Introduction

The germ theory of disease was initiated in the 19th century by Louis Pasteur. Lord Lister promoted the idea of antisepsis while Semmelweis focused on hand washing identifying the spread of infection by objects (in this case contaminated hands) moving from infected patient to uninfected ones. This gave the conceptual basis for infectious disease and its management and set the stage for development of modern anti-infective therapy, one of the major medical advances of the 20th century.

Modern anti-infective therapy was started by Paul Ehrlich's group systematically making and testing several series of related compounds in the 1920s to treat syphilis. Domagk and his group developed sulfonamides using the same systematic methods in the 1930s. Fleming saw the zones of inhibition of bacterial growth around molds in a culture plate and recognized that the mold was secreting an anti-bacterial substance. But it took another 10 years before Chain and Florey tested this secretion in infected mice. The reason for the delay of a decade is that it was known that germicides did more damage to tissue than to bacteria. It was assumed that the secretion of the *Penicillium* was also a germicide. This error in automatically considering penicillin a germicide delayed its development for 10 years. This delay in developing penicillin supports the adage that it is better not to know something than to know something that is wrong.

The papers selected for this book in the Pharmacotherapy Revisited series are my personal choices for "the papers that were seminal in the development of antimicrobial therapy". Either the first paper describing a discovery or use of a substance or the paper describing a new way of thinking about an antimicrobial topic are what I selected. All papers but one are anti-microbial. One is anti-parasitic to illustrate that the same systematic way that antimicrobials were discovered applied to anti-parasitic drugs as well. If fact, this systematic approach to drug discovery and development started by Ehrlich in the 1920s

is the model for most of 20th century drug discovery and development for all of medicine.

The reasons for selecting each paper are:

I. **Green M. Cod liver oil and tuberculosis. BMJ. 2011;343:d7505. doi: 10.1136/bmj.d7505.**

This is a reprint and analysis of a controlled clinical trial in 1848. It found that giving cod liver oil to patients with tuberculosis improved their outcomes compared to those patients not given cod liver oil. This is the first controlled clinical trial for an anti-infective therapy and only the second published clinical trial after the first one by Lind assessing the various treatments for scurvy published in 1748.

II. **Fitzgerald JG. Ehrlich-Hata remedy for syphilis. CMAJ. 1911;1(1):38-46.**

The first publications by Ehrlich and others about their research to find better treatments for syphilis was in a book. The series, Pharmacotherapy Revisited, is to include journal papers so this is the first paper in a journal describing the discovery of the first "modern" medicine, an arsenical named 606 or Salvarsan after a systematic search of a series of chemicals using structure-activity relationships to select the best drug for its intended purpose, treating syphilis. Ehrlich's work is the start of modern systematic pharmaceutical drug discovery.

III. **Domagk G. Chemotherapie der bakteriellen Infektionen. Angewandte Chemie. 1935;48(42):657-67.**

This is the first paper describing sulfonamides, the first of the modern anti-infective drugs with good efficacy and low mammalian toxicity.

IV. **Colebrook L, Kenny M. Treatment with Prontosil of puerperal infections: due to haemolytic streptococci. Lancet. 1936;228(5910):1319-22.**

This paper describes the use of Prontosil, the first sulfonamide, in the treatment of puerperal sepsis. It showed that this drug worked in humans.

V. **Marshall EK Jr, Emerson EK Jr, Cutting WC. Para-aminobenzenesulfonamide: Absorption and excretion: method of determination in urine and blood. JAMA. 1937;108(12):953-7.**

A method for measuring concentrations of drug in plasma and urine is described here. The drug was a sulfonamide. Drug level measurements were made in animals and in patients showing that variable pharmacokinetics explained some of the difference in dose-response of this drug. The investigators even showed the difference in drug levels in patients with normal kidneys compared to those with impaired renal function showing that impaired excretion led to high levels for a dose and suggested modifying the dose for patients with poor renal function. This paper, in 1937, is the first description of the individualization of drug therapy based on a laboratory measurement. This concept of individualization of drug therapy, now called "personalized medicine", goes back over 60 years.

VI. **Fleming A. On the antibacterial action of cultures of a Penicillium, with special reference to their use in the isolation of *B. influenzae.* Br J Exp Pathol. 1929;10(3):226-36.**

Fleming describes his discovery of penicillin in this paper.

