Righting the Antibiotic Record

Most people think that Alexander Fleming discovered the first clinically useful antibiotic, but that honor should really go to Rene Dubos, science historians say

QUESTION: What was the first antibiotic put to clinical use, and who discovered it?

If you answered penicillin and Alexander Fleming, you would be wrong on both counts. The correct answers are gramicidin and Rene Dubos.

It was 50 years ago that Dubos isolated a substance from a soil microbe and discovered that it protected animals from massive doses of some types of bacteria. His work helped pave the way for widespread use of antibiotics, which have revolutionized the treatment of infectious disease. "But Dubos's role has never been fully recognized," says Carol Moberg, a research associate at Rockefeller University.

To help set the record straight, Moberg organized a 1-day symposium last month to mark the 50th anniversary of the discovery of gramicidin.* "Fleming often gets the credit [for discovering antibiotics] thanks to his work with penicillin, but that's just not right," says Moberg. "We wanted to correct the British bias in the story as it is usually told."

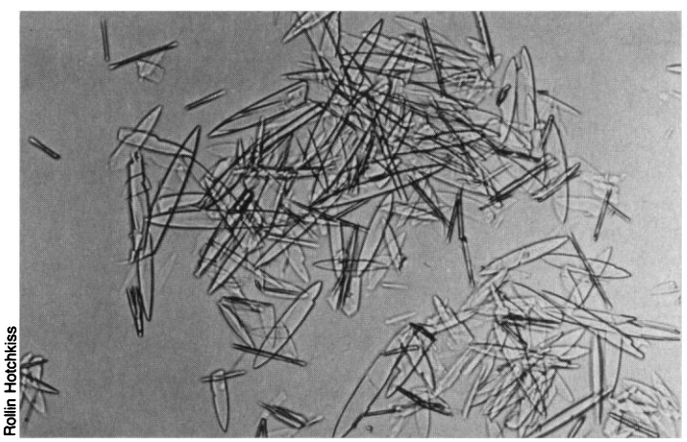
The penicillin story, as recounted at the symposium by Norman Heatley of Oxford University's Dunn School of Pathology, is well known. One day in 1928 Alexander Fleming leaves his laboratory at St. Mary's Hospital in London for summer vacation. A spore happens to waft in from somewhere and lands on one of several unincubated petri dishes, giving rise to a circular mold colony. Fleming returns in September and discards the lot of contaminated plates. To illustrate a point in conversation with a colleague, he happens to pick up just the dish with the circular mold and notices that staphylococcus colonies are undergoing lysis in the area of the mold. He names the mold "penicillin," but originally misidentifies it, misunderstands its properties, and never succeeds in isolating it. Subsequent attempts to reproduce the event reveal how enormously fortuitous it was, requiring a specific weather sequence of limited temperature range. In fact, Fleming himself loses interest in penicillin and publishes nothing on it after 1931. By the mid-1930s nobody believes penicillin to be of practical value. But Howard Florey and Ernst Chain rekindle interest in it and discover its value as an antibiotic. Then, pharmaceutical companies and governments leap on the discovery, learning how to stabilize and expand penicillin production during World War II. And finally, penicillin becomes an irreplaceable therapeutic agent.

This is a classic story of how science often combines serendipity with hard work—and it is regularly recounted to illustrate Pasteur's remark that "fortune favors the prepared mind." But, as other speakers at the Rockefeller symposium related, Dubos played a key role in the story—albeit one that is hardly ever mentioned—and his life and achievements were equally marked by the combination of serendipity and preparation.

