

DR SUSAN
PRESCOTT

...

**The
Allergy
Epidemic**

...

*A Mystery
of Modern Life*



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This book is for the countless millions who suffer
the many burdens of allergic diseases, and for all those
who are working so hard to solve the mystery of
this epidemic.



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THE ALLERGY EPIDEMIC

PREFACE

Allergies have emerged as a major public health problem. This enormous rise in disease has been most apparent in developed countries, and nowhere is this 'epidemic' more evident than in Australia and New Zealand, which have among the highest prevalence of allergic disorders in the world. Published studies indicate that the prevalence of allergies is continuing to increase, with a doubling in the rate of hospital admissions for potentially life threatening, severe allergic food reactions (anaphylaxis) in Australia over the past decade. The impact is even greater on preschool children who have experienced a five-fold increase in serious food allergy. It is now concerning to see the same trends beginning to emerge in many developing regions of the world.

The burden of the allergy epidemic is felt at every level. The personal impact and social costs are growing and the mounting economic costs are unparalleled. In a report published by Access Economics and the Australasian Society of Clinical Immunology and Allergy (ASCIA) it was estimated that the financial cost of allergies in Australia was \$7.8 billion in 2007; and other developed countries are showing similar trends. This report also emphasised that raising awareness of allergies is an important factor in facilitating the early recognition and control of allergic disease.

We therefore commend Professor Susan Prescott in publishing this important book, which we believe will raise awareness of

allergies by providing current, accurate and evidence-based information in a language that a lay person can understand.

Associate Professor Jo Douglass
President
Australian Society of Clinical Immunology
and Allergy

Associate Professor Richard Loh
President Elect
Australian Society of Clinical Immunology
and Allergy

FOREWORD

Allergy is one of the most common non-infectious diseases. The global increase in this disease is unprecedented, it affects all societies and brings with it vast personal, social and economic costs. The greatest burden of this 'epidemic' is borne by young children, who account for the most dramatic increase in disease. Already, about 30–40 per cent of the world's population is affected by one or more allergic conditions, including food allergies, eczema, allergic rhinitis and asthma. As the younger generations reach adulthood, the burden of allergic diseases is expected to increase even more. Many of these conditions can be serious and life threatening. It is therefore very important that allergy is recognised as a major public health problem and that continuous efforts are made towards its prevention and optimal treatment.

Promoting public awareness is an essential part of this process, and that is exactly what Professor Susan Prescott does in *The Allergy Epidemic: A Mystery of Modern Life*. In a time of uncertainty and confusion, she provides much needed clarity and hope, as she tells the fascinating yet serious story of allergy in the modern world. Not only does she describe and explain each allergic disease and its treatment, she also delves into the intriguing story that lies behind the epidemic rise in immune diseases and explains how and why this may be happening. She provides insights and information as she takes her readers into the world of the immune system in a way that captures the imagination and makes a very complex area of

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medical science immediate and accessible. At the cutting edge she explains the very latest research, and introduces important concepts that underpin many modern diseases including the new fields of ‘developmental origins’ and ‘epigenetics’, which are changing the way we understand the effects of modern environmental changes on our immune systems. Research in all these areas may provide new answers and solutions to the mystery of the allergy epidemic.

An allergy specialist and a pediatrician, Susan Prescott is also a leading research scientist, internationally recognised and highly regarded for her research into the developing immune system and how this system gets ‘sidetracked’ in allergic disease. She is also at the forefront of efforts to understand the environmental factors that are driving this epidemic, including approaches that might help reverse this through prevention strategies early in life.

The Allergy Epidemic coincides with another very important initiative: the release of the first ever, international *WAO White Book on Allergy*, published by the World Allergy Organization (WAO). The *WAO White Book on Allergy* targets governments and health care policy makers of the world, and makes high-level recommendations to address this growing international crisis. A key recommendation of the *WAO White Book on Allergy* is to ‘increase public awareness of allergic diseases and their prevention’. In the light of this, Susan Prescott’s highly accessible book on this central mystery of our modern life is a relevant and logical companion to the core objectives of the *White Book*.

Professor Ruby Pawankar,
MD PhD FAAAAI
President Elect
World Allergy Organization

In the trenches

We have never been so busy. I arrive to see the allergy clinic waiting room as overcrowded as usual. Brimming with children. Some scared, some screaming, some just bored. All ages. All with serious allergies. There are record numbers of new referrals. Our lists are so long that many have been waiting over a year for their appointment. And they just keep coming. We overbook them. We do extra clinics. But still we can't keep up.

There is no better place to see first-hand evidence of the allergy epidemic.

I momentarily close my door on the chaos to review my first chart. And I smile. I have known Ben since he was a small baby when he had a life-threatening reaction to cow's milk. He only had a mouthful. Karen, his mother was completely bewildered as her six-month-old son reacted almost instantly before her eyes. His lips swelled. His eyes swelled so much, he could hardly open them. A blotchy rash spread over most of his body and he started coughing and gasping for breath. Although panic stricken, Karen still had the presence of mind to call the ambulance. She had never been so relieved as when the paramedics came bursting through her door. Ben received a life-saving dose of adrenaline and Karen watched, amazed, as his symptoms settled almost as quickly as

they had started. She had never heard of an ‘anaphylactic’ reaction before, but now she had first-hand experience.