VII. **Chain E, Florey HW, Gardner AD, Heatley NG, Jennings MA, Orr-Ewing J, et al. Penicillin as a chemotherapeutic agent. Lancet. 1940; 236(6104):226-8.**

This is the paper showing penicillin can cure infected mice without being toxic to the mice. Penicillin is not a germicide like Lister's carbolic acid, the erroneous analogy used for 10 years until this study.

VIII. **Mahoney JF, Arnold RC, Harris AD. Penicillin treatment of early syphilis – A preliminary report. Am J Public Health Nations Health. 1943;33(12):1387-91.**

Syphilis could be effectively treated with penicillin, a huge advance over mercury and arsenic therapy, the standard treatment at that time.

IX. **Schatz A, Bugie E, Waksman SA. Streptomycin, a substance exhibiting antibiotic activity against Gram-positive and Gram-negative bacteria. Proc Soc Exp Biol Med. 1944;55(1):66-9.**

The initial discovery of streptomycin, the second antibiotic after penicillin isolated from culture broth from fungi, is described in this paper. Culture broths from microbes became the initial substances used to screen for pharmacologically active compounds. Even the first statin, lovastatin, was discovered by screening culture broths.

X. **Weinstein L. The treatment of meningitis due to *Haemophilus influenzae* with streptomycin; a report of nine cases. N Engl J Med. 1946;235(4):101-11.**

This paper discusses the treatment of *Haemophilus influenzae* meningitis with streptomycin followed by the development of infections with streptomycin-resistant *Staphylococcus aureus* in some of these patients. It may be the first paper widely read describing superinfections, infections with new species of bacteria resistant to the antibiotic used initially in antibiotic-treated patients.

XI. **Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. BMJ. 1948;2(4585):769-82.**

The first randomized controlled trial of a drug and the first drug to show efficacy in tuberculosis is described here. The studies by Lind on treatment of scurvy and the study described by Green about vitamin D and tuberculosis were controlled but not randomized.

XII. **Faget GH, Pogge RC, Johansen FA, Dinan JF, Prejean BM, Eccles CG. The promin treatment of leprosy – A progress report. Public Health Rep. 1943;58(48):1729-41.**

This is the first description of the first modern drug to treat leprosy.

XIII. **Kaufman HE, Nesburn AB, Maloney ED. IDU therapy of herpes simplex. Arch Ophthalmol. 1962;67(5):583-91.**

This paper describes the first drug to treat a viral infection effectively. It was given locally to the eye since it was too toxic to give systemically.

XIV. **Davies WL, Grunert RR, Haff RF, McGahen JW, Neumayer EM, Paulshock M, et al. Antiviral activity of 1-adamantanamine (amantadine). Science. 1964;144(3620):862-3.**

This is the first drug effective for a systemic viral infection and safe enough to give systemically.

XV. **Merigan TC, Reed SE, Hall TS, Tyrrell DAJ. Inhibition of respiratory virus infection by locally applied interferon. Lancet. 1973;301(7803):563-7.**

This paper describes the first human testing of the first cytokine, interferon.

XVI. **Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. N Engl J Med. 1987;317(4):185-91.**

This is the first clinical trial for the first drug to be effective in HIV-AIDS.

XVII. **Rogers L. The rapid cure of amoebic dysentery and hepatitis by hypodermic injections of soluble salts of emetine. BMJ. 1912;1(2686):1424-5.**

An early study of an effective drug for amoebic dysentery is described here.

XVIII. **Hazen EL, Brown R. Fungicidin, an antibiotic produced by a soil actinomycete. Proc Soc Exp Biol Med. 1951;76(1):93-7.**

This is the first drug effective against fungi. The drug is now known as nystatin.

XIX. **Loeb RF, Clark WM, Coatney GR, Coggeshall LT, Dieuaide FR, Dochez AR, et al. Activity of a new antimalarial agent, chloroquine (SN 7618): Statement approved by the Board for Coordination of Malarial Studies. JAMA. 1946;130(16):1069-70.**

While chloroquine was discovered in 1934, it was not developed for malaria until nearly a decade later.

XX. **Hewitt RI, Kushner S, Stewart HW, White E, Wallace WS, SubbaRow Y. Experimental chemotherapy of filariasis. III. Effect of 1-diethylcarbamyl-4-methylpiperazine hydrochloride against naturally acquired filarial infections in cotton rats and dogs. J Lab Clin Med. 1947;32(11):1314-29.**

This is the one paper in this list that is about parasites. I though it important to show that parasitic chemotherapy could also be advanced by using the same systematic structure-activity studies of chemical compounds as was found to be effective in discovering 606 and Prontosil.

