Second Edition

The Practice of MEDICINAL CHEMISTRY

Edited by CAMILLE GEORGES WERMUTH

This book is printed on acid-free paper

First published 1996
Reprinted 2001
Second edition 2003

Academic Press
An Imprint of Elsevier
84 Theobald's Road, London WC1X 8RR, UK
http://www.academicpress.com

Academic Press
An Imprint of Elsevier
525 B Street, Suite 1900 San Diego, California 92101-4495, USA
http://www.academicpress.com

ISBN 0-12-744481-5

Library of Congress Catalog Number: 2003104296

A catalogue record for this book is available from the British Library

Typeset by Alden Dataset
Printed and bound in Great Britain by the Bath Press, Avon

Contents

Biography viii

Contributors ix

Foreword xi

Preface to the First Edition xiii

Preface to the Second Edition xv

Part I General Aspects of Medicinal Chemistry

1 A brief history of drugs: from plant extracts to DNA technology
François Chast 1

2 Medicinal chemistry: definition and objectives, the three main phases of drug activity, drug and disease classifications
Camille G. Wermuth 29

3 Measurement and expression of drug effects
Jean-Paul Kan 41

4 Drug targets: molecular mechanisms of drug action
Jean-Pierre Gies and Yves Landry 51

Part II Lead Compound Discovery Strategies

5 Strategies in the search for new lead compounds or original working hypotheses
Camille G. Wermuth 67

6 Natural products as pharmaceuticals and sources for lead structures
David Newman, Gordon Cragg and David Kingston 91

7 Basics of combinatorial chemistry
Cécile Vanier and Alain Wagner 111

8 The contribution of molecular biology to drug discovery
Kenton H. Zavitz and Adrian N. Hobden 121

9 Electronic screening: lead finding from database mining
Lothar Terfloth and Johann Gasteiger 131

10 High-speed chemistry libraries: assessment of drug-likeness
Alexander Polinsky 147

11 Web alert—using the internet for medicinal chemistry
David Cavalla 159

Part III Primary Exploration of Structure–Activity Relationships

12 Molecular variations in homologous series: vinylogues and benzologues
Camille G. Wermuth 173
13 Molecular variations based on isosteric replacements
Camille G. Wermuth 189
14 Conformational restrictions and/or steric hindrance in medical chemistry
Camille G. Wermuth 215
15 Conformational restriction and/or steric hindrance in medicinal chemistry
André Mann 233
16 Identical and non-identical twin drugs
Jean-Marie Contreras and Jean-Jacques Bourguignon 251
17 Optical isomerism in drugs
Camille G. Wermuth 275
18 Application strategies for the primary structure–activity relationship exploration
Camille G. Wermuth 289

Part IV Substituents and Functions: Qualitative and Quantitative Aspects of Structure–Activity Relationships

19 Specific substituent groups
Camille G. Wermuth 301
20 The role of functional groups in drug–receptor interactions
Peter Andrews 327
21 Compound properties and drug quality
Christopher A. Lipinki 341
22 Quantitative approaches to structure–activity relationships
Han van de Waterbeemd and Sally Rose 351

Part V Spatial Organization, Receptor Mapping and Molecular Modeling.

23 Stereochemical aspects of drug action I: conformational restriction, steric hindrance and hydrophobic collapse
Daniel H. Rich 371
24 Pharmacophore identification and receptor mapping
Hans-Dieter Höltje 387
25 Three-dimensional quantitative structure–property relationships
Gabriele Cruciani 405
26 Protein crystallography and drug discovery
Jean-Michel Rondeau and Herman Schreuder 417
27 Protein homology modelling and drug discovery
Tom Blundell and Charlotte Deane 445
28 The transition from agonist to antagonist activity: symmetry and other considerations
David J. Triggle 459
29 Design of peptidomimetics
Hiroshi Nakanishi and Michaël Kahn 477

Part VI Chemical Modifications Influencing the Pharmacokinetic Properties

30 The fate of xenobiotics in living organisms
Franz Belpaire and Marc G. Bogaert 501
31 Biotransformation reactions
Jacques Magdalou, Sylvie Fournel-Gigleux, Bernard Testa and Mohamed Ouzzine 517
32 Chemical mechanisms of toxicity: basic knowledge for designing safer drugs
Anne-Christine Macherey and Patrick M. Dansette 545
33 Designing prodrugs and bioprecursors
Camille G. Wermuth 561
34 Macromolecular carriers for drug targeting
Etienne H. Schacht, Katleen De Winne, Katty Hoste and Stefan vansteenkiste 587

