Plant Food Allergens
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Preface
Historical and Cultural Background to Plant Food Allergies
PAUL J. DAVIS

This book is concerned with a paradox of immense, potentially life-threatening significance to about 1 in 100 adults and nearly 1 in 10 children, within the European Union. The paradox is that certain nutritious proteins from wholesome foods can act as if they were harmful, sometimes deadly, poisons to otherwise normal people unfortunate enough to possess a food allergy. And, although immunologists have been occupied with the whole problem of allergy throughout the twentieth century, we enter the twenty-first century with a vast number of questions still unanswered. Whilst the lives of food-allergic patients have certainly been improved through the understanding gained so far, an allergic individual is still haunted by the ever-present threat of inadvertent exposure to the allergen – an event that could have devastating consequences. The impact of this constant fear on the lives of caring parents with a food-allergic child, for example, is immense, and can only be appreciated by those who have experienced at first hand the torment involved. There can be no doubt that food allergy is a major, unsolved problem of great economic, social and personal significance. And the problem is getting even worse, because of the current trend in the developed world for an increasing diversity of foods to be routinely available, with an ever-increasing variety of complex recipes and formulations.

So, there is still much to do, and the EU-funded European network, called PROTALL, brought together over 30 scientists with a particular blend of expertise relevant to studying the complex problems of food allergy. In order to shed new light on this persistent problem, the network deliberately combined the diverse insights of clinicians, food scientists and plant biologists, with a focus on the relationship between the allergenic potential of plant food proteins, their molecular structures, their biological activities, their processing history and their interactions with other food components, such as fats. Such diverse groups of experts are rich sources of creative insights and fresh thinking – a far cry from the old, restricted membership of the New York Allergy Roundtable Discussion Group founded between the World wars. Typical of the attitudes of the time, this august and ground-breaking body was restricted entirely to clinicians until 1949, when the first basic scientist, Merrill W. Chase, PhD, was admitted!

The PROTALL network concluded at the end of 2000, and this book is largely based on the outcome of its investigations. Whilst the literature is rich with information on the topic of food allergy, this is the first book to present a coherent account of plant proteins as allergens to humans. It begins to make sense of why some types of proteins are more allergenic than others, and provides a unique source of information on particular groups of proteins in relation to their structure, function and phylogenetic relationships. These insights can bring us closer to the elusive but much to be prized ability to predict the allergenicity of food proteins. The mysteries are gradually being unravelled by identifying key physicochemical properties common to known allergens and by working out which particular chemical structures (epitopes) are
recognised by immunoglobulin E (IgE) antibodies. These types of study have already shown that if a protein is stable through processing (e.g. acid and heat-treatments) and resistant to digestion, it is more likely to be an allergen than one that is easily degraded.

Usually, food allergy research has (for very good reasons) involved the use of purified proteins, following the typical reductionist approach that helps to make sense of complex problems. But now it is time to move on, for this grossly simplified situation does not resemble that which results from the ingestion of food as eaten, when complex mixtures of proteins, usually in a highly processed form, interact together and with other food components during cooking, eating and digestion. For example, lipid-binding proteins will normally be associated with lipids when they occur within food, rather than being in a free state or dissolved in water. For this reason, the PROTALL studies have included investigations of the interactions and fate of key proteins within realistic mixtures and processes, thus getting to grips with what actually happens in food.

It is important to appreciate that the allergic reactions studied in this project relate to the most common and easily diagnosed food allergies, known as Type I-hypersensitivity reactions. It includes neither the less clear-cut condition defined as food intolerance, nor those adverse reactions caused by other immunological and toxicological mechanisms. Type I-hypersensitivity reactions are mediated by IgE antibodies, and have a rapid onset and, usually, a brief duration. Judged by the vanishingly small amounts of IgE in the serum, IgE would have seemed an insignificant player in the complex drama of the immune system. But the low serum levels of IgE are very deceptive, for most of the IgE in the body is to be found on the surface membranes of the vast population of mast cells in the tissues and basophils in the blood, held in place by specific receptors. More dramatically, the true significance can be judged by the overall effects on the whole body.

