1 Immunology of the Allergic Response

1 Allergy and Hypersensitivity: History and Concepts

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Summary

The study of allergy ("allergology") and hypersensitivity, and the associated allergic diseases, have their roots in the science of immunology but overlap with many disciplines including pharmacology, biochemistry, cell and molecular biology, and general pathology, particularly the study of inflammation. Allergic diseases involve many organs and tissues such as the upper and lower airways, the skin, and the gastrointestinal tract and therefore the history of relevant discoveries in the field are long and complex. This chapter gives only a brief account of the major milestones in the history of allergy and the concepts which have arisen from them. It deals mainly with discoveries in the 19th and early 20th century, particularly the events which followed the description of anaphylaxis and culminated in the discovery of IgE as the carrier of reaginic activity. An important conceptual landmark that coincided with the considerable increase in knowledge of immunologic aspects of hypersensitivity was the Coombs and Gell classification of hypersensitivity reactions in the 1960s. This classification is revisited and updated to take into account some newer finding on the initiation of the allergic response.

The story of anaphylaxis

Untoward reactions to external agents, which were harmless to most people, were recognized even in ancient times. The Egyptian pharaoh Menes (2641 BC) was reported to have died from a wasp (*kehb*) sting and is thus the first recorded case of anaphylactic shock (although interpretation of hieroglyphics is apparently controversial) (Avenberg & Harper 1980). Hippocrates (born 375 BC) is attributed with the first description of allergy to goats' milk and cheese and Britannicus (born AD 41) was said to be afflicted by acute allergic reactions to horses.

During the 19th century there were a number of reports describing violent or fatal reactions to repeated injections of foreign proteins to various species including dogs (Magendie 1839), guinea pigs (Von Behring 1893, quoted in Becker 1999, p. 876) and rabbits (Flexner 1894, reviewed in Bulloch 1937). However it was not until the discovery of anaphylaxis by Charles R. Richet (1850–1935) and Paul J. Portier (1866–1962) (Fig. 1.1) in 1901 that the concept of hypersensitivity reactions having a possible immunologic basis was put on a firm scientific footing.

Fig. 1.1 A commemorative postage stamp to mark the discovery of anaphylaxis by Charles R. Richet (1850–1935) and Paul J. Portier (1866–1962).

The story of the discovery of anaphylaxis is provided by Richet (1913) and goes as follows:

> During a cruise on Prince Albert of Monaco's yacht, the Prince suggested to Portier and myself a study of the toxin production of *Physalia* (the jelly-fish known as Portuguese Man-of-War) found in the South Seas. On board the Prince's yacht, experiments were carried out proving that an aqueous glycerine extract of the filaments of *Physalia* is extremely toxic to ducks and rabbits. On returning to France, I could not obtain *Physalia* and decided to study comparatively the tentacles of *Actinaria* (sea anemone) . . . While endeavouring to determine the toxic dose (of extracts), we soon discovered that some days must elapse before fixing it; for several dogs did not die until the fourth or fifth day after administration or even later. We kept those that had been given insufficient to kill, in order to carry out a second investigation upon these when they had recovered. At this point an unforeseen event occurred. The dogs which had recovered were intensely sensitive and died a few minutes after the administration of small

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Fig. 1.2 Clemens von Pirquet (1874–1929). von Pirquet conceived the term "allergy" (see Appendix). He meant it to include any situation where there was "changed reactivity" irrespective of whether this resulted in immunity or hypersensitivity (see Chapter 2). He also introduced tuberculin skin tests in diagnosis. (From Cohen & Samter 1992, with permission.)

> doses. The most typical experiment, that in which the result was indisputable, was carried out on a particularly healthy dog. It was given at first 0.1 mL of the glycerine extract without becoming ill; 22 days later, as it was in perfect health, I gave it a second injection of the same amount. In a few seconds it was extremely ill; breathing became distressful and panting; it could scarcely drag itself along, lay on its side, was seized with diarrhoea, vomited blood and died in 25 minutes.

It is difficult to overstate the importance and ramifications of this seminal discovery. Our present understanding of immediate-type hypersensitivity reactions, the antibody involved together with the pharmacologic mediators released, as well as the treatments for allergic diseases which have followed, have their roots in the discovery of anaphylaxis. However the concept that foreign proteins could induce hypersensitivity as well as immune reactions was difficult for early investigators to accept. It was out of this controversy that the word "allergy," first coined by Clemens von Pirquet (Fig. 1.2) in 1906, was introduced (von Pirquet 1906).

The word "allergy"

Von Pirquet and others had noticed that as well as the protective effects of passive immunotherapy with vaccinia and horse antiserum, many patients experienced adverse reactions. Thus the word "allergy" arose from his attempts to reconcile the two apparently contradictory phenomena of immunity and hypersensitivity. Working with Bela Schick in the scarlet fever wards of Escherich's Paediatric Department in Vienna, he observed that some patients receiving antiserum developed a spectrum of systemic and local symptoms, notably, fever, skin rash, arthropathy, and lymph node swelling, which they termed "serum sickness" (von Pirquet *et al*. 1905; Wagner & von Pirquet 1968). Earlier accounts in the hospital records described similar symptoms with diphtheria and tetanus antisera. Therefore serotherapy appeared to have produced not only immunity (protection) but also hypersensitivity (or "supersensitivity" as was the then more favored word). Von Pirquet realized that in both situations an external agent had induced some form of "changed or altered reactivity" for which he proposed the term "allergy" from the Greek *allos* ("other") and *ergon* ("work"). The critical passage from his article in *Munchener Medizinische Wochenschrift* (von Pirquet 1906) is as follows:

> The vaccinated person behaves toward vaccine lymph, the syphilitic toward the virus of syphilis, the tuberculous patient toward tuberculin, the person injected with serum towards this serum in a different manner from him who has not previously been in contact with such an agent. Yet, he is not insensitive to it. We can only say of him that his power to react has undergone a change.

The problem of reconciling the protective effect of antitoxin with the adverse reactions associated with the administration of foreign agents came to a climax in 1903 with three important discoveries. Firstly, Maurice Arthus (Fig. 1.3) found that repeated injections of horse serum to rabbits

Fig. 1.3 Nicholas-Maurice Arthus (1862–1945). The Arthus reaction is an experimental localized acute necrotizing vasculitis first described as local anaphylaxis. (From Cohen & Samter 1992, with permission.)

produced hypersensitivity reactions that were antigenically specific, so challenging the currently held view that these reactions to foreign proteins were essentially toxic (Arthus 1903). Second, von Pirquet and Bela Schick (1905) observed that a child who had received a second injection of antitoxin had clinical symptoms the same day, though, on the first injection, given some time previously, her clinical symptoms appeared only after the tenth day. As a result they hypothesized that "the time of incubation is the time necessary for the formation of these antibodies." These two observations, together with the third discovery by Hamburger and Moro (1903) of precipitating antibody in the blood during serum sickness, led von Pirquet to speculate that the disease-producing factor produces symptoms only when it had been changed by antibody. Thus, although not explicitly stating so in his original definition, in a later work von Pirquet (1911) made it clear that he intended the term "allergy" to be applied only to immunologic reactions.

Von Pirquet also suggested that the word "allergen" should be used to describe the agent which, after one or more applications, induced this changed reactivity. Therefore von Pirquet had brilliantly laid the foundation for the modern science of immunology by appreciating that a foreign substance "sensitizes" the organism in a way that produces a different response on the second and subsequent administration. Unfortunately with the passage of time the word "allergy" became corrupted and is now used incorrectly and with a limited usage, i.e., to describe hypersensitivity mechanisms that are operative transiently, or persistently, in a limited group of conditions, particularly the IgE-mediated allergic diseases. Such a restricted meaning was not von Pirquet's original intent and in fact it misses his point by, in a sense, merely substituting "allergy" for "hypersensitivity" (Kay 2006).