Part VII Pharmaceutical and Chemical Formulation Problems

35 Preparation of water-soluble compounds through salt formation
P. Heinrich Stahl 601
36 Preparation of water-soluble compounds by covalent attachment of solubilizing moieties
Camille G. Wermuth 617
37 Drug solubilization with organic solvents, or using micellar solutions or other colloidal dispersed systems
P. Heinrich Stahl 631
38 Improvement of drug properties by cyclodextrins
Kaneto Uekama and Fumitoshi Hirayama 649
39 Chemical and physicochemical solutions to formulation problems
Camille G. Wermuth 675

Part VIII Development of New Drugs: Legal and Economic Aspects

40 Discover a drug substance, formulate and develop it to a product
Bruno Galli and Bernard Faller 687
41 Drug nomenclature
Sabine Kopp-Kubel 697
42 Legal aspects of product protection — what a medicinal chemist should know about patent protection
Maria Souleau 707
43 The consumption and production of pharmaceuticals
Bryan G. Reuben 723

Index 751

Contributors

Andrews, Peter, Center for Drug Design and Development, The University of Queensland, Brisbane, Queensland 4072, Australia
Belpaire, Franz, JF&C Heymans Institute for Pharmacology, University of Gent Medical School, De Pintelaan 185, B-9000 Gent, Belgium
Blundell, Tom, Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Cambridge, CB2 1GA, UK
Bogaert, Marc G., JF&C Heymans Institute for Pharmacology, University of Gent Medical School, De Pintelaan 185, B-9000 Gebt, Belgium
Bourguignon, Jean-Jacques, Laboratoire de Pharmacochimie de la Communication Cellulaire, Faculté de Pharmacie, 74 Route du Rhin, 67401 ILLKIRCH-Cedex, France
Cavalla, David, Arachnova, St John's Innovation Centre, Cambridge CB4 4WS, UK
Chast, François, Hôpital de l'Hôtel-Dieu, 1 Place du Parvis de Notre-Dame, 75004, Paris, France
Contreras, Jean-Marie, Prestwick Chemical Inc., Rue Tobias Stimmer, Bâtiment Tycho, Brahé, 67400 Illkirch, France
Cragg, Gordon M., Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Frederick Cancer Research and Development Center, P.O. Box B, Frederick, MD 21701-1013, USA
Cruciani, Gabriele, Laboratory for Chemometrics, Chemistry Department, University of Perugia, Via Elce di Sotto 10, Perugia I-06123, Italy
Dansette, Patrick, Laboratoire de chimie et Biochimie, Pharmacologiques et toxicologiques, CNRS UMR 8601, 45 rue des Saints-Pères, 75006 Paris, France
Deane, Charlotte, Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Cambridge, CB2 1GA, UK
Faller, Bernard, Novartis Pharma AG, Werkklybeck, Klybeckstrasse 141, CH-4057, Basel, Switzerland
Fournel-Gigleux, Sylvie, UMR 7561 CNRS/UMP, Faculté de Médicine, Boite Postale 184, 54505 Nancy, France
Galli, Bruno, Novartis Pharma AG, Postfach, Ch-4002, Basel, Switzerland
Gasteiger, Johann, Computer-Chemie-Centrum, Institut für Organische Chemie, Universität Erlangen-Nürnberg, Naegelbachstrasse 25, D-91052 Erlangen Germany
Gies, Jean-Pierre, Laboratoire de Pathologie des Communications entre Cellules Nerveuses et Musculaires, Université Louis Pasteur, Faculté de Pharmacie, 74 Route du Rhin, 67401 ILLKIRCH-Cedex, France
Hirayama, Fumitoshi, Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe Honmachi, Kumamoto 862, Japan
Hirschmann, Ralph S., University of Pennsylvania, Philadelphia, USA
Hobden, Adrian N., Myriad Genetics, Inc., 320 Wakara Way, Salt Lake City, Utah 84108, USA
Höltje, Hans-Dieter, Institut für Pharmazeutische Chemie, Heirich Heine Universität, Universitätstrassse 1, Düsseldorf 40225, Germany
Hoste, Katty, University of Gent, Department of Organic Chemistry, Polymer Materials Research Group, Krijgslaan 281 54 Bis, Ghent, Belgium
Kahn, Michaël, Department of Pathobiology, Box 35 72 38, University of Washington, Seattle, WA 98195, USA
Kan, Jean-Paul, Sanofi-Synthelabo Recherche, Département Système Nerveux Central, 371 Rue du Professeur J. Blayac, 34082 Montpellier-Cedex 04, France
Kingston, David G.I., Department of Chemistry College of Arts and Sciences, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061-0212, USA
Kopp-Kubel, Sabine, DMP-RGS World Health Organization, 20 Avenue Appia, 1211 Genève-27, Switzerland
Landry, Yves, Laboratoire de Neuroimmuno-Pharmacologie Pulmonaire INSERM U425, Université Louis Pasteur, Faculté de Pharmacie, 74 Route du Rhin, 67401 ILLKIRCH-Cedex, France
Lipinski, Christopher A., Pfizer Global Research and Development, Mail Stop 8118W/220, Eastern Point Road, Groton, Connecticut 06340/0177, USA
Macherey, Anne-Christine, UPS 831-Institut de Chimie des Substances Naturelles, Avenue de la Terasse, 91198 Gif sur Yvette-Cedex, France
Magdalou, Jacques, UMR 7561 GNRS/UMP, Faculté de Médecine, Boite Postale 184, 22 Rue de Vandoeuvre, 54505 Nancy, France

