Enrique Raviña

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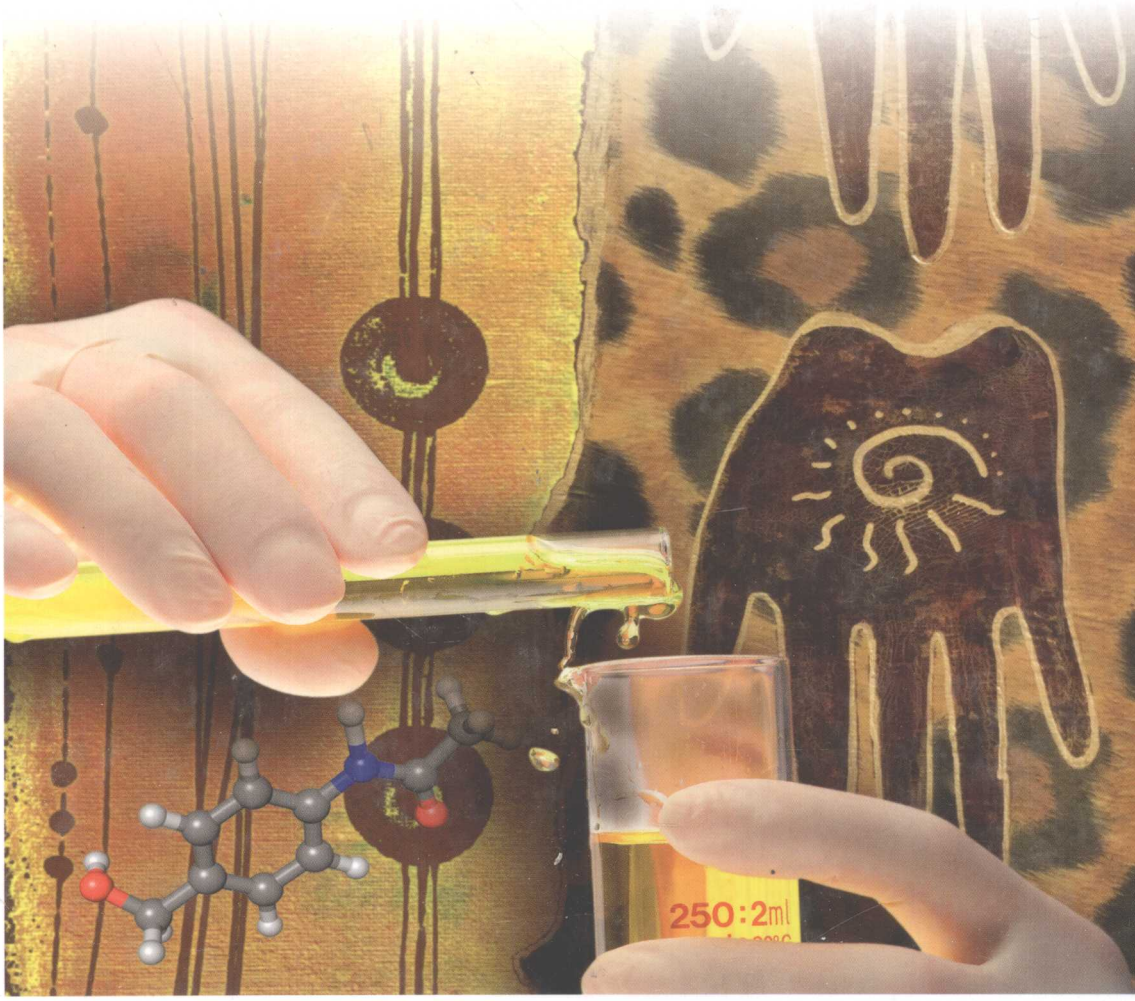
The Evolution of Drug Discovery

From Traditional Medicines to Modern Drugs



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The Evolution of Drug Discovery

From Traditional Medicines to Modern Drugs

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This book is dedicated to the memory of my father, José Raviña Valdés (1903–1979), physician in a rural village of Spain (Council of Teo, province of La Coruña) between 1929 and 1978.

A special dedication also for my three daughters: María, Elena and Ana.