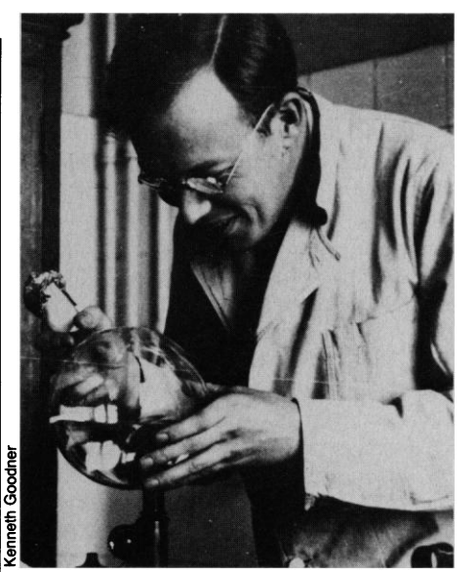
Born in a small town outside Paris, Dubos wound up at the Institut National Agronomique largely because an attack of rheumatic fever kept him from taking the entrance exams to other universities. In 1924, aboard a cruise ship bound for the United States, Dubos met bacteriologist Selman Waksman; by the time the ship docked, Waksman had persuaded Dubos to come to Rutgers University as his graduate student.

Meanwhile, an article by Russian soil microbiologist Serge Winogradsky convinced Dubos that microorganisms are best studied not in laboratory isolation but in the environment where their complex interactions with their surroundings are exhibited and where important clues about the microorganisms are disclosed. This approach strongly affected Dubos throughout his life, and he promptly committed himself to developing soil manipulation techniques as a means of isolating microbes suited to almost any given purpose.

Yet another chance event brought him to what was then called the Rockefeller Institute for Medical Studies. While visiting a fellow French scientist at Rockefeller, Dubos happened to sit next to the eminent bacteriologist Oswald Avery at lunch, and the two promptly hit it off. ("My suspicion



Rollin Hotchkiss



Kenneth Goodner

The first antibiotic. *Gramicidin (crystals shown above) was discovered 50 years ago this year by Rene Dubos, portrayed here in a photograph taken in 1932.*

*"Launching the Antibiotic Era," held at Rockefeller University on 23 October.

is that if it had not been for the dining room at the Rockefeller," Dubos later recalled, "I would not have been as rapidly successful in science.") Dubos explained his soil manipulation techniques, while Avery related his interest in discovering a microbe to dissolve the polysaccharide coating of the deadly Type III pneumococcus; what made the bacteria deadly was precisely the fact that the coating was not dissolved by host defenses. Dubos reasoned that such a microbe *must* exist, or else the polysaccharide would have accumulated in nature in vast quantities. So confident was he of his techniques that he told Avery he could find the microbe.

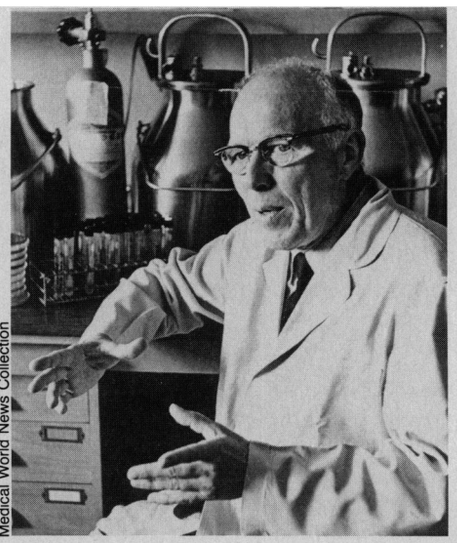
Avery offered the audacious 26-year-old a job at Rockefeller. Within 3 years, Dubos discovered the desired microbe in a soil sample from a New Jersey cranberry bog and extracted from it the enzyme that dissolved the coating. This enzyme was not really an antibiotic, since it did not actually kill the bacteria but only removed the polysaccharide coating, leaving the infected host's defenses to do the rest. Still, it was effective enough to cure pneumonia-infected mice [*Science* **72**, 151 (1930)].

Though the enzyme was never used on humans—the new, chemically based sulfa drugs were superior—Dubos's work was a stunning display of the potential of systematically using microbiological techniques as a rational approach to chemotherapy. "Dubos set the stage for the exploration of nature as a source of antibiotics," said George B. Mackanness, president emeritus of the Squibb Institute for Medical Research, at the symposium. "Dubos showed how you could look for antibacterial products in nature by defining what you are hoping to discover and devising the test systems to reveal their presence."

