What are the chemicals that trigger allergies? How can chemists help prevent allergies?

Ethan Harris - 31 January 2021

There is an increasing occurrence of allergies in the developed world and it is one of the most chronic diseases in Europe. By 2025 it is predicted that half the population of Europe will have an allergy. Food allergies currently affect 7% of children in the United Kingdom and 9% in Australia. However, across Europe only 2% of adults have food allergies. Considering older people are less allergic, it is clear that the number of children suffering with this condition is increasing. Approximately 2.5% of three-year-old children in the UK currently have a peanut allergy and, in the UK, this has increased fivefold between 1995 and 2016.[1] There is no clear single reason for this increase, yet improved hygiene may be a factor, with less childhood exposure to infections. A robust immune system is critical for maintaining health but when it fails, for example in Severe Combined Immunodeficiency (SCID) syndrome[2] or overreacts, as in severe atopy, it can be life-threatening.

This essay explores the mechanisms and chemicals that cause allergic reactions and the science behind preventing allergies.

What are allergies?

Allergic disease, or atopy, is a condition caused by a hypersensitive immune system to chemicals, known as allergens (commonly proteins), found in the environment.[3] There are different categories of allergies: food allergies, respiratory allergies and allergies caused from medication. The chemicals that trigger allergies are harmless to people who are not considered to be allergic. The majority of people with allergies will only have mild symptoms for example, sneezing, red and itchy watery eyes, or worsening of asthma and eczema. More severe symptoms include facial swelling, called angioedema (see Fig 1). However, occasionally an intense immune reaction can occur with extensive vasodilatation causing blood pressure to drop and airways to narrow which can prove to be fatal – known as anaphylactic shock.

How do allergies happen?

When the body is first exposed to an allergen (a foreign chemical that the body does not recognise) a subtype of T-Lymphocytes known as type 2 helper T-Cells produce the antibody immunoglobin

Allergen	Protein
Peanut	Ara h 2, Ara h 6 (group of 2S albumins – storage proteins that exists in various seeds)
English walnut	Jug r 1
Hazelnut	Cor a 9
Almond	AMP
Yellow mustard	Sin a 1
Soybean	Alpha subunit of beta conglycinin
Lentil	Ses l 2

Table 1: common allergens in food [4, 5]

E or IgE. IgE antibodies that are chemically complementary to the antigen of the allergen, bind to the receptors on the cell surface of mast cells and basophils (see Fig 2).[6] This exposure to the allergen does not result in allergic symptoms, however, the person is now sensitised to the allergen. Upon re-exposure to the same allergen, the antigen binds to neighbouring IgE molecules on the mast cells and basophils, causing cross-bridges and joining their receptors. This triggers a signalling "cascade" producing the release of inflammatory chemicals, for example, histamine.[7] This can precipitate a life-threatening anaphylactic reaction.

Figure 1: Picture of a child showing severe facial swelling (angioedema).

Sensitisation from one specific protein may also cause sensitisation to similar antigens. This is called "cross sensitivity" and is often seen in people allergic to one type of nut.

Examples of Allergenic Chemicals:

There is a huge range of allergenic chemicals, some natural (see Table 1) and some man-made. Some artificial food colourings have been reported to be allergens and can have negative effects on children, for example hyperactivity.[8] The most commonly consumed food dyes are Red 40 ($C_{18}H_{14}N_2Na_2O_8S_2$)[9], Yellow6 ($C_{16}H_{12}N_2O_7S_2$ •2 Na)[10] and Yellow 5 ($C_{16}H_9N_4Na_3O_9S_2$)[11]. Yellow 5, known as tartrazine (see Fig 3), has been shown to cause hives (see Fig 4) and asthma symptoms and

