Introduction

The allergology just began over 100 years ago around a new knowledge, a new name and new therapeutic interventions that required a high degree of specialization. The new knowledge was organized around the recently discovered immune system and the group of strange diseases it caused in response to harmless agents. The new name was taken from the neologism 'allergy' coined in 1906 by the Viennese paediatrician Clemens von Pirquet, in fact a poorly understood but appealing word. The new therapeutic interventions were mainly non-pharmacological, aimed to reinforce or change the natural immunity. Not many drugs were included in them, in part because a new understanding of the therapeutics and because a shortage of really effective drugs in that time.

In view of this background, it could seem difficult to write an issue of *Pharmacotherapy Revisited* dedicated to allergology. But the next decades of the twentieth century witnessed the development of powerful new drugs that eventually became as important as immunological techniques in the therapeutic armamentarium of allergists. Nowadays, both types of interventions complement one another in the treatment of the complex and prevalent diseases of the immune system studied by allergists.

In this book, the major allergological therapeutic interventions, pharmacological and non-pharmacological, will be presented along with its historical development. Furthermore, we will highlight the authors and seminal papers that contributed to the modern therapeutic in allergology and in this way we will know better the main advances occurred in the history of this young medical discipline. This will be the best way to understand the exciting new therapeutic discoveries about to arrive.

Allergen-specific immunotherapy

Allergen specific immunotherapy is the more distinctive modality of treatment linked to the speciality of allergology. We can certainly say that allergology was developed around immunotherapy and that probably it would not exist without it, at least as now we know it.

Early in the 20th century, with the recent introduction of antitoxins in the treatment of infectious disease, some American authors like H. Holbrook Curtis (1865-1920) and Ephraim Fletcher Ingalls (1849-1918), and the English physician A. T. Schofield made the first attempts to administer pollen to immunize patients affected from hay fever, a disease considered in that time the result of a "pollen toxin" acting on idiosyncratic patients.

But the most outstanding among them was the American physician William Phillips Dunbar (1836-1922), who worked most his life in Hamburg. He devised techniques for collecting pure pollen and analysing its "toxic" content, developed special tests to assess the individual sensitivity of patients and made the first attempts of actively immunizing patients by inoculating pollen extracts. Unfortunately, he employed too high doses that elicited severe systemic adverse reactions, which finally discouraged him to continue this therapeutic modality.

I. **Dunbar WP. Weiterer Beitrag zur Ursache und spezifischen Heilung des Heufiebers. Deutsche Med Wochenschr. 1903;9(29):149-51.**

II. **Dunbar WP. Etiology and specific therapy of hay fever. Ann Otol Rhinol Laryngol. 1903;12(3):487-506.**

As a result, Dunbar changed to a less aggressive treatment and selected to passively immunize patients by administering an antitoxin obtained from animals previously injected with pollen extracts. The antitoxin was marketed in Europe and USA as Pollantin™ by Schimmel & Company with a great success. Much of the Dunbar's work on immunotherapy is summed up in his 1913 English publication:

III. **Dunbar WP. The present state of our knowledge of hay-fever. J Hyg (Lond). 1913;13(2):105-48.**

But the most important feature of Dunbar's work was its determinant influence on two young English allergists belonging to the Inoculation Department of St. Mary's Hospital led by Almroth Wrigth (1861-1947). They were Leonard Noon (1877-1913) and John Freeman (1876-1962). Both adopted Dunbar's pollen toxin theory and his methodology of work, but in opposition to him, they were committed to direct immunization, loyal to the spirit of the Inoculation Department. In 1911, they published two seminal articles formally considered the beginning of allergen-specific immunotherapy, in which they described their positive experience with the pre-seasonal inoculation of progressive doses of a grass pollen extract in a patient cohort:

IV. **Noon L. Prophylactic inoculation against hay fever. Lancet. 1911; 177(4580):1572-3.**

V. **Freeman J, Noon L. Further observation on the treatment of hay fever by hypodermic inoculation of pollen vaccine. Lancet. 1911;178(4594):814-7.**

After the premature death of Noon, Freeman concentrated on the practical issues of extracting pollen, formulating vaccines and developing schedules of administration, a work that ended in the marketing of Pollacine™, the first commercial pollen vaccine and the base of all futures ones. The old toxin pollen theory was soon overcome and substituted by the anaphylactic theory, but inoculations (from then called hyposensitization) went on growing an extended to other allergens. In 1920s, 1930s and 1940s they became part of mainstream medical practice for hay fever and asthma treatment in USA and Europe.