Mann, André, Laboratoire de Pharmacochimie de la Communication Cellulaire, Faculté de Pharmacie, 74 Route du Rhin, 67401 ILLKIRCH-Cedex, France
Nakanishi, Hiroshi, Department of Pathobiology, Box 35 72 38, University of Washington, Seattle, WA 98195, USA
Newman, David, Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Frederick Cancer Research and Development Center, P.O. Box B, Frederick, MD 21701-1013, USA
Ouzzine, Mohamed, UMR 7561 CNRS/UMP, Faculté de Médecine, Boite Postale 184, 22 Rue de Vandoeuvre, 54505 Nancy, France
Picot, André, UPS 831-Institut de Chimie des Substances Naturelles, Avenue de la Terasse, 91198 Gif sur Yvette-Cedex, France
Polinsky, Alexander, Pfizer Global R&D, La Jolla Laboratories, 10770 Science Center Drive, San Diego, CA 92121, USA
Reuben, Bryan G., 7 Clarence Avenue, London SW4 8LA, UK
Rondeau, Jean-Michel, Novartis Pharma Research, WSJ-88.9.09A, 4002 BASEL, Switzerland
Rose, Sally, BioFocus plc., Sittingbourne Research Centre, Sittingbourne, Kent ME9 8AZ, UK
Rich, Daniel H., School of Pharmacy, 425 North Charter Street, Madison, WI 53706-1508, USA
Schacht, Etienne H., University of Gent, Department of Organic Chemistry, Polymer Materials Research Group, Krijgslaan 281 54 Bis, Ghent, Belgium
Schreuder, Herman, Aventis Pharma Deutschland GmbH, Building G 865 A, 65926 Frankfurt am Main, Germany
Seymour, Len, University of Birmingham Clinical Oncology, Queen Elizabeth Hospital, Edgbaston Birmingham, B15 2TH UK
Souleau, Maria, Sanofi-Synthélabo, Departement Brevets, 174 Avenue de France, 75 013-Paris, France
Stahl, P. Heinrich, Cosmas Consult, Lerchenstrasse No. 28, D-79104 Freiburg im Breisgau, Germany
Steenkiste, Stefan van, University of Gent, Department of Organic Chemistry, Polymer Materials Research Group, Krijgslaan 281 54 Bis, Ghent, Belgium
Terfloth, Lothar, Computer-Chemie-Centrum, Institut für Organische Chemie, Universität Erlangen-Nürnberg, Nägelbachstrasse 25, D-91052 Erlangen, Germany
Testa, Bernard, Université de Lausanne, École de Pharmacie, B.E.P., CH-1015 Lausanne-Dorigny, Switzerland
Triggle, David J., State University of New York, School of Pharmacy, Amherst Campus, Buffalo, NY 14260, USA
Uekama, Kaneto, Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe Honmachi, Kumamoto, 862, Japan
Vanier, Cécile, Graffinity Pharmaceuticals AG Im, Neuenheimer Feld 518-519 69120, Heidelberg, Germany
Wagner, Alain, Laboratoire de Synthèse Bioorganique, UMR 7514 du CNRS, Université Louis Pasteur, Faculté de Pharmacie, 74 Route du Rhin, 67401 ILLKIRCH-Cedex, France
Waterbeemd, Han van de, Pfizer Global Research and Development, PDM, Department of Drug Metabolism, Director and Head of Discovery and Preclinical Development, IPC 331, Sandwich, Kent CT13 9NJ, UK
Wermuth, Camille G., Laboratoire de Pharmacochimie de la Communication Cellulaire, Université Louis Pasteur, Faculté de Pharmacie, 74 Route du Rhin, 67401 Illkirch-Cedex, France
Winne, Katleen de, University of Gent, Department of Organic Chemistry, Polymer Materials Research Group, Krijgslaan 281 54 Bis, Ghent, Belgium
Zavitz, Kenton H., Myriad Pharmaceuticals Inc., Salt Lake City, UT 84108, USA

