Chapter 1
Introduction

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Abstract Since the first description of hay fever by John Bostock in 1819, the role of pollen in the pathogenesis of allergic diseases is well established now. Most important allergic diseases are asthma and rhinitis, which affect from 5 to 30% of the population in industrialized countries. The standardization of pollen count protocols and the creation of wide and coordinated networks have provided an invaluable tool for epidemiological and clinical studies and, more recently, for a better understanding of the effects of climate change on plants producing allergenic pollen and on allergic diseases. Significant advances occurred in allergy diagnostic with the use of recombinant molecules. Thanks to new methods for airborne allergen measurement, the same development occurred in aerobiology, thus shedding a new light on the relationship between pollen and allergic diseases.

Keywords Allergic diseases • Asthma • Rhinitis • Pollen • Aerobiology

1.1 Allergenic Pollen

"About the beginning or middle of June in every year … A sensation of heat and fullness is experienced in the eyes …. To this succeeds irritation of the nose producing sneezing. To the sneezing are added a further sensation of tightness of the chest, and a difficulty of breathing" (Bostock 1819). This is the first description of hay fever, published in 1819 by John Bostock. More than 50 years later, in 1873, pollen was recognized as the cause of this clinical picture by Charles Harrison Blackley (1873), who also performed the first skin prick test on his own arm. Since then, thousands

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of papers have been published on this issue and nowadays the role of pollen in the pathogenesis of allergic rhinitis, asthma and conjunctivitis is well established. Epidemiological studies and clinical trials designed with the aim to evaluate the efficacy of antiallergic drugs and specific immunotherapy confirmed early results about the importance of pollen in the seasonal allergic disorders, although inconsistently in some cases. Indeed, several questions are still open.

Aerobiology (from Greek ἠρ, aēr, "air"; βίος, bios, "life"; and -λογία, -logia) is a branch of biology that studies organic particles, such as bacteria, fungal spores, pollen grains and viruses, which are passively transported by the air. Aerobiologists played a key role in the understanding of the relationship between allergic diseases and pollen, especially through the standardization of the procedure for the assessment of pollen concentration in the atmosphere. Pollen count has being used for over 50 years for the assessment of allergen exposure both in clinical practice and clinical and experimental studies. The method, proposed by Hirst (1952) is based on the identification and count with a microscope of pollen and spores collected with a volumetric trap and provides the standard for the national networks which are currently covering most of the European continent. This type of airborne particle assessment presents several advantages: it allows a comprehensive evaluation of airborne particles with a wide spectrum of applications; long time-series are now available, which can be used for pollen calendars and for research purposes. To this regard 20–25 years long datasets provide an extraordinary tool for climate change studies, showing both changes in the past decades and providing the basis for modelization of future scenarios (Cecchi et al. 2010). However, proof is insufficient that pollen count is representative for allergen exposure, thus providing the explanation of some controversial results of epidemiological studies aimed at showing the effects of pollen on respiratory allergic diseases, especially on asthma.

1.1.1 Pollen-Related Allergic Diseases

Rhinitis, conjunctivitis and asthma are the typical clinical pictures of allergy to pollen and they often occur in the same patient simultaneously during the pollen season.

Asthma is a chronic inflammatory disease of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness and coughing (GINA 2009). Exposure to allergens represents a key factor among environmental determinants of asthma, which also include air pollution (Eder et al. 2006). Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose. Symptoms of rhinitis include rhinorrhea, nasal obstruction, nasal itching and sneezing which are reversible spontaneously or under treatment (Bousquet et al. 2001). Pathophysiological and clinical studies have strongly suggested a relationship between rhinitis and asthma. However, epidemiology provides the most convincing data, showing that the prevalence of asthma in patients with rhinitis varies from 10 to 40 % depending on the study. Moreover, allergic rhinitis is correlated to, and

constitutes a risk factor for, the occurrence of asthma (Bousquet et al. 2008). Taken together, these data have lead to the concept that upper and lower airways may be considered as a unique entity influenced by a common, evolving inflammatory process. Conjunctivitis is also commonly associated to pollen-induced rhinitis.

1.1.2 Mechanisms

Type I allergies are mediated by the production of IgE specific for otherwise harmless environmental substances, most of which are proteins. Most allergenic molecules that elicit IgE-mediated immune responses are derived from plants, animals and fungi.

Sensitization occurs at the site of allergen exposure, such as the airways and skin, but can also occur through the gastrointestinal tract. However, not everybody who is exposed will become sensitized and have allergies. Aside from the individual exposure conditions, there is a high variability in the individual responsiveness to a given allergen dose.

The most important allergen carriers in the outdoor air are pollen – with a diameter between 15 and 60 μm – from anemophilic plants such as trees, grasses and weeds. However, whole pollen grains are too large to penetrate the small airways. Since pollen is able to evoke IgE-mediated allergic reactions within seconds after contact with the mucosa, pollen allergens must be extremely water soluble and readily available. In fact allergen liberation from pollen grains can occur on the mucosal surface of the upper respiratory tract after exposure to pollen (Behrendt and Becker 2001). Symptoms can be explained by the interaction between the antigen and its corresponding IgE antibody and this phase is situated at the end of a cascade of events leading to allergy.