The "corruption" of allergy

So why has the term "allergy" become misused, and are "allergists" themselves largely to blame? As Elmer Becker (1999) described in his erudite paper "Elements of the history of our present concepts of anaphylaxis, hay fever and asthma," part of the confusion lay in attempts to "classify" allergy. Doerr (1914) initially divided allergy into hypersusceptibility to antigenic substances as well as altered reactivity to nonantigens in which he included morphine addiction. By 1926 Arthur Fernandez Coca (Fig. 1.4) advised the abandonment of the term "allergy" on the basis of its then numerous conflicting meanings. More confusingly he did not consider "anaphylaxis" as part of allergy because it was a phenomenon in which the antigen–antibody reaction was established. Instead Coca classified under "allergy" all those conditions where he considered an antibody mechanism had not been demonstrated, e.g., drug "idiosyncrasies," serum sickness in man, and hay fever. In fact the view that allergy was all forms of hypersensitivity *except* anaphylaxis was to persist until the 1940s. By this time a medical subspecialty practiced by clinicians diagnosing and treating hay fever, asthma, serum sickness, drug reactions, etc. and involving treatment with desensitization injections was already then well established. As Becker (1999) explained:

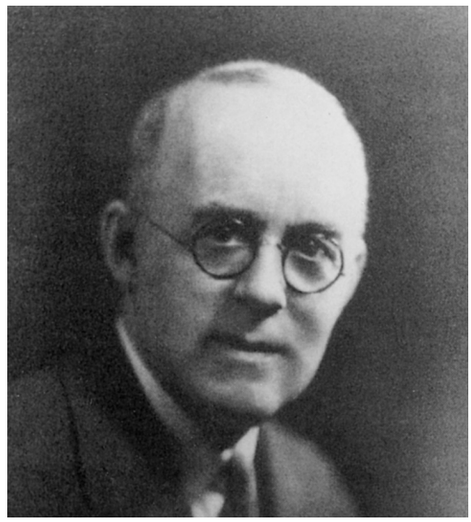


Fig. 1.4 Arthur Fernandez Coca (1875–1959). Coca introduced the term "atopy" (now recognized as IgE-mediated hypersensitivity). (From Cohen & Samter 1992, with permission.)

> [clinicians] desired a brief, convenient, not too limiting group of terms describing what their specialty was and what it was about. As a consequence, they turned more and more to the use of "allergy", "allergic", etc. so that these terms became embedded in clinical usage. This was recognized by the editors of the *Journal of Allergy* when in the first issue they stated, "We believe that it [allergy] does not possess an established meaning in scientific usage. [They then quoted Karsner and Ecker (1921) as the source for this belief.] However, the term is very generally employed by clinicians who apply it to conditions of specific hypersensitiveness exclusive of anaphylaxis in lower animals . . . it seems the title of this journal corresponds to current medical usage."

In hindsight the *Journal of Hypersensitivity and Hypersensitivity Disorders* would have been more historically correct and still have served the clinicians' purpose.

In the 1960s Robin Coombs (Fig. 1.5) and Philip Gell attempted to restore the term "allergy" to its original meaning (Coombs & Gell 1963). They pointed out that "hypersensitivity" is a general term to describe an adverse clinical reaction to an antigen (or allergen). Such an antigen could be bacterial-derived as in a classical delayed-type hypersensitivity reaction to tuberculo-protein or derived from allergen such as pollen giving rise to IgE-mediated hypersensitivity. They argued that limiting the term "allergy" to any exaggerated

Fig. 1.5 Robin A. Coombs (1921–2006). Described the antiglobulin (Coombs') test and, with Philip Gell, classified the hypersensitivity reactions.

response of the immune system to external (antigenic or allergenic) substances was illogical as, by definition, the role of the immune system is to effect immunity. By way of example they pointed out that a deleterious effect to autoantigens should more properly be termed "autoallergic" rather than "autoimmune."

As suggested later (Kay 1997), most of this difficulty is removed if instead of "allergy" we refer to "allergic diseases" and confine the word "allergy" (as von Pirquet originally intended) to the uncommitted biological response. In the individual this uncommitted response may lead to either immunity (which is beneficial) or allergic disease (which is harmful). Therefore, the allergic response, in producing antibodies and specifically reacting (sensitized or allergized) lymphocytes, supplies a common armamentarium for both the reactions of immunity as well as those of the hypersensitivity reactions (allergic diseases).

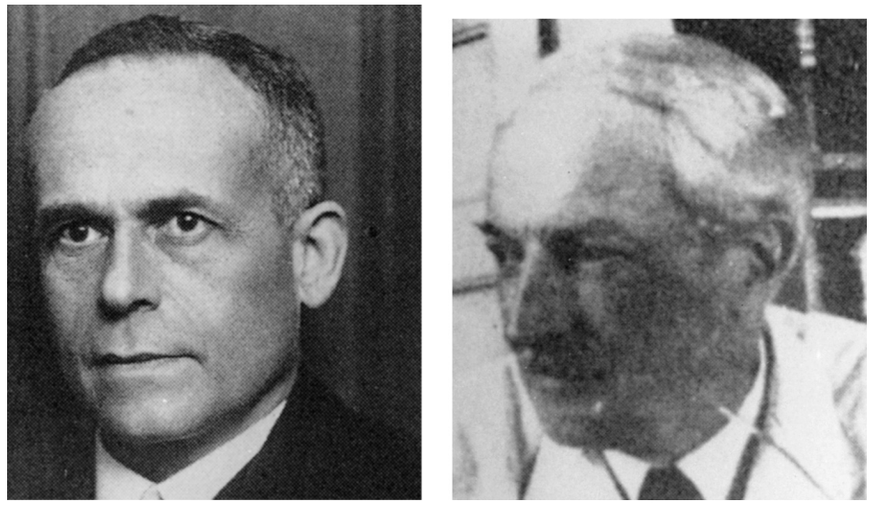
The restricted usage of the term "allergy" (allergic disease) is reflected in the practice of the clinical allergist, where physicians diagnose and treat only selected examples of hypersensitivity states rather than the wide spectrum of immunologic disorders. In many countries this is confined to the IgE-mediated ("atopic") diseases, e.g., summer hay fever, perennial rhinitis, allergic asthma, allergy to stinging insects, food anaphylaxis, and atopic dermatitis. Other "hypersensitivity diseases" such as celiac disease and contact dermatitis are frequently managed by the relevant organ-based specialist. Furthermore, the clinical allergist also deals with patients whose signs and symptoms mimic those of true allergic disease, i.e., where there is evidence of local or generalized release of histamine and other pharmacologic reagents but where an "immunologic" abnormality often cannot be identified (i.e., pseudoallergy).

Is anything to be gained by attempting to restore von Pirquet's word to its original meaning? Probably not. Words lose, or change, their meaning according to custom. Semantics can bury communication. We say that a T cell is "sensitized" but it would be more correct (in the von Pirquet sense) to call it an "allergized" lymphocyte. However this would only cause further confusion and so current imprecision may have to be accepted. What is important is to appreciate that von Pirquet introduced not so much a word but a fundamental biological rule which, arguably, marked the modern approach to immunology.

From reagin to IgE

In the years after Portier and Richet's discovery numerous unsuccessful attempts were made to transfer anaphylactic sensitivity to experimental animals using the serum from patients with hay fever or asthma. However in 1919, Ramirez reported that a normal nonallergic recipient of a blood transfusion 2 weeks previously from a donor sensitive to horse serum developed asthma upon being exposed to horses when riding in an open carriage in Central Park, New York (Ramirez 1919). This was the prelude to the classical experiments of Otto Carl Prausnitz and Heinz Küstner (Fig. 1.6) who, in 1921, demonstrated the presence of a tissue-sensitizing antibody in humans. Küstner was a fish-sensitive individual. When his serum was transferred to the skin of Prausnitz, a nonallergic recipient, there was a positive reaction at the skin site when this was subsequently injected with fish extract. They suggested that the sensitizing agent should be called "reagin" because they were not sure it was an antibody (Prausnitz & Küstner 1921).

The eventual identification of human reagin as IgE antibody was one of the most important biological discoveries of the 20th century. For some years reaginic activity was believed to be a property of IgA that had been discovered in the 1950s. However, Mary Loveless (Fig. 1.7) in 1964 reported the presence of reagin in an individual who formed no detectable IgA (Loveless 1964). In 1966, Kimshige and Teruko Ishizaka (Fig. 1.8) (Ishizaka & Ishizaka 1966) found that reaginic activity was associated with an immunoglobulin other than IgG and IgA and went on to develop an antiserum which, after absorption with IgG and IgG subclasses, IgA, IgM, and IgD (a new immunoglobulin whose discovery had been reported by Rowe and Fahey in 1965), still precipitated protein in immunoglobulin fractions and also precipitated skin-sensitizing activity. As they stated "the results suggest the presence of a unique immunoglobulin as a carrier of reaginic activity." The protein was tentatively designated IgE-globulin and in a series of remarkably thorough and brilliant experiments in which they laboriously checked and cross-checked their



(a) (b)

Fig. 1.6 (a) Otto Carl W. Prausnitz (Giles) (1876–1963) and (b) Heinz Küstner (1897–1963). The passive transfer of immediate skin reactivity by interdermal injection of serum from an allergic patient ("reagin") is called the Prausnitz–Küstner (or P–K) test. (From Cohen & Samter 1992, with permission.)

findings, they finally left no doubt of the validity of their conclusions (reviewed in Ishizaka & Ishizaka 1968).

