René Dubos: unearthing antibiotics

In 1939, René Dubos discovered gramicidin—the first clinically tested antibiotic agent. This discovery helped revive the stalled interest in penicillin and launched the era of antibiotics.

The notion that microbes can inhibit other microbes dates back to the late 1800s, when Louis Pasteur showed that anthrax cultures were robbed of their virulence when exposed to aerobic microbes. Dubos based his early experiments on this principle of “antibiosis” and “the supremely simple working hypothesis that soil as a self-purifying environment could supply an agent to destroy disease-causing bacteria” (1).

Digging in the dirt
In 1927—two years before Alexander Fleming discovered penicillin—Oswald Avery recruited Dubos, a young soil microbiologist, to The Rockefeller Institute. Avery challenged Dubos to find a soil microbe that could destroy the durable polysaccharide capsule of type III pneumococcal bacteria—a deadly bacterial strain that was resistant to neutralization by type-specific antiserum and was thus impervious to the serum therapy then used to treat patients with pneumococcal pneumonia.

Dubos accepted Avery’s challenge and set out in search of capsule-killing microbes. His approach was simple. Dubos put soil samples on a high-carb diet of purified type III pneumococcal polysaccharide and, over time, coaxed out a capsule-devouring bacterium. From this new bacterium, Dubos isolated the capsule-degrading S III enzyme.

The S III enzyme, which worked by stripping the bacteria of their sugary coats and rendering them vulnerable to attack by phagocytic cells, protected mice against infections with type III pneumococci. This discovery was first announced in Science (2), but was published in detail in two papers in The Journal of Experimental Medicine (3, 4). Despite its promise in animal models, the S III enzyme could not be used to treat patients, as the enzyme was difficult to purify and detoxify and worked poorly in patients with immune systems weakened by disease.

Although Dubos later used rabbits to raise type III-specific antibodies that ameliorated disease in patients with type III pneumonia (5), the use of serum therapy became passé by 1940 with the development of antibacterial sulfa drugs.

A kinder, gentler drug
But Dubos forged ahead, turning back to the soil in search of new agents to combat other bacterial infections. Among such infections were those caused by Gram-positive bacteria, such as hemolytic streptococci, identified in 1931 as the causative agent of rheumatic fever—a disease that afflicted both Dubos and his first wife (1).

Dubos’s tactics remained largely the same, except he fed the soil a more complex diet of whole bacterial particles. Soil reared for two years on a mixture of staphylococci, pneumococci, and hemolytic streptococci yielded a spore-forming bacillus (Bacillus brevis) that could attack and kill most Gram-positive bacteria. These findings were also published in The Journal of Experimental Medicine (6, 7).

Dubos turned to biochemist Rollin Hotchkiss for help in defining the chemical nature of the antibacterial substance produced by B. brevis. The duo’s analysis revealed that the active substance (dubbed tyrothricin) contained two distinct polypeptides. One (referred to by Hotchkiss as the “roughneck” tyrocidine) was a lysin that attacked the membranes of both Gram-positive and Gram-negative bacteria. The second was gramicidin (“the gentle protector”), a subtil, bacteriostatic agent that selectively inhibited the growth of Gram-positive bacteria (8, 9).

Reviving penicillin
“We had high hopes,” recalled Hotchkiss in 1990, “that we had [found] a power-ful new curative and preventative medicine” (1). But although a single intraperitoneal injection of gramicidin protected mice against fatal bacterial infections, the compound was toxic when administered intravenously and thus could not be used to treat systemic infections. Topical gramicidin, however, proved highly effective and was used during World War II to treat wounds and ulcers. Indeed, gramicidin is still an ingredient in some modern-day topical antibiotics.

Although ultimately of limited practical use, gramicidin was the first natural antibiotic discovered through a deliberate, systematic search for antibacterial compounds. And without it, penicillin might have been left to languish. Howard Florey (Oxford University) credited Dubos for reviving his research on penicillin, which was shelved for nearly a decade after its uncelebrated discovery by Fleming in 1929 (10).

REFERENCES