In contrast with the early success of hyposensitization, along these first decades the acceptance of it was only based on the anecdotal experience of physicians. The formal and essential demonstration of its efficacy came in 1950's with two controlled trials, one from England and other from USA:

VI. **Frankland AW, Augustin R. Prophylaxis of summer hay-fever and asthma: A controlled trial comparing crude grass-pollen extracts with the isolated main protein component. Lancet. 1954;i:1055-7.**

VII. **Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. N Engl J Med. 1965;273(13):675-9.**

The definitive name of immunotherapy was not introduced until 1968:

VIII. **Lichtenstein LM, Norman PS, Winkenwerder WL. Clinical and in vitro studies on the role of immunotherapy in ragweed hay fever. Am J Med. 1968;44(4):514-24.**

Beside the subcutaneous route, another ways of administration were investigated to increase immunotherapy safety and facilitate its administration with mixed results. Undoubtedly, sublingual immunotherapy has enjoyed the most success. The first double-blind placebo-controlled randomized trial proving its efficacy was conducted in 1986:

IX. **Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. Clin Allergy. 1986;16(5):483-91.**

Nowadays, the investigation on allergen-specific immunotherapy is continuously advancing, looking for new allergenic extracts, schedules of administration and new indications, including food allergies and atopic dermatitis.

Adrenaline

It was not until the 19th century that the adrenal glands received attention from physicians. Specifically, the French physician Alfred Vulpian (1826-1887) and the German pharmacologist Oswald Schmiedeberg (1838-1921) observed that there was something unique about them.

But the discovery of the existence of an active substance inside adrenal glands, even before the coining of term 'hormone', was demonstrated independently in 1893-4 by the English physicians George Oliver (1841-1915) and Edward A. Schäfer (1850-1935). Both observed potent constrictive effects on blood vessels after oral administration of extracts of adrenal glands of animals, that communicated to The Physiological Society in London on March 10, 1894:

X. **Oliver G, Schäfer EA. Proceedings of the Physiological Society, March 10, 1984. No. I. On the physiological action of the suprarenal capsules. J Physiol. 1894;16(3-4):i-iv.**

The next year, it followed a comprehensive description of many individual experiments on the vascular effects of the extracts:

XI. **Oliver G, Schäfer EA. The physiological effects of extracts of the suprarenal capsules. J Physiol. 1895;18(3):230-76.**

The findings of Oliver and Schäfer were confirmed one year later by two Polish physicians, Wladyslaw Szymonowicz (1869-1939) and Napoleon Cybulski (1854-1919), who additionally showed that the adrenal substance was secreted into the adrenal veins:

Szymonowicz L. Die Function der Nebenniere. Plüggers Arch Ges Physiol. 1895;64:97-164.*

Two pharmacologists, John Jacob Abel (1857-1938) and Otto von Fürth (1867-1938), independently advanced in the process of purification of the active substance present in adrenal glands. The first called the partially purified substance "epinephrine" ("on top of the kidneys" in Greek). But was the Japanese industrial chemist Jokichi Takamine (1854-1922) working in New York who definitively obtained it in 1901 basing on Abel's procedure:

XII. **Takamine J. Adrenalin the active principle of the suprarenal glands and its mode of preparation. Am J Pharmacy. 1901;73:523-31.**

Takamine called the substance "Adrenalin" (with capital "A" and without the "e"; meaning also «on top of the kidneys» but in Latin) and licensed the exclusive production rights to a large US pharmaceutical company, Parke Davis, which marketed it with that trademark.

