antibody, definitely named IgE in 1968 by the WHO (37), attracted much attention on the type I of immune reactions. Perhaps for this reason, a wide group of physicians started using 'allergy' as equivalent only to type I or IgE-mediated hypersensitivity diseases. So, in spite of the strong and long-lived influence of Gell and Coombs' classification, the word 'allergy' gradually returned to its confused

[4]Subsequently, it was named the 'Department of Allergy' under John Freeman and 'Allergy Clinic' under A. W. Frankland. Curiously, Freeman always rejected the word 'allergy' and preferred the term 'toxic idiopathy'.

and vague role. Increasingly, physicians showed their preference for the shorter expression 'hypersensitivity reactions' over 'allergic reactions producing tissue damage', and they used 'allergy' as equivalent to IgE-mediated or any type of hypersensitivity reactions, depending on their membership of different clinical and scientific groups.

The topic became even more confusing in the mid-1970s when the influential American physician Jack Pepys gave the name 'atopic allergy' to the IgE-mediated allergic reactions (38), recovering in this way the Coca's older term and mixing it with allergy. Coca himself had rejected the term a few decades earlier, but many physicians went on using atopy as an useful clinical term referring to the personal or family tendency to produce IgE antibodies. It would have been difficult for an old and rejected term together with an ambiguous one to have added clarity and definition to the terminology.

About at the same time, the direct histamine release evoked by several agents, like dextran or codeine, led to the development of the interesting concept of 'pseudo-allergy' by the Hungarian immunologist Paul Kallos (39). Pseudo-allergic responses, occurring at the first contact with the agent without prior sensitization, are acute systemic reactions arising via a non-IgE-dependent mechanism, but clinically very similar to them. This new variation in the term 'allergy' had a rapid success in scientific literature and is still in force today. In 2001, the European Academy of Allergology and Clinical Immunology (EAACI) proposed to use 'nonallergic anaphylaxis' instead of 'pseudo-allergic reaction' (40, see below), but today both coexist in harmony.

At the end of twentieth century, the word 'allergy' was used more inaccurately than ever before. This was even more noticeable in medicine outside of the specialized field of clinical immunology. 'Allergy' had been transformed into an 'umbrella' term commonly use to describe immunological and nonimmunological unexpected reactions, including side-effects of drugs, psychological reactions blamed on environmental factors, controversial adverse reactions to food and food additives, and others.

Allergy in 21st century

The new century began with the publication of the first institutional attempt to standardize the nomenclature for allergology. The EAACI appointed a Task Force to perform this mission, and the result was published in 2001 as a Position Statement (40). The declaration was supported by the World Allergy Organization and slightly revised 3 years later (41). The report defined hypersensitivity as 'objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons'. These hypersensitivity reactions were divided into nonallergic hypersensitivity when immunological mechanism cannot be proven and allergic hypersensitivity when a type of immunological mechanism is found. Here, 'allergy' is considered 'a hypersensitivity reaction initiated by specific immunological mechanisms'. Both antibody-mediated and cell-mediated reactions are considered then under the term 'allergy'.

Despite this laudable attempt, inaccuracy has continued to govern the use of terminology in this new century. Physicians seem to prefer to use 'hypersensitivity' as equivalent only to undesirable reactions produced by the immune system in their papers, in contrast to the 2001 EAAIC report's criterion. And 'allergy' is almost always synonymous with an adverse immune reaction, although the exact nature of this is variably considered from different standpoints. This changing understanding of 'allergy' can be easily analysed reviewing the currently applied clinical guidelines.

In the field of respiratory diseases, for instance, major guidelines seem to agree with the exclusive use of 'allergy' to define IgE-mediated rhinitis and/or asthma (42, 43). In dermatologic diseases, the position depends on the specific condition considered. In the case of urticaria, 'allergy' always connotes an IgE-mediated hypersensitivity disease (44, 45), but in the case of contact dermatitis (46, 47) 'allergy' is related to both delayed and cell-mediated hypersensitivity diseases. 'Allergy' is always an IgE-mediated condition in latex adverse reactions (48, 49), but it can be any type of