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Foreword

Drug discovery strategies developed in an evolutionary manner. Starting from folk medicine and accidental observations, the first "drugs" were plant extracts and minerals, but also materials of animal origin. The famous theriak ("Venice treacle"), therapeutically used over almost two millennia, was a mixture of hundreds of different ingredients; it was supposed to avoid poisoning and to be beneficial in all other diseases, including the plague. The isolation of morphine from poppy in the early nineteenth century marks the beginning of drug discovery based on pure organic compounds. The narcotic action of laughing gas and some volatile organic liquids was discovered in the mid-nineteenth century, enabling painless surgery. In the following decades chemical industry developed, due to a boom in synthetic dyestuffs. However, close to the end of this century industry ran into a crisis due to competition and low prices. Drug discovery offered a promising alternative: analgesics, sedatives, and other drugs resulted from the investigation of a variety of chemicals in animals and humans. Even dyestuffs made it into therapy (e.g., phenolphthalein as a laxative and other dyestuffs as antiparasitic agents). It was another dyestuff that marked a breakthrough in antibacterial therapy: sulfamidochrysoidine, also called prontosil rubrum. Gerhard Domagk, who discovered this first antibacterial sulfonamide, was lucky to have it tested in animals – in bacterial cultures its activity would not have been detected. Jacques and Therese Trefouel realized that the compound is a prodrug of the active agent sulfanilamide. For this reason both are cited as the discoverers of the antibacterial sulfonamides in French textbooks, whereas Domagk is celebrated in German textbooks; in 1939, the Nobel Prize Committee decided to award the Nobel Prize in Medicine to Domagk. At the time of the sulfonamides Alexander Fleming had already observed the antibacterial activity of penicillin. However, it took another 13 years before penicillin could be isolated in pure form and applied to humans. Fortunately, no toxicity study was performed in guinea pigs – penicillin is toxic in this species! In the following years many other antibiotics were isolated from various microorganisms.

The decades following World War II, especially the 1950s, 1960s, and 1970s, mark the so-called "golden age" of drug discovery. Antihistamines were discovered and were praised as "wonder drugs;" many other receptor agonists and antagonists followed, enabling dedicated therapy of many diseases. Animal models still

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dominated biological testing, sometimes leading to drug candidates that were inactive in humans or missing potential drugs that do not show up in animal tests. Correspondingly, huge progress was made when gene technology enabled biologists for the first time to test their compounds against human targets. Possibly this is, so far, the most important contribution of gene technology to the wealth of mankind. Automation of test models allows high-throughput screening (HTS) of hundreds of thousands of compounds within a short time. In parallel, combinatorial chemistry as well as structure-based and computer-aided ligand design were introduced into drug discovery. Whereas combinatorial chemistry failed completely in the early years, due to the neglect of physicochemical properties and drug-likeness of chemical structures, 3D structure-based approaches were and still are successful in designing well-fitting ligands. However, in time medicinal chemists learned that ligand affinity is only a necessary, but not sufficient property – many of the designed ligands had poor or no bioavailability at all. Nowadays virtual screening (i.e., filters for certain properties), pharmacophore screening, and docking and scoring, dominate projects in which protein 3D structures are available. With access to several 3D structures of G-protein-coupled receptors (GPCRs), this approach is not only applicable to soluble enzymes and ligand-binding domains of nuclear receptors, but also to GPCRs. The first 3D structures of ion channels have been determined and within a short time more structures should follow. The latest promising developments in drug design are fragment-based design and scaffold hopping.

There was not only an evolution in the strategies and methods of drug discovery. Each drug discovery itself is an evolutionary process. On the way from hit to lead and finally to a clinical candidate, several rounds of optimization are needed. In each round the best candidates are selected for further structural variation, following Darwin's principle of "survival of the fittest." Only in this manner can the final goal be achieved with the least effort. Nowadays, the first hits in a new drug discovery project result from HTS or virtual screening. However, the pearls are most often hidden in a large number of false positives – compounds that are not suited to be further developed. A lead series results only after retesting interesting compounds in advanced biological models and investigating chemically similar compounds for their potential activity. Such leads should already have sufficient activity (i.e., at least micromolar) and they should show some target selectivity, if needed. In addition, they should possess high ligand efficiency, low lipophilicity, and the potential for further chemical modification. Once a lead or a lead series is defined, chemical optimization starts, based on evolutionary rounds. Whenever a new molecule shows improved activity, target selectivity, better oral bioavailability, and lack of antitarget activities or toxic groups, this candidate "survives" – it now becomes the starting point for further optimization. After several such rounds it has to be proven whether a preclinical candidate results, whether another lead series should be selected, or whether the project has failed. Let us assume, however, that a preclinical candidate results, having all the expected properties. Then preclinical profiling starts: tests are performed against a large panel of enzymes, receptors, transporters, and ion channels, including tests for cytochrome P450 inhibition and

induction; absorption, distribution, metabolism, and excretion (ADME) properties are investigated in different animal species; metabolic patterns are compared, using microsomes and hepatocytes from different species, including humans. Optimally, the species that corresponds in its metabolism most closely to humans is selected for toxicity studies. Whenever problems arise in one of these investigations, the project is thrown back to an earlier stage and new evolutionary optimizations have to be performed.