The existence of different names for the same substance (epinephrine, Adrenalin™, adrenaline –the name widely used in Britain–, suprarenin, and many others) triggered numerous conflicts and discussions, which ended in the preferred current use of "adrenaline" in UK and majority of the rest of Europe and of "epinephrine" in USA referring to the pharmaceutical compound. When considering the natural hormone, the IUPAC recommends the exclusive use of adrenaline.

Nowadays, adrenaline/epinephrine is a very useful drug widely employed in many conditions as shock, cardiac arrest and superficial bleeding. In allergology, this drug is the treatment of choice of anaphylaxis by a parenteral

*Note: Articles over 60 pages have not been reprinted in this volume.

route because its immediate action on α1 and β2 adrenergic receptors. This preeminent role of the drug in anaphylaxis was definitively confirmed in 1986 by Malcolm Fischer in a series of 225 patients who experienced anaphylaxis related to anaesthesia:

XIII. **Fisher MM. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. Anaesth Intensive Care. 1986;14(1):17-21.**

Its initial use in asthma treatment was overtaken by the use of the more selective β-adrenergic agonists.

β_2-Adrenergic agonists

The first attempt to use adrenaline in asthma treatment, occurred in 1903, was erroneously based on the vasoconstrictor effect of the drug, which was hoped to alleviate the turgidity of bronchial mucosa. The authors used Adrenalin™, from Parke Davis, by subcutaneous route and observed a fast response in acute asthma attacks:

XIV. **Bullowa JGM, Kaplan DM. On the hyperdermatic use of adrenalin chloride in the treatment of asthmatic attacks. Med News (NY). 1903;83(14):787-90.**

However, its efficacy was associated with many systemic adverse effects. The inhaled route was later tried and gave fewer adverse effects but did not abolish them.

In the meantime, relevant authors as Thomas Renton Elliot (1877-1961), Otto Loewi (1873-1961), Henry Dale (1875-1968), Hermann Blaschko (1900-1993), Peter Holtz (1902-1970) and many others advanced in the physiology and biochemistry of catecholamines (the chemical group to which adrenaline belongs) and the heterogeneity of their putative receptors. Various adrenergic agonists were synthetized. Outstanding among them became isoprenaline, with a particularly potent action on bronchus and a significant one on heart. Boehringer introduced it for subcutaneous or inhaled use in asthma in 1940. It became a very good bronchodilator but overdosage caused numerous deaths due to cardiac side effects.

In 1948, an important advance took place. The American pharmacologist Raymond P. Ahlquist (1914-1983) defined the α and β types of adrenergic receptors:

XV. **Ahlquist RP. A study of the adrenotropic receptors. Am J Physiol. 1948;153(3):586-600.**

The discovery was additionally refined by the definition of subtypes of β-adrenoceptors, being the β_2 subtype responsible for bronchodilator and vasodilator effects of the group of drugs called from then β_2-agonists. The discovery was made by A.M. Lands et al. working at Winthrop Research Laboratories (USA):

XVI. **Lands AM, Arnold A, McAuliff JP, Luduena FP, Brown TG. Differentiation of receptor systems activated by sympathomimetic amines. Nature. 1967;214(5088):597-8.**

The searching of a more selective β_2-adrenergic agonist culminated in the synthesis of salbutamol (Ventolin™) in 1967 by the group of David Hartley at Allen & Hamburys Ltd (later Glaxo), a drug derived from the molecule of isoprenaline. Almost simultaneously, the team of researchers of Astra Co. led by Kjell Wetterlin developed terbutaline, with similar structure and pharmacologic profile. Both drugs showed fewer side effects than isoproterenol because a weaker action on cardiac receptors and a stronger action on bronchial receptors but a similar short duration of the bronchodilator effect. In the 1990's were finally introduced the long-acting β_2-agonists salmeterol (marketed by Glaxo) and formoterol (marketed by AstraZeneca), today mainly used in association with glucocorticoids as inhaled combination therapy. The last marketed β_2-adrenergic agonist for asthma treatment is the salmeterol-derived drug vilanterol, an extra-long-acting β_2-agonist with 24 hours of action launched by Glaxo in 2014.