That was thirteen years ago and I have been seeing Ben every year since. I call his name across the bedlam. It takes several attempts before they hear me. Then I see a strapping teenager, with his mother and younger sister Amy in tow, fighting their way across a floor strewn with toys and toddlers. As they settle themselves in the quiet of my consulting room, Karen presents some home-baked cakes. She proudly announces that they are made without eggs, dairy or nuts, for me to share with the other doctors in our tea break.

I take them gratefully, but don’t tell her that we rarely have time for a break together these days. We are an all-girl team today. Each of us working behind a door in the long row of consulting rooms that surround the large clinic waiting room. Although I can’t remember the last time we all sat down together for a tea-break, we still regularly drop into each other’s rooms to discuss our more difficult and puzzling patients. And there seem to be more and more of those.

Things have changed so much, even since Ben first developed his allergies. Back in 1995, when I first started working in the allergy clinic, food allergies were already becoming common, but still nothing like they are now. And although some allergies like peanut and shellfish often persisted into adulthood, most other common forms of food allergy, like egg and milk allergy, were almost always transient. So, when I first met them, I confidently told Karen that Ben’s milk allergy would likely be gone by the time he reached school age. That might have been the case then, but I have since had to eat those words more times than I care to remember. Not only are these food allergies becoming more common, they also seem to be becoming more persistent.

With each passing year Karen would wait expectantly to see the results of Ben’s latest allergy tests. And each time my heart



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would sink as I prepared to disappoint her again. I am glad to say that many of our patients do still outgrow their egg and dairy allergies, but with the growing number of people who don't, we are now more cautious with our predictions!

Ben and his family have not had an easy journey. It was not long before he also developed an allergy to egg. And then peanuts. The level of vigilance needed while buying, preparing and eating food is very difficult, time-consuming and stressful, because the consequence of a mistake can be life threatening. And yet, like so many others, Karen and her family have taken this in their stride. It becomes a way of life.

Today we are checking that Ben is learning to take more responsibility for his own diet. We will update his adrenaline auto-injectors and make sure he knows how to use them himself. The teenage years can bring new challenges. Ben is very good but he still refuses to wear the medical alert bracelet, which warns of his allergies.

Even though Ben's allergies seem to be here to stay, we have never given up hope. So, once again, I key the computer to see the results of the blood tests he had last week. I look down the list of his allergic antibody levels to egg, milk and peanut. None of us is optimistic, but as always, there is an air of expectancy. Amy is just as interested, as everyone in the family is affected by Ben's restrictive diet. They are all watching my face and I try not to give too much away.

Just at that moment, there is a knock at the door, which opens before I can even answer. With an apologetic look, Terri, the allergy nurse, calmly announces that I am needed urgently in the treatment room. One of the food challenge patients is going into anaphylaxis.

Karen and Ben need no explanations for my hasty departure. Karen's look of understanding says it all, and reflects the memory of her own experience many years before. I arrive in the treatment



room to find the situation already well in hand. Val, the nurse specialist has already given an injection of adrenaline and the junior doctor is monitoring the recovery of a two year old girl, Chloe. Another nurse is consoling Chloe's mother Madeleine, who is quietly in tears. Chloe also has milk allergy, but her recent allergy tests had shown such promising improvement; down to a level where we all felt it was worth trying a test feed or a 'food challenge' to see if she might be growing out of it. Madeleine had been very keen to try this. But, although Chloe has had more milk than she ever had before, she is clearly not ready yet.

We always do food challenges very slowly, starting with tiny amounts, so we can detect any reaction early. Chloe had been doing well, but on her third increment symptoms started to develop. First came the red blotchy rash. Then her eyes and nose started streaming. While these symptoms are not serious, the cough was the first sign that this might be evolving into anaphylaxis. The adrenaline, which was ready just in case, was given without delay. Red faced, but now settled, Chloe is looking happier than Madeleine. With everyone's heart rate returning to normal, I reassure Madeleine and arrange to see them momentarily, after I have finished seeing Ben.

Satisfied that all is well, I make my way back to where Karen, Ben and Amy are waiting patiently. Back in front of my computer screen, I re-inspect Ben's numbers. As expected, Ben's peanut antibodies are still so high they are above the laboratory's detection scale. No one is surprised, but there is still disappointment. But then I happily add some good news: that the milk and egg levels are looking better than ever. Finally, we may be able to strike these two foods off Ben's avoidance list. But first he will have to go through two food challenges, and after avoiding certain foods for so long, this can be quite a psychological obstacle.

No one speaks. This is a moment that they have all been waiting for. But Ben looks uncertain. Karen stunned. She quickly

recovers and turns to Ben saying that she thinks this is great news. Trying to sound convincing, she tells him that she thinks that the challenges are worth trying and that this is the only way to find out. Life would be so much easier if they didn't have to avoid milk and eggs.

Ben still looks unsure, and I spend some time explaining the challenge procedure: how we do this gradually, starting with only a rub of food on the lip, and that we stop if there is any sign of a reaction, adrenaline always at the ready. I also explain that he will have plenty of time to think about it, because the waiting time for challenges is at least six months now. This seems to satisfy Ben, who gives the okay to start the paperwork and the bookings. In the meantime he actually seems relieved to continue with the avoidance diet that he has become so used to.

