History of Antimicrobial Therapy

Early 20th century:	PAUL EHRLICH pioneers "chemotherapy"
1929:	ALEXANDER FLEMING demonstrates inhibition of bacterial growth with penicillin moulds
Early 1930s:	CARL DOMAGK discovers "prontosil" a prodrug to sulfanilamide
1936:	Sulfanilamide, the first synthetic sulfonamide in human medicine
1940:	First therapeutic use of "penicillin" by FLOREY
1944:	Streptomycin
1947:	Chloramphenicol, the first broad-spectrum antibiotic
1948:	Chlortetracycline
1960:	Cephalosporines
1962:	GEORGE Y. LESHER discovers nalidixic acid during chloroquine synthesis
1970s:	New 4-quinolones (pipemidic acid, oxolinic acid, cinoxacin)
1980:	Norfloxacin, the first fluoroquinolone
1980:	Enrofloxacin synthesized by GROHE and PETERSON

At the beginning of the 20th century, Paul Ehrlich, one of the pioneers in research on antiinfectives, studied the interaction of different substances with infectious protozoans and bacteria. Ehrlich used chemicals for his in vitro experiments, and thus, this therapy of infectious disease became known as chemotherapy.

In the early 1930s, Bayer researcher Gerhard Domagk, discovered a substance called prontosil, which was effective in treatment of bacterial infections in vivo.

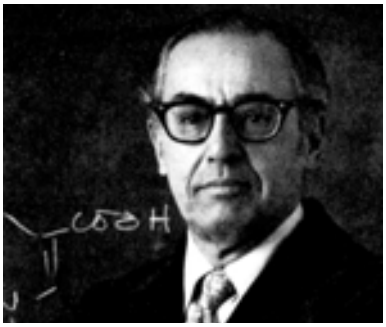
Gerhard Domagk

Prontosil was safe enough to be used clinically and it was the first effective chemotherapeutic agent against infectious disease in human medicine. A short time later, it was discovered that prontosil was a prodrug, which had to be hydrolyzed in the organism to become effective. The active metabolite was identified as sulfanilamide, the first synthetic sulfonamide introduced to the market in 1936.

In 1929, Alexander Fleming coincidentally found that penicillin moulds inhibit the growth of bacteria in vitro. Florey, an Australian researcher, first used penicillin for therapy in humans in 1940. Today, synthetic penicillins and other members of the group of beta-lactam antibiotics, such as cephalosporines (discovered 1960), are still among the most important chemotherapeutic agents.

History of Antimicrobial Therapy 2/2

Research for new substances to fight bacterial and protozoal infections rapidly went on. Streptomycin (1944), the first aminoglycoside, chloramphenicol (1947), the first broad spectrum antiinfective, and chlortetracykline (1948) are examples of this rapid development.



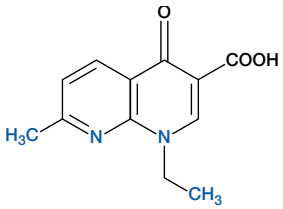
George Y. Lesher

The area of quinolones began with the introduction of nalidixic acid in 1962 for treatment of kidney infections in humans. The substance was discovered by George Lesher and coworkers in a distillate during chloroquine synthesis. Nalidixic acid, predecessor of all members of the family of topoisomerase inhibitors, is thus a by-product of antimalarial research. Due to modest serum and tissue kinetics, a consequence of high protein binding, and unfavourable antibacterial activity, the benefits of therapy with nalidixic acid were limited to Gram-negative infections of the urinary tract in humans.

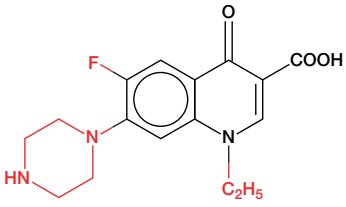
New 4-quinolones such as pipemidic acid, oxolinic acid and cinoxacin, introduced in the 1970s, were only marginal improvements over nalidixic acid. Rapid progress came with the introduction of a fluorine atom at the C6 position and C7 piperazine substituents into the basic molecular structure. Since the discovery of norfloxacin (1980), around 10,000 new analogues have been described. The so-called third generation quinolones have a broad spectrum against Gram-negative as well as Gram-positive bacteria and an excellent tissue distribution. They have since become the most important agents in systemic therapy of infections of the urinary and respiratory tract, skin, bones and numerous additional indications.

Enrofloxacin, which was first synthesized by Bayer researchers Grohe and Peterson in 1980, has been developed exclusively for use in veterinary medicine. Introduced to the market in 1988, it has become the most important quinolone for the therapy of bacterial infections in dogs and cats worldwide.

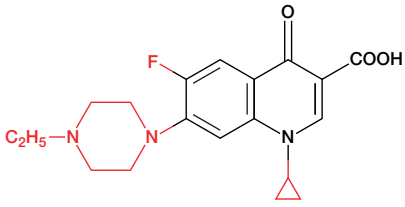
Nalidixic Acid (1962)



Norfloxacin (1980)



Enrofloxacin (1980)



References:

(1) Norris S, Mandell GL: The quinolones: history and overview, in Andriole VT (ed): The quinolones, San Diego, Academic Press Inc: 1- 22, 1988.

(2) Wentland MP: In memoriam: George Y. Lesher, Ph.D., in Hooper DC, Wolfson JS (eds): Quinolone antimicrobial agents, ed 2., Washington DC, American Society for Microbiology : XIII - XIV, 1993.