The experimental data of Bacsi et al. (2005, 2006), Boldogh et al. (2005) and Traidl-Hoffman et al. (2002) provide additional evidence that pollen fragments, containing NAD(P)H oxidases and lipid particles, can amplify the immune response by producing reactive oxygen species (ROS) as well as chemo-attractants. To this regard, this pollen-mediated mechanism seems to be able to induce a non-specific inflammatory response at the mucosal level (Traidl-Hoffmann et al. 2009), providing a possible explanation of some data showing an association between pollen count and hospital admissions of nonallergic diseases (Besancenot 2011).

Patients affected by respiratory allergy are subjected to inhalation of aerosols of pollen, pollen fragments, air pollutants and other caustic chemicals. The relative importance of this mixture of pro-inflammatory agents in the airways and their interactions still needs to be clarified.

Numerous studies have shown that air pollution is consistently associated with adverse health effects and it has a quantifiable impact on respiratory diseases, on cardiovascular diseases and stroke (Dockery and Stone 2007). Positive associations have been observed between urban air pollution and respiratory symptoms in both adults and children (D'Amato et al. 2010), and the literature reports of a relation

between motor vehicle exhausts and acute or chronic respiratory symptoms in children living near traffic (Ryan et al. 2005). Air pollution can also negatively influence lung development in children and adolescents (Gauderman et al. 2007).

In the so called thunderstorm, asthma fragments of pollen might play a role. A thunderstorm is an extreme weather event with dramatic consequences on respiratory asthma, as showed in the last 15 years with asthma outbreaks during thunderstorms worldwide (D'Amato et al. 2007a). Despite some uncertainties, a mechanism underlining asthma epidemics might be pollen grains that rupture by osmotic shock and release part of their content, including respirable, allergen-carrying starch granules (0.5–2.5 mμ) into the atmosphere (Taylor and Jonsson 2004).

Thunderstorms have often been linked to epidemics of asthma, especially during the grass and molds season (Marks and Bush 2007), even if other pollens might be involved (D'Amato et al. 2008).

1.1.3 Epidemiology

Type I hypersensitivity reactions, such as allergic rhinitis and asthma, are the most common allergic diseases, with current prevalence rates ranging from 5 to 30 % in industrialized countries (Asher et al. 2006).

Pollen allergy has a remarkable clinical impact all over Europe and there is a body of evidence suggesting that the prevalence of respiratory allergic reactions induced by pollens in Europe is on the increase (D'Amato et al. 2007b; ECRHS 1996; ISAAC, 1998; Burney et al. 1997). In fact, for the past 40 years, the prevalence of asthma has increased, and it is still increasing worldwide in parallel with that of allergy (Law et al. 2005) even if recent findings of the phase three of ISAAC study showed the absence of increases or little changes in prevalence of asthma symptoms, allergic rhinoconjunctivitis and eczema for European centres with existing high prevalence in older children (Asher et al. 2006). This data suggests that it might possible be that the increase is coming to an end especially in some western countries (von Hertzen and Morais-Almeida 2005).

Since airborne-induced respiratory allergy does not recognize national frontiers, the study of pollinosis cannot be limited to national boundaries, as obviously happens with most diseases that can be prevented by avoiding exposure to the causative agent. In Europe, the main pollination period covers about half the year, from spring to autumn.

1.1.4 Towards a Molecular Era of Allergology and Aerobiology

Thanks to the development and progress made in the field of recombinant allergens, allergy diagnostic has changed in the last 10–15 years, moving from the use of extracts for both *in vivo* and *in vitro* diagnostic to the so called "Component Resolved

Diagnosis" (CRD), a tool that characterises each patient's IgE antibody profile to individual allergen components, thereby discriminating between genuine sensitisation to certain specific allergen sources and cross-reactivity (Sastre 2010). This new approach is particularly useful for a better identification of patients to be treated with specific immunotherapy. To this regard, companies are now producing extracts for immunotherapy standardized according to the content of major allergens expressed in mcg/ml, as suggested by the last guidelines for sublingual immunotherapy (Canonica et al. 2009).

As expected, Aerobiology is developing in the same direction. Allergen count is based on the measurement of the concentration of single allergenic components in the air, collected with special devices which suck a higher volume of air than the classic Hirst-type pollen trap. After the early observations by Schäppi et al. (1999) a number of papers have been published in the last 10 years. Nowadays we use to call "molecular aerobiology" this new branch of Aerobiology. So far, research focused on grass pollen (Phl p 5 and Lol p 1), birch (Bet v 1), olive (Ole e 1), wall pellittory (Par j 1 and Par j 2) allergens mainly in Australia (Schäppi et al. 1999), Germany (Buters et al. 2008, 2010) and Spain (De Linares et al. 2007, 2010; Jato et al. 2010; Moreno-Grau et al. 2006). In these studies different methods for allergen measurement and collection were used which explains several inconsistencies between the papers published in this field. However, almost all authors indicate that allergen concentration deviates from pollen count and that this is due to a number of factors.

Despite several questions are being left, it is now clear that monitoring the allergen itself in ambient air might be an improvement in allergen exposure assessment. These new methods are already contributing to the clarification of some aspects of exposure to airborne allergens, such as the debated importance of pauci- and sub-micronic particles or the clinical thresholds.

Even if it is the time to move towards the allergen count, we still need "classic" pollen count and the combination of the two methods seems to be the best choice in the medium term. Allergen count is still limited by cross-reactivity between allergens, lack of homogenization of methods and devices, unavailability of long time-data sets and high costs.

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