ANTIBIOTIC DEVELOPMENT

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1 BIRTH OF THE ANTIBIOTIC ERA

It is easily forgotten that antibiotics as we know them have only been available for about 70 years. Death from infection was a feared eventuality before quite recently, whereas now society almost seems to have the opposite problem—expecting easy cures from antibiotic therapy for nearly all infectious diseases. The early discoveries that were keystone events in antimicrobial development were due to combinations of luck, skill, ingenuity, and Nobel-Prize-winning research.

The antibiotic era was primed to begin after Alexander Fleming's famous observation in 1929 of a zone of inhibition around a *Penicillium notatum* mold on a Petri dish of staphylococci in his laboratory [1]. Fleming was wise enough to recognize that a natural substance was being secreted from the mold, and for the sake of convenience he named this substance *penicillin* to avoid calling it "mold broth filtrate," which is what his experiments began working with [1]. To Fleming, penicillin's greatest potential was to assist in the selection culturing of organisms that were penicillin resistant to prevent overgrowth of organisms such as streptococci and staphylococci on culture medium from samples taken in areas of mixed human flora. His paper only briefly mentioned its possible utility in treating infections, and the editor's first revision of the paper actually removed mention of this [1, 2].

The utility of penicillin as a therapeutic agent was first described by Chain et al. in 1940 [3]. By this point, sulfonamides had already been discovered and were being used therapeutically in the treatment of infections [4]. A group under the leadership of Gerhard Domagk experimented with a antimicrobial dye named prontosil that was eventually determined to be a prodrug of sulfanilamide [4]. Experiments in mice revealed prontosil's in vivo activity against streptococcal infections, and Domagk himself administered the drug successfully to his child when she developed a dangerous streptococcal infection. After the publication of Domagk's results, the discovery and development of many active sulfonamides followed with numerous compounds becoming commercially available [4]. Domagk won the Nobel Prize in Medicine in 1939 for his discovery of prontosil's antimicrobial effects, though he was prevented from receiving it until 1947 due to Hitler's policies [4, 5].

Chain et al. described penicillin's antimicrobial activity in a paper written in 1940 [3]. By this point, the active penicillin molecule had still not been isolated, but several researchers were working with active penicillin preparations in a similar manner to Fleming. Chain and co-workers were the first to investigate penicillin as a chemotherapeutic agent. They tested this by injecting groups of healthy mice with one of three bacteria: *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Clostridium septicum* (formerly *C. septique*) [3]. Half of the mice were then given penicillin for different durations. Penicillin dramatically saved the lives of the treated mice, while all controls expired. This led to testing in human patients and the eventual availability of the refined drug for Allied soldiers in World War II. For their work in the discovery and development of

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