Biography

Camille-Georges Wermuth PhD, Prof. and Founder of Prestwick Chemical, was Professor of Organic Chemistry and Medicinal Chemistry at the Faculty of Pharmacy, Louis Pasteur University, Strasbourg, France from 1969 to 2002. He became interested in Medicinal Chemistry during his two years of military service in the French Navy at the "Centre d'Etudes Physio-biologiques Appliquées à la Marine" in Toulon. During this time he worked under the supervision of Dr Henri Laborit, the scientist who invented artificial hibernation and discovered chlorpromazine.

Professor Wermuths' main research themes focus on the chemistry and the pharmacology of pyridazine derivatives. The 3-aminopyridazine pharmacophore, in particular, allowed him to accede to an impressive variety of biological activities, including antidepressant and anticonvulsant molecules; inhibitors of enzymes such as mono-amine-oxidases, phosphodi-esterases and acetylcholinesterase; ligands for neuro-receptors: GABA-A receptor antagonists, serotonine 5-HT_3 receptor antagonists, dopaminergic and muscarinic agonists. More recently, in collaboration with the scientists of the Sanofi Company, he developed potent antagonists of the 41 amino-acid neuropeptide CRF (corticotrophin-releasing factor) which regulates the release of ACTH and thus the synthesis of corticoids in the adrenal glands. Professor Wermuth has also, in collaboration with Professor Jean-Charles Schwartz and Doctor Pierre Sokoloff (INSERM, Paris), developed selective ligands of the newly discovered dopamine D_3 receptor. After a three-year exploratory phase, this research has led to nanomolar partial agonists which may prove useful in the treatment of the cocaine-withdrawal syndrome.

Besides about 300 scientific papers and about 60 patents, Professor Wermuth is co-author or editor of several books including; *Pharmacologie Moléculaire*, Masson & Cie, Paris; *Médicaments Organiques de Synthèse*, Masson & Cie, Paris; *Medicinal Chemistry for the Twenty-first Century*, Blackwell Scientific Publications, Oxford; *Trends in QSAR and Molecular Modeling*, ESCOM, Leyden, two editions of *The Practice of Medicinal Chemistry*, Academic Press, London and *The Handbook of Pharmaceutical Salts, Properties Selection and Use*, Wiley-VCH.

Professor Wermuth was awarded the Charles Mentzer Prize of the Société Française de Chimie Thérapeutique in 1984, the Léon Velluz Prize of the French Academy of Science in 1995, the Prix de l'Ordre des Pharmaciens 1998 by the French Academy of Pharmacy and the Carl Mannich Prize of the German Pharmaceutical Society in 2000. He is Corresponding Member of the German Pharmaceutical Society and was nominated Commandeur des Palmes Académiques in 1995. He has been President of the Medicinal Chemistry Section of the International Union of Pure and Applied Chemistry (IUPAC) from 1988 to 1992 and from January 1998 to January 2000 was President of the IUPAC Division on Chemistry and Human Health.

Foreword

It is a privilege to write a Foreword to *The Practice of Medicinal Chemistry* written by a distinguished group of contributors. It is also a privilege because this book will be read by medicinal chemists from diverse backgrounds, interests and expertise. What these scientists share is a chosen career in medicinal chemistry, surely one of the most satisfying, because it is dedicated to improving mankind's quality of life and also because it provides an intellectually satisfying environment.

The eight general topics discussed insightfully in forty-three chapters of this textbook were wisely selected and do indeed describe medicinal chemistry as it is practiced today. This Foreword does not analyze or summarize these chapters, but offers instead some personal reflections which, it is hoped, have some relevance to the volume.