Gunnar Johansson and Hans Bennich (Fig. 1.9) had used a completely different approach to arrive at the same conclusion. They discovered in 1965 (but reported in 1967) a myeloma protein (IgND) which did not belong to any of the four known immunoglobulin classes (Johansson & Bennich 1967). IgND was shown to block skin-sensitizing activity and an antiserum prepared against it had the same specificity as the anti-IgE globulin prepared by Ishizaka. At an international conference held in 1968 it was agreed to call the new class of proteins to which reagins belonged "immunoglobulin E" (IgE) (Bennich *et al*. 1968).

Fig. 1.7 Mary Hewitt Loveless (1899–1991). Major contributions to immunotherapy including the identification of blocking antibody (with Robert Cooke) and the use of pure venoms in Hymenoptera allergy. (From Cohen & Samter 1992, with permission.)

Fig. 1.8 (Left) Teruko Ishizaka (1926–) and (right) Kimshige Ishizaka (1925–). Characterized reaginic antibody as IgE.

Mediator cells and mediators

The *mast cell* was discovered by Paul Ehrlich (Fig. 1.10) while still a medical student at the University of Freiburg. He was testing a new basic synthetic dye, "dahlia," and discovered that some connective tissue cells contained large granules which avidly took up the dye and changed its color to a reddish purple (metachromasia) (Ehrlich 1877). He named these cells "mast" cells, i.e., well-fed cells, giving them this name because he believed the cell granules were products of cell overfeeding.

Fig. 1.9 (Left) Hans Bennich (1930–) and (right) Gunnar Johansson (1938–). Identification of IgND as IgE immunoglobulin and with L. Wide developed the radioallergosorbent technique (RAST). (Courtesy of Pharmacia, Uppsala, Sweden.)

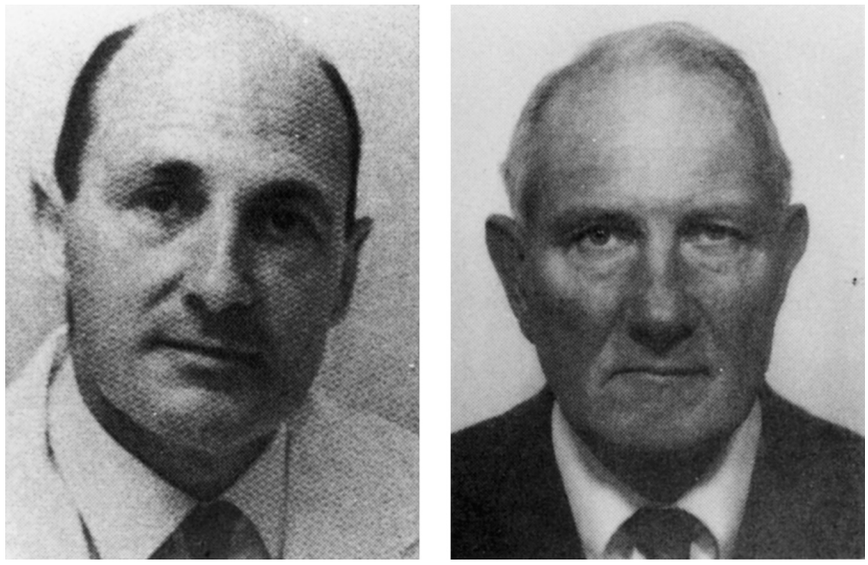
Fig. 1.10 Paul Ehrlich (1854–1915). An exceptionally creative bioscientist who, along with many other accomplishments, described the side-chain theory of antibody formation and discovered the mast cell and the eosinophil. (From Mahmoud & Austen 1980, with permission.)

James Riley and his coworker Geoffrey West (Fig. 1.11) were the first to provide convincing evidence that tissue mast cells contained histamine (Riley & West 1952, 1953; Riley 1959), and Stuart (1952) reported that anaphylaxis in the mouse, rabbit, and guinea pig was associated with degranulation of mast cells. By approximately the mid-1950s, evidence was available that mast cells contained the mediators histamine, serotonin, and heparin, and that mast degranulation was related to the release of these mediators during anaphylaxis in several species. By that time, moreover, it was also evident that the tissue mast cell was not the only mediator cell.

Two years after describing the mast cell, Ehrlich (1879a) noted the presence of cells with metachromatic granules in blood. Although he termed them "blood mast cells," he proposed that unlike the tissue mast cells the blood cells were derived from bone marrow and were essentially equivalent to the neutrophil and eosinophil, cells he had also described. Later workers renamed the blood mast cell, the *basophil*.

Eosinophils were discovered by Paul Ehrlich in 1879 and so called because they stained with negatively charged dyes including eosin (Ehrlich 1879b). He also suggested that the bone marrow was their site of origin. Some time earlier (1846) an anatomist at Charing Cross Hospital, London (Thomas Wharton-Jones) described granulated blood cells from several species using a simple compound microscope and no staining methods. His drawings indicate that these were almost certainly eosinophils (Wharton-Jones 1846).

Histamine was the first substance to be considered an anaphylactic mediator. Sir Henry Dale (Fig. 1.12) demonstrated the presence of histamine in various tissues (Best *et al*. 1927). It was not until 1932 that others (Gebauer Fuelnegg in Dragstedt's laboratory, Bartosch working with Feldberg and Spinelli) were finally successful in demonstrating the release of histamine during *in vitro* and *in vivo* anaphylaxis (Bartosch *et al*. 1932; Gebauer-Fuelnegg *et al*. 1932; Spinelli 1932). Histamine could explain some but not all the features of anaphylaxis. Schild (1936), for example, pointed out that a hundred times more histamine had to be administered to the guinea-pig lung than was released from shocked lungs to have the same effect in contracting the bronchi. This



(a) (b)

Fig. 1.11 (a) James F. Riley (1912–85) and (b) Geoffrey B. West (1916 –). Riley and West discovered that the mast cell granule was the major source of histamine in tissues. (From Cohen & Samter 1992, with permission.)

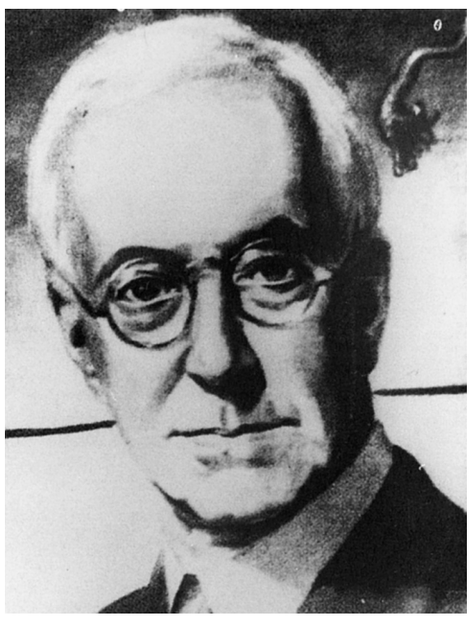


Fig. 1.12 Sir Henry H. Dale (1875–1968). Established the role of histamine in anaphylaxis and demonstrated chemical transmission of nerve impulses. (From Cohen & Samter 1992, with permission.)

and many other observations led to the discovery of slow-reacting substance of anaphylaxis.

Charles Kellaway and Everton Trethewie (Fig. 1.13) reported that the lungs or jejunum of sensitized guinea pigs perfused with antigen released a substance which gave a slow sustained contraction of guinea-pig ileum (Kellaway & Trethewie 1940). This was unlike the sharp short contraction given by histamine and, accordingly, they named the substance slow-reacting substance (SRS). It was not until 1953 that Walter Brocklehurst confirmed earlier work showing that perfusates of sensitized guinea-pig lungs challenged with antigen gave a slow contraction of guinea-pig ileum even in the presence of an antihistamine in the organ bath (Brocklehurst 1953, 1962). He renamed the agent SRS-A, the slow-reacting substance of anaphylaxis. SRS-A was eventually chemically characterized by Robert Murphy and Bengt Samuelsson (Fig. 1.14) as leukotriene D and E (later reclassified as LTC_4, LTD_4, and LTE_4) (Borgeat & Samuelsson 1979; Murphy *et al*. 1979). Leukotrienes and many analogs were totally synthesized by E.J. Corey and with K. Frank Austen (Fig. 1.15) the range of biological activities in humans and experimental animals was established (Weiss *et al.* 1982). (See *Clinical and Experimental Allergy Reviews*, volume 1(3), November 2001 for the history of leukotrienes.)