Antihistamines

In 1910, Henry Dale (1875-1968) performed some investigations on the physiological properties of histamine (then called β-iminazolylethylamine), a recently discovered putrefaction product of histidine. He initially believed that this amine was a transmitter in the autonomic nervous system, although it resulted to be a more complex amine than he originally thought:

XVII. **Dale HH, Laidlaw PP. The physiological action of β-iminazolylethylamine. J Physiol. 1910;41(5):318-44.**

Simultaneously, Dale was interested in the topic of anaphylaxis and its mechanisms, and the similarities between manifestations of anaphylaxis and physiological effects of histamine led him to link both in a seminal article published in 1919:

XVIII. Dale HH, Laidlaw PP. Histamine shock. J Physiol. 1919;52(5):355-90.

The central role of histamine in anaphylaxis in man would be confirmed years later by several authors. It was in this context that Daniel Bovet (1907-1922) started in 1930s to look for some substance which exerted a specific antagonism toward histamine, like it occurred with respect to others naturally occurring amines as acetylcholine and epinephrine. Thymoxyethyldiethylamine (929 F), an amine with a phenolic ether function, was the first of such a substances. It also possessed sympatholytic properties.

XIX. Bovet D, Staub AM. Action protectrice des éthers phénoliques au cours de l'intoxication histaminique. CR Seances Acad Sci. 1937;124:547-9.

But the first antihistamine introduced in clinic was an aniline compound, also with sympatholytic actions. Its name was N-diethylaminoethyl-N-benzylaniline (Antergan™) and was discovered by Bernard Halpern from the Institute Pasteur in Paris:

Halpern BN. Les antihistaminiques de synthèse. Essais de chimiothérapie des états allergiques. Arch Int Pharmacodyn Ther. 1942;681:339-408.*

In the next decade, it followed diphenhidramine, chlorpheniramine and promethazine, and afterwards many new ones. These earliest antihistamines resembled histamine in their chemical structure, but progressively chemicals with different structures showed antihistamine properties, as ethanolamines, ethylene diamines, alkylamines, piperazines, piperidines and phenothiazines. Furthermore, the diverse "anti-amine" actions of these substances led to develop other drugs with new indications, as antipsychotics and antidepressants.

The last major advance in antihistamine development was the introduction of more selective second-generation antihistamines from the 1980s, with fewer side effects and longer half-lives.

Glucocorticoids

In 1900, the American physician Solomon Solis-Cohen (1857-1948) first reported the beneficial effect of an orally administered adrenal gland extract in asthma, a benefit erroneously attributed at first to its content in the recently discovered substance called adrenaline (which cannot be orally absorbed):

XX. **Solis-Cohen S. The use of adrenal substance in the treatment of asthma. JAMA. 1900;XXXIV(19):1164-6.**

The real cause of its effect was discovered several years after thanks to the collaborative efforts of two men: Philip Showalter Hench (1896-1965) and Edward C. Kendall (1896-1972). In 1930s, Hench, a rheumatologist at the Mayo Clinic, noted that several patients with "arthritis" started to improve when they became jaundiced:

XXI. **Hench PS. Analgesia accompanying hepatitis and jaundice in cases of chronic arthritis, fibrositis and sciatic pain. Proc Staff Meet Mayo Clin. 1933;8:430-7.**

He postulated that an innate 'substance X' was responsible for the effect, and a number of observations led him to suspect in adrenals as possible source of it. Fortuitously, Hench became friends with the American chemist E. C. Kendall and, from 1935, they collaborated attempting to isolate and purify the adrenal hormones. By 1940, 28 compounds had been isolated; among them, compound E (17-hydroxycorticosterone or "cortisone") appeared particularly active and was identified as the mysterious 'substance X'.