Modern medicinal chemistry began in the 1950s when organic chemists began to apply newly developed steric and electronic concepts to an understanding of the structure-activity relationships of the steroids. During the second half of the twentieth century, chemistry and biology made possible the discovery of a steady stream of important new medicines. Chemistry contributed to these discoveries through impactful advances in both theory and practice of this art/science. Notable examples include invaluable advances in physical measurements, computational techniques, inorganic catalysis, stereochemical control of synthesis and the application of physical organic chemical concepts, typified by the transition state analog principle, to enzyme inhibitor design. At the same time, biology continued to contribute through the discoveries of new concepts and understanding at a rate that may well be termed explosive.

Specifically, in 1953 Watson and Crick had proposed the double-helical structure of DNA, and suggested that the sequence of nucleotide units in DNA carries encoded genetic information that determines the amino acid sequence of proteins. These discoveries proved to be a revolutionary event in biology with a profound impact on the vitality of all biomedical research. In the early 1970s, biochemical research made possible the application by Herbert W. Boyer of this new understanding to the introduction of recombinant DNA research, a new technology. This in turn led to the Boyer and Cohen collaboration on prokaryotic and eukaryotic DNA research, early cloning successes, and the founding of Genentech, Inc. in 1976. The beginning of the successful commercialization of the recombinant DNA technology by Boyer and Robert A. Swanson thus occurred twenty-three years after the discovery of the double-helix. The early (and subsequent) successes of Genentech, Inc. amply validated DNA technology as an industrial enterprise. Biotechnology became a household word and with it the search for new biotechnology came to be accepted as a desirable end in itself.

During the 1970s, target validation became an important consideration in the selection of therapeutic programs explored by the pharmaceutical industry. In the strictest sense this strategy holds that intervention in any particular biochemical or pharmacological pathway has been fully validated only if it has been shown to work in human subjects. Any research program that does not pass this definitive test is therefore thought to be a 'long shot.' In practice, this leads to the conclusion that a conservative portfolio of an organization's research programs should strike some appropriate balance between 'validated' and 'long shot' targets. In recent years successful use of antibodies in neutralizing a target protein or other substance has come to be accepted as adequate validation; this is also the case for another validated technology, the use of 'knock-out' or 'knock-in' mice.

At the end of the twentieth century there was every reason to expect that the flow of new drugs from the laboratory stages, *via* clinical trials, to the expected regulatory approval would continue to accelerate. As this book goes to press, the pipelines of both the pharmaceutical industry and of the biotechnology companies are, however, relatively dry. This is at the very time when spectacular advances in biology such as genomics and proteomics seemed to have laid the basis for the discovery of many new breakthrough drugs.

Surprisingly, there has been relatively little discussion of the causes of this paradoxical state of affairs. It is believed by some that the growing impact of marketing departments on the choice of clinical targets may have played a role in bringing about this disappointing state of affairs. Perhaps so, but it seems prudent to suggest that scientific decisions originating within the research organizations themselves may also deserve scrutiny (see below).

The unexpectedly dry pipelines of the industry raise the interesting question of whether it might be wise for any company to also 'validate' *new technologies* on a modest scale before they are extensively embraced by any organization. Two examples serve to illustrate this concern. In the 1980s the recognition that 'rational design' of enzyme inhibitors is a fruitful approach to drug discovery, led to the belief that knowing the tertiary structure of the active sites of such enzyme targets would greatly facilitate the discovery process. Significant time and effort was invested in this approach by several companies before it was recognized that the X-ray structure of the *uninhibited* enzyme is likely to be misleading, because the important role of water molecules and of conformational effects on molecular recognition was not appreciated.

More importantly, the extensive early commitment by the pharmaceutical industry to the use of combinatorial chemistry as the principal source of new chemical entities for lead discovery may be an even more serious issue. Combinatorial chemistry has proven to be an effective tool for lead optimization, but its use as the principal source of compounds for screening for lead discovery has been problematic. At the present time, very few – if any – compounds that are approved drugs or that are in Phase III clinical trials, are thought to owe their existence solely to leads generated by combinatorial chemistry. If this assessment is indeed a valid one, the extensive reliance by the industry on this unvalidated technology may well have contributed to the current disappointing status of the pipelines. For combinatorial chemistry to become a useful source of compounds for lead discovery, two requirements must be met. (1) The successive reactions must proceed sufficiently well to afford the expected final product in good yield. This requirement has generally been met. (2) It is equally important, however, that the chosen synthetic targets incorporate sufficient complexity to have a good chance that some of them will become true leads. The bar for this second objective may often have been lowered too much in order to achieve the first requirement – the desired purity. There is reason to hope that now-a-days both requirements are being met, but only time will tell.