The story of *bradykinin* dates back to the experiments of Rocha e Silva, Beraldo, and Rosenfield who added trypsin or snake venom to serum globulin and obtained a peptide which was hypotensive, stimulated smooth muscle, and was also a vasodilator (Rocha e Silva *et al.* 1949). They termed the peptide "bradykinin" because it gave a contraction of smooth muscle that was somewhat slower than histamine. Beraldo (1950) demonstrated the liberation of bradykinin into the blood of dogs undergoing anaphylaxis. These results over the succeeding 10 years were confirmed and extended to other species.

Asthma and hay fever

Asthma (meaning "panting") has been recognized since ancient times. Moses Maimonides (1135–1204) (Fig. 1.16) wrote a *Treatise on Asthma* which described the disease and recommended certain lifestyle changes, especially diet, as

(a)

(b)

Fig. 1.13 (a) Charles H. Kellaway (1889–1952) and (b) Everton R. Trethewie (1913–84). First description of a "slow-reacting substance of anaphylaxis" causing smooth muscle contraction. (From Cohen & Samter 1992, with permission.)

Fig. 1.14 Bengt I. Samuelsson (1934–). Identification and chemical characterization of the SRS-A leukotrienes. (From Cohen & Samter 1992, with permission.)

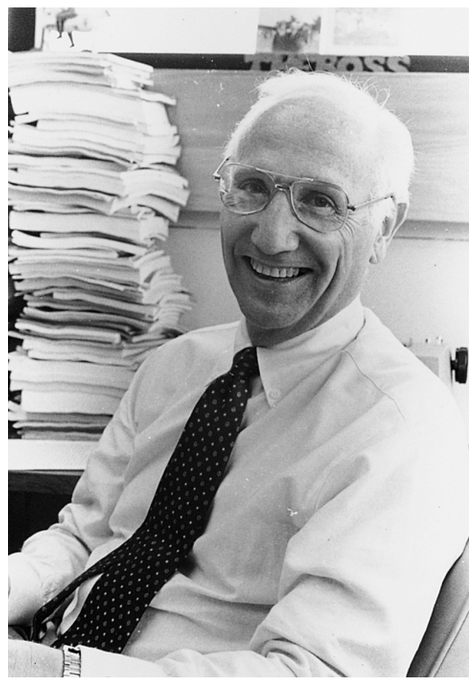


Fig. 1.15 K. Frank Austen (1928–). Pioneered the biochemistry of mast cell mediator release and the biological properties of leukotrienes.

beneficial. The first description of occupational asthma was made by Bernardino Ramazzini (1633–1714) (Fig. 1.17). Thomas Willis (1621–75) (Fig. 1.18) suggested that asthma may have a nervous or neural component, a concept clearly valid to this day. Throughout the 19th and early 20th century asthma was generally believed to be due to spasm of the bronchial musculature either as result of heightened neural pathways or the result of anaphylaxis due to specific sensitization. Although John Floyer (1649–1734) (Fig. 1.19) recognized that asthma had many triggers, as well as a hereditary component, it was Henry Hyde Salter (1823–71) (Fig. 1.20) who made the first attempts to understand asthma mechanisms (McFadden 2004). Salter, himself an asthmatic, noticed that asthma attacks could be triggered by "extrinsic" factors such as exercise, cold air, laughing, coughing, sneezing, chemical and mechanical irritants, and animal and vegetable products. He also realized that other causes were operating and suggested that asthma involved both neural and vascular

Fig. 1.16 Moses Maimonides (1135–1204). A prolific writer and author of a famous *Treatise on Asthma*. (From Cohen & Samter 1992, with permission.)

Fig. 1.17 Bernardino Ramazzini (1633–1714). First description of occupational diseases, in particular baker's asthma. (From Cohen & Samter 1992, with permission.)

mechanisms and wrote with amazing accuracy, "The inflammation or congestion of the mucous surface appears to be the stimulus that, through the nerves of the air tubes, excites the muscular wall to contract." On the other hand, Sir William Osler (1849–1919) taught that asthma was a psychoneurosis and because of his prestige this opinion was accepted by many physicians for decades after. It was many years before this view was put in perspective.

Fig. 1.18 Thomas E. Willis (1621–75). Recognized the importance of bronchial innervation in asthma; and asthma as a "nervous disease." (From Cohen & Samter 1992, with permission.)

Fig. 1.19 Sir John Floyer (1649–1734). Recognition of asthma as a multifactorial disease with many triggers (e.g., tobacco smoke, dust, foods, exercise, emotions, environmental factors). First description of heredity in asthma. (From Cohen & Samter 1992, with permission.)

In studies on the pathology of asthma, Ernst von Leyden (1832–1910) (Fig. 1.21) described colorless, needle-like crystals in the sputum of asthmatics and used the observation to "prove asthma was not a nervous disease." Much earlier Jean Martin Charcot (1825–93) (Fig. 1.21) had noted similar crystals from a leukemic spleen, hence Charcot–Leyden crystals.

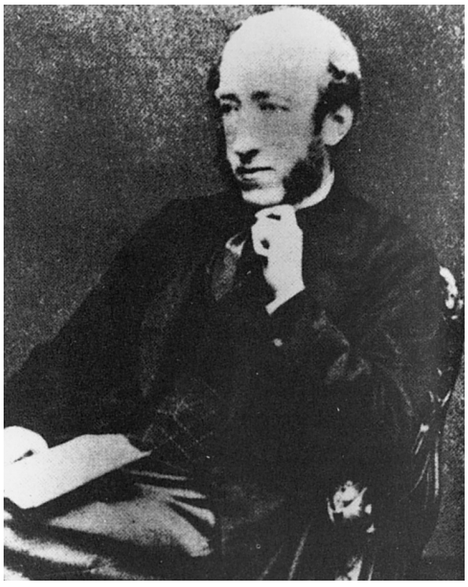


Fig. 1.20 Henry Hyde Salter (1823–71). Description of the various causes of asthma and of cells (now known as eosinophils) in sputum. (From Cohen & Samter 1992, with permission.)

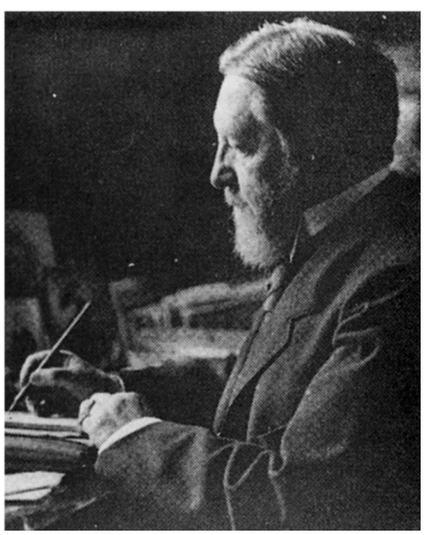
Fig. 1.22 Francis M. Rackemann (1887–1973). Introduced the term "intrinsic asthma." (From Cohen & Samter 1992, with permission.)

Many clinicians appreciated that asthma had an allergic component but it was Francis Rackemann (1887–1973) (Fig. 1.22) who introduced the term "intrinsic asthma" to describe patients who gave no history of "allergy" and who were skin test negative to common allergens.

There was a well-recognized association between asthma and hay fever but it was John Bostock (Fig. 1.23) who in 1819 was the first to describe hay fever as a disease with distinct symptoms. Much later, in 1873, Charles Blackley (Fig. 1.24), in experiments carried out largely on himself, showed that hay fever was due to pollen. He was the first to use conjunctival and skin tests and also showed a relationship between the number of pollen grains collected in 24 hours on sticky glass slides and the intensity of symptoms.

Dunbar thought that hay fever was caused by a toxin in pollen and he produced an "antitoxin" in horses which he called "Pollatin" which was widely used therapeutically. But it was Leonard Noon (1911) (Fig. 1.25) who successfully introduced specific injection therapy for hay fever. After his premature death from tuberculosis, his colleague John

(a)



(b)

Fig. 1.21 (a) Jean Martin Charcot (1825–93) and (b) Ernst V. von Leyden (1832–1910). The needle-like (eosinophil-derived) crystals characteristic of asthmatic sputum are named after Charcot and Leyden. (From Cohen & Samter 1992, with permission.)

