

Impact of the introduction of the first systemic chemotherapeutic agents in a major pharmacology textbook

E Seres¹, F Bosch^{1,2}

¹Esteve Foundation, 08032 Barcelona, Spain, ²Universitat Pompeu Fabra, Department of Experimental and Health Sciences, 08003 Barcelona, Spain

Introduction. Without any doubt, the major advances in drug therapy occurred during the 20th century. A good example illustrating this would be the development of the first effective chemotherapeutic agents that were incorporated into the therapeutic arsenal early in that century. Increasingly, these and other therapeutic advances were incorporated into the pharmacology literature of the time. This study aims to analyze when and how the first chemotherapeutic agents were included in the pharmacology reference texts of the day and why, in consequence, it was necessary to make several changes in how these drugs were classified.

Methods. The first three editions of the pharmacology reference book, “*Goodman & Gilman’s Pharmacological Basis of Therapeutics*”, corresponding to the years 1941, 1956 and 1965, were reviewed. The different classifications of drugs were analysed and, in particular, attention was focused on those sections where references to chemotherapeutic agents were included. A comparison was made of the sections, chapters, pharmacological groups and subgroups, active compounds, route of administration and the agents’ principal therapeutic indications.

Results. In all three editions of the book, both quantitative and qualitative changes in the classification of the agents were observed. Overall, the number of sections increased from 16 in the 1st edition, to 18 in both the 2nd and 3rd editions. There were also changes to the titles of sections; the titles of seven sections were changed in the 2nd edition and six in the 3rd edition. In the 2nd edition a new section was incorporated dealing with antineoplastic drugs (“*Drugs Used in the Chemotherapy of Neoplastic Diseases*”) and in the 3rd edition, two new sections appeared as part of the chemotherapy group (“*Chemotherapy of Parasitic Diseases*” y “*Chemotherapy of Microbial Diseases*”). Arsenicals, as antisyphilitics, were included in two different sections of the 1st edition: in “*Heavy Metals*” and in “*Antiseptics, Disinfectants and Drugs Used in the Chemotherapy of Infectious Diseases*”. This last section of the 1st edition also contained sulfonamide derivatives as antisyphilitics. The 2nd edition, again in this same section, incorporated penicillin and other antibiotics such as streptomycin, chloramphenicol and tetracycline, and the 3rd edition introduced the new sections “*Chemotherapy of Parasitic Diseases*” and “*Chemotherapy of Microbial Diseases*”. The section “*Chemotherapy of Microbial Diseases*” of the 3rd edition eventually included three large groups of antimicrobial agents: sulfonamides, antibiotics and chemotherapy against leprosy and tuberculosis.

Conclusions. The 1st editions of pharmacology reference texts reflected the availability of the first chemotherapeutic agents, arsenicals and sulfonamides. In later editions, such drugs lost prominence with the introduction of new and more effective antimicrobial agents, which necessitated substantial changes in the classification of chemotherapies during the first half of the 20th century.



IMPACT OF THE INTRODUCTION OF THE FIRST SYSTEMIC CHEMOTHERAPEUTIC AGENTS IN A MAJOR PHARMACOLOGY TEXTBOOK

Elisabet Serés¹, Alba Farrés², Marc Aguilar², Fèlix Bosch^{1,3}

¹Esteve Foundation, Barcelona; ²Human Biology Degree, School of Health and Life Sciences, Universitat Pompeu Fabra, Barcelona; ³Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona

INTRODUCTION

Therapeutic decisions in the second half of the 20th century were undoubtedly shaped by the reference book created by L.S. Goodman and A. Gilman. Successive editions of this book offer a unique tool to evaluate the unfolding of several therapeutic fields, and in this study we focus on

