Dr. Ward

AMI Work for Advanced Biology

1. Read the following article.
2. Write a brief summary.
3. Write a 1 paragraph discussion of the importance of this scientist's work today.

Paul Ehrlich (1854–1915)

In 1906 Paul Ehrlich prophesied the role of modern-day pharmaceutical research, predicting that chemists in their laboratories would soon be able to produce substances that would seek out specific disease-causing agents—"magic bullets," as he called them. Ehrlich himself met with signal successes in the emerging fields of serum antitoxins and chemotherapy.

Ehrlich was born near Breslau—then in Germany, but now known as Wrocław, Poland. He studied to become a medical doctor at the university there and in Strasbourg, Freiburg im Breisgau, and Leipzig. In Breslau he worked in the laboratory of his cousin Carl Weigert, a pathologist who pioneered the use of aniline dyes as biological stains. Ehrlich became interested in the selectivity of dyes for specific organs, tissues, and cells, and he continued his investigations at the Charité Hospital in Berlin. After he showed that dyes react specifically with various components of blood cells and the cells of other tissues, he began to test the dyes for therapeutic properties to determine whether they could kill off pathogenic microbes. Classmates and others recalled Ehrlich as the man with blue, yellow, red, and green fingers.

After a bout with tuberculosis—probably contracted in the laboratory—and his subsequent cure with Robert Koch's tuberculin therapy, Ehrlich focused his attention on bacterial toxins and antitoxins. At first he worked in a small private laboratory, but then he was invited to work at Koch's Institute for Infectious Diseases in Berlin. The post-Pasteur world was an exciting time to be looking for cures and preventives, and Koch's Institute was one of the best places to be. Among Ehrlich's new colleagues were Emil von Behring and Shibasaburo Kitasato, a Japanese scientist whose fellow countrymen were to play a critical role in Ehrlich's research. Von Behring and Kitasato had recently developed sera therapies—first for tetanus, then for diphtheria (for which Behring would win the first Nobel Prize in physiology or medicine)—and evolved the concept of antitoxin to explain the immunizing properties of sera. Whereas Pasteur's vaccines and Koch's tuberculin were made from weakened bacteria, von Behring used the serum, or cell-free blood liquid, from naturally or artificially immunized animals to induce immunity. One of Ehrlich's jobs at the institute was to make von Behring's diphtheria antitoxin in quantity and later to review the quality of the product produced by the chemical-pharmaceutical company Hoechst. In carrying out this work, he learned how to boost immunity systematically and how to produce high-grade sera. Although Ehrlich and von Behring often quarreled, they maintained a lifelong relationship, for better or worse.

In recognition of Ehrlich's accomplishments and of his promise as a researcher, in 1896, the Institute for Serum Research and Serum Testing was established for him in a Berlin suburb. In 1899 the institute, which was originally housed in a one-story ramshackle building, was moved to the city of Frankfurt to more suitable quarters and renamed the Royal Prussian Institute for Experimental Therapy. In 1908 Ehrlich shared the Nobel Prize in physiology or medicine with Élie Metchnikoff for their separate paths to an understanding of the immune response: Ehrlich presented a chemical theory to explain the formation of antitoxins, or antibodies, to fight the toxins released by the bacteria, while Metchnikoff studied the role of white blood corpuscles in destroying bacteria themselves. By that time most scientists agreed that both explanations of the immune system were necessary.

Early in his career Ehrlich began to develop a chemical structure theory to explain the immune response. He saw toxins and antitoxins as chemical substances at a time when little was known about their exact nature. Up to that time those scientists, like Felix Hoffmann (p. 10), who were synthesizing therapeutic agents came at their tasks with few hypotheses about where and how these agents interacted with living systems. Ehrlich supposed that living cells have side chains much in the way that dye molecules were known to have side chains that were related to their coloring properties. These side chains can link with particular toxins, just as the organic chemist Emil Fischer had said that enzymes must bind to their receptors "like a key in a lock." According to Ehrlich, a cell under threat from foreign bodies grows more side chains, more than are necessary to lock in foreign bodies in its immediate vicinity. These "extra" side chains break off to become antibodies and circulate throughout the body. It was these antibodies, in search of toxins, that Ehrlich first described as magic bullets. Serum therapy was for him the ideal method of contending with infectious diseases. In

those cases in which effective sera could not be discovered, Ehrlich would turn to synthesizing new chemicals, informed by his theory that the effectiveness of a therapeutic agent depended on its side chains. These chemotherapies were to be the new magic bullets.

Over time Ehrlich elaborated his theory of the immune system, supposing, for example, that a disease-causing substance must have special chemical groups that enable it to link to cells and others that account for the toxic action of a substance. Sometimes in explaining his theories, Ehrlich became so excited that he wrote on virtually any available surface, covering tablecloths, shirt cuffs, picture postcards, and laboratory walls with diagrams.

In Frankfurt, Ehrlich returned from his work on sera to chemotherapies and dyes. First targeting trypanosomes—the protozoa that were known to be responsible for certain diseases such as sleeping sickness—he and the Japanese bacteriologist Kiyoshi Shiga synthesized trypan red as a highly effective cure for that disease.

In 1906 Georg-Speyer-Haus, a research institute for chemotherapy, was established with its own staff under Ehrlich's direction. Soon this institute and the Hoechst and Cassella chemical companies reached an agreement that gave the companies the right to patent, manufacture, and market preparations discovered by Ehrlich and his colleagues. The companies further agreed to supply chemical intermediates for the syntheses that the staff of the institute would undertake.

The researchers, now including an organic chemist, Alfred Bertheim, and a bacteriologist, Sahashiro Hata, broadened the targeted microorganisms to include spirochetes, which had recently been identified as the cause of syphilis. Beginning with an arsenic compound, atoxyl, in three years' time and three hundred syntheses later—for that day an amazingly large number—they discovered salvarsan (1909), or dihydroxydiaminoarsenobenzenedihydrochloride (see introduction to chapter 5, p. 64). Salvarsan was first tried on rabbits that had been infected with syphilis and then on patients with the dementia associated with the final stages of the disease. Astonishingly, several of these "terminal" patients recovered after treatment with salvarsan. More testing revealed that salvarsan was actually more successful if administered during the early stages of the disease. Salvarsan and Neosalvarsan (1912) retained their role as the most effective drugs for treating syphilis until the advent of antibiotics in the 1940s.