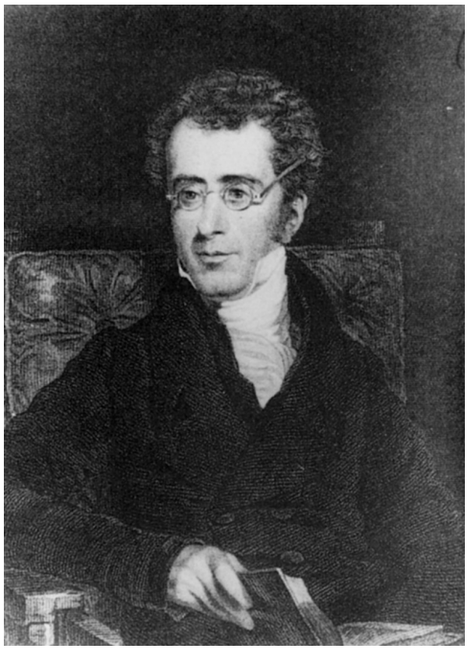


Fig. 1.23 John Bostock (1773–1846). Described "catarrhus aestivus," later recognized as summer hay fever. (From Cohen & Samter 1992, with permission.)

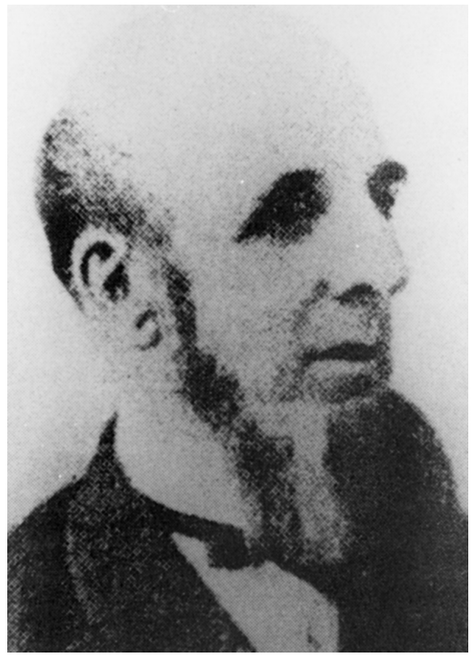
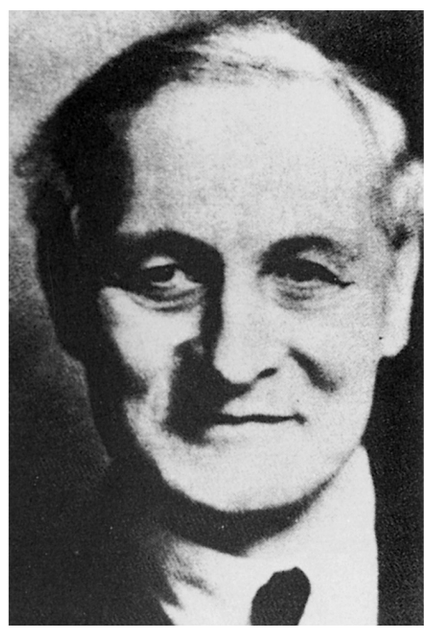


Fig. 1.24 Charles H. Blackley (1820–1900). Identified pollen as a cause of hay fever and devised methods for pollen counts and clinical challenge tests. (From Cohen & Samter 1992, with permission.)

Freeman (Fig. 1.25) continued the work (Freeman 1914) and by 1920 it was a standard method of treatment among allergists. Cooke (Fig. 1.26) and Vander Veer then recognized a hereditary component to hay fever and other conditions associated with sensitization and, later, Coca and Cooke (1923) introduced the term "atopy" (meaning "out of place") which they considered to be a peculiarly human condition in which there was hereditary predisposition to produce reagin but which was quite separate from anaphylaxis.

Another antibody beside IgE found in human immediate-type allergic disease is the so-called "blocking antibody." This was discovered by Cooke *et al.* (1935) in attempting to find

(a)



(b)

Fig. 1.25 (a) Leonard Noon (1877–1913) and (b) John Freeman (1877–1962). Noon and Freeman introduced the treatment of hay fever by immunization with pollen extracts. (From Cohen & Samter 1992, with permission.)

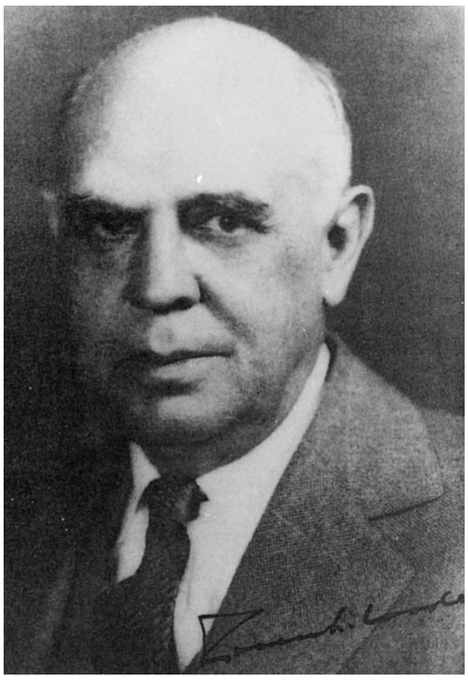


Fig. 1.26 Robert A. Cooke (1880–1960). Introduced the protein nitrogen unit (PNU) for standardization of allergen extracts, realized the role of hereditary factors in hay fever and described allergic drug reactions. Cooke also discovered "blocking antibody" with Mary Loveless. (From Cohen & Samter 1992, with permission.)

out why the injection treatment for hay fever was successful. The concept that the blocking activity was due to binding of the antibody with the allergen was first explicitly stated by Mary Loveless when she found that blocking activity, unlike the skin-sensitizing activity, was heat stabile, withstanding heating at 56°C (Loveless 1940). Blocking antibody seemed to offer a respectable, "scientific" reason for the efficacy of the injection treatment of hay fever, although doubt continues to be expressed as to whether the development of blocking antibody was responsible for the therapeutic relief claimed for the treatment.

Many other "allergy landmarks" are listed in chronologic order in Table 1.1. All were crucial observations even though in many instances their full importance was not recognized at the time.

The Coombs and Gell classification of hypersensitivity reactions

Until the 1960s there had been difficulties in relating the various models of hypersensitivity in humans and experimental animals, as well allergic diseases themselves, to some form of systematic classification in order to study disease processes in an ordered fashion. Coombs and Gell (1963) described a "classification of allergic reactions which may be deleterious to the tissues and harmful to the host". This still remains useful to practicing physicians, scientists, and students today because it relates mechanisms to disease entities. Coombs and Gell predicted correctly that in any one disease it was likely that more than one kind of allergic process was involved. They also emphasized the fact that their classification was primarily one of initiating mechanisms and not of the subsequent events or the diseases themselves.

The type I–IV hypersensitivity reactions of Coombs and Gell, with some modification in the light of more recent knowledge, are shown in Fig. 1.27. The *type I reaction* is initiated by allergen or antigen reacting with tissue cells passively sensitized by antibody produced elsewhere, leading to the release of a wide range of biological agents including pharmacologically active substances, proteases, cytokines, and chemokines. These anaphylactic reactions include general anaphylaxis in humans and other animals as well as local manifestations of anaphylaxis, such as that observed in the skin following diagnostic skin-prick tests, and local responses in the respiratory and gastrointestinal tracts. IgE was discovered shortly after the Coombs and Gell classification was published. The high-affinity IgE receptor was discovered some 15 years later (Lanellopoulis *et al.* 1980; Perez-Montfort *et al.* 1983) and was a landmark observation leading to the later elucidation of signal transduction pathways involved in IgE-dependent mediator release.

More recently it has been shown that in mice antigen-specific light chains can sensitize mast cells for subsequent antigen-induced release of mediators (Kraneveld *et al.* 2005). This observation is yet to be confirmed in humans. *Type II reactions* (cytolytic or cytotoxic) are initiated by antibody reacting either with an antigenic component of a tissue cell or with an antigen or hapten intimately associated with these cells. Complement was usually, but not always, necessary to effect the cellular damage. Examples include drug-induced hemolytic anemia in association with chlorpromazine or phenacetin and thrombocytopenic purpura caused by the now obsolete sedative Sedormid. There are many examples of type II reactions outside the province of the clinical allergist, including incompatible blood transfusion reactions and autoallergic (autoimmune) hemolytic anemia.