On the other hand, a change in tactics in lead optimization has allowed for huge advances, especially in the discovery of ligands for G-protein coupled receptors. As their first objective, medicinal chemists used to seek to optimize *in vitro* potency. Given the hydrophobic nature of many of these receptors, it is not surprising that the most potent compounds to emerge from this tactic proved to be equally hydrophobic, and thus to display poor pharmacokinetic properties. Attempts to deal with this matter in the so-called 'endgame' more often than not proved to be futile. The program had thus become a victim of the 'hydrophobic trap.' By the end of the twentieth century we had learned to appreciate that measurements or calculations that relate to solubility, and thus to oral bioavailability such as log P and polar molecular surface properties, should guide the synthetic program from the very beginning.

I shall close this Foreword by returning to the theme of medicinal chemists in the service of humanity and illustrate it with two examples: the first relates to AIDS. In the mid-1980s, the human immunodeficiency virus (HIV) had been identified as the cause of AIDS. By 1996 medicinal chemists, in collaboration with biologists, had discovered reverse transcriptase inhibitors and later HIV protease inhibitors, which were combined to provide cocktails of therapy. Various regimes of what was termed 'highly active antiretroviral therapy' (HAART) reduced the viral load below detection levels — an enormous advance. Today there are sixteen approved drugs against AIDS which include seven nucleoside reverse transcriptase inhibitors (NRTIs), three non-nucleoside inhibitors of these enzymes (NNRTIs) and six protease inhibitors (PIs). These medicines thus represent an enormous step forward, although they have failed to eliminate the virus entirely from patients, resulting in the need to continue these therapies, along with their considerable side effects, for life. Resistance to these anti-AIDS medications represents an even more serious challenge, as is our inability to make anti-AIDS therapy readily available to patients in developing nations.

In contrast, the drug Mectizan has all but eliminated another dreaded disease, river blindness, in both Latin America and in West Africa. In other parts of Africa where progress varies on a country-by-country basis, success has been less dramatic. Surely there is every reason for medicinal chemists to be proud of this drug, first discovered and developed as an animal health anthelmintic, and which ultimately proved to have a far more glorious role to play in human medicine. Almost miraculously, oral administration of this drug is required only three times a year, an enormous plus in an environment where patient compliance is so poor. It should be a source of great pride and satisfaction to all medicinal chemists, whether working in the pharmaceutical industry or in other organizations, that at the time of writing Merck & Co., Inc. continues to donate 150 million tablets annually to patients in the developing world.

Looking to the future, great challenges remain including cancer, AIDS and — as life expectancy increases — Alzheimer's disease. It is exciting to contemplate that in the twenty-first century medicinal chemists will, in addition, become increasingly successful in using small molecules to block undesired protein–protein interactions. It is surely the hope of the scientists who have contributed to this book that *The Practice of Medicinal Chemistry* will become a much-consulted adjunct to the medicinal chemists in their search for the drugs of the future.

Ralph Hirschmann
Philadelphia, Pennsylvania

Preface to the First Edition

The role of chemistry in the manufacture of new drugs, and also of cosmetics and agrochemicals, is essential. It is doubtful, however, whether chemists have been properly trained to design and synthesize new drugs or other bioactive compounds. The majority of medicinal chemists working in the pharmaceutical industry are organic synthetic chemists with little or no background in medicinal chemistry who have to acquire the specific aspects of medicinal chemistry during their early years in the pharmaceutical industry. This book is precisely aimed to be their 'bedside book' at the beginning of their career.

After a concise introduction covering background subject matter, such as the definition and history of medicinal chemistry, the measurement of biological activities and the three main phases of drug activity, the second part of the book discusses the most appropriate approach to *finding a new lead compound or an original working hypothesis*. This most uncertain stage in the development of a new drug is nowadays characterized by high-throughput screening methods, synthesis of combinatorial libraries, data base mining and a return to natural product screening. The core of the book (Parts III to V) considers the *optimization of the lead in terms of potency, selectivity, and safety.* In 'Primary Exploration of Structure-Activity Relationships', the most common operational stratagems are discussed, allowing identification of the portions of the