This book by Enrique Raviña covers the history of drug discovery up to the most recent developments. It describes the evolution of drug discovery strategies, from ancient time to the current structure-based drug discovery methodologies. All this is nicely illustrated by many fascinating drug discovery stories. Especially valuable are the many illustrations, including the cultural history of drug discovery. In this manner, it follows a phrase attributed to Thomas Morus: "Tradition is not to preserve the ashes but to pass on the flame." What we need today in drug discovery is the merger between the rich empirical treasure of medicinal chemistry and the various "rational" approaches. Compared to other textbooks on medicinal chemistry, this one is unique in considering both aspects. Due to the fact that the current English version goes back to his Spanish two-volume book *Medicamentos: Un viaje a lo largo de la evolución histórica del descubrimiento de fármacos*, published in 2008, several illustrations are of Hispanic origin.

Special thanks go to the author and to the publisher Wiley-VCH, especially to Frank Weinreich and Nicola Oberbeckmann-Winter, for making this book available outside of Spain.

December 2010

Hugo Kubinyi
Weisenheim am Sand

Preface and Acknowledgment

"Quand on est tombé sur un bon produit il n'a jamais fini d'être interessant"
"[When you stumble upon a good product it never ceases to be of interest]"
Dr Ernest Fourneau

"For my part I believe that medicines are one of the blessings of our age, perhaps the greatest of them all"
Sir Ernest Boris Chain (Nobel Prize for Physiology and Medicine, 1945)

"The most fruitful basis for the discovery of a new drug is to start with an old drug"
Sir James Black (Nobel Prize for Physiology and Medicine, 1988)

Throughout the thirty years, approximately, that we have been imparting Pharmaceutical/Medicinal Chemistry in the Faculty of Pharmacy in the University of Santiago de Compostela (Spain), we have been noticing that the level of the student's attention increases when to the explanation of the origin of a drug we add a brief description of the historical, scientific and human scenery in which the discovery has taken place. This motivation of the students in a core subject of the Degree in Pharmacy is what has induced us to lay down in a book a scientific story in the form of a journey that will allow us to contemplate with perspective and in necessarily succinct manner the evolution of drug discovery in the different historical sceneries and social contexts during the 19th and 20th centuries.

We intended to write a book on drugs with a medium-high scientific level. We have intended that any student or graduate from health related disciplines (Pharmacy, Medicine, Dentistry, Veterinary Science, Nursing) or experimental science disciplines (Chemistry, Biology, ...) can satisfy his/her curiosity regarding the medicines which make possible the level of health that we enjoy today: their origin, the context in which they have been discovered and the trajectory of their development.

Also, we wanted to transmit to students and the new generations of drug professionals the extraordinary role of historic old crude drugs from plant origin, or those of animal origin (e. g. insulin). The old drugs are the origin of many drugs now widely used. In fact, morphine has not been superseded as a painkiller

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medication for the relieve of severe pain, the most feared physiological response amongst humans and animals.

We have endeavoured to produce an approachable and inviting book. It is for this reason that we include photographs that we feel will contribute to motivate the reader to enter the world of medicines and their historical evolution. We have also attempted to highlight the humanity of the scientists that have participated in or contributed to the discovery of medicines in a decisive manner and the photographs of many of them are included in recognition of their meritorious work.

Included in the text there are formulae and chemical outlines. We cannot produce a book on drugs without showing their chemical representations. A drug is an organic-chemical product (90–95% of cases) and its formula and name identifies it in the same way as an identity card identifies a person. Also, many drugs were discovered by manipulating other ones, so that, in the interest of academic clarity, chemical outlines, if simplified, are unavoidable. On the other hand, understanding chemical general structures is within the reach of most educated people.

The diversity of existent medicines in the therapeutic arsenal is such (fortunately), that in a journey of these characteristics there will inevitably be aspects regarding therapeutic innovation that will not be commented on. We would try to fill those gaps in successive editions, if there were any.

