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Editorial

Paul Ehrlich : father of three

The antigen is presented to a cell. The cell has on its surface accurate samples of all the antibodies which it can manufacture. These samples act as receptors for antigens. A particular antigen selects the appropriate receptor. Antigen-receptor interaction stimulates the cell to manufacture and secrete antibodies to the antigen. In this description, for cell, read B lymphocyte. For selection of appropriate receptor, read selection of appropriate B cell. And you have a condensed but uptodate version of the mechanism of antibody formation. The slightly inaccurate description given above is not from a student's answer book, but based on the "side chain theory" of antibody formation propounded by Paul Ehrlich exactly a century ago (1). How he reached these conclusions without any tracers or probes is a mystery which can be "explained" only in terms of intuitive leaps which some rare individuals are specially good at. No wonder, Ehrlich is considered the father of immunology. For his work on immunology, he shared the Nobel Prize with Metchnikoff in 1908 (2). The two gaints had worked on different aspects of body defence, and did not acknowledge adequately the significance of each other's work. It goes to the credit of the Nobel Prize Committee that they have often honoured scientists with divergent viewpoints, one more example in the same category being Golgi and Cajal (3).

Ehrlich's first love, however, was not immunology, but dyes. He knew that the dyes are organic compounds, with benzene rings. Cells also have benzene rings. A dreamer that he was, Ehrlich thought that the similarity should allow him to see structural details better if the cells are stained with the dyes (4). He played with all sorts of dyes, and all types of cells, specially blood cells. He developed methods for staining which allowed him to distinguish different types of cells in peripheral blood and the bone marrow. Besides, he developed a simple diagnostic test for paroxysmal cold haemoglobinuria, studied pernicious anemia and coined the terms megaloblast and normoblast. Hence Ehrlich is also considered the father of hematology. Little did Ehrlich realise that his two 'children' actually had a 'blood relationship'. When he talked of antibody-secreting cells, he had in mind *all* cells of the body. He assigned to lymphocytes, as did many scientists after him, no significant function.

Ehrlich is best known through his third child, chemotherapy. Ironically, he achieved success in this direction through a series of far-fetched arguments and erroneous theories. Fond of dyes as he was, he once injected methylene blue into a rabbit. To his surprise, although the dye travelled through all tissues, it stained only the nerve endings. From this, he argued that methylene blue could possibly be used as a pain killer. He did inject the dye into some groaning patients but failed to relieve their pain. Then he came up with a still more imaginative idea on the basis of the rabbit experiment. Since methylene blue selectively stained nerve endings, there could also be substances which would kill the microbes which infect man without doing any harm to human tissues. He called such substances "magic bullets". This dream of Ehrlich forms the basis of chemotherapy, and he made the dream come true during his life time. The microorganisms he chose to work on were the trypanosomes. The reason was that trypanosomes killed one hundred percent of the mice infected. This made evaluation of "treatment" easier–even if one treated mouse out of several infected survived, the treatment could be considered beneficial. The method adopted was that of

'trial and sweating' (4). Ehrlich would try a compound, fail, and then think of some small change in its chemical structure which might make it an effective treatment. He was an imaginative chemist, but not very good at synthesising compounds with the desired structure; for that, he depended on his assistants. His enthusiasm, inspiring leadership and endearing ways made them go through the ordeal of trying hundreds of chemical transformations. It was ultimately 'compound no. 606', an unstable arsenic containing compound, which was rather dangerous to make because its synthesis carried the risk of ether explosions, which turned out to be effective against trypanosomes. Around that time Ehrlich read somewhere Schaudin's theory that the spirochaetes which cause syphilis are closely related to trypanosomes, and that spirochaetes may sometime turn into trypansomes. This was a wrong theory, as we know today, but it gave Ehrlich the idea that compound 606 may also be effective as treatment for syphilis. This was a stroke of good luck. The drug turned out to be effective beyond expectations. Ehrlich assumed messianic proportions for the thousands afflicted with the dreaded killer, the punishment for sin. Ehrlich's lab turned into a chemical factory, churning out millions of doses of the wonder drug for patients scattered worldwide. The achievement was followed by bouquets and some brickbats too, because a small proportion of patients reacted to the drug with unacceptably serious side effects.

Paul Ehrlich was one of the most brilliant products of european enlightenment. He was born on 14 March 1854 at Silesia in Germany (5). He did not get good marks as a student because he gave full freedom to his fertile imagination but refused to memorize arid facts. His initial work was in association with Robert Koch. He went about his work so enthusiastically that he contracted tuberculosis. His lab was simple, with little equipment but hundreds of bottles, the contents of each of which he knew by heart. All available space in his rooms had mountains of books and journals piled on one another. He was an uncommonly voracious reader, but what was still more uncommon about him was that when the read material stewed in his brain, the outcome was a string of extraordinary ideas. His mannerism was thoroughly informal. His hands and clothes were always stained with his favourite dyes. He scribbled chemical formulae on his clothing and sometimes even on his colleagues' clothing, long before the Americans started doing it on T-shirts. To explain a point, he would sit down with a chalk and start drawing a diagram on the floor. He reinforced the statistical approach to biological experiments. He used 50 mice for an experiment for which only one was used before, but the result was that he could deduce mathematical laws predicting biological phenomena. He was a modest and kind man, which made it easy for him to win friends and influence people. He smoked 25 strong cigars a day. His love for cigars and books kept him poor all his life. Among his hobbies was reading adventures of Sherlock Holmes by Arthur Conan Doyle, which went well with the detective-like approach required in research. Ehrlich was much distressed by the first world war. He suffered a mild stroke in 1914, and another one on 20 August 1915, to which he succumbed. We may end this tribute with his oft-quoted Gs which are required for success in research : Geld (money), Geduld (patience), Geschick (cleverness) and Gluck (luck).

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