If the challenges go well, that might leave only peanut. And I have more good news on that front too.

They have heard there may be a cure for peanut allergy on the horizon and they want to know more about it. I begin to explain that there are new research trials under way using oral immunotherapy (OIT), aimed at potentially curing peanut allergy; how they are enrolling patients just like Ben, with very high allergic antibody levels and a history of anaphylaxis (Chapter 11). By starting with very tiny amounts of peanut and gradually building up the amount over weeks and months, the immune systems 'learn' to tolerate peanut and the patient can eventually cope with a sizeable portion each day. But this can be very dangerous and most children have reactions along the way. The aim of OIT is to change the underlying immune responses. This is quite different from the oral challenge, which is a short term 'test' of allergy that does not continue for long enough to change the immune responses to the food. Understandably, these procedures are only done under strict medical supervision because of the potential for life-threatening reactions. Even so, in studies done so far, many

children eventually tolerate peanut as a regular part of their diet. The same technique has been used for other foods, such as milk and egg. At the moment this is still in the ‘experimental stages’ until the safest and most effective methods have been determined. It is not yet clear how long the effects will last, and how this may vary between children. With many unanswered questions, it will be some years before this may become available to patients in everyday practice. Even then, it won’t be suitable for all patients with food allergy. Nonetheless, this provides a future hope that we could not offer before.

Ben is tuning out by now, and the idea of eating peanuts is too much to contemplate. I suspect he is grateful that this will not be any time soon.

Although the new ‘oral immunotherapy’ treatments are the first hope of a real cure for food allergy, they will create new difficulties in the clinic. In their current experimental form, they are very labour-intensive and require extended periods of medical observation. Most hospital clinics barely have the resources to cope with their current services. At the moment, none of us can imagine the logistics of how these treatments can be delivered to the thousands of children who could benefit. Still, with so many families affected by persistent food allergies, it is good to finally provide some light at the end of the tunnel, even if we are not yet sure how we will overcome the logistics of doing so.

It is something special to see the new hope in Karen’s eyes. With a spring in my step, I see them back to the waiting area. Ben finally cracks a smile as he turns around to say goodbye.

By now Madeleine is also back in the waiting room, still looking shell-shocked, but much calmer. And Chloe is playing as though nothing has happened. When I call them in to my waiting room Chloe has a change of heart and starts screaming, clearly worried that we are about to do something else unpleasant. Struggling to be heard, we spend a few minutes going through Chloe’s allergy

management plan. She clearly needs to avoid all dairy products for a while yet. But unlike Ben, the early and progressive drop in her allergic antibody levels to milk still holds some promise that she will eventually grow out of it. And she has no signs of other food allergies. This might be because we have made sure that she started eating most other 'allergenic' foods, like peanut butter, regularly as early as possible. It initially took some convincing for Madeleine to do this because of the well-known previous approach of avoiding these foods in the hope of preventing new allergies. However, since new studies have suggested that avoidance is not effective, we now recommend that allergenic foods are included in the weaning diet without any specific avoidance (see Chapter 9).

Madeleine is convinced it was worth it. Now that Chloe has virtually all common foods as part of her regular diet, it is unlikely that she will develop allergies to any of them. Her immune system has already 'learned' to tolerate them. She remains at risk of other kinds of allergic diseases, like asthma and rhinitis as she gets older, but once the milk allergy is outgrown she should be free of any food allergies.

Like so many parents, Madeleine is still full of questions:

- Why did Chloe develop food allergy when no one else in the family has food allergy?
- What went wrong with her immune system to cause this?
- Is it genetic?
- Why are allergies on the increase?
- Are there factors in the environment that are causing this?
- Could we have done anything to prevent this?

She has her own theories. Most parents do. Many are convinced the modern environment is to blame. Some blame unseen toxins in the modern world, some blame antibiotics and cleaner living, and some blame more processed refined diets. And there is probably truth to all of these ideas.

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Helpless to explain our current scientific ideas about these complex issues in the remaining moments we have left, I feel guilty in my cursory and superficial attempts. All I can do is agree wholeheartedly that our modern lifestyle is a driving force behind the allergy epidemic.

And I start to question what I am doing. I am a clinician, but I am also a researcher, a scientist and a teacher. I travel the world as an expert in this field, giving lectures and talking to many other international experts. I write research papers, editorials, opinion papers and book chapters. All for other clinicians and scientists. Suddenly it seems illogical and extraordinary that I am not bringing my roles together more; teaching and writing for the very people who ask these questions of us every day in the clinic, the people who are actually living the effects of the allergy crisis on a daily basis.

There have been so many fascinating and exciting developments in our understanding of the immune system, the environment, our genes and how these all interact to produce the rise in many modern diseases. We might not have all the answers yet, but the rate of recent discovery is cause for great optimism. The problem is that there is still so much misinformation and misconception out there. It is no wonder that many parents and patients get confused. We are so busy dealing with the effects of the epidemic that we often don't take the time to explain what we know about it. Unless experts at the cutting edge of research take the time to communicate more of these things to the people who really want to know, none of this will get any clearer.

This small revelation dawns on me in the few moments that it takes to see Madeleine and Chloe back to the waiting area. I pick up the next chart, ready for the next story. And as I look at the sea of faces and the many charts piled up in my box, I feel a new sense of purpose.

