

REVIEW ARTICLE

Fifty years of allergy: 1965–2015

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Abstract: The last 50 years in allergy could almost be considered the first 50 years. Over this time period, we have witnessed the emergence of allergy as a subspecialty, have seen and continue to observe a tremendous change in prevalence of allergic disease and have gained insight into the mechanisms that underlie allergic predisposition and disease manifestation. We have improved the care of children with many forms of allergic disease and now sit poised to be able to alter the natural history of allergic disease with the use of specific immunotherapy. There is much left to do in the next 50 years including understanding what underlies both the predisposition to atopic disease and its natural resolution and identifying the environmental cofactors involved in the 'allergic epidemic' and therefore targets for effective primary prevention.

Key words: advances; allergy; future; history.

1965 in Snapshot

The year 1965 could be considered a turning-point year for science and public health in general. It saw the first space walk, the establishment of Medicare and Medicaid in the United States, banning of cigarette advertising on British television and the Nobel Prize for medicine awarded for advances in understanding genetic control of cellular enzymes and transcription.

In politics and popular culture, 1965 saw in the Thunderbirds TV series and the Beatles 'Help' album, the first Australian soldiers in Vietnam and Martin Luther-King Jr. marching with

25 000 supporters for civil rights in the United States. It saw out Winston Churchill and TS Eliot at a time when the world population was just over 3 billion. It saw the birth of the *Journal of Paediatrics and Child Health* (JPCH), so the origins of the JPCH coincide with the changing of an era.

The Discovery of Immunoglobulin E and Some Other Interesting Stuff

As 1965 was in full swing, a Japanese couple Teruko and Kimishige Ishizaka were working hard in their Denver research laboratory and the following year would publish their discovery of immunoglobulin E (IgE).¹ Almost simultaneously, Johansson and Bennich from Sweden also described the elusive 'reagin antibody'.² These publications are landmark events in the evolution of allergy as a subspecialty and perhaps delineate the change in the external view of 'allergy' from dark arts and magic to the world of science. There are even rumours of paediatric respiratory physicians being overheard whispering (during a reflective moment) that allergy may play a role in some forms of asthma.

An understanding of the mechanism by which IgE-mediated sensitisation and allergic reactions could occur was a big leap forward. This discovery would be the basis for identification of IgE directed against allergens and the diagnostic testing still used today.

An avalanche of mechanistic publications have followed in the past 50 years, and we now understand much of how dysregulation of T cells, antigen-presenting cells and the innate immune system play a role in allergic responses. These discoveries have moved allergy firmly into the arena of immunology and in many countries, training for these two inter-related specialties is combined.

Key Points

- 1 Rates of allergic disease have risen dramatically over the last 50 years.
- 2 Key environmental drivers of the current allergy epidemic have yet to be fully elucidated.
- 3 Immunotherapy is the only current treatment for allergic disease that offers the potential for disease modification and cure.

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All authors have contributed significantly to this paper and all authors are in agreement with the content of the manuscript.

Precautionary advice: This review may contain traces of irony, sarcasm and bad jokes, and was produced in an environment that may be at risk of cross-contamination from other subspecialties.

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The Prevalence of Allergic Disease over the Last 50 Years

When 'hay-fever' was first described in 1819, it was a rare medical oddity and it, along with other forms of allergic disease, remained so for at least another 100 years. Allergic diseases were still relatively rare in 1965. The first case reports of anaphylaxis to foods, insects and drugs appeared in the literature in the 1960s. A PubMed search of 'anaphylaxis' today results in 23 955 hits.

The so-called tsunami of allergic disease is real and is not an artefact of over-diagnosis or increased disease awareness. There is now robust epidemiological data that support a real and alarming increase in IgE-mediated food allergy in particular, but also atopic dermatitis and allergic rhinitis and non-IgE-mediated food allergy.³ The asthma epidemic of the 1990s appears to have stabilised and plateaued,⁴ albeit at a much higher rate than that described in 1965. The increase in allergic disease prevalence was first observed in the developed world, but is now becoming a major problem in emerging economies and the developing world.⁵ This is likely related to a complex interplay of western life-style influencing genetic predisposition and although plausible theories abound on the most likely suspects for this (hygiene hypothesis, vitamin D, microbiome, infant feeding practices, exposure to pollutants, etc.), there is currently no definitive one culprit answer.

Australia has the unenviable top place in current IgE-mediated food allergy prevalence. Up to 1 in 10 infants has challenge-proven IgE-mediated food allergy,⁶ falling to around 2–5% for school-aged children. Admissions to hospital for anaphylaxis, and in particular for food-related anaphylaxis, have doubled to trebled over the past decade in Australia, the United States and the United Kingdom, as have reported rates of peanut allergy.^{7,8} This rise has been most marked in the 0–4-year age group, suggesting a wave of burden of disease that has yet to be fully realised by the health system, already struggling to cope with the increasing demands of disease prevalence. There are a few early signs that the rapid rise in food allergy in Australia and in the United Kingdom may be slowing, with rates of admissions to hospital for food allergy-related anaphylaxis still rising over the last 5 years, but at a slower rate than the previous decade.

The Emergence of a Specialty

The last 50 years has seen allergy societies grow from small, often add-on groups within existing societies to large societies with an important role in public health and policy. Training around the world in allergy (often combined with immunology) as a specialty is now commonplace.

Specialty allergy societies have been in existence since the 1920s in the United States and 1940s in the United Kingdom with a very respiratory focus, often as part of asthma societies. Similarly, the World Allergy Organization was founded in 1951 and has grown over the last 60 years to include 95 member regional and national allergy and clinical immunology societies from around the world.