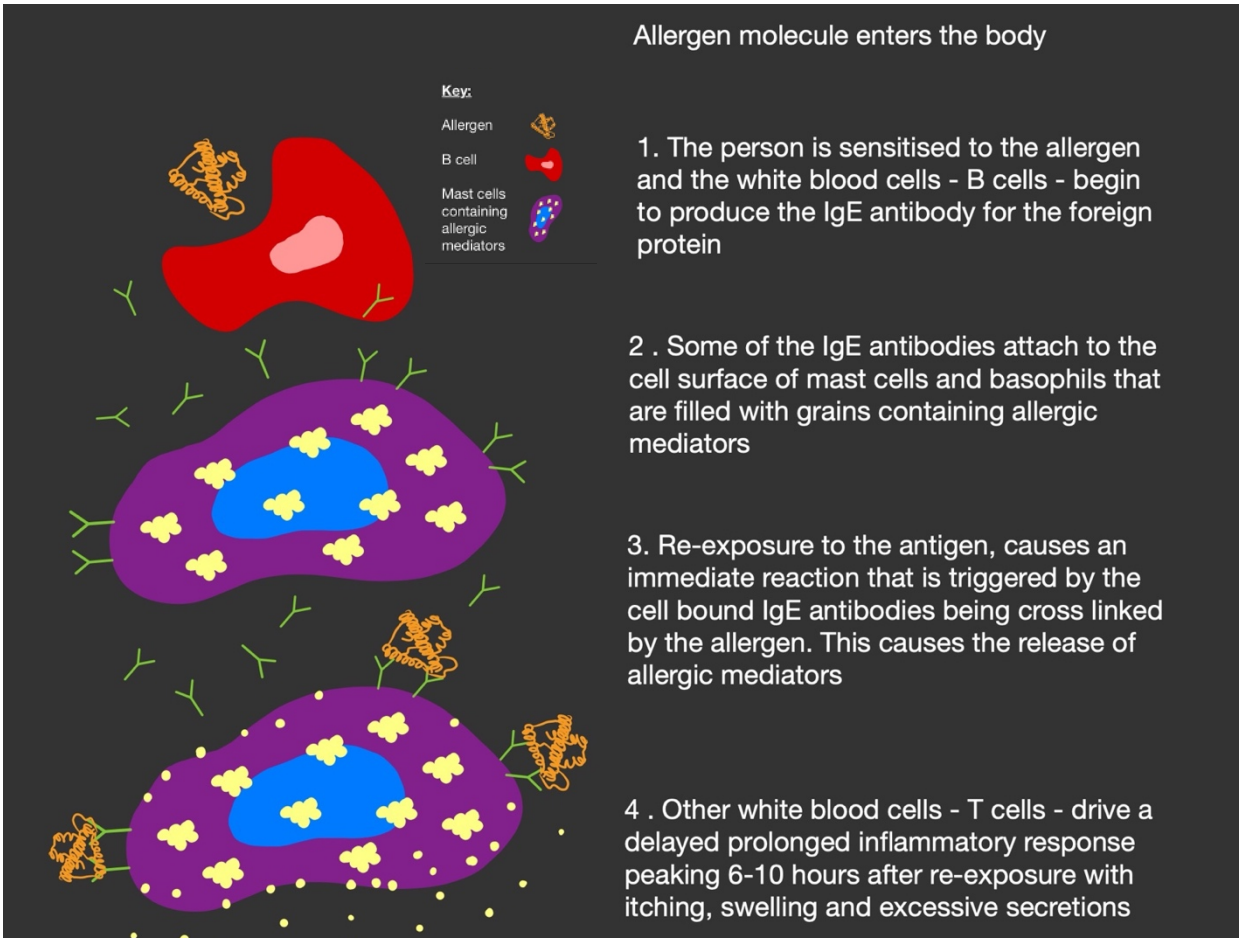

Figure 2: Schematic diagram illustrating the steps in sensitisation in the first stages of developing an immune reaction

Yellow 6 and Red 40 may cause reactions in sensitive individuals.

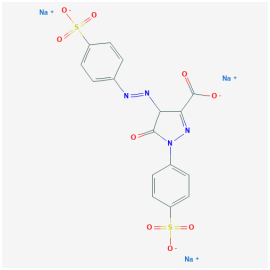

Figure 3: Structure of Yellow 5 - tartrazine ($C_{16}H_9N_4Na_3O_9S_2$)[11]

Figure 4: An example of hives – red, blotchy, itchy swellings that occur due to the release of histamine in an immune reaction.

Sensitisation can also occur through skin contact, for example with latex rubber gloves used by healthcare workers. Over 4000 environmental chemicals have been identified as contact allergens and rubber glove chemicals are among highest cases of contact allergens.[12] The accelerators used in the gloves, to speed up vulcanisation, are what primarily cause the allergy. These accelerators include carbamates, thiurams, 2-mercaptobenzothiazole (MBT), and 1,3-diphenylguanidine (DPG). The antioxidants used to prevent rubber deterioration, for example, p-phenylenediamines (the black rubber mix chemicals) can also cause allergic reactions to rubber gloves. The allergy may manifest as a contact dermatitis on the surface of the skin where the gloves have been in contact, causing patchy and itchy red sores, particularly on the dorsal surface of the hands, wrists and forearms (see Fig 5).

Figure 5: Patchy dermatitis on the hands due to allergic reaction to the accelerators in rubber gloves

In addition to skin contact, allergic reactions can occur by inhaling the allergen. A very common example of this is hay fever, caused by pollen. The sugar beet plant (*Beta vulgaris*) produces the allergen Beta v 2 in its pollen.[13] The chemical Zoy m 1 is released in the pollen of *Zoysia matrella* (manilla grass) which can also trigger hay fever. Symptoms include a runny nose, sneezing, coughing, throat itching and watery eyes. Pet dander also contains allergens that often trigger asthma symptoms - wheezing, chest tightness and coughing. Domestic dogs[13] (*Canis familaris*) and domestic cats *(Felus catus*)[13] induce allergic reactions due to the allergen Can f and Fel d, respectively. Fel d is a uteroglobin protein, which is also referred to as a secretoglobin. These are a group of small, dimeric, disulphide bridged proteins secreted by mammals and can cause asthma. Although all of these chemicals are foreign to the human body, they are safe to many people as only a low-grade immune reaction may occur without symptoms. However, in the case of allergy, the immune system overreacts, sometimes with severe allergic symptoms.