In the 19th century, science progressed in all its branches. Pasteur discovered microbes and created Bacteriology. Buchheim and Schmiedeberg laid the foundations for Pharmacology, Wöhler broke with the theory of the vital force and led the way for Organic Chemistry and Synthesis. As a consequence, the first chemical products derived from natural sources (animals, plants) were isolated and identified by the use of synthetic methods. These products are evaluated following the experimental assay methods provided by Pharmacology (or Bacteriology) in its development.

Throughout the 20th century, the development of the chemistry of drugs (Pharmaceutical Chemistry) has taken place evolving from the progress of Organic Chemistry.

One of the first Pharmaceutical Chemistry treatises is that of Prof. Ernst Schmidt, professor of *Pharmazeutische Chemie* at the University of Marburg and Director of the Institute of the same name. The first edition of *Pharmazeutische Chemie* dates from 1879 and the fifth from 1907. Schmidt's treatise was followed by others as the *Grundriss der Modernen Arzneistoff-Synthese* by K. H. Slotta (Enke, Stuttgart, 1931).

In the 1950s, the great compilation treatises (fundamentally synthetic) on Pharmaceutical Chemistry began to be published in Germany. We would like to highlight the work of H. P. Kaufmann, *Arzneimittel-Synthese*, published in 1953 by Springer Verlag, Berlin (French translation by Professor Ph. F. Winternitz as *Médicaments de Synthése*. Office International de Librairie, Buxelles, 1957); *Syntheticka Léciva* (CSAV. Prague, 1954) by Z. Budesinsky and M. Protiva translated into German as *Synthetische Arzneimittel* (Akademie Verlag, Berlin, 1961). In 1968, the first edition of *Arzneimittel. Entwicklung, Wirkung, Darstellung* (*Drugs. Development, Action, Preparation*) (Verlag Chemie. Weinheim), by Gustav Ehrhart and Heinrich

Ruschig, was published in two volumes. It was updated and extended to five volumes in a second edition (1972). A. Kleemann, E. Lindner and J. Engel continued this work with *Arzneimittel Fortschritte* 1972 bis 1985. After, *Erhart/Ruschig* (as it will be denoted in the book), two works followed: *Pharmazeutische Chemie* (two volumes) by E. Schröder, C. Rufer and R. Schmiechen (Georg Thieme Verlag. Stuttgart, 1982) (Published also in Italian: *Chimica Farmaceutica*, Societá Editrice Scientifica. Napoli, 1990) and, in 2000, *Pharmaceuticals. Classes, Therapeutic Agents, Areas of Application* edited by Dr. J. L. McGuire (Wiley-VCH). This book, in four volumes, has been written by more than a hundred co-authors, mostly members of the pharmaceutical industry, coordinated by Dr. J. L. McGuire (cited in the text as McGuire, J. L. Pharmaceuticals). For Dr. Jürgen Drews [1] who reviewed volume IV, this volume, like the whole series to which it belongs, looks like a remake of an earlier version of the same topic: *Arzneimittel* also published by Verlag Chemie (Weinheim) in 1968, at that time in German.

In 1978, the work of Drs. Axel Kleemann and Jürgen Engel began to be published with *Pharmazeutische Wirkstoffe: Synthesen, Patente, Anwendungen* (Georg Thieme Verlag). The third edition of Kleemann/Engel was published in 1998 entitled *Pharmaceutical Substances* with B. Kutscher and D. Reichert as co-authors and the fourth, with the same title, in two volumes in 2003. It describes with outlines the synthesis of 2267 active substances or medicines (*pharmaceutical substances*) with abundant detail, references to patent's documentation, therapeutic usage, names, registered trademarks for several countries and more. It constitutes compulsory reference material for every professional working in the field of the chemistry of drugs. The last edition has been published in 2008 in a volume of over 1700 pages.

In America, the most historically significant work was probably the first edition of *Medicinal Chemistry* by Alfred Burger[1] (Interscience Publishers Inc. New York, 1951). This work contains all the existing relevant knowledge on Medicinal Chemistry up to that point. Another five editions have been published since then: the 2nd in 1960 and the 3rd in 1970, edited by A. Burger; the 4th in 1980 and the 5th in 1995, edited by M. E. Wolf (*Burger's Medicinal Chemistry and Drug Discovery*) and, the 6th in 2003, *Burger's Medicinal Chemistry and Drug Discovery*, edited by D. J. Abraham. These volumes significantly cover the change of direction of the evolution of Medicinal Chemistry from synthesis towards design and study of the structure-activity relationships and the action of drugs.