But many technical problems had yet to be overcome in the next years. Only after an important investment from Merck and Company, a group of patients with diverse arthritis was successfully treated with compound E and the results firstly presented at the regular Wednesday night meeting of the Mayo Clinic in 1949:

XXII. **Hench PS, Kendall EC, Slocumb CH, Polley HF. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and the pituitary adrenocorticotrophic hormone on rheumatoid arthritis. Preliminary report. Proc Staff Meet Mayo Clin. 1949;24(8):181-97.**

Afterward, they published their findings in a prestigious medical journal:

> **Hench PS, Kendall EC, Slocumb CH, Polley HF. Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions. A study in clinical physiology. Arch Intern Med. 1950;85(4):545-666.***

In the same year of 1950, and because their discovery, Hench and Kendall won the Nobel Prize in Medicine or Physiology with T. Reichstein, who had separately isolated cortisone prior to them but without recognizing its biological relevance. Cortisone was first produced commercially in 1949 and soon became a standard treatment for several conditions.

One of them was asthma. The first formal attempt to treat this entity was made by the UK Medical Research Council through a placebo-controlled multicentre trial that, surprisingly, got disappointing results because of the inclusion of patients with chronic obstructive pulmonary disease:

> XXIII. **Controlled trial of effects of cortisone acetate in status asthmaticus. Report to the Medical Research Council by the Subcommittee on Clinical Trials in Asthma. Lancet. 1956;268(6947):803-6.**

One of the investigators, Jack Pepys, allergist at the Brompton Hospital, carefully selected asthma patients and showed a marked clinical improvement in this subgroup, but this was not published. Despite the poor results of the published trial, the efficacy of oral glucocorticoids became obvious to physicians and was increasingly used in patients with asthma and allergic disease worldwide.

The efficacy of oral cortisone in asthma was soon associated with significant adverse effects on metabolism, bones and growth in children immediately suggesting the need of an inhalational route of administration. Cortisone and the next commercially available glucocorticoid, dexamethasone, proved to be of little benefit by inhalation, but this was not the case of another new compounds. The first glucocorticoid developed for inhalation was beclomethasone dipropionate by the group of David Jack (1923-2011) at Allen/Hanburys/Glaxo, and its efficacy and safety was proved by Harry Morrow in 1972:

> XXIV. **Morrow Brown H, Storey G, George WHS. Beclomethasone dipropionate: a new steroid aerosol for the treatment of allergic asthma. Br Med J. 1972;1:585-90.**

Afterwards other topical glucocorticoids were developed for treating both asthma and rhinitis with different pharmacodynamic profiles and potencies.

Today, glucocorticoids remain the most effective anti-inflammatory drugs available for the treatment of allergic disease.

Chromones

The development of the chromones took place in the 1950's at Benger Laboratories in England. This company marketed an organic compound called khellin extracted from the seed of *Ammi visnaga*. A soup made from this plant has been used in Egyptian folk medicine to relieve renal colic for centuries and, after the later identification of khellin, the compound was marketed as smooth muscle relaxant by the aforementioned laboratory with the name of Benecardin™. The efficacy of khellin by parenteral route in bronchial asthma was demonstrated in 1947 by G. V. Anrep:

XXV. Anrep GV, Kenawy MR, Barsoum GS, Misrahy G. Therapeutic uses of khellin. Method of standardisation. Lancet. 1947;249(6452):557-8.

This prompted Benger Laboratories to develop a research program to synthesise derivatives of khellin that could be administered orally or by inhalation for the treatment of asthma. First, they screened various khellin analogues by pre-treating guinea pigs and then challenging them with an aerosol of histamine. But in 1956, Roger E. C. Altounyan (1922-1987), an asthmatic physician, joined to Benger Laboratories, and the screening method was extended to a human model: himself. From that moment, every new compound was screened studying its ability to prevent the anaphylactic release of histamine and slow reacting substance (SRS) from guinea pigs and then its ability to reduce the severity of an induced asthmatic attack on Altounyan. In 1961, over 130 compounds have been obtained, and the one called BLA8 seemed the more suitable (83% of inhibition of histamine release and 78% of SRS release in the model animal and >70% of protection of asthmatic attack at 1 hour and 30% at 6 hours).

