MILESTONE 2

The many sides of Paul Ehrlich

In the final decade of the 19th century, Emil von Behring and Shibasaburo Kitasato developed serum therapy for the treatment of diphtheria and tetanus (MILESTONE 1). The contribution of the Berlin-based bacteriologist Paul Ehrlich was vital for the production of high-quality anti-diphtheria serum that could be used to passively vaccinate humans against this deadly disease. Ehrlich proceeded to show that feeding laboratory animals low doses of a toxin protected them against an otherwise lethal dose of the same toxin, and he formulated the concept of active and passive immunization. However, the basis of the immunological protection involved was unknown.

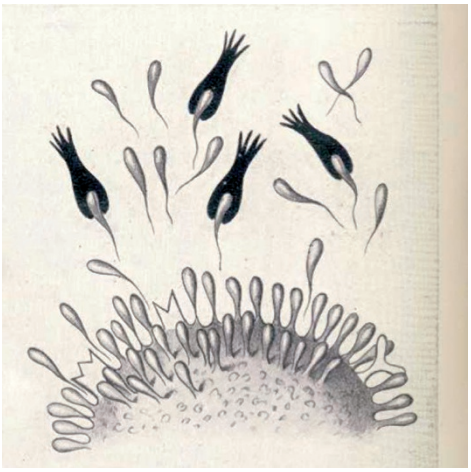
In 1897, Ehrlich proposed the side-chain model of immunity to account for his experimental observations. He imagined that harmful compounds (toxins) could mimic nutrients for which cells express side chains that he called 'nutriceptors'. Each cell would express multiple types of side chains to allow the specific uptake of essential nutrients. During an infection, the side chains would bind to microbial toxins instead of nutrients and would thereby block the physiological functions of the side chains. To compensate, the cell would produce more side chains; these would be shed into the bloodstream, where they would accumulate and act as antitoxins or 'antibodies', protecting against subsequent exposures to the same infection. Ehrlich would later introduce the term 'receptor' to replace 'side chain'.

Ultimately, the side-chain hypothesis of immunity proved to be incorrect. Ehrlich envisaged that all cells express the receptors that can give rise to antibodies and that any single cell expresses multiple receptor types. When the sheer scale of the potential antibody repertoire was later realized, it became improbable that any single cell could express all of the required receptors. Furthermore, Karl Landsteiner's studies showing that antibodies can be generated against chemically synthesized haptens also suggested cracks in Ehrlich's model—why would cells express pre-formed receptors for non-organic substances?

> "the side-chain model … paved the way for the subsequent correct description of antibody formation…"

It is now appreciated that plasma cells are the dedicated antibody-producing cells of the immune system, developing from B cells that express a single antigen-receptor type and undergo clonal expansion (MILESTONES 3, 5). Furthermore, B cell receptors for antigen are randomly generated (giving rise to a highly diverse receptor repertoire), and B cells that express self-reactive receptors are purged to prevent harmful autoimmune responses. In fact, Ehrlich himself observed that animals could not be immunized against their own blood, and he introduced the term 'horror autotoxicus' to describe the host's aversion to autoantibody production. Despite its shortcomings, the side-chain model was ground-breaking; it paved the way for the subsequent correct description of antibody formation (MILESTONES 3, 5) and introduced the 'lock-and-key' concept that became the basis of our understanding of adaptive immunity.

Ehrlich had many other notable 'side projects'. He developed chemical dyes for selective cell staining, described mast cells, basophils, eosinophils and neutrophils, and showed how the passive transfer of antibodies via breast milk protects infants. Moreover, he devised the concept of the 'magic bullet', proposing that invading microbes could be specifically targeted without damage to the host. His discovery of Salvarsan as a 'magic bullet' for the treatment of syphilis (through the use of a high-throughput screening system now routinely employed by the pharmaceutical industry) founded the field of chemotherapy. In 1908, he was jointly awarded the Nobel Prize in physiology or medicine, with Élie Metchnikoff, in recognition of their work on immunity. Not bad for a Jewish scientist considered a 'non-person' during the Nazi regime, a period that saw his manuscripts scattered throughout Europe and lost for almost a century. Mercifully, Ehrlich's papers were eventually tracked down by his grandson and are now safely deposited in the Rockefeller Archive Center—a lasting tribute to perhaps the greatest medical scientist of the late 19th and early 20th centuries.



Ehrlich's side-chain model looks spookily like our modern understanding of antibody production. Adapted from: Ehrlich, P. Croonian lecture: on immunity with special reference to cell life. *Proc. Royal Soc. Lond.* **66**, 424–448 (1900). Courtesy of Stefan H. E. Kaufmann.

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