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Evolving concepts of allergy

Further reading

The concept of allergy evolved and more and more new phenomena were described and documented in the beginning of the 20th century. Nowadays, we are able to classify them based on the different cellular mechanisms underlying the distinct reactions. Read below how Type III and IV allergic reactions were discovered.

Arthus reaction (nowadays Type III allergic reaction)

In 1903, the French physiologist Nicolas Maurice Arthus observed local skin reactions (i.e. redness, swelling, overheated tissue and later necrosis) after subcutaneously injecting repeated doses of sterile horse serum in his patients. This actually resembled the classical signs of any skin inflammation. Surprisingly, this reaction occurred after injection of non-infectious and non-toxic substances. He called the phenomenon 'local anaphylaxis'. Today it is known to be caused by an immune complex reaction (type III allergic reaction by Coombs and Gell). It still may happen today in individuals with high titers of protective IgG anti-tetanus antibodies. If they receive another dose of tetanus toxoid in case of a contaminated wound, the high antibody concentration interacting with the locally injected antigen form immune complexes resulting in a large local reaction (sometimes accompanied by fever).

Delayed hypersensitivity (nowadays Type IV allergic reaction)

Eczemas have already been known by the ancient Greeks. The word 'eczema' means to burn or boil and refers to the itchy and burning skin eruptions. Before the concept of allergy was established, the term 'Dermatitis venenata' was coined by the American Charles White in 1887. Different skin reactions upon contact with plants (including poison ivy, lacquer or primula) have been documented at that time. Joseph Jadassohn for the first time used the patch testing method to elicit local reactions to mercury ointments in patient with a widespread dermatitis. He noticed that allergic contact eczema took one to two days as opposed to the immediate reactions in IgE-antibody mediated allergies.

In analogy to the immune reaction known from tuberculosis, this cell-mediated immunity was also not readily transferable from one animal to another or among humans. A subcutaneously-injected first agent to treat tuberculosis, called *Tuberculine*, was developed by Robert Koch in 1890. It did not allow to treat tuberculosis as Koch proposed, but could be used for diagnostic purposes. Later in 1907, Clemens von Pirquet developed the Pirquet reaction – a test where the skin was superficially scratched and *Tuberculine* was applied. Based on their work in 1912, Charles Mantoux described this intradermal technique, called the Mantoux test, which is till used today for the diagnosis of tuberculosis (although in vitro tests measuring cytokine production are now available). Only in the 1940s, it became clear that specific lymphocytes are relevant in both diseases: in the immune defense against tuberculosis as well as in the elicitation of allergic contact dermatitis. The delayed hypersensitivity (mediated by specific T lymphocytes) was later incorporated into the classification scheme by Coombs and Gell as type IV reaction.