The clinical trials made at Brompton Hospital by Jack Pepys with BLA8 and BLA13 were not good enough, and finally, after many new attempts, disodium cromoglycate was synthetized late in 1964, a new derivative that provided >50% of protection in Altounyan for 6 hours through the inhalational route.

The new chromone was tested associated with isoprenaline in a double-blind trial in ten patients and showed a significant clinical improvement:

XXVI. **Howell JBL, Altounyan REC. A double-blind trial of disodium cromoglycate in the treatment of allergic bronchial asthma. Lancet. 1967;290(7515):539-42.**

In a time when the standard asthma treatment consisted on inhaled bronchodilators as isoprenaline and, in severe cases, oral glucocorticoids, the discovery of cromoglycate was a very important advance. This article showed for the first time the efficacy and safety of a new class of drug and led to the launch of Intal Compound™ by Benger Laboratories (20 mg of cromoglycate and 0,1 mg de isoprenaline). Numerous additional clinical trials confirmed the efficacy of cromoglycate, which finally was marketed without the isoprenaline due to clinicians and regulatory authorities criticisms.

The real mechanism of action of cromoglycate, the stabilisation of mast cells, was definitively demonstrated by Goose and Blair in 1969:

XXVII. **Goose J, Blair AMJN. Passive cutaneous anaphylaxis in the rat, induced with two homologous reagin-like antibodies and its specific inhibition with disodium cromoglycate. Immunology. 1969;16(6):749-60.**

However, the use of inhaled cromoglycate in asthma has declined in recent years because the introduction in therapeutic armamentarium of newer and more potent drugs. But this chromone remains widely used in allergic conjunctivitis, allergic rhinitis, food allergy and systemic mastocytosis and its interest and relevance are notorious in allergic disease and allied conditions.

Antileukotrienes

The history of antileukotrienes dates back to 1940s, when an unidentified substance apart from histamine was found by Kellaway and Trethewie in the perfusate of the lungs of sensitised animals after the anaphylactic response:

XXVIII. **Kellaway CE, Trethewie ER. The liberation of a slow-reacting smooth muscle-stimulating substance in anaphylaxis. Q J Exp Physiol Cogn Med Sci 1940;30(2):121-45.**

In contrast with histamine, this substance induced a slow contraction of smooth muscle; this was the reason why the authors called it "slow-reacting substance" (SRS) of anaphylaxis. The structure of SRS remained unknown waiting advances in purification technology until 1979, when the group of Bengt Ingemar Samuelsson (1934-) of Karolinska Institute found that it consisted of a mixture of arachidonic acid metabolites, which they called leukotrienes (A to C; at a later time named LTC4, LTD4 and LTE4). Samuelsson later won the Nobel Prize in Medicine and Physiology in part for this discovery.

XXIX. **Murphy RC, Hammarström S, Samuelsson B. Leukotriene C: a slow-reacting substance from murine mastocytoma cells. Proc Natl Acad Sci U S A. 1979;76(9):4275-9.**

The discovery and the compelling evidences of the importance of leukotrienes in asthma led several pharmaceutical companies to establish programs to develop programs looking for substances with antileukotrienic properties. One of them, Merck Frosst of Dorval, played a central role by making synthetic leukotrienes available to asthma researchers around the world. By the early 1990s, several compounds had been developed but a few were disappointing because of the lack of potency and specificity. The antileukotrienes finally available to treat asthma were three receptor antagonists for leukotriene D_4 (montelukast, zafirlukast, pranlukast) and one 5-lypoxygenase inhibitor (zileuton), all formulated to the oral route for children and adults.

From 1993, various published controlled trials showed the efficacy and safety of antileukotrienes in asthma, and of all of them seemed comparable and equivalent to a low-dose of inhaled corticosteroids. When administered in association with inhaled corticosteroids, antileukotrienes permitted a decrease in the dosage of them and were specially effective in ASA-sensitive asthmatic patients. The oral administration was particularly advantageous in young children.