In the early '60s, the Australian Society broke free from its colonial ties with the British Medical Association and became

the Australian College of Allergists. Several merges and name changes later, we now have a strong and vibrant Australian Society for Clinical Immunology and Allergy, which has led the world in terms of standardisation of written 'action management plans' for the recognition and management of anaphylaxis and in country-wide e-training for anaphylaxis, food allergy, allergic rhinitis and immunotherapy.⁹

Immunotherapy for Respiratory Allergic Disease and Insect Allergy

Immunotherapy is more than 50 years old. Unlike many other therapies in medicine, immunotherapy has the potential to alter the natural history of disease, rather than just providing symptomatic relief. Aero-allergen immunotherapy spawned in the early 1900s as a result of the dual recognition that pollens were potential triggers of respiratory allergic symptoms and the success of vaccinations against infectious diseases. In 1911, Leonard Freeman, an English immunologist, and John Freeman, an English physician, developed a regime of incremental injections to prevent allergic rhinitis; this we now refer to as subcutaneous immunotherapy (SCIT).¹⁰

Clinics for the management of allergic disorders were soon established and SCIT, typically with crude extracts, was offered to those with allergic rhinitis or asthma. In 1927, the first allergy clinic in Australia was established at the Alfred Hospital, Victoria. Sublingual immunotherapy (SLIT) was then investigated as an alternative means of desensitisation, a modality which has seen significant resurgence in the past decade, particularly in the paediatric setting with its ease of home administration and good safety profile. There is now robust evidence for the efficacy of immunotherapy in the management of childhood seasonal and perennial allergic rhinitis and asthma, where clinically relevant aero-allergens are identified.¹¹

Over the last 50 years, immunotherapy has matured. Allergists in 2015 have a better understanding of who to desensitise and which allergens to use. Purified allergen extracts have become widely commercially available. Component-resolved diagnostic testing to aero-allergens and insect venom can now be used in patients with allergen poly-sensitisation, enabling better selection of clinically important allergens in these poly-sensitised patients.^{12,13} Immunological mechanisms of desensitisation are now better understood than they were 50 years ago.¹⁴ Immunotherapy has become available for a number of insect venoms. Immunotherapy to jack jumper ant is an Australian innovation, providing a useful and potentially life-saving therapy for subjects who have experienced anaphylaxis to previous bites.¹⁵ Perhaps the biggest advance in immunotherapy over the last 50 years has been the establishment of a firm evidence base for efficacy and safety of SCIT/SLIT by meta-analysis of multiple randomised control trials. This is a great leap forward compared with the first 50 years of immunotherapy, where 'evidence' was typically based on anecdote, case reports or observational studies.¹⁴

Immunotherapy still remains an imperfect science. High-level evidence for immunotherapy efficacy is only currently available for certain aero-allergens (house dust mite, common grasses), yet companies make available a myriad of allergen extracts for which little or no evidence exists. Moreover, Australian practice

relies upon allergen extracts made for the US/European markets, but our patients often have unique aero-allergen sensitisation profiles specific to the Australian and Asia Pacific region.

It is likely that in the next 50 years, SLIT/SCIT will become more refined, with targeted selection of purified allergens, improved protocols and a better understanding of what aero-allergens can be combined in the one regime.

Specific Oral Immunotherapy for Food Allergy

There has been a recent swell of interest in the use of specific oral tolerance induction (SOTI) in those with immediate IgE-mediated food allergies. However, the idea is not new. In 1939, Gert Sydow published a series of children who most likely had IgE-mediated cows milk allergy.¹⁶ He showed desensitisation to cows milk (i.e. the ability to ingest a food without reacting but with the food needing to be ingested at regular doses) was possible, that desensitisation did not equate to tolerance (i.e. food could now be eaten sporadically) and that cows milk allergen could be modified by heating, rendering it non-allergic in some children. This oral approach to desensitisation for food allergy was lost in the annals of dusty journals.

A paradigm shift in food allergy has occurred over the last decade. The previous 'allergy mantra' of strict avoidance of the food allergen has been challenged increasingly. It is now established that up to 70% of children with IgE-mediated egg and milk allergy can tolerate heat-modified allergen without symptoms.^{17,18} Indeed, many allergic services now offer baked egg/milk challenges to children allergic to whole egg/cows milk, improving quality of life of patients, and possibly accelerating tolerance.^{19,20} Who else but allergists can legitimately prescribe at least one cupcake per week?

SOTI has become of intense interest to patients, the media and the food industry. Randomised controlled trials have shown SOTI to egg, cows milk and peanut can induce desensitisation in a significant proportion of allergic children.²¹ The process, however, is not without risk, and most importantly whether it induces sustained tolerance rather than transient desensitisation remains unclear. In Australia and most of the world, access to SOTI for patients is currently limited to enrolment in clinical trials. This is likely to change within the next 3–5 years, with selected patients being offered SOTI to egg, dairy and peanut. In the next 50 years, SOTI protocols, patient selection and safety will invariably improve, and SOTI will most likely become part of routine clinical care.

Allergy has often been relegated to the back row of the immunology family portrait, while immunodeficiency and autoimmunity have taken the front row limelight. The last 50 years has been witness to an allergy epidemic, the application of evidence-based medicine to allergy therapies including immunotherapy, and improved understanding of the immunologic mechanisms that underlie allergic disease. In accord with these changes, allergy has moved a long way from a magical art to its current firm footing in science.

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