Dubos refined and extended his soil manipulation methods throughout the 1930s, trying to discover microbes to digest whole bacteria outright. Rollin Hotchkiss, an early associate of Dubos at Rockefeller, described the techniques and recalled being banished to the roof of the Rockefeller hospital building in order to fractionate "an unpleasant brownish material, incompatible with water, under organic solvents congealing into a sticky substance resembling uncouth ear wax."

In February 1939, Dubos published the first reports of his isolation of the bacteria-attacking microbe *Bacillis brevis* [*Proc. Soc. Exp. Biol. Med.* **40**, 311 (1939)], manufacturer of the chemical substance tyrothricin. This proved to be composed of the polypeptides tyrocidene and gramicidin; the latter was discovered to exert a protective effect on infections in animal bodies.

Until then, chemotherapeutic agents were almost all based on poisons such as arsenic, mercury, phenols, and the like, which medical researchers strove to transform into "magic bullets" to attack disease through chemical group substitutions that made them less poisonous to hosts. Gramicidin was different, for it involved a natural process initiated by living bacteria with enough specificity to be toxic to one kind of cell and none for almost all others. "It was the first antibacterial principle that resulted from a deliberate, systematic search for antagonistic principles among soil microorganisms," Hotchkiss said.



"So Human an Animal." *Rene Dubos was also noted for his environmental concerns.*

When Florey and Chain, who had been preparing a purely academic survey of antimicrobial mechanisms, learned of Dubos's work, it not only increased their appreciation of the importance of systematic techniques in studying microorganisms such as penicillin but also made them aware of their chemotherapeutic potential.

Gramicidin proved too toxic to be used systemically on humans, but it was successfully used on animals to protect them from otherwise fatal doses of Gram-positive pathogenic organisms such as pneumococcus, staphylococcus, and streptococcus. Indeed, when the Borden cow herd on exhibit at the 1939 World's Fair (which included the famous Elsie) came down with mastitis and sulfa drugs proved ineffective, gramicidin saved the day.

Hotchkiss was followed by Sir Edward P. Abraham of the Dunn School who purified and determined the structure of penicillin as a member of Florey's group. Abraham reported that Florey and Chain's early penicillin work was initially of purely academic interest: "I don't think the idea of helping suffering humanity ever entered our minds," he quoted Florey as saying. Norman Heatley, another of Florey's collaborators at the Dunn School, recalled the combination of luck and preparation in the work of Fleming and later penicillin researchers. He noted that the massive efforts to develop penicillin were based on the slimmest of evidence—a toxicity test in rodents and a clinical trial in six subjects, two of whom died—and suggested that penicillin certainly would have been rejected had the regulations currently promulgated by the British Committee on the Safety of Medicine been in effect. "Is it too whimsical to suggest," he concluded, "that our greatest piece of luck so far might be the fact that this worthy body did not exist in 1941?"

A few speakers mentioned Dubos's environmentalist works, which included *So Human an Animal*, for which he won the Pulitzer Prize in 1969. "He was the first of the hard scientists I encountered who had a sense of the need for a humanistic approach to the limits of science and to the consequences of scientific innovation," said Rockefeller University president Joshua Lederberg.

Characteristically, the British speakers at the symposium came prepared with carefully crafted papers available for distribution, while the U.S. participants tended toward anecdotal speeches delivered from recently composed notes—reflecting, perhaps, the national differences in the valuation of the history of science that had conspired to disguise Dubos's role in the first place. The conference attracted about 350 people, including a great number of historians of medicine, former colleagues and friends of Dubos, and individuals who had worked in infectious diseases. A dozen or so white-coated individuals dropped in briefly, evidently doctors and researchers from nearby Memorial Sloan Kettering or Cornell University Medical Center who were squeezing in time from their other investigations. Their presence implicitly raised the question of the value of the history of science to ongoing research. "Well," said Lederberg when this question was directed to him during a break in the symposium, "that raises the question of the value of history itself. Science is often thought of as an automatic process, whereas in fact it profits from an immense diversity and richness of styles, personalities, approaches, and so forth. Histories such as that of the development of antibiotics—and of Dubos in particular—are valuable because they remind us of that." ■ **ROBERT P. CREASE**

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