Nowadays, the main advantages of antileukotrienes are the oral route of administration, its action on a different site in inflammation cascade from glucocorticoids and its very good safety profile. The main pitfall is to predict which patients will respond to them.

Anti-IgE monoclonal antibody and new biological agents

Since its discovery in 1967, the long-time elusive IgE was considered a major potential therapeutic target in allergic diseases. Twenty years after, in 1987,

the Taiwanese physician Tse Wen Chang, then in Baylor College of Medicine in Houston, was the first to rationalize the concept of using an antibody targeting free IgE and membrane-bound IgE on B cells to treat allergic diseases. In order to not trigger anaphylaxis nor cause lysis of cells bearing IgE receptors, the antibody should recognize only that part of the IgE molecule that interacts with the IgE receptor. The first steps in the development of this monoclonal antibody were made in the biotechnology company Tanox founded by Tse Wen and his wife and also researcher Nancy T. Chang. The description of the production of the monoclonal antibody was published in 1990 in a seminal article:

XXX. **Chang TW, Davis FM, Sun NC, Sun CRY, MacGlashan DW, Hamilton RG. Monoclonal antibodies specific for human IgE-producing B cells: a potential therapeutic for IgE-mediated allergic diseases. Bio/Technology. 1990;8(2):122-6.**

In 1990, Tanox signed a collaborative agreement with Ciba-Geigy (which merged with Sandoz to form Novartis in 1996) to develop the anti-IgE program. After extensive *in vitro* and animal experiments, one murine antibody called CPG 51901 was selected to clinical trial. For the first time, Jonathan Corne et al. demonstrated that this anti-IgE antibody was safe and effective in reducing levels of circulating IgE in allergic patients:

XXXI. **Corne J, Djukanovic R, Thomas L, Warner J, Botta L, Grandordy B, et al. The effect of intravenous administration of a chimeric anti-IgE antibody on serum IgE levels in atopic subjects: efficacy, safety, and pharmacokinetics. J Clin Invest. 1997;99(5):879-87.**

Several subsequent Phase II trials confirmed these results and CPG 51901 was further developed into a humanized antibody, TNX-901. While this anti-IgE program was evolving, one American group led by the immunologist Leonard G. Presta, from a competing company named Genentech, presented in 1993 an anti-IgE humanized monoclonal antibody called omalizumab. Tanox soon reacted filling a lawsuit against Genentech for trade secret violation, because the first had disclosed its anti-IgE technology to the latter a few years before to evaluate a potential corporate partnership. After years of legal entanglement, in 1996 Tanox, Novartis and Genentech formed a tripartite partnership to develop the anti-IgE program, and omalizumab was selected to further development because a better manufacturing process. From then, many clinical trials have confirmed the efficacy and safety of omalizumab in severe allergic asthma. The next one was especially relevant for this purpose:

XXXII. **Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005;60(3):309-16.**

Omalizumab was approved by the U.S. FDA in 2003 to treat patients over 12 years old with moderate to severe allergic asthma, and soon many other countries followed. The antibody is now being tested in many other allergic diseases as allergic rhinitis and food allergy. In 2014, the indication was even expanded to include chronic spontaneous urticaria, a non-allergic disease. This has opened the possibility to treat with omalizumab other relevant non-allergic diseases, like IgE-independent asthma, in which IgE could play an important and sometimes unknown role. The only major disadvantage of omalizumab are its high cost and the requirement for long-term administration, but it certainly represents the major therapeutic advance in last two decades in allergology. Furthermore, and perhaps more important, it has opened the door to new monoclonal antibodies for the treatment of allergic disease.

At the moment of editing this book, a new monoclonal antibody against interleukin 5, named mepolizumab, has been approved for the treatment of refractory severe eosinophilic asthma, and two more, reslizumab and benralizumab, are on the way, like many others against several relevant interleukins. This type of biological agents will permit a more individualized treatment of severe asthmatic patients matching the patient disease characteristic with the very specific biological therapeutic effect. This will allow an unknown precision in the treatment of allergic and related diseases.