The making of an allergist

After my clinic I head back to my University office on the other side of the Children's Hospital campus to prepare for a teaching session. Another part of my role as a University Professor is to teach the next generation of doctors. The medical students rotate through our hospital to study Paediatrics and Child Health and this is an opportunity to teach them about the common allergies that begin in childhood, such as eczema, food allergy, rhinitis ('hay fever') and asthma. As I collect my teaching materials, I hear the boisterous students returning from the wards for our classroom session. We have about thirty students on this rotation and the seminar room is packed and raucous when I arrive. Standing in front of the next generation of doctors, I remember sitting in those same classroom chairs, with my own unformed, innocent enthusiasm.

• • •

I suppose we all have moments when we zone out and suddenly wonder: how the hell did I get here? As a very young child I had many high ambitions, and these changed daily: I wanted to be a teacher, a writer, a performer, a doctor, a leader, an artist, an actor, a scientist. Anything seemed possible. Only when I consider it from where I am now do I see that, in strangeness, I do indeed do all of

these things. It might seem more by accident than by design, but I suspect that even after they slip into our subconscious, untamed childhood dreams have more power than we realise. There are certainly things I never planned to do, and might have even shied away from; I never thought to be a fundraiser, an account manager or a peace maker but somehow these roles are always on my 'to do' list as well. But none of this was clear to me at sixteen when I finished high school.

Poised on the threshold of an uncertain future, I wanted to make a difference on any scale that had meaning. It was exciting to have an entirely blank slate in front of me. I felt I could put anything on it, but I hesitated to make a commitment. Rather than find uncertainty daunting, I loved the feeling of an open horizon of endless possibilities. That was my problem. I did not want to narrow my horizons by making choices. At least that was my excuse. I *liked* having possibility, uncertainty. A strong sense of purpose, yet undefined; a wanting without shape. My naïve enthusiasm had grown under the nurturing care of my new-age parents, who also went to great lengths not to taint, bias or influence my choices in any way.

It was my more traditional grandparents that gave focus to my passion. My grandmother, Monica, was one of the very few women to study medicine in the 1930s. From a family of adventurers, explorers and missionaries, she had taken inspiration from her father who believed that 'travel was the best education'. As one of the first protestant missionaries to Peru in the early 1900s, he had travelled the dangerous mountain passes of the Andes by mule to provide basic medical care. His exotic tales and sometimes hair-raising journeys became bedtime stories for Monica and her sister throughout their childhood. They revelled in his adventures, inspired to believe that anything was possible. Although they were very poor, they always lived by the motto that 'where there is a will, there is a way', and Monica set her heart on medicine from

an early age. Following in her father's footsteps, she sailed out to China as a medical missionary as soon as she finished medical school in 1937, just as war was breaking out.

I first came to hear Monica's stories of working as a doctor in Japanese-occupied China when I was sixteen. Just finished high school, still uncertain and waiting for my exam results, Monica announced that she would like to honour her father's belief that 'travel is the best education' and take me to Europe for several months as her travelling companion. It was during those travels that I got to know her more and my own plans to study medicine were set, not to mention my own love of travel. I was enthralled by her passion and how she had always known she wanted to study medicine and become a medical missionary. Because her family had been so poor and scholarships were very difficult to get, she had to be creative. She found a scholarship given to somebody who didn't drink, didn't smoke, and went to church regularly, and joked that she might have been the only eligible candidate. Monica then seemed to approach her medical training with much the same spirit of enthusiasm and fearlessness as she approached every other aspect of her life. There was never any sense that she might be at all intimidated by the establishment, or by the social class, gender or intelligence of her mainly male peers. As one of so few women, I once asked her if she experienced any prejudice or intimidation. I was surprised by her answer. She said that it just never occurred to her that this might be an issue, and because she did not make it an issue she did not experience it. She delighted in the company of her male colleagues and they delighted in hers. They all just 'got on with it'. This is a philosophy that I have tried to hold onto in my own career.

Monica's eyes always shone when she recalled her days of medicine, and I think this played a large part in my decision. I am equally determined when I set my goals but I tend to follow my heart more than my head when opportunities arise. Listening to

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Monica there came a moment when I suddenly just knew in my heart that medicine was for me too. When I look back I cannot imagine doing anything else.

She told me of how she had seen medicine transform the world in a very short span of years. It had been a world still at the mercy of bacterial infection, with hospital wards then filled with women dying of the 'childbed fever'. She was there to watch the most extraordinary transformation as antibiotics were widely introduced, and countless lives were saved. In perhaps the greatest irony, I am now working at the frontier of a new epidemic, which may have its origins in this victory over the bacterial world. But back as I listened to these stories, the allergy epidemic was only beginning to show and was still not recognised by most.