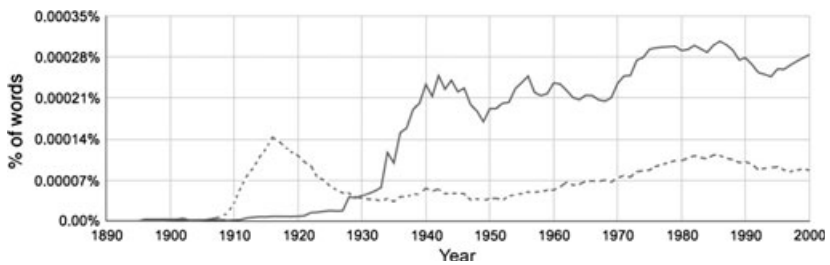

Figure 4 The use of the term 'allergy' (*solid line*) from 1890 to 2000 compared with the use of its competitor term 'anaphylaxis' (*dotted line*) employing culturomics. The *x*-axis show the years evaluated and the *y*-axis the usage frequency, or number of instances of the given term in a year by the total number of words in the corpus of books in that year. The corpus analysed contains about 4% of all books printed in this period, a percentage considered sufficient to observe cultural trends. For instance, the word 'allergy' appeared in 0,0002333599% of the words printed in 1940 and 'anaphylaxis' only in 0,0000566214%. The most important aspect of the analysis is not in the figures themselves, but the temporal evolution of them (a complete description of the methodology of this type of analysis can be found in reference 52; Source: Google Books Ngram Viewer, http://books.google.com/ngrams).

hypersensitivity in drug (50) and food (51) adverse reactions. As we can see, criteria vary according to the context.

The extension of the idea of 'allergy' to the streets, which started in 1930s as we showed above, has continued expanding in the new century. As we could expect, in this context the ambiguity of the word 'allergy' is broader than in the medical one, even when used in reference to health and disease. Herein, 'allergy' is applied to a wide variety of physical disorders and even to anything bothersome, uncomfortable or upsetting. However, this imprecision is clearly less worrying and significant than that of health professionals.

A quantitative analysis of the use of the word allergy

New technologies have made it possible to make a quantitative analysis of the use of the word 'allergy' from its birth in the literature. The 'n-gram' project (52) – included in the modern science of culturomics – permit us to assess a big corpus of books digitalized by Google Inc. (Mountain View, CA, USA) with the purpose to observe trends in the use of any word. The corpus contains approximately 5,2 million of books published between 1800 and 2000, about 500 billions of words (361 billion in English); this corresponds to over 4% of all books edited in this period, sufficient to show significant cultural trends. Most books were drawn from over 40 university libraries around the world. Periodicals, manuscripts and other human creations are not included.

As we can see, in Fig. 4 the use of the word 'allergy' in English-written books between 1890 and 2000 is compared with the use of its more important competitor 'anaphylaxis'. The word 'allergy' began to appear in books slowly after being coined in 1906, and it was not until the middle of 1920s that the term initiated a striking development that became stabilized in 1940s. The last half of the twentieth century showed a less significant growth of the use of 'allergy' in the literature. By contrast, the use of 'anaphylaxis' grew rapidly from its birth in 1902, being well above the use of allergy in these first years. But in the middle of the 1910s, precisely by the time the discovery of the phenomenon of anaphylaxis received the Nobel Prize, the use of this other new word began to decline. Since then, the use of 'anaphylaxis' has maintained a parallel evolution to the use of 'allergy', but in a very lower level. In conclusion, this quantitative analysis of the use of the terms 'allergy' and 'anaphylaxis' supports the qualitative historical analysis undertaken in this article.

Conclusion

Pirquet developed a new idea that constituted the foundation for modern clinical immunology. He raised the theory of the ambivalent harmful and/or protective nature of the immune response and summarized both in the word 'allergy'. Unfortunately, the strength of the old idea of immunity, historically understood as a protection against the disease, hindered and delayed the acceptance of the new one. After several years of competition with the idea of 'anaphylaxis' and others, 'allergy' finally earned its place in medicine, but at the cost of corrupting its original meaning: it became limited to describing only hypersensitivity conditions, mainly (but not always) IgE-mediated diseases. Its success led even to the creation of an autonomous medical discipline based on its name. Pirquet would have been very proud of the long and productive life of his word, but perhaps would show his disagreement with its perverted meaning and its current and unavoidable imprecision. The Roman poet Horace clearly explained it 2000 years ago in his Arts Poetic: 'Many a word long disused will revive and many now high in esteem will fade if custom wills it, in those power lie the arbitrament, the rule and the standard of language' (53).

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Conflict of interest

The author declares that he has no conflict of interest writing this manuscript.

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