In 1983, Prof A. Burger published the book *A Guide to the Chemical Basis of Drug Design* (Wiley-Interscience, 1983). Throughout its three hundred pages, concisely structured and incorporating 1521 bibliographic references, this book constitutes, in our opinion, the cornerstone work of Medicinal Chemistry.

1) Alfred Burger (Vienna, 1905-Virginia 2000). PhD with Späth, emigrated in 1929 to USA where he was Chemistry Professor at the University of Virginia (Charlottesville). Prof. Burger, as well as a writer, has been the founding editor of *Journal of Medicinal Chemistry*. He narrates his autobiography in a little book (167 pages) published by himself, entitled *Searching, Teaching and Writing-What Fun!* (1988).

We should mention two American pioneer works in the field of the Organic Chemistry of drugs published before Burger's first edition (1951). *The Chemistry of Organic Medicinal Products* by J. G. Jenkins and W. H. Hartung (Wiley, first edition, 1941, fourth edition, 1957) was in a way the precursor of the Medicinal Chemistry treatises by Wilson and Gisvold, in 1949, and Foye in 1972. The *Textbook of Organic Medicinal and Pharmaceutical Chemistry* by Professors Charles Wilson and Ole Gisvold (first edition 1949 as *Organic Chemistry in Pharmacy*) is a classic work in the field of American Medicinal Chemistry literature. From the 6th edition (1971), Prof. R. F. Doerge participates as editor. The 8th edition (1982) is denoted *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry* and edited by Doerge. Professors Jaime N. Delgado and William A. Remers edited the 9th and 10th editions and, after Delgado's death, the 11th edition (Lippincott Williams & Wilkins, Philadelphia, 2003) is edited by Professors John Beale and John Block.

The first Edition of *Principles of Medicinal Chemistry* by Professor William Foye, was published in 1970. It has been printed in successive editions until the current sixth edition entitled *Foye's Principles of Medicinal Chemistry* and edited by Professors D. A. Williams, Th. Lemke, V. F. Roche and S. W. Zito (Wolters Kluwer/Lippincott Williams & Wilkins, Philadelphia, 2008).

Chemical-synthetic aspects of drugs are covered in the American literature by the extensive series *The Organic Chemistry of Drug Synthesis* by Dr. Daniel Lednicer and Dr. Lester Mitscher (the latter, Professor of Medicinal Chemistry at the University of Kansas is a co-author of the volumes 1–5, also Gunda I. Georg for the volume 4). The series, in seven volumes, published by J. Wiley & Sons (Volumes 1–7; 1977–2008) provides a thorough overview of the synthetic routes to therapeutic agents.

A very useful selection of drug synthesis from the first five volumes in the series has been published by Dr. Daniel Lednicer with the title *Strategies for Organic Drug Synthesis and Design* (Wiley, 1998).

In 1990, a *Comprehensive Medicinal Chemistry* in five volumes was published by Professors C. Hansch, P. G. Sammes and G. B. Taylor (Pergamon, 1990). *Comprehensive Medicinal Chemistry II* (eds D. Triggle and J. Taylor) was published in 2006 (Elsevier, eight volumes).

We should also highlight the important and copious French contribution to reference bibliography in this area. *Chimie des Médicaments* by Albert Lespagnol (Entreprise Moderne d'Edition. Technique et Documentation Volumes 1–3; P.I.C Perfectionement Industrielle des Cadres. Genéve, 1974) has been a basic reference book for numerous Pharmaceutical/Medicinal Chemistry academics. Professor Albert Lespagnol, *Professeur de Pharmacie Chimique* at the Faculty of Medicine and Pharmacy at the University of Lille, was a French medicinal chemistry pioneer. He had published the treatise *Pharmacie Chimique. Avec les Preparations Industrielles des Medicaments* (Vigot Frères Eds. 3ème Ed. Paris, 1950) and, with D. Bar, Ch. Lespagnol and M. Dautrevaux, in 1966, he published *Quelques aspects de la chimie des Médicaments* (Masson) (250 pages). In his books, Prof. Lespagnol

describes the origin and chemistry of medicines and he masterfully analyses the relationship between chemical structure and pharmacological activity.

We should also point out the series *Médicaments Organiques de Synthèse* edited by G. Valette (Masson et Cie., Vol. I, 1969; Vol. VII, 1974), as well as the work in three volumes *Pharmacie Chimique* by P. Lebau and M.M-Janot and other professors at the Faculty of Pharmacy in Paris (Masson et Cie, 1955–1956).