I also learned that it was there in medical school that Monica met my grandfather, Stanley. He fell in love with her immediately. Until he met Monica, Stanley had not planned to leave England. But her passion was contagious and he soon went to China to learn the language while she finished her medical training. A year later, Monica sailed to Hong Kong to be reunited with her fiancé, only days before war broke out in North China. The Japanese invasion left Stanley stranded in the heart of the war zone. I loved hearing how the newspapers told of Stanley's perilous 1300 mile journey down the Chinese coast in small Chinese junks and fishing boats, slipping past Japanese warships at Shanghai in the dead of night, to claim his bride. It was even more incredible to hear how, together, they braved the typhoons and returned to the war zone of North China where Monica set to work as a doctor and Stanley became the youngest medical superintendent of the Qilu Hospital. For the next three years they provided much needed medical care to the war-ravaged Chinese, always under the watchful eyes of the Japanese soldiers. This was where my father, David, was born. He was only eighteen months old when hostilities escalated and they had to join the British evacuation or face life in a concentration

camp. Stanley chose to stay behind to keep the hospital running as long as he could, while Monica and David joined the other refugees on a very long, crowded and uncertain ocean journey south. They arrived safely in Australia before their ship was sunk in Darwin harbour by the Japanese. After many months of uncertainty, Stanley finally escaped on one of the last boats out. Leaving their home in China, they made a new life in Australia. Stanley went on to become one of the longest serving Vice Chancellors of the University of Western Australia (UWA), where I now work. From humble beginnings, Sir Stanley and Lady Prescott found themselves at Royal garden parties, and when the queen visited Australia, they were invited to dine with her on the *Britannia*. But they never lost their humility or their sense of what was important.

Through this, I could see how a passion for helping people find love, health and spiritual sustenance molded my family and brought us to Australia. Monica had succeeded in igniting my passion and a strong commitment to study medicine. I just had to hope for good enough exam results, and wished I had thought of this *before* I sat my exams. My conviction further deepened when Monica told me that it was Stanley who founded the first Medical School in Western Australia.

I think Monica was as nervous as I during the wait for my exam results. We were dining in a hotel in London when my father called me from Australia with the news. He could hardly speak and started by telling me that the numbers were so low that he had to call the authorities to see if there was some mistake. I was already feeling sick as he explained that he had been looking at my state ranking and not my aggregate score, which was so large that he also could hardly believe it. Neither could I. Although I had always done well in school, I had no way of knowing how I might do in the state ranking. Still in happy shock, I returned to the dining table to tell my good news. I had never seen Monica look so proud and that was the best moment. So, with the sense of

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anticipation, wonder and adventure I share with my ancestors, I set off on my own path. A door of the universe had opened to me and I felt my own calling to go through. How could I not?

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I clearly needed to use my head to study medicine, but my philosophy has always been to follow my heart first and foremost, to do what felt right and what made me happiest. One of Stanley's final duties as the Chairman of Royal Perth Hospital was to recruit a new and brilliant Professor of Medicine, Professor Lawrie Beilin, who was also to play a critical role in my career. As a fourth year medical student in 1985, I somehow found myself in Prof. Beilin's office, metres from where Stanley had presided over the opening of the medical school. I can't really remember how I came to be sitting alone before his desk without my fellow students. I think he was reflecting fondly of how he appreciated my grandfather's belief in him. Perhaps he wanted to repay the favour in some way. In any case, he gave me an opportunity for which I will be forever grateful. I took it, without question. In my heart I knew it was the right thing to do. My fellow students did not understand the attraction of taking a year off from my medical training to undertake a year of research, and write an honours thesis. Incomprehensible. Studying medicine took long enough as it was. But it was my first taste of academic life, and I don't regret it for a moment. Monica, as ever, was pleased and excited by my decision. Many years later in 1999, when I was appointed as a tenured academic at UWA, one of my first and most fruitful collaborations was with Lawrie Beilin's group. Although we worked in very different fields by then, that very diversity paved the way for some quite novel research.

I worked very hard when I returned to the ranks of medical school, but I tried to not take life too seriously and do what I

could to retain perspective. Two weeks before my final medical exams, when my classmates were all madly cramming in a climate of growing stress and paranoia, I decided to follow a different tack. We had a series of written and oral exams. Standing alone in front of examiners, who had the power to throw almost anything at us, was the moment of intimidation that we had all been dreading for six years. We could not even imagine life after that moment. I knew I had done the work. What I really needed now was perspective, clarity and a sense of humour. The best way to achieve all of these was immediately obvious. I needed to travel. Travel to the other side of an unknown universe. So off I went with Douglas Adams and his *Hitchhikers Guide*. Ten days before my exams I embarked on this grand journey reading every book in the *Hitchhikers Guide*, before returning to Earth just in time to meet my examiners. Fresh. Inspired. Ready for anything. It certainly gave me another perspective. And I never expected to have so much fun. I had a great time and did well. And I am sure that a universal perspective mixed with humble confidence helped.

The intern year was another challenge. I picked up my first pager with all the other nervous interns and ran to hide in the toilets as I waited for it to go off for the first time. It did not take long. A few major traumas and cardiac arrests later and soon I was in the full swing of things. It was also not long before my classmates started to choose specialty-training programs. But after a full year of internal medicine I still had not found my calling. It was overwhelming, exhausting and I was just too tired and disillusioned to feel inspired. Being assaulted by intoxicated and uncooperative patients in the Emergency Department did not help. I started to wonder if I might be on the right path after all. This might have contributed to my decision to take a dramatic detour in my second year. Struggling for direction and involved with a boy about to go overseas, I considered dropping out for a year, maybe more, hoping that things would clarify. I just knew I didn't want to stay