In some instances antibodies against cell-surface receptors have cell-stimulatory (agonist) effects without necessarily being cytotoxic. An example is Graves' disease (hyperthyroidism, autoallergic thyroiditis) in which IgG antibodies directed against the thyroid-stimulating hormone (TSH) receptor is produced. These have agonist effects by stimulating thyroid hormone production with subsequent thyrotoxicosis and goitre formation. Similarly, some patients with chronic urticaria have histamine-releasing IgG autoantibodies against the ε subunit of the high-affinity IgE receptor (FcεRIα) (Hide *et al.* 1993). The antibody is believed to activate normal mast cell function by receptor cross-linking

Table 1.1 Hypersensitivity reactions: Landmark findings and theories throughout the ages (adapted from De Weck (1997)).

28th BC	Shen Nung	First reference to an anti-asthmatic plant ("ma-huang"), shown later to contain ephedrine, in the first herbal compendium Pen Ts'ao
2698 BC 2641 BC	Huang Ti Menes	First decription of asthma ("noisy breathing") in the Nei Ching, oldest treatise of internal medicine. Egyptian pharaoh reported to have died from a wasp ("kehb") sting (first report of an anaphylactic shock?) However, interpretation of hieroglyph controversial (Avenberg & Harper, 1980)
460–365 BC	Hippocrates	Description of asthma, eczema and allergy to goats' milk and cheese
25 BC–AD 40	Aulus Celsus	Thorough description of dyspnoea, asthma and orthopnoea in treatise "De medica"
AD c. 40	Marcus Terrentius Varro	Very small animals invisible to the eye, floating in the air, growing in damp places, inhaled and giving rise to serious diseases (mites?)
AD b.41	Britannicus	Reported to be afflicted by acute allergic reactions to horses
AD c. 60	Pedanius	Remedies for asthma in classical pharmacology treatise
120–AD 180	Aretaeus of Cappadocia	First detailed description and coining of the word asthma
AD b.131	Galen	Description of untoward reactions to various milks (goat, cow, ewe, camel, ass): allergy?
AD b.865	Rhazes	Description of seasonal catarrh due to roses in Persia
1135–1204	Moses Maimonides	Author of famous "Treatise on Asthma". Physician to Sultan Saladin
b.1306	John of Arderne	Prescription of a "syrup" for asthma
1530	Thomas Moore	Report on acute skin eruption of King Richard III due to ingestion of strawberries (Shakespeare!)
1552	Girolamo Cardano	Cures asthma of Archbishop Hamilton of St Andrew by elimination of bedding feather pillows
1565	Leonardhus Botallus	Description of "rose cold" in Pavia
1570	Pietro Mattioli	First reported challenge of a cat allergic patient by stay in a room containing a concealed cat
c. 1584	Johann Schenk	Coins the term "idiosyncrasy"
b.1603	Kenelm Digby	Blister to rose petal applied on cheek of English court lady hypersensitive to roses (first patch test?)
1603	Felix Platter	Asthma due to obstruction of small pulmonary arteries or to nerve disturbances
c. 1630	Sanctorius	Description of asthma to cat hair
1656	Pierre Borel	Weakness, fainting and asthma upon contact with cats, mice, dogs and horses (particularly in Germans?) Blister upon applying egg on skin of hypersensitive patient (first skin test?)
1662	K.V. Schneider	Nasal catarrh caused by exudation from nasal mucosa, not by secretion from the brain (!)
1665	Philipp Jacob Sachs	Description of a case of urticaria caused by strawberries and of shock upon ingestion of fish
1673	Johannes Binneringus	Description of seasonal rose coryza in Basle
1675	Theophile Bonet	Idiosyncrasies to bread, strawberries and wine
1680	Thomas Willis	Studies of asthma as bronchial disease and role of bronchial innervation; asthma as nervous disease
c. 1680	Nehemiah Green	First microscopic studies of pollen grains
1682	Joan van Helmont	Description of seasonal asthma with itching skin eruption (atopic dermatitis?) and of psychosomatic asthma
1691	Jacob de Rebecque	Coryza due to rose scent but only at the end of spring
1698	John Floyer	Description of asthma causes (tobacco smoke, dust, foods, exercise, emotions, environmental factors) First description of heredity in asthma
1713	Bernardino Ramazzini	First systematic description of occupational diseases, in particular baker's asthma
1765	Debrest	Description of sudden death by bee sting in Montpellier
1775	William Cullen	Hereditary idiosyncrasy to eggs in "Historia de Materia Medica"

Continued p. 16

Table 1.1 (*Cont'd*)

1776	Johann Murray	Ipecac root (emetine), causes asthma attacks in pharmacists
1778	Stolpertus	Description of acute angioneurotic oedema following ingestion of eggs
1783	Friedrich Schademantal	Allergic urticaria due to ingestion of fresh pork meat
1783	Philipp Phoebus	Comprehensive monograph on hayfever. First epidemiological enquiry
1802	William Heberden	Description of summer catarrh and asthma; differentiation from common cold
1816	Henri Laennec	Invents stethoscope. Identifies bronchospasm as important component of asthma
1819	John Bostock	Description of 28 cases of "estival catarrh" or hay-fever, disease restricted to upper classes of society
1839	François Magendie	Description of sudden death of dogs repeatedly injected with egg albumin
1853 1886	Jean Martin Charcot and Ernst van Leyden	Description of Charcot–Leyden crystals in sputum of asthmatics
1868	Henry Hide Salter um	Description of asthma with various causes (animal emanations, foods, hayfever), intrinsic asthma, cells in sputum (later identified as eosinophils)
1872	Heinrich Quincke	First description of angioneurotic oedema
1872	Morrill Wyman	Description of autumnal catarrh in USA and identification of ragweed pollen as cause
1873–80	Charles Blackley	Experimental demonstration of role of grass pollens in hayfever, first pollen counts
1877	Paul Ehrlich	Description and staining of mast cells (1877) and eosinophils (1879)
1894	Samuel Flexner	Experimental "toxic death" whilst injecting dog serum into rabbits
1895	Josef Jadassohn	Establishment of patch tests in contact dermatitis
1895	Josef Jadassohn	Description of various types of drug reactions in the skin
1900	Solomon Solis-Cohen	Role of autonomic imbalance in allergic diseases. Use of adrenal substance in hayfever and asthma
1902	Charles Richet Paul Portier	Discovery of experimental anaphylaxis in dogs
1903	Theobald Smith	Observations of anaphylactic reactions of guinea pigs to horse serum
1903	Maurice Arthus	Experimental localized acute necrotizing vasculitis, first described as local anaphylaxis
1905	Bela Schick	First description of serum sickness disease: skin test for diphtheria susceptibility
1905	Clemens von Pirquet	Studies on serum sickness, coins the term "allergy": introduces tuberculin skin test in diagnosis
1906	A. Wolff-Eisner	Relationship of human hayfever and urticaria to experimental anaphylaxis
1909	William Schultz	Detection of anaphylaxis by contraction of isolated smooth muscle *in vitro*
1909	William B. Osler	Asthma associated with neurotic disease
1910	S. Meltzer	Bronchial asthma as a phenomenon of anaphylaxis
1910	William Dunbar	Methodology for pollen extraction; first approaches to pollen immunotherapy
1911	Leonard Noon John Freeman	Wide use of immunotherapy with pollen extracts in hayfever patients
1911	Henry Dale	Role of histamine in anaphylaxis and studies on chemical transmission of nerve impulses
1911	Tomaso Casoni	Skin test in patient infected with *Echinococcus*
1912	Oscar M. Schloss	Use of scratch test in allergy to foods
1913	William Dunbar	Methodology for pollen extraction, identification of allergenic protein
1914	A.T. Waterhouse	Anaphylactic reactions of beekeepers to stings

Table 1.1 (*Cont'd*)