Lastly, we need to mention the very thorough *Traité de chimie thérapeutique* written by a group of French professors of *Chimie Thérapeutique* in five volumes (Association Française des Enseignants de Chimie Thérapeutique. Tec & Doc Lavoisier. Vols. 1–5. París, 1992–2003 (vol. 5).

The Italian contribution to Medicinal Chemistry literature is also worth mentioning and, among others, we can highlight two outstanding treatises: *Chimica Farmaceutica* by Professor Giordano Giacomello (two volumes, UTET, Torino, 1974) and *Fondamenti di Chimica Farmaceutica* by Profesor Carlo Runti (four volumes, Ed. Lint., Trieste, 1972).

In a work such as this it is imperative to include Pharmacology treatises and references to them are made throughout the book.

The successive editions of the celebrated Pharmacology treatise by Louis Goodman and Albert Gilman *The Pharmacological Basis of Therapeutics* (1st edition 1940), Brunton, L. C., Lazo, J. S., Parker, K. (editors) *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (11th edition 2006, Mc Graw Hill), as well as the *Rang and Dale's Pharmacology* (6th edition 2007, Churchill Livingstone Elsevier) have constituted a source of great value in the writing of parts of the book.

Similarly, the Pharmacology treatise (in Spanish) by Professor B. Lorenzo Velázquez, *Terapéutica con sus Fundamentos de Farmacología Experimental* (Volumes I and II. Editorial Científico Médica, Madrid 1950), has been very helpful as a source of great historical relevance. Also, the following editions of Velazquez's textbook (18th edition, 2008) have been of great value.

Readings in Pharmacology, a now historical publication by B. Holmstedt and G. Liljestrand, Professors at the Karolinska Institute in Stockholm (Pergamon Press, 1963), has been very useful as reference to highlight the biographical and professional aspect of the professors and researchers who have made the advance of Pharmacology possible.

Other valuable sources have been used:

Paris, R., Mayse, H. *Matiére Medical.* Masson, Paris 1967.

Samuelsson, G. *Drugs of Natural Origin. A Textbook of Pharmacognosy* 4th ed. Apotekarsocieteten/Swedish Pharmaceutical Society, 1999.

Kirkiacharian, S. *Guide de Chimie Thérapeutique.* Ellipses, (1996).

Nogrady, Th., Weaver, D. F. *Medicinal Chemistry. A molecular and biochemical approach.* Third Edition. Oxford University Press (2005).

Sneader, W. *Drug Discovery. The Evolution of Modern Medicines.* John Wiley & Sons, 1985.

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Meyers, R. A. (editor) (2008) *Pharmacology. From Drug Development to Gene Therapy* Vols. I and II. Wiley-VCH (Weinheim, Germany).

Mukund S. Chorghade (2006) *Drug Discovery and Development* Vols. 1 and 2. John Wiley & Sons.

Landau, R., Achilladelis, B., Scriabine, A. (Editors) *Pharmaceutical Innovation. Revolutionizing Human Health.* Chemical Heritage Press, Philadelphia, 1999.

The Merck Index. 14th edition. Merck & Co (Whitehouse Station) New Jersey, USA.

US Parmacopoeia/National Formulary (Edition in Spanish). (2008) (USP 29/NF 24). Vols. 1–3.

European Pharmacopoeia (Sixth Edition, 2007) *Council of Europe,* Strasbourg, France.

Physician's Desk Reference (2005) 59th ed. Thomson PDR. Montvale, New Jersey, USA.

Drug Facts and Comparisons 2008 ed. Wolters Kluwers Health Facts & Comparisons. St. Louis, Missouri USA.

Except for some cases, because the very extensive literature covering a multidisciplinary subject as a book on drugs, no primary literature has been incorporated. Instead, we have used the above mentioned literature together with the following documented collections or series:

Drugs of the Future (Editor J. R. Prous, Prous Science, now Thomson Reuters, editor J. Prous Jr.), *Annual Reports in Medicinal Chemistry* (Academic Press), as well as *Progress in Drug Research* (Birkhäuser Verlag, Basel Switzerland), *Progress in Medicinal Chemistry* (Elsevier), *and Chronicles in Drug Discovery* (American Chemical Society), which are cited throughout the text. These valuable collections provide the reader with comprehensive content regarding selected topics and new drugs. The literature cited therein will be extremely useful and valuable to interested reader.

The interested reader can also check databases such as *MedLine, Sci Finder, Prous Integrity* (now *Thomson Reuters Integrity)* and others.

Finally, I will welcome comments, suggestions and constructive criticism. Despite careful revision the book will still have errors and omissions. I hope that the readers' leniency will forgive these errors and omissions and hope for their generous collaboration in correcting them.