So what are these effects, usually summarised rather blandly as the allergic reaction? It was Carl Prausnitz and Heinz Kustner, two clinicians at the Institute of Hygiene in Breslau, who first began to make the link between an undetectable serum component and the symptoms of food allergy (termed by them supersensitivity), when they published in 1921 a remarkably insightful paper that brought about a step change in understanding [1]. They were intrigued by the observation that Kustner was supersensitive to cooked fish (not raw), and decided to undertake some bold, novel experiments in order to shed light on this mysterious idiosyncrasy. The closely observed, meticulously described account of Kustner’s reaction on eating the merest trace of marine or freshwater fish is as good an account of the symptoms of food allergy as any that have been written, and it is repeated it here, exactly as translated by Prausnitz, himself [2], from the original German:

After half an hour there is itching of the scalp, neck and lower abdomen, with a dry sensation in the throat; soon afterwards, there is swelling and congestion of the conjunctivae, severe congestion and secretion of the respiratory mucous membranes, intense fits of sneezing, irritating cough, hoarseness merging into aphonia and marked inspiratory dyspnoea. The skin of the entire body, especially the face, becomes highly hyperaemic, and all over the body there are numerous very itching wheals, 1–2cm large, which show a marked tendency to confluence. Increased
perspiration has not been noted. After about 2 hours, heavy salivation starts and is followed by vomiting, after which the symptoms gradually fade away. Temperature, cardiac and renal functions have always been normal. After 10 or twelve hours, all the symptoms have disappeared; only a feeling of debility persists for a day or so. After each attack, there is a period of oliguria and constipation; this may be due to dehydration and vomiting, but perhaps it is better explained by retention of water similar to what occurs in serum sickness.

Despite this dramatic sequence of events, they concluded that, although they could not identify the cause (there were no detectable precipitins nor complement-binding and neutralising antibodies), the effect could be transferred with the serum. This meant that when a little of Kustner’s serum was injected into the skin of Prausnitz, a typical wheal and erythraema reaction occurred at the injection site, when appropriate allergen was locally administered 24 hours later. To their surprise, this local hypersensitivity persisted for more than four weeks, leading to the conclusion that the transferable serum factor was binding to the cells in the injection site. They were, of course, transferring without knowing it, human IgE.

At last, Prausnitz and Kustner were beginning to shed light on this mystery for, even though they had not demonstrated the nature of the allergy-causing agent, the effect bore all the hallmarks of an antibody, as shown in other antibody-dependent passive transfer experiments known at the time. The name of Prausnitz continued to be associated with allergy research and diagnosis for many decades, partly because the Prausnitz–Kustner test (or P–K test), derived from this classic experiment, became a standard investigative tool, until it was appreciated that the risk of transferring hepatitis with the test serum was too great to justify its use. But there was another way in which Prausnitz came to exercise a benign and helpful influence on the international allergy research community, which adds a fascinating footnote to the history of allergy research. During the 1920s and 1930s he enjoyed a sparkling academic career in Germany, holding the Chair of Hygiene and Bacteriology in the University of Breslau from 1926–1933 and becoming Director of the State Institute of Hygiene. His next move was almost certain to have been to the Prime Chair of Bacteriology in Berlin but, finding it impossible to live and work under the curse of Nazism, he and his family moved to England, where he had a license to practise medicine. After just a couple of difficult years performing research on respiratory dust disease in Manchester, he chose a completely different career path and became a country GP at Ventnor on the Isle of Wight. At this point, he adopted his mother’s family name and he became known locally simply as Dr C.P. Giles, earning the epitaph of beloved physician. He worked in this role until about 1960, and the author is privileged to have been one of his patients in childhood on the Isle of Wight. At the local level, very few of his patients knew of the academic stature of this great man in their midst, but he did sometimes attend meetings of the influential Collegium Internationale Allergologicum in the 1950s, where he was known affectionately as Father Giles [3]. A photograph taken at this time is shown in Fig. 1, together with a photograph taken at the height of his academic career when he was about 50. He continued to exercise a wise and helpful influence on allergy research throughout his years on the Isle of Wight, recognised by the fact that he was invited to write the Foreword of the first
edition of the hugely influential book Clinical Aspects of Immunology by Gell and Coombs, which appeared in 1963, a few weeks after his death. Not only had he written the Foreword, but also he had read all the proofs and made many helpful suggestions. It is fascinating to observe that the Isle of Wight has now become well known again in the area of food allergy research, with the long-term child population studies that are conducted there. Prausnitz would have been delighted by this work, and it seems fitting that it should take place in the locality he had chosen to make his home.