1915	Warfield T. Longcope	Experimental lesions in organs from animals repeatedly injected with foreign proteins
1916	Robert A. Cooke	Standardization of allergen extracts – protein nitrogen unit (PNU), role of hereditary factors in hayfever, description of allergic drug reactions
1918	Francis Rackemann	Description of intrinsic and extrinsic asthma: asthma is not always of allergic origin
1919	M.A. Ramirez	Horse dander asthma following blood transfusion
1921	Carl Prausnitz Heinz Küstner	Passive transfer of immediate skin reactivity of fish allergen by intradermal injection of serum from allergic patient ("reagins")
1921	Arent de Besche	Passive transfer of serum from horse asthmatics sensitized to horse proteins by injection of diphtheria vaccine
1922	Fernand Widal Pierre Abrami J. Lermoyez	Described triad of asthma, vasomotor rhinitis (with or without nasal polyps) and intolerance to aspirin and aspirin-like medicines (also known as Samter's syndrome)
1923	Arthur Coca	Reagent for allergen extraction
1923	Arthur Coca	Coined the term "atopy"
1924	F.T. Codham	First description of mould allergy
1924	Ko Kuei Shen Carl F. Schmidt	Systematic investigations of pharmacological actions of ephedrine, the active component of "ma-huang"
1927	Thomas Lewis	Description of similarities between urticaria and skin vascular reactions to histamine (vasodilatation, flare and local oedema as triple response)
1927	Bret Ratner	Experiments on allergic sensitization *in utero*
1928	Storm van Leeuwen	Inhalation allergy to house dust
1928	Edward Dienes	Induction of cellular delayed hypersensitivity by protein antigens
1934	Mataso Masugi	Experimental glomerulonephritis with anti-kidney antiserum
1935	Ulf von Euler	Discovery of the activity of lipid fraction of seminal fluid on smooth muscle ("prostaglandins")
1937	Daniel Bovet	First synthesis of antihistaminic drugs
1939	Harry H. Donally	Transmission of food allergens in breast milk
1940	Charles H. Kellaway Everton T. Trethewie	First description of "a slow-reacting substance of anaphylaxis" causing smooth muscle contraction
1940	Mary Loveless	Description of blocking antibodies arising during immunotherapy with pollen extracts. Use of pure venoms in immunotherapy for hymenoptera allergy
1941	Louis B. Jaques	Relationship between mast cells and anaphylaxis in dogs: mast cells as source of released heparin
1941	Joseph Harkavy	Bronchial asthma with recurrent pulmonary eosinophilic infiltration and polyserositis
1942	Merrill W. Chase	Transfer of tuberculin sensitivity by cells from immunized animals
1945	Merrill W. Chase	Transfer of contact dermatitis to simple chemicals by sensitized leukocytes
1945	Robin A. Coombs	Described the antiglobulin ("Coombs") test
1949	Philip S. Hench Edward C. Kendall	Isolation of cortisone from adrenals for therapy of rheumatoid arthritis
1952	Zoltan Ovary	Development of passive cutaneous anaphylaxis (PCA) for quantification
1953	James F. Riley Geoffrey B. West	Mast cell granules as major source of histamine in tissues
1954	William Frankland Rosa Augustin	First placebo-controlled clinical trial of desensitization (allergen-injection immunotherapy)

Continued p. 18

Table 1.1 (*Cont'd*)

1957	Ernest Witebsky	Experimental autoallergic thyroiditis: pathology and criteria of immune diseases
1958–60	Zoltan Ovary Herman N. Eisen	Elicitation of immediate anaphylactic reactions requires bridging of antibody molecules by bi- or multivalent allergen
1960	Bernard. B. Levine Alain L. de Weck	Identification of major and minor antigenic determinants in penicillin allergy
1962	Alain L. de Weck Charles W. Parker	Diagnostic skin testing for penicillin allergy with synthetic penicilloyl-polylysine polymers
1963	Robin A. Coombs Philip Gell	Classification of the hypersensitivity reactions
1963	K. Frank Austen	Biochemistry of mast cell mediator release
1963	Jack Pepys	Identification of moulds and anti-*Thermosopora* IgG antibodies as cause of farmer's lung
1964	Lawrence M. Lichtenstein Abraham G. Osler	Development of allergen-specific histamine release test
1964	T.E. King	Identification of major allergen in ragweed
1966	Barry R. Bloom John R. David	Description of lymphokine-induced cell interaction: macrophage migration inhibitory factor (MIF)
1966	David Marsh	Identification of major grass allergens
1966	J.J. Curry	Asthmatics more sensitive than normals to the action of histamine on the respiratory tract
1967	Kimishige Ishizaka Teruko Ishizaka	Characterization of reagins as IgE immunoglobulins
1967	Hans Bennich Gunnar Johansson	Identification of myeloma ND as IgE immunoglobulin
1967	L. Wide Gunnar Johannsson	Development of a RAdioSorbent Test (RAST) for detection of allergen-specific IgE
1967	Reindert Voorhorst Frederick Spieksma	Identification of *Dermatophagoides mites* as major allergen source in house dust
1967	Bernard Halpern	Lymphocyte stimulation test in drug allergy
1967	Roger Altounyan	Discovery of sodium cromoglycate as anti-asthmatic drug
1981	K. Frank Austen	Biological properties of leukotrienes
1983	Bengt I. Samuelson	Identification of leukotrienes as slow-reacting substance of anaphylaxis, role in allergic diseases

and in this sense is cytostimulating rather than cytolytic (in which there is destruction of the cells with liberation of preformed histamine). In myasthenia gravis, on the other hand, autoantibodies directed against acetylcholine receptors have been identified. These have antagonist properties leading to a failure to sustain maintained or repeated contraction of striated muscle. Although, in both situations, the initiating event is IgG bound to cell-surface antigen, the outcome is quite different, giving on the one hand cytolytic or cytotoxic reactions, and on the other a cytostimulating hypersensitivity reaction in which there is altered cell function (or cell signaling) with IgG antibody acting either as an agonist or an antagonist. For these reasons, Janeway and Travers (1995) proposed that cytotoxic or cell-stimulatory reaction are subdivided into type IIa (cytotoxic) and type IIb (cell-stimulating) responses (Fig. 1.27).

Type III reactions (Arthus reactions and "immune complex" or toxic complex syndrome) occur when antigen and antibody, reacting in antigen excess, form complexes which, possibly with the aid of complement, are toxic to cells. As shown by Jack Pepys (1914–96) (Fig. 1.28), this mechanism operates, at least in part, in farmer's lung (and other forms of extrinsic allergic alveolitis). Other examples of type III reactions include erythema nodosum leprosum, serum sickness,

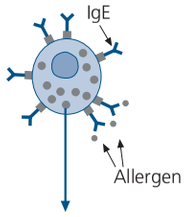
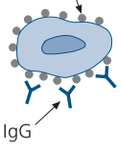
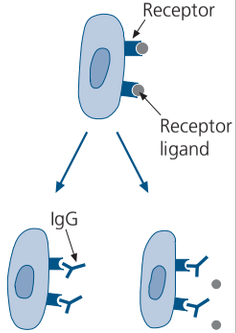
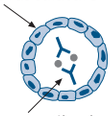
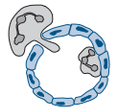
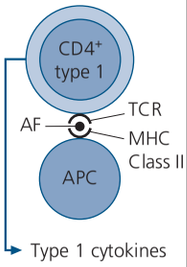
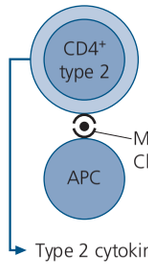
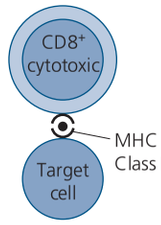
	Type I	Type II		Type III	Type IV	Type IV	Type IV
		a	b		Th1	Th2	cytotoxic
Descriptive term	Immediate-type (IgE-dependent, or anaphylactic) hypersensitivity	Cytolytic, or cytotoxic, reactions	Cell-stimulating reactions involving altered cell function (or signaling)	Arthus type (or antigen-antibody complex) – often called 'immune complex' – hypersensitivity reaction	Classical delayed-type hypersensitivity	Cell-mediated eosinophilic hypersensitivity *or* chronic allergic inflammation	Tissue injury by cytotoxic T lymphocytes
Initiating event	Antigen (allergen) interacting with mast cells or basophils passively sensitized by IgE	IgG antibody interacting with cell surface antigen	IgG cell-stimulating antibody interacting with cell surface receptors involved in cell signaling	Antigen-antibody complexes, in and around the micro-vasculature, which activate complement	Antigen presentation to sensitized $CD4^+$ type 1 T lymphocytes (also called T helper (Th) type 1 cells)	Antigen presentation to sensitized $CD4^+$ type 2 T lymphocytes. *Sensitized $CD8^+$ type 2 T lymphocytes (also called T cytotoxic (Tc) type 2 cells) may also participate*	Cytotoxic $CD8^+$ T lymphocytes recognize fragments of antigen on the surface of target cells
Antigen	Soluble	Cell-associated	Cell-associated	Soluble	Soluble	Soluble	Cell-associated
Simplified scheme of the proposed mechanism	Mast cell/basophil  Release of granule-associated mediators (e.g. histamine) and membrane-derived lipid mediators of hypersensitivity	Target cell Cell surface antigen  +/– complement Complement lysis or removal by the RE system	Target cell  	Microvasculature  Antigen-antibody complexes + complement  Neutrophil-rich inflammatory response	T Lymphocyte  Macrophage-rich inflammatory response	T Lymphocyte  Eosinophil- and basophil-rich inflammatory response	T Lymphocyte  Cytotoxicity (apoptosis)
Examples in humans	• Acute symptoms of allergic rhinitis • General and local anaphylaxis • Early-phase allergic reactions (in experimental models of atopic allergic disease)	• Certain allergic drug reactions (e.g. penicillin) • Incompatible transfusion reactions • Autoallergic ("autoimmune") hemolytic anemia	• Chronic urticaria (Anti-FcεRIα antibody – agonist) • Graves disease (Thyroid stimulating antibody – agonist) • Myasthenia gravis (Anti-acetylcholine receptor antibody – antagonist)	• Serum sickness • Extrinsic allergic alveolitis • Antigen-antibody complex ("immune complex") glomerulonephritis	• Tuberculin reaction • Contact dermatitis • Rheumatoid arthritis	• Chronic asthma • Chronic allergic rhinitis • Atopic eczema • Late-phase allergic reactions (in experimental models of atopic allergic disease)	• Early-onset, insulin-dependent diabetes • Graft rejection