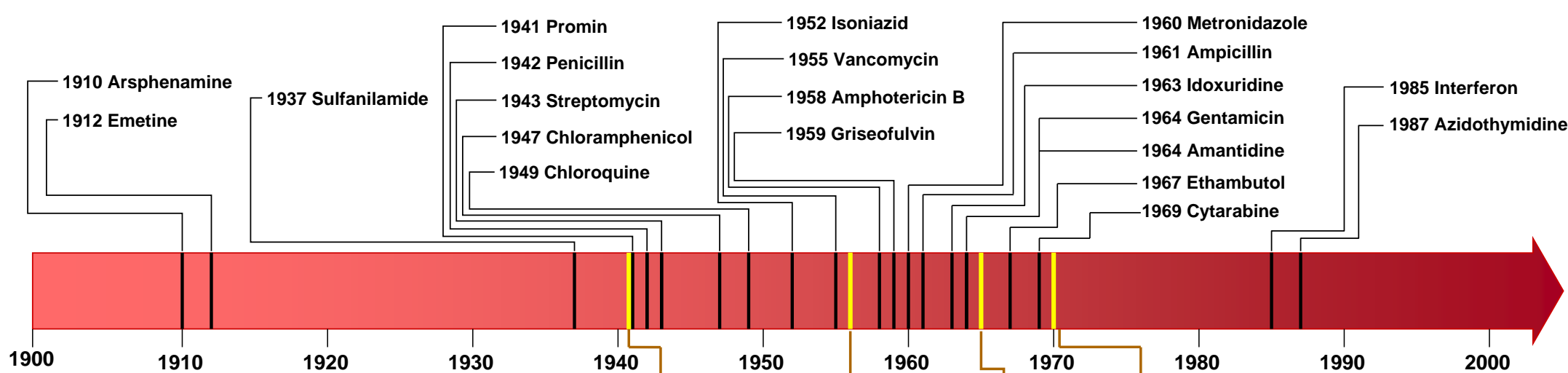
the area of antimicrobial chemotherapy from its beginnings up to its full maturity. The aim of this study is to analyse the changes on antimicrobial chemotherapy in the four first editions of the reference book "Goodman & Gilman's Pharmacological Basis of Therapeutics".

MATERIALS AND METHODS

The first four editions of "Goodman & Gilman's Pharmacological Basis of Therapeutics", corresponding to the years 1941, 1956, 1965 and 1970, were reviewed. Although the focus was on the appearance of the different drugs and the milestones that this represented, we

analysed the general information given about chemotherapeutic agents. A comparison was made of the sections, chapters, pharmacological groups and subgroups, active compounds, route of administration and the agents' principal therapeutic indications.

RESULTS



1st edition, 1941

- 16 sections in total: 1,387 p.
- Antimicrobial drugs present in 3 sections:
 - XI "Heavy Metals and Metalloids" (49 p.)
 - XII "Drugs Acting Locally on the Skin and Mucous Membranes" (57 p.)
 - XIII "Antiseptics, Disinfectants and Drugs Used in the Chemotherapy of Infectious Diseases" → the biggest section in the book with 12 chapters (281 p.):
 - "Antiseptics, Germicides, Fungicides and Parasitocides" (55 p.): phenol, salicylic acid
 - "Drugs Used in the Chemotherapy of Helminthiasis" (25 p.)
 - "Drugs Used in the Chemotherapy of Malaria" (27 p.)
 - "Drugs Used in the Chemotherapy of Amebiasis" (13 p.)
 - "Drugs Used in the Chemotherapy of Leprosy" (3 p.)
 - "Drugs Used in the Chemotherapy of Syphilis", (3 chapters, 56 p.)
 - "Sulfanilamide and related sulfonamide drugs" (4 chapters, 102 p.): **sulfonamides** as the first effective and safe antimicrobial group.
- **Arsenicals** (arsphenamines) as antisiphilic, cover a full chapter (32 p.) in section XIII.
- Natural compounds like quinine for malaria and chaulmoogra oil for leprosy also appear.

2nd edition, 1956

- 18 sections in total: 1,831 p. → 5 titles have changed
- 2 new sections appear:
 - VI "Histamine and its Antagonists" (24 p.) from 1st edition's section VI "Cardiovascular Drugs"
 - Completely new section XV "Drugs Used in the Chemotherapy of Neoplastic Diseases" (36 p.)
- Section XIV "Antiseptics, Disinfectants and Drugs Used in the Chemotherapy of Infectious Diseases" → the biggest section again, with 12 chapters (340 p.) including 7 new chapters:
 - "Antiseptics, Germicides, Fungicides, Virucides and Ectoparasitocides" (58 p.) includes similar drugs than section XIII in 1st edition
 - "Drugs Used in the Chemotherapy of Helminthiasis" (28 p.)
 - "Drugs Used in the Chemotherapy of Malaria" (47 p.)
 - "Drugs used in the chemotherapy of amebiasis" (20 p.)
 - "Miscellaneous Drugs Used in the Treatment of Protozoal Infections" (5 p.)
 - "Penicillin Therapy of Syphilis" (17 p.)
 - "Drugs Used in the Chemotherapy of Tuberculosis and Leprosy" (26 p.)
 - "Sulfonamides" is reduced to 1 chapter (45 p.)
 - "Antibiotics" (4 different chapters, 94 p.): introduction of new **effective antimicrobial agents**:
 - "Penicillin" (39 p.)
 - "Streptomycins" (18 p.)
 - "The tetracyclines" (16 p.)
 - "Miscellaneous antibiotics: chloramphenicol, erythromycin, carbomycin, polymyxin B, neomycin, bacitracin and tyrothricin" (21 p.)
- Section XIV also includes topical products and drugs used in malaria, amebiasis and helminthiasis, with new some drugs:
 - Quinacrine, chloroquine, pyrimethamine, pamaquine, pentaquine, primaquine (for malaria)
 - Gentian violet and piperazine (as anthelmintics)
- Section XIV also includes **new drugs for tuberculosis and leprosy**:
 - Isoniazid and streptomycin (tuberculosis)
 - Sulfones like dapsone and promin (leprosy)
- Arsphenamine only included in section XII "Heavy metals and Heavy-Metal Antagonists" (inside Arsenicals chapter, 22 p.)