It might have seemed that the progress made by Prausnitz and Kustner in 1921 was well overdue, for the symptoms experienced by Kustner had first been seen by Magendie in 1839 [4], when he observed the sudden death of dogs resulting from repeated injections of egg albumin. The same basic effect was rediscovered in 1902 when two French clinicians, Portier and Richet [5] observed similar effects when trying to prepare an antitoxin against jellyfish venom from the Portuguese man-of-war. In model experiments with toxin from sea anemones, they found that immunised dogs developed a rapid sequence of allergic symptoms (recognisable now as anaphylaxis), when challenged several weeks later with an identical sub-lethal injection. It was these two workers who coined the term anaphylaxis (greek, ana-against and phylaxis-protection), and in 1913 Richet was awarded a Nobel prize for his work on this condition.

Even with these important advances in understanding through the first 21 years of the twentieth century, the pace of development was not fast. It was not until the mid-1960s that the husband and wife team of Kimishige Ishizaka and Teruko Ishizaka [6] in the USA and Johanssen & Bennich [7] in Sweden would identify this elusive class of antibody, which became known as IgE (deriving the E from erythaema). Subsequently,
it became possible to work out the immunological mechanisms and pharmacological pathways involved in human allergy, leading to our present awareness of the way in which IgE antibodies bind tightly to basophils and mast cells, where they in turn bind their specific allergens (Fig. 2). When the allergen is multivalent, it binds simultaneously to several IgE molecules, thus cross-linking the antibodies involved. Such cross-linking triggers an intracellular signal cascade that causes the basophil, or mast cell, to degranulate, resulting in the release of histamine and other pharmacologically active agents that together directly cause all of Kustner’s symptoms, so clearly described in 1921.

Now that we have a more complete knowledge of the fine structure and mode of action of IgE, we are still left with the deeper question of its purpose. Why has such a dangerous and apparently unhelpful mechanism evolved? What is the benefit of IgE-mediated reactions? Perhaps, the clearest answer to these questions can be seen in the role that IgE and its related accessory mechanisms (especially eosinophils, which also increase in number during allergic reactions) play in the response to helminth (worm) parasites. The exact role of IgE in the protective immune response to these types of parasite is still not fully clear, but the association between worm infections, elevated levels of IgE and dramatic increases in the eosinophil population of blood has long been known [8]. It has been shown that eosinophils can actually bind to the surface of parasites through worm-specific IgE, whereupon they degranulate and damage the target parasite through the released biochemicals [9]. Clearly, the kind of immune response involved in a Type I allergy is deeply involved in anti-parasitic reactions, and IgE working in concert with eosinophils and other factors seems to have a particular ability to take on the difficult problem of killing large parasites.

![Fig. 2](image)

**Fig. 2** Diagrammatic representation of IgE-mediated degranulation of mast cells. Four individual IgE antibodies are depicted in a form in which each domain (about 110 amino acids) is represented by an oval. The IgE antibodies are anchored to the mast cell membrane by high affinity Fc ε I receptors. Two of the antibodies are shown binding to two different epitopes on a polyvalent allergen—a situation in which the antibodies are said to be crosslinked. This effect (crosslinking) causes a signal to be transmitted into the cell, with the result that the preformed granules (containing histamine and other pharmacologically active ingredients) are caused to expel their contents to the outside. Other (short- and longer-term) changes take place as a consequence of the allergen binding, including changes to the lipid composition of the cell membrane and the induction of certain genes.