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Allergy black box

Allergenic substances in everyday products are abundant and the mechanisms in the body to deal with them are complex. There is a great need for research.

Vienna, 1902 at St. Anna's Children's Hospital: Clemens von Pirquet, paediatrician and hospital director, discovers side effects in individual children after injecting a vaccine serum against diphtheria. He observes harmless rashes and itching, but also dizziness, breathing problems and fainting. A few children die. Von Pirquet observes that the adverse effects of the second injection do not appear after several days as with the first, but within a few minutes. The Viennese paediatrician coins the term *"allergy"*, which is still used today to describe various clinical scenarios.

Substances are varied

Whether in eggs and nuts or in creams and earrings, numerous substances in food and everyday products, such as cosmetics or jewellery, can trigger an allergy in certain individuals. "Allergies represent a serious and increasing health problem. This notably applies to industrialised countries," says senior lecturer Dr. Hermann-Josef Thierse. About 15 to 25 percent of the population in Germany suffer from allergies. Thierse, an immunologist and biochemist, has been working on allergic diseases for more than 20 years. At the BfR, he supervises complex risk assessments and toxicological research on the safety of consumer products, for example, latex components in textiles or preservatives, such as methylisothiazolinone.

Immune system reactions

Clinical medicine is typically aware of four types of reactions (see box p. 32), which are the body's responses in the event of an allergy. For most types of allergy (types I to III), *antibodies* are produced in response to a substance. These antibodies, together with the specific T-lymphocytes (T-cells), form a crucial component of the acquired immune system and normally fight against infections caused by viruses and bacteria. In the case of a type I allergic reaction, IgE antibodies in particular react to a foreign substance. They can trigger a rapid and powerful immune response. Type IV reactions are different: delayed-type skin allergy symptoms may occur many hours or days after secondary contact with an allergen. After the initial contact, allergen-specific T-lymphocytes can form special T-cells (memory cells) that "remember" the foreign substances so that they are able to fight them more effectively and quickly, after repeated contact. These T-cells may contribute to triggering a clinically visible allergic reaction, such as a rash.

T-cells react to nickel

There are over 4,000 known substances that can trigger a contact allergy in products that we use every day. These include nickel. The immune system reaction to this metal is regarded to be of type IV. For example, when the skin repeatedly comes into contact with jewellery, jeans buttons, or piercings that contain nickel, the result can be skin inflammation. In the process, T-cells respond to nickel ions, which can be released from the products through oxidation. "Of the more than 100 million different T-cells that every human being has, each has a unique docking site, which is known as a "T-cell receptor". Through them, all kinds of allergenic pathogens or substances can be recognised and fought off," says Dr. Katherina Siewert, biochemist in the Department Chemicals and Product Safety at the BfR and one of the two heads of the Dermatotoxicology Study Centre. "At the BfR, we have now been able to shed light on certain mechanisms of how nickel is recognised by the body." Siewert and her team examined blood and skin samples in the laboratory. They discovered that a large proportion of the T-cells

Allergy
(Greek: allos – different; Greek ergon – work, reaction) A normally innocuous, non-invasive substance triggers an allergic reaction in predisposed persons after repeated contact. This is sometimes referred to as a misdirected or exaggerated immune response.

Antibody
This is an immune defence protein (protein molecule, immunoglobulin, such as IgG, IgE) that can specifically bind to an extraneous or endogenous structure – an antigen. Within the context of an allergy, the antigen is an allergen.

that bind nickel have the amino acid histidine at the corresponding docking site and that nickel is presumed to bind to this location. Furthermore, a surprisingly large number of T-cells reacted to the metal with a very specific receptor. According to Siewert, this is an important indication in explaining why so many people develop a nickel allergy. Another research success: "Our research method does not use animal experiments and produces results relatively quickly."

Hair dyes as allergy triggers

Similar to nickel, hair dye ingredients can also trigger a type IV allergy. The BfR has assessed the substance *para*-phenylenediamine (PPD) to be of particularly high-risk. This substance can be found in higher concentrations in hair dyes. In particular to PPD, it is important to mention that it not only can it trigger type IV skin inflammations in predisposed allergic persons, but also type I allergic reactions – in very rare exceptional cases with symptoms that may culminate in a life-threatening reaction. "All the more reason to explicitly reject the suggestion (as proposed by some companies) that consumers do a self-test on their skin before dyeing their hair," says allergy expert Thierse.

Ban on methylisothiazolinone

Another critical substance is methylisothiazolinone (MI), which is used, among other things, as a preservative in cosmetics, liquid detergent and wall paints. Since the mid-2000s, research teams in Europe have observed that allergic skin reactions caused by MI were increas-

Types of allergic reaction (mixed forms exist)

TYP I	TYP II	TYP III	TYP IV
The type I reaction is the most common form of allergy and is known as an immediate type reaction. Examples are quick IgE-mediated hypersensitivity reactions to certain substances from food, pollen, bee venom or animal hair. In addition to wheals and localised itching, a life-threatening reaction (anaphylactic shock) may occur in rare individual cases.	**The type II reaction** is also known as cytotoxic (cell-destructive) and usually leads to damaged antigen-binding blood cells, in a process mediated by antibodies. Examples are adverse reactions to drugs caused by analgesics or antibiotics.	**Type III reactions** are caused by immune complexes (consisting of antigen and antibody). These include allergic vasculitis triggered by antibiotics or infections.	**The type IV reaction** is known as a delayed type hypersensitivity reaction (with reactions occurring 48 to 72 hours after exposure) and includes T-cell dependent contact allergies of the skin, reactions to drugs, and transplant rejections.

ing. A regulatory ban, based on extensive studies, was introduced in the EU in 2017 for use in hand creams and body lotion, for example. MI is still allowed in shampoos or shower gels since it does not remain on the skin for a longer period and is washed off again immediately. According to the EU Commission's Scientific Committee on Consumer Safety (SCCS), a concentration of 0.0015 percent is considered safe for these kinds of products to avoid an allergic reaction.

Legal regulations are necessary

Research on substances like PPD or MI shows that legal regulations are necessary to improve consumer protection. This requires internationally agreed rules, such as the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) developed by the United Nations or the European Chemicals Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

Another example is the constantly evolving Regulation (EC) No 1223/2009 of the European Parliament and of the Council on Cosmetic Products ("Cosmetics Regulation"). This provides precise information on permitted, restricted, or forbidden substances in cosmetics, which the SCCS has previously identified as part of its assessment. These assessments also help regulate allergenic substances. The BfR assists in these international committees. Moreover, the BfR develops recommendations, independent of the law, on how the allergy risks from everyday products can be minimised. For example, corresponding professional associations follow these recommendations, such as when dealing with potentially allergenic latex components in textiles.

Challenges for risk assessment

There remains however, a fundamental problem: the general public often wants to have clear and explicit specifications, especially limit values, although it is not always possible to determine these. According to Hermann-Josef Thierse, it is important that potentially allergenic substances are always assessed individually because of the variety and chemical diversity of allergens and the highly variable reactions of consumers to these allergens. This also means that individual differences and uncertainty factors must be considered, similar to modern, personalised medicine. It is also necessary to see to which extent allergens are released (if at all) from products that come into contact with the skin.

The complex mechanisms that trigger allergies are still a black box for science in many cases. When, why, and how strongly does someone react to certain substances? How do genes and environmental conditions influence allergy development? What role do they play in tolerance mechanisms in healthy individuals or therapeutically in desensitisation? There is still a great need for research in this field. ◘

More information:
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