Fig. 1.27 A modification to the Coombs and Gell classification (1963) of hypersensitivity reactions based on more recent knowledge of the initiating events but restricted to human allergic disease. Immediate-type (type I) reactions involve soluble antigen interacting with cell-bound IgE. Type I reaction involves IgE antibodies bound to high-affinity (FcεRI) IgE receptors on mast cells or basophils (and possibly macrophages or even eosinophils). Antigen (allergen) induces the release of granule-associated and membrane lipid-derived mediators of hypersensitivity as well as several cytokines including interleukin (IL)-5, IL-3, and granulocyte–macrophage colony-stimulating factor (GM-CSF). Type II reactions are subdivided into type IIa, cytolytic or cytotoxic reactions originally described by Coombs and Gell, in which antibody-sensitized cells are destroyed by complement lysis or removed by the reticuloendothelial (RE) system; and type IIb, those in which antibodies directed against cell-surface receptors cause altered cell function or signaling. In type IIb, antibody is cell-stimulating (cytostimulatory) and acts as either an agonist or antagonist. (From Janeway & Travers 1995.) The type III Arthus-type reaction, or antigen–antibody complex reaction (mostly called immune-complex reaction), is mediated by soluble antigen and involves IgG, complement, and an inflammatory reaction which initially is neutrophil-rich. Type IV reactions are subdivided into (i) classical delayed-type hypersensitivity initiated by $CD4^+$ Th1-type lymphocytes (type IV Th1), (ii) cell-mediated eosinophilic hypersensitivity or chronic allergic reactions involving $CD4^+$ (and sometimes $CD8^+$) Th2-type cells (type IV Th2) and (iii) reactions in which tissue damage is evoked by $CD8^+$ cytotoxic T lymphocytes (type IV cytotoxic).

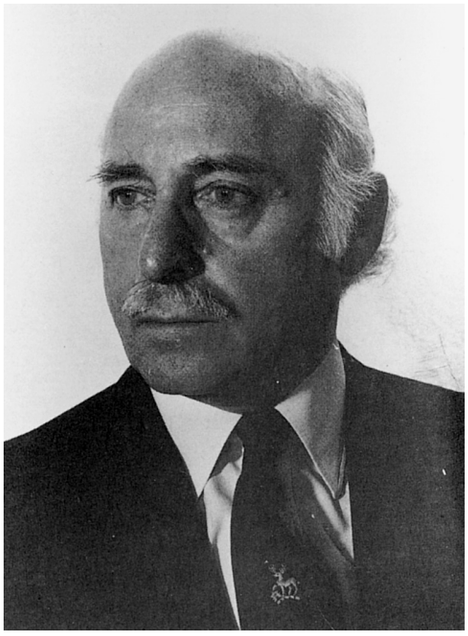


Fig. 1.28 Jack Pepys (1914–96). Identified thermophilic actinomycetes as a cause of farmer's lung. Major contributions to our understanding of the etiology and pathogenesis of allergic alveolitis, occupational asthma, and allergic bronchopulmonary aspergillosis. (From Cohen & Samter 1992, with permission.)

antigen–antibody complex glomerulonephritis, and deposition of antigen–antibody complexes at other sites such as the skin as in certain vasculitic skin rashes.

Type IV reactions refer to situations where specifically sensitized T cells react with allergen or antigen deposited at the local site, as in delayed- or tuberculin-type hypersensitivity. Classical delayed-type hypersensitivity involves predominantly $CD4^+$ T cells with antigen presented in a major histocompatibility complex (MHC) class II restricted fashion. These reactions are characterized by infiltration of T lymphocytes with a restricted cytokine profile. As described below, and in detail elsewhere (see Chapters 3 and 4), these cells preferentially produce interferon (IFN)-γ and interleukin (IL)-2 and are therefore characteristic of the T helper type 1 (Th1) lymphocyte. Contact dermatitis, an important allergic disease, is another example of a type IV reaction with a prominent Th1-type cytokine response. Th2 cells on the other hand elaborate IL-4, IL-5, IL-9, and IL-13 and are involved in atopic allergic reactions as well as parasitic helminthic disease. Some T lymphocyte-mediated hypersensitivity reactions, of which early-onset (insulin-dependent) diabetes is an example, involves $CD8^+$ cytotoxic T cells. These recognize cell-surface antigen presented to T cells in an MHC class I restricted fashion. After cell–cell contact, programmed cell death (apoptosis) of the target is initiated. Although in health, cytotoxic T cells provide a basic "immune" mechanism for dealing with viruses and other insoluble antigens, in the context of insulin-dependent diabetes and graft rejection they mediate a variant of type IV hypersensitivity, termed type IV cytotoxic (see Fig. 1.27). As stated, the effector cell in classical delayed-type hypersensitivity is the CD4 type 1 (or Th1) lymphocyte whereas allergic tissue damage is mediated by Th2 cells. For this reason it is logical that these two forms of cell-mediated hypersensitivity are referred to as type IV Th1 and type IV Th2 respectively, since the initiating event involves T lymphocytes with distinct characteristics (see Fig. 1.27).

The involvement of other classes of T cells or T-cell subsets in allergic reaction is also of current interest and is described in Chapters 3 and 4. Akbari *et al.* (2006) found that 60% of $CD4^+$ T cells in the airways of asthmatics were invariant natural killer (NK)T cells. This finding remains controversial since others have found low numbers of NKT cells in asthma, chronic obstructive pulmonary disease, and controls (Vijayanand *et al.* 2007). There is growing interest in the possible role of Th17 cells in allergic disease although their role remains ill-defined in humans. As discussed in Chapter 3, they are distinct from Th1 and Th2 cells are involved in the initiation of a predominantly neutrophil-rich inflammatory response (Romagnani 2006). Control of allergic inflammation by natural and inducible T regulatory cells is discussed in Chapter 4.

Some hypersensitivity reactions do not fall neatly into the type 1–IV classification. For example, activation of the plasma cascade via factor XII, prekallikrein, and high-molecular-weight kininogen leads to bradykinin formation, the critical mediator of hereditary angioedema (Fields *et al.* 1983).

Concluding comments

The full history of allergy is long and complex and only a relatively superficial account can be given here. The story of direct relevance to atopic allergic disease ranges from the first full description of anaphylaxis in 1903 to the discovery of IgE in the 1960s. Side by side is the unraveling of the structure and biological properties of various biological agents released in the allergic cascade. The coining of the word "allergy" itself, although often misunderstood, laid the foundation for a fundamental rule of immunology, with the concept that humans and animals "alter" their reactivity to antigen when they meet it on second and subsequent occasions.

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(1992); and "A short history of allergological diseases and concepts" by Alain de Weck (1997).

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