Explanatory Notes

Drugs can be broadly defined as any chemical (or biological) agent that affects living processes. Specifically, a drug is defined as a chemical substance or substances (or active ingredient or ingredients) of known structure, other than a nutrient or an essential dietary ingredient, which when administered to a living organism is able to diagnose, prevent, alleviate or cure a pathological break condition.

Drugs may be chemicals obtained from plants, animals, microorganisms or from the sea, synthetic chemicals or products obtained by DNA recombinant technology.

The active principle or ingredient or active drug must be delivered in the proper dosage form to reach at the intended site of action. That is, it must be formulated in any one of the many dosage forms available: tablets, capsules, *parenteral* (injectable) product, ointments, liquid oral dosage, etc. This is a *medicine*. A medicine contains the active drug together with excipients, solvents, stabilizers, conservatives, which are necessary to the adequate administration and delivery of the active principle or active drug.

Unless otherwise stated, from 1980 the year of introduction of a drug (as generic name) mentioned in the book is that given in the Annual Reports in Medicinal Chemistry.

The X-ray crystal structural data can be downloaded from Protein Data Bank http://www.pdb.org. The access code appears below each picture along with the corresponding reference. The renderings of the X-ray crystal structures were kindly developed by Dr. Hugo Gutiérrez de Terán (University of Santiago de Compostela, currently in the Fundación Pública Galega de Medicina Xenómica, Spain) by using software PyMOL Molecular Graphics System, Version 1 2r3pre, Schrödinger, LLC http://www.pymol.org/. His generous contribution is gratefully acknowledged.

In the United States, all food, drugs, cosmetics and medical devices for both humans and animals are regulated under the authority of the U.S. Food and Drug Administration (http://www.fda.gov). The interested reader is referred to Chapter 11 of Foye's textbook.[2)]

In the European Union, the regulatory agency for drugs is EMEA (European Medicines Evaluation Agency, http://www.emea.eu.int).

Aclaratory Note

Given the nature of this work, regarding historical evolution of drugs, administration details, doses, dosage regimens and a comprehensive list of administration routes are not included. To obtain more information or check recommended dosages forms, administration routes, treatments, adverse/side effects, contraindications, precautions, etc. the reader must check manufacturer's product information, pharmacology and/or therapeutic treatises, comprehensive drug information compendium, data bases, regulatory agency statements and all other sources which the reader may consider appropriate.

Acknowledgments

This book is a revised version, not a mere translation, of the Spanish book *Medicamentos. Un viaje a lo largo de la evolución histórica del descubrimiento de fármacos* published in 2008 by the University of Santiago de Compostela (Spain). A substantial part of the content from the Spanish version is included in this English

2) Pisano, D. J. U.S. Drug regulation: An overview in *Foye's principles of Medicinal Chemistry* Sixth edition (cited in the Preface) Chapter 11, pp. 327–338.

version, especially photographs, images and illustrations. The author and publisher wish to thank The University of Santiago de Compostela (Universidad de Santiago de Compostela) and its Principal Prof. Senén Barro Ameneiro for their generosity in authorizing the use of said content in both the printed and electronic versions of this book.

Also, I would to like to acknowledge the assistance and collaboration of many individuals and institutions which provided very valuable help and encouragement. The list would be very long. Many thanks are given to the Pharmaceutical Companies which provided me with very valuable graphic material or granted permission to reproduce it.

Also, specially, I want to acknowledge the generosity of Dr. Tomás Adzet Porredón, Retired Professor of Pharmacology and Pharmacognosy at the University of Barcelona (Spain) who provided very valuable graphic material (coca and peyolt), a selection of which is shown in the book. In the study and practice of Ethnopharmacology, Prof. Tomás Adzet (in several occasions with Dr. Josep Lluis Massó i Lago) travelled through the American continent, from Mexico to Peru, Argentina and Chile living by periods of time in several regions of Latin America.

Also, I want to acknowledge the generosity of Pharmacists Ricardo Bescansa (Santiago de Compostela, Spain) and Eduardo Esteban, José Luis Domínguez, and Carlos Montero (Pontevedra, Spain) who provided very nice images of old historic drugs. From generation to generation they maintained and preserved in their pharmacies old drug collections which illustrate the long journey of drug evolution.

I would like to thank the courtesy of botanists Drs. Iñigo Pugar, Modesto Luceño and Xosé Ramón García who provided most of the plants photographs that the reader can see throughout the book as well as the good work by Miguel Suárez, experienced informatic illustrator.