3rd edition, 1965

- 18 sections in total: 1,785 → 3 section titles have changed and 3 new sections appear
- Sections II and III from the 2nd edition are merged into one new section: II "Drugs Acting on the Central Nervous System" (330 p.)
- 2 new sections appear from previous 2nd edition's XIV section:
 - XIII "Chemotherapy of Parasitic Diseases" (86 p.) including drugs for:
 - Helminthiasis
 - Malaria
 - Amebiasis
 - Protozoal Infections
 - XIV "Chemotherapy of Microbial Diseases" (201 p., two thirds of the information given about antimicrobials in the book) which includes three large groups of antimicrobial agents:
 - Sulfonamides (1 chapter, new reduction to 27 p.)
 - Chemotherapy against leprosy and tuberculosis (1 chapter, 37 p.)
 - Antibiotics (5 chapters, 137 p.): 1) General Considerations (22 p.); 2) Penicillins (37 p.); 3) Streptomycin (12 p.); 4) The tetracyclines (18 p.); Miscellaneous antimicrobial agents (48 p.)
- Main changes in antibiotic chapters:
 - Penicillins are now divided into two groups: natural (penicillin G) and semisynthetic penicillins (ampicillin and others)
 - Some highly toxic antibiotics have disappeared (carbomycin)
 - Cephalosporins as well as vancomycin and gentamicin appear
 - **First effective antifungal agents** as amphotericin B (parenteral), nystatin (topical and oral) and griseofulvin (oral) appear in chapter 5 as "Miscellaneous antifungal agents"
- Arsphenamine is not included; only some arsenic derivatives are cited but no longer used
- Section XIV, chapter on "Drugs Used in the Chemotherapy of Leprosy and Tuberculosis" (37 p.), includes now a clear difference between tuberculosis and leprosy treatments and new drugs:
 - Ethambutol and others (tuberculosis)
 - Dapsone (leprosy)

4th edition, 1970

- 18 sections in total: 1,794 → no changes in titles and sections
- XIII "Chemotherapy of Parasitic Diseases" (87 p.), introduction of a new antiamebiasis compound: metronidazole
- XIV "Chemotherapy of Microbial Diseases" (190 p.) with:
 - "The Sulfonamides" (1 chapter, 27 p.): sulfisoxazole appears
 - "Antibiotics", 4 chapters (107 p.): the chapter on "General Considerations" (23 p.) is now the first chapter of section XIV
 - The penicillins (38 p.)
 - Streptomycin (11)
 - The tetracyclines (16)
 - Miscellaneous antimicrobial, antifungal and antiviral agents (42 p.)
 - "Drugs used in the Chemotherapy of Leprosy and Tuberculosis" (1 chapter, 33 p.): **rifampicin as a new drug**
- Main changes in antibiotic chapters:
 - Former chapter on "Miscellaneous antimicrobial agents" in 3rd edition has changed into "Miscellaneous antimicrobial, antifungal and antiviral agents"
 - New antifungals: tolnaftate
 - **First antivirals**: idoxuridine (topical), amantidine, cytarabine (interferons only cited)

CONCLUSION

After the first uses of arsenicals in syphilis, the chemotherapy of bacterial diseases took off with the introduction of the sulfonamides. These drugs blossomed and reached maturity in the mid-50s and lead to the introduction of the effective antimicrobial agents in the second half of the century which necessitated substantial changes in the classification of chemotherapies.

REFERENCES

1. Raviña E. The Evolution of Drug Discover: From Traditional Medicines to modern Drugs. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA; 2011.
2. Serés E, Bosch F. Impact of Paul Ehrlich's discoveries as reported by *The New York Times*. Eur J Clin Pharmacol. 2010; 66(Suppl.1):S119. Poster Communication PO-93. XXXII Congress of the Spanish Society of Pharmacology. León, 15-17 September 2010.
3. Sneader W. Drug discovery. A history. Chichester: John Wiley & Sons; 2006.
4. Thomson-Reuters Integrity [Internet]. Philadelphia: Thomson-Reuters [cited 2012 July 9]. Available from: <https://integrity.thomson-pharma.com/integrity/xmlsl/>