where I was. In what most of my friends and family believed was a misguided choice; I decided to follow the boy. It was an ill-fated relationship and a detour that could have turned into a cul-de-sac. But it didn't. As life often does, the painful and seemingly pointless detour actually led me far more quickly to purpose and direction. Within a few months I found myself stranded, literally, on an island in the middle of the Pacific. No boy. No money. No idea. To make ends meet I worked for the Fiji School of Medicine doing some basic research. This achieved important two things. It reinforced my love of research. And it was there that I met the man who inspired my passion to study paediatrics, Professor Ian Lewis, a retired Australian paediatrician heading the Fiji medical school. Seeing my interest and clear attraction to paediatrics, he mapped it all out clearly for me. Go back to Perth. Enter into paediatric residency for three years of basic training. Sit my paediatric exams. Pass the first time, although that is hard to do. Enter three more years of advanced training. Oh, and do a PhD at the same time. Sure. I nodded. Like hell! After seven years of medical school this did not sound like much fun.

But paediatrics 'felt' like a good idea, so why not? I decided to do that for a while to see what might happen. Unfortunately I discovered paediatrics was so popular that when I initially applied all the jobs were taken, with no prospects for at least a year. So I actually had to trudge back to Royal Perth Hospital and work in the Emergency Department again. Not my favorite place. But now my intentions were set and I was happy. As chance would have it, I was almost immediately and unexpectedly seconded to the Emergency Department at the Children's hospital. I literally came in the back door, and I never left. So I like to think of it as destiny that, within six months of setting my intentions in Fiji, I found myself back in Perth studying paediatrics. And six years later I took great joy in writing to Ian Lewis to let him know that everything had unfolded *exactly* as he planned, with the PhD thrown in for

good measure. His soothsaying had not extended to what my chosen specialty should be, so I had to figure that out for myself.

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Immunology and Allergy was one of the most intimidating and the most hated specialties when we were in medical school. A little later you will see why. After graduation it did not get any more popular in attracting specialty trainees. No one in my cohort was drawn to specialise in this field. But I like a challenge. At that stage there were many new and confusing discoveries about the immune system, and its role in so many diseases and conditions was starting to become more recognised. The current crisis of food allergy was still unheard of, but asthma was becoming more common, and the first speculations that this might be related to the decline in bacterial infectious diseases were only just starting to emerge. Still, very little was known about the developing immune system in early life, when bacterial exposure seemed most critical for maturation of immune function. And around the time I was starting my advanced training, I had the chance to research this topic and answer this important question. By working in the allergy clinics and undertaking a PhD at the same time, I had the perfect opportunity to study exactly how the immune system develops and how this goes wrong in allergic children. I got that ‘feeling’ again. It was the right thing to do.

And it was. Under the inspiring tutelage of Professor Patrick Holt, I undertook important work that was soon published in the *Lancet* and which had great impact on our understanding of the early immune system and how we think about allergic disease. The enormous interest in my work launched my international career. So although I am still not exactly sure what I want to be when I grow up, this seems to be a good start.

It is hard not to be amazed when I reflect on just how much

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medicine has changed since my grandmother Monica was in medical school fifty years before me. From a world plagued with infectious diseases, to a much cleaner world now plagued with allergy and many other immune diseases. My specialty did not even exist in Monica's day. Now looking at the new generation of medical students in front of me, I can't help but wonder what lies in store for them.

In the classroom: some basics of allergy

Time to get down to business and learn more about allergic disease. I like to start by reminding the medical students just how common and serious allergies can be, and how fast this problem has been increasing. When I started medical school in the early 1980s, allergy was hardly mentioned at all. There was some teaching on asthma but without much focus on the underlying inflammation or the links with the immune system. Even long after I graduated, many respiratory specialists remained doubtful about the relevance of allergy. As medical students we did learn about skin inflammation in eczema, but our dermatology teachers were equally skeptical about any link with allergy. And I did not even hear about food allergy until some years after I graduated. At that stage, the field of Allergy was a very, very poor cousin to the fairly new field of Immunology, which was more focussed on immune deficiencies. There were very few advocates for Allergy and only a few took it seriously. That has certainly changed. Now most community doctors are seeing evidence of the allergy epidemic on a daily basis, and the medical curriculum has caught up with this change in disease profile.

Before the students learn about disease they need a basic understanding of the normal immune system and a general grounding in what causes the allergic response. These students have already

done some of the basics in their earlier training, so we begin by reviewing the following basic points about allergy and what happens during an allergic reaction.

WHAT IS ALLERGY?

We remind the students that in the most basic terms, allergy occurs when there is a seemingly pointless immune response to completely harmless factors in the environment.

One of the main functions of the immune system is to protect our bodies from infections and other possible dangers in the environment. Allergic individuals direct this immune attack at things that do not present any real threat, such as proteins in foods and pollens. In this case the attacker is the only one that suffers in this misdirected assault. This self-damaging allergic response causes inflammation, which leads to the signs and symptoms of allergic disease. These symptoms depend on where in the body the reaction occurs.

As allergic reactions are directed to the external environment, it makes sense that the areas of the body affected are those that are in most immediate contact with the environment: the skin, the airways and the gut. Reactions that occur mainly in the skin lead to hives or to eczema, a form of dermatitis. Reactions to inhaled environmental particles can be seen in the nose as rhinitis and in the lower airways of the lungs as asthma. While reactions to ingested foods are seen in the gut, the effects are often more extensive with more generalised symptoms (see Chapter 11) which can even be life threatening. Severe and generalised reactions can also occur when allergens directly penetrate tissues or the blood stream, as we commonly see with insect sting allergies.