XXI. **Huguley CM, Erslev AJ, Bergsagel DE. Drug-related blood dyscrasias. JAMA. 1961;177(1):23-6.**

This paper reports the first organized study of adverse drug reactions. The multiple case reports of chloramphenicol-induced aplastic anemia lead to the formation of the American Medical Association Blood Dys-

crasia Registry. This was the start of using systematic epidemiologic methods to study adverse drug effects.

XXII. **Mohler DN, Wallin DG, Dreyfus EG. Studies in the home treatment of streptococcal disease. I. Failure of patients to take penicillin by mouth as prescribed. N Engl J Med. 1955;252(26):1116-8.**

This is the first study to my knowledge in which compliance/adherence with the prescribed treatment regimen was evaluated and lack thereof described.

XXIII. **Landy M, Larkum NW, Oswald EJ, Streightoff F. Increased synthesis of p-aminobenzoic acid associated with the development of sulfonamide resistance in *Staphylococcus aureus.* Science. 1943;97(2516):265-7.**

This paper is the first describing a mechanism for the development of antimicrobial drug resistance.

XXIV. **Jawetz E, Gunnison JB, Speck RS, Coleman VR. Studies on antibiotic synergism and antagonism; the interference of chloramphenicol with the action of penicillin. AMA Arch Intern Med. 1951;87(3):349-59.**

This experimental study showed that two drugs, each of which has efficacy against an organism, can antagonize each other when given concurrently.

XXV. **Lepper MH, Dowling HF. Treatment of pneumococcic meningitis with penicillin compared with penicillin plus aureomycin: studies including observations on an apparent antagonism between penicillin and aureomycin. AMA Arch Intern Med. 1951;88(4):489-94.**

This paper shows that the antagonism can occur in actual treatment and caused increased mortality in the patients getting both antibiotics instead of the more effective one alone.

XXVI. **Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998;26(1): 1-10.**

The first group to publish that antibiotics could be divided into concentration-dependent or time-dependent killing was Shah, et al. (Dtsch Med Wochenschr. 1976;101(9):325-8). This paper by Craig discusses this concept of two types of antibiotic pharmacodynamics in the context of antibiotic pharmacokinetics. It articulates the conceptual basis for antibiotic dosing regimens.

XXVII. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

This paper presented a simple way to estimate glomerular filtration rate (GFR) at the bedside using only measurements readily available: gender, weight, age, and serum creatinine concentration. It made individualizing the therapy for patients with varying degrees of renal impairment practical. Rapid adoption of the Cockcroft Gault method for estimation GFR enabled physicians to adjust aminoglycoside doses for renal impairment preventing renal failure and deafness. Its concept and use has spread to all of drug therapeutics.

Marcus M. Reidenberg
Weill Cornell Medical College
New York City, United States of America

PS/ Unfortunately, the American College of Physicians, owners of the Annals of Internal Medicine, has set a policy for this journal that "prohibits including articles published in the Annals of Internal Medicine from republication in an anthology". The reason stated was to "protect the integrity of articles especially in the event of any changes or retractions" and to prevent using the articles "outside of its original context". For this reason, the following articles that shaped modern anti-infective therapy, are not printed in this volume:

- **Appelbaum E, Shtokalko S. Cryptococcus meningitis arrested by amphotericin B. Ann Intern Med. 1957;47(2):346-51.**

  The first description of amphotericin is in Antibiotics Annual for 1953-1954. This is the first journal publication of its efficacy in cryptococcal meningitis.

- **Rich ML, Ritterhoff RJ, Hoffmann RJ. A fatal case of aplastic anemia following chloramphenicol (chloromycetin) therapy. Ann Intern Med. 1950;33(6):1459-67.**

  The first case report of aplastic anemia from chloramphenicol. This was the start of considering the topic of adverse drug reactions as worthy of study.

- **Kunin CM. A guide to use of antibiotics in patients with renal disease. A table of recommended doses and factors governing serum levels. Ann Intern Med. 1967;67(1):151-8.**

  This is the first systematic coverage of adjusting the dose of excreted drugs to correct for impaired excretion rates in patients with impaired renal function.