Thanks are given also to my daughter María for her continuous help and encouragement. María, an English teacher, supervised the language of this English version.

I am deeply indebted to Prof. Jorge Christian Fernández Masaguer, Professor of Organic Chemistry, for proofreading all the chapters and making useful comments and improvements as well as for his constant encouragement and support.

I acknowledge the assistance and encouragement throughout the course of this project of Wiley-VCH editorial staff, especially to Dr. Nicola Oberbeckmann-Winter, Dr. Waltraud Wüest and Dr. Frank Weinreich.

Finally, I want to express my gratitude to Dr. Hugo Kubinyi for his help and encouragement and for accepting to write a foreword for this book.

April 2010 *Enrique Raviña*

Reference

1. Drews, J. (2001) *Drug Discovery Today*, **6**, 1100.

List of Credits for Images

We wish to acknowledge the generous collaboration of Individuals, Institutions and Pharmaceutical Laboratories for providing us these valuable images. [(USC, abbreviation of Universidad de Santiago de Compostela/University of Santiago de Compostela, Spain). See, also Acknowledgements at Preface].

Chapter 1

Figure 1.1	(left) Universitätsbibliotek Leipzig. Papyrus Ebers, Tf. 20, Kol. 69 (right). Aconitum in *the Dioscorides.*
Figure 1.2	Cover of Dioscorides (1554). (University of Santiago de Compostela Library). © USC.
Figure 1.3	Monastery garden. [San Domingos de Bonaval Monastery (Santiago de Compostela). [Recreation/Exposition, July-August 2004). © USC.
Figure 1.4	Cover of Francisco Hernandez's *Rerum Medicarum Novae Hispaniae Thesaurus.* [signature BH FG 2756]. Historic Complutense University of Madrid Library.
Figure 1.5	(left) *Radix Ipecacuanha.* Laboratory of Pharmacognosy Faculty of Pharmacy. University of Santiago de Compostela (Spain). (Right) Cinchona (quina) in powder. From Farmacia Esteban's old drugs collection (Photography by Carlos Montero) (Pontevedra, Spain).
Figure 1.6	Covers. Magendie and Schmiedeberg's books. University of Santiago de Compostela Library. © USC.
Figure 1.10	*Bluevac®*. Provided by Courtesy of CZ Veterinaria. Porriño, Pontevedra. (Spain).

Chapter 2

Figure 2.4	Coca leaves. Images provided by courtesy of (Retired) Professor of Pharmacology and Pharmacognosy Dr. Tomás Adzet Porredón. University of Barcelona, Spain.

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Figure 2.6 *Orthoform®*. From "*Museo de la Farmacia de Galicia/Museo da Farmacia Galega Aniceto Charro*", USC. Reproduced with permission from sanofi-aventis (Spain). *Novocaina®*. Author's collection (Reproduced with permission from Bayer Schering Pharma. Química Farmacéutica Bayer, S. L., Barcelona. Spain).

Figure page 34 *Luminal ®*. From Farmacia Esteban's old drugs collection (Photography by Carlos Montero). Pontevedra, Spain. (Reproduced with permission from Bayer Schering Pharma. Química Farmacéutica Bayer, S. L., Barcelona. Spain).

Figure 2.9 *Penthotal sódico®*. Author's collection (Reproduced with permission from Abbott Laboratories,. Madrid, Spain).

Figure 2.11 Paul Ehrlich and Sahachiro Hata portrait. Courtesy of the Paul Ehrlich Institute (Langen, Germany).

Figure 2.15 *Neosalvarsan®*. From Farmacia Esteban's old drugs collection (Photography by Carlos Montero) (Pontevedra, Spain). Reproduced with permission from Bayer Schering Pharma. Química Farmacéutica Bayer, S. L., Barcelona. Spain).

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Chapter 3

Figure 3.2 Drugs from Specia (Rhône-Poulenc, 1951). (Announcement in "Boletín cultural e informativo del Consejo General de Colegios Médicos de España", Vol. X. No 49, 1951) (Reproduced with permission from sanofi-aventis, Spain).

Figure 3.3 (left) Activity cages (with permission from Panlab, Barcelona. Spain). *Largactil®*. Author's collection (Reproduced with permission from sanofi-aventis, Spain).

Box 3.1 *Trional®*. From Farmacia Bescansa's old drugs collection. Santiago de Compostela (Spain). Reproduced with permission from Bayer Schering Pharma. Química Farmacéutica Bayer, S. L., Barcelona. Spain).