How can allergies be treated:

There are three methods to treat and prevent allergies. The first is to prevent re-exposure to the allergen/antigen by avoiding the food or trigger. This can be done by educating people with allergies to check ingredients and manufacturers clearly labelling their food products. Alternative products can be provided, for example, those who are allergic to latex gloves (see above) could find alternatives that do not trigger allergic reactions, for example gloves made from neoprene and poly vinyl chloride.

Secondly, chemists can modify the allergen to make it acceptable to the body. Dr Chris Mattison, a molecular biologist, using the knowledge that the immune system recognised a specific protein in food and releases the IgE antibody, set out to overcome this challenge.[14] He approached the problem from an agricultural perspective, rather than a medical one. He treated proteins from cashew nuts – a common allergen (2S albumin, Ana o3) – with heat and sodium sulphite, a commonly used food preservative. This breaks down the proteins into smaller fragments in attempt to prevent

the IgE antibody from recognising the protein's epitope (to where the IgE binds). When mixed with IgE from people allergic to cashews, Mattison found a significant reduction (about 50%) of the altered protein bound to IgE compared to the normal cashew protein, reducing the chances of the immune cascade of inflammatory chemicals.

Drugs used:

Thirdly, chemists can use specific drugs to help prevent the symptoms of allergies. However, these drugs do not cure the person of their allergy. As mentioned earlier histamine is an important chemical responsible for allergic symptoms.[15] Antihistamine drugs compete with histamine for receptors on cells as they are competitive inhibitors with a similar structure to histamine. They block the action of histamine and can prevent and reduce the swelling, itching and other histamine related symptoms. However, a common side effect of first-generation antihistamines is drowsiness as the drug can pass through the blood brain barrier (BBB). Chemists have also developed second generation antihistamines with fewer side effects as they cross the BBB to a much lesser extent. There are different sub-types of histamine receptors and chemists have designed drugs to target specific receptors, for example, the H_1– antihistamines ($C_{23}H_{24}FN_5$)[16] (see Fig 6) are used to ease allergic symptoms as they inhibit the H_1-receptor. Epinephrine/adrenaline ($C_9H_{13}NO_3$) was the first drug marketed for the treatment of asthma. It is found in inhalers and relaxes the muscles in the bronchi, therefore increasing the lumen diameter and reduces wheezing. Steroids, for example adrenocorticoids and hydrocortisone, are very important in treating allergies as they reduce the immune response. They help relieve the redness, swelling and fluid build-up associated with allergic reactions like eczema.

Figure 6: Molecular Structure of H_1-antihistamines ($C_{23}H_{24}FN_5$)[16]

Immunotherapy:

Desensitisation

Desensitisation involves a gradual exposure to larger quantities of an allergen. This can either be through subcutaneous immunotherapy - injections or sublingual immunotherapy - tablets that are placed under the tongue. This immunotherapy does not cure the patient of their allergy but is simply there to protect the patient in a situation of undesired exposure, for example, foods that may contain allergens could trigger immune responses. If the patient is desensitised, they are less likely to react to when exposed to smaller, accidental, quantities of the allergen.

Immune deviation

Immunotherapy can be used to treat allergies by reducing sensitivity to allergens, lessening the severity of allergic reactions. Immunotherapy has different responses in different people, some people are cured, some are less sensitive and for some there is no change in the allergic reaction. It is recommended for people who are extremely allergic or cannot avoid the allergen.[17] During a dose of immunotherapy (specifically immune deviation), the person is exposed to approximately 100 times the estimated yearly intake of the allergen. This massive intake of allergens in such a short time period presents unique effects on the immune system known as immune deviation or a modified immunological response to an allergen exposure by induction of regulatory T cells. During immune deviation, allergen-specific T helper type-1 (Th1) cells are released instead of Th2. Unlike the Th2 cells, Th1 produce interferon gamma, stimulating B cells to release IgG antibodies and not IgE which cannot trigger allergic reactions. The IgG4 antibodies block the allergen from the Th2 cells therefore inhibiting mast cell degranulation, so no allergic mediators are released, preventing allergic reactions.

Conclusion:

An understanding of how allergies occur and how to treat them is an increasingly important health issue due to the ever-increasing number of people with allergies. Allergies are a greater medical problem in the developed world and as more

emerging countries gain wealth with improvements in general hygiene, their populations too are likely to experience allergies. In addition, with the introduction of GM foods, new foreign proteins may be encountered, possibly causing new hypersensitivity reactions to unrecognised chemicals.

How can chemists face these challenges? In addition to developing new treatments, prevention of allergies should also be prioritised. Perhaps by using the same bio-chemical technology used in gene modification, the allergens inside the product can be altered to create an "allergen free" alternative with a different epitope. Also, we know that older people suffer less with allergies presumably due to an aging effect on the immune system. Perhaps understanding the mechanisms behind the natural reduction in the immune system could be used to prevent allergies. However, any modifications in our biological defences needs continued careful research as the immune system is a hugely complex system there to protect us from foreign and dangerous chemicals and diseases.

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