WHAT ARE ALLERGENS?

'Allergen' is the name we give to virtually *anything* that triggers an allergic response. So potentially *anything* in the environment can

be an allergen. In other words, allergens are the 'target' that the immune system illogically singles out. However, there do appear to be certain things that are more 'allergenic' than others, making them more likely targets of the immune system. This is the reason that certain allergies are more common. For example, the most common food proteins to cause reactions are found in eggs, cow's milk, peanut, soy, tree nuts and seafood, and the inhaled proteins most likely to induce reactions are found in dust mites, animal dander and pollens. The 'top ten' allergens vary according to geographical region, depending on which allergens are most prevalent in that environment. Allergens are usually proteins, although there are a few rare exceptions, and the pattern of response is generally similar regardless of the trigger.

The allergic response is very selective. An allergic person will encounter countless different proteins over their lifetime, and they will produce perfectly normal responses to virtually all of these potential allergens. They only mount an allergic immune response to a select few. Even the most allergic people only make allergic antibodies to a tiny fraction of the possible allergens that they encounter in the environment.

There are a number of possible reasons that some substances are more allergenic. Some allergenic proteins have been shown to have chemical or enzymic properties that might make them more irritating. This seems to fool the immune system into thinking that the allergen poses a threat. Some of these allergens, such as dust mite proteins, also have structural elements similar to bacterial products, which normally induce an immune response. One theory is that when our immune system is too busy fighting real infection, as it was in centuries gone by, it is less likely to be distracted by any of these allergen protein imposters. But this does not fully explain exactly why the allergens evoke allergic antibodies, and not typical defensive antibodies.

ALLERGENS ARE NOT TO BLAME

One thing we must remember is that allergens are just the ‘target’ of the immune response; they themselves do not appear to cause the underlying allergy. Allergens can certainly not explain the epidemic rise in allergy, which is more likely to be due to other environmental forces effectively ‘loading the gun’ by altering the immune system such that allergic responses are more likely. We should be looking for what is loading the gun rather than at the target.

Allergenic foods like milk and eggs have been part of our diets for thousands of years, but allergies to these have only appeared very recently. Although it might seem obvious now that allergens could not possibly be responsible for the general rise in allergy and other immune diseases, this has been a common and longstanding misconception. In fact, it has only been quite recently, in 2008, that experts around the world stopped recommending ‘allergen avoidance’ in early life to prevent the development of allergic disease.¹ After nearly twenty years of failed attempts to avert the allergy epidemic by avoiding the most allergenic foods and inhaled allergens, it is not surprising that this change in approach has been quite confusing for the community. But we must remember that these guidelines were based on the best evidence available at the time (see Chapter 9).² As we learn more, our perspective changes. It has taken time and research to revise these practices. Importantly, as we gain more knowledge, we need to prepare for further possible changes. But at least we have the insight to know we are nowhere near the end of this story yet.

WHAT HAPPENS DURING AN ALLERGIC REACTION?

There are several different kinds of reactions to allergens. In broad terms, allergic reactions are mediated by antibodies or cells that have been conditioned to attack allergens. We will come back later to how these responses get conditioned, but once these antibodies

and cells are present in significant numbers, any encounter with an allergen will typically trigger a reaction.

The most common kind of reaction is the sudden (acute) reaction, which is mediated by allergic antibodies. These antibodies are from the immunoglobulin E (IgE) group of antibodies, which induce sudden swelling, rashes and itching along with other symptoms depending on where the reaction occurs. Each antibody can only recognise a particular allergen. Unless they come across that allergen, absolutely nothing happens. Everyone has some IgE to various things, but whereas non-allergic individuals only have low levels, allergic individuals have much higher levels of IgE that are directed to the particular allergen(s) they are allergic to. These antibodies circulate in the blood and are found in tissue where they bind to histamine containing cells called 'mast' cells (Figure 1).

When we do allergy tests, we are looking for the presence or levels of IgE antibodies to specific allergens (see Chapter 10). IgE antibodies were not discovered until the 1960s and are quite different to the IgG antibodies which fight bacterial infections and which do not cause histamine release.

The allergic response only occurs when an allergen binds to the IgE on the cell surface and sets off a rapid 'chain reaction'. Even tiny amounts of allergen can trigger this response.

For example, the child with peanut allergy will have a large number of IgE molecules in their blood (Figure 1a) and on their mast cell surfaces (Figure 1b) and a high proportion of these will be directed to peanut. Nothing happens until this child comes into contact with peanuts. When the peanut allergens bind the many peanut-specific IgE receptors in the mast cell surface, these IgE molecules become interlinked into a matrix, which induces the cell to spill histamine and other chemical mediators into the tissues (Figure 1c). Other cells called eosinophils also play a major role in the acute allergic response pouring more inflammatory chemicals into the tissues.

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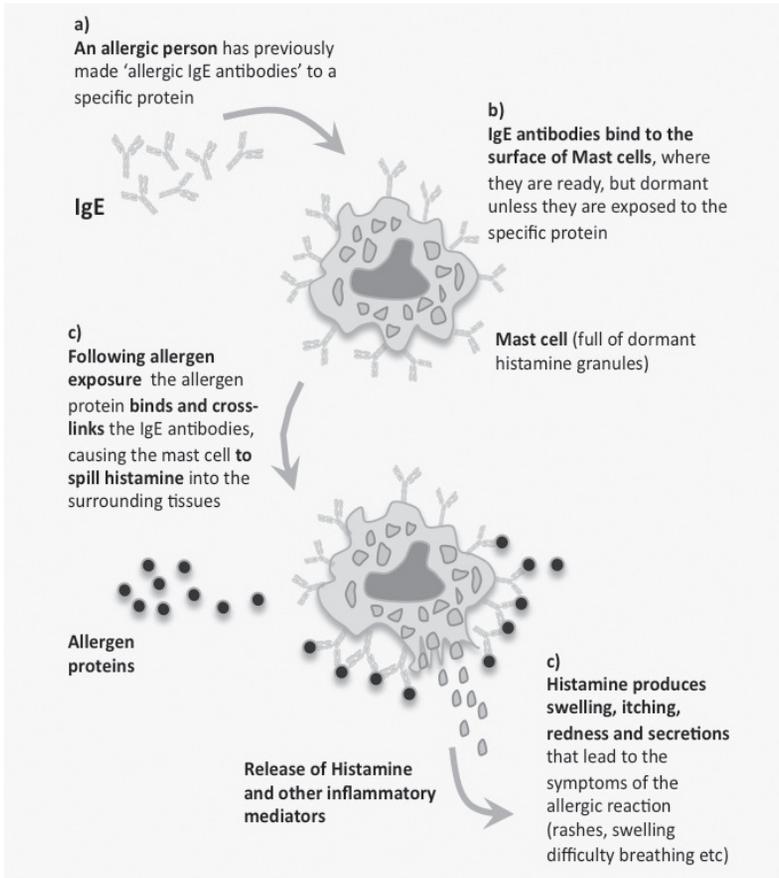


Figure 1 Events that occur during an acute allergic attack

It is the histamine and related mediators such as leukotrienes that cause all the signs and symptoms of the allergic reaction such as itching, redness and swelling (Figure 1d). As discussed later, the effects can range from unpleasant (such as itching or vomiting) to life threatening (if it occurs in the throat and blocks breathing). Once a reaction has occurred, the symptoms usually settle spontaneously, although serious reactions should be terminated quickly with treatment.

It is very reasonable to question why these IgE antibodies evolved in the first place, if they cause so many problems. This

family of antibodies is actually a normal part of our body's defense systems, and they have evolved to particularly attack parasites. In societies that encounter very few parasites, these antibodies appear more likely to be misdirected to attack allergens (see Chapter 8).

Sometimes the IgE reaction also induces a secondary delayed 'late-phase' reaction that can evolve over the following hours or days. This is more common in persistent allergic conditions such as asthma and eczema, where tissues are prone to chronic (long-standing) inflammation. It is generally mediated by immune cells rather than by antibodies. The chemical mediators released during the IgE reaction recruit more immune cells to the site of the reaction where they can perpetuate the inflammation. The IgE response is the most common kind of allergic reaction, but there are others. These are much less common and are driven by cellular responses which do not involve IgE at all. The best examples of these kinds of cell-mediated reactions are seen in the gut. They generally occur hours after ingesting the food trigger and are still not fully understood. As IgE is not involved, the patients do not experience histamine-related symptoms. Instead they have diarrhoea, vomiting and related symptoms. This can be harder to diagnose because the IgE allergy test is usually negative (see Chapter 11).

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All of the students have had some lectures on these basics earlier in their courses, so once we have completed the review, we get down to business and focus on allergy case studies. The students take turns to present cases of real patients with common allergies that they have just seen in the clinics. After telling the patients' stories, students discuss the research evidence that applies to each case. Some of these cases are outlined later in Chapters 11–15.

They do the work. They quiz each other. My role at this

point is to make sure that the discussions are dynamic and the facts are correct. I often supervise role-playing where one student will act as a doctor giving advice or explaining how to use an adrenaline auto-injector to another student pretending to be a patient or a parent. We create real-life scenarios that they are likely to encounter in general practice.

The idea of this kind of learning is that the students are actively engaged rather than passively dozing in a lecture. Their practical exams at the end of the year run in a very similar role-play scenario format. As always, the students are more focussed on passing exams than on their future practice, but at least we make sure that the skills they learn are directly relevant for both.

Each group of students is different, which keeps it interesting for me too. The underlying issues might be the same, but there are always so many new patients to discuss. Many changes have happened in the field over the last ten–fifteen years that I have been teaching, and this form of dynamic, evidence-based learning ensures the students are keeping up to date with the latest approaches.

I love it most when I see the students discover controversies and uncertainties. And there are still plenty. Although it is unsettling at first, it is critical for students to realise that we don't have all the answers. Above all, they must learn that ongoing research is essential to understand both the big picture of the allergy crisis as well as all of the specific questions that it raises.

When they come to the edge of the unknown, their interest is most stimulated. They realise that what they are learning now is only the beginning of a story that will continue to evolve over their lifetime. With any luck, we always hope to find a few who choose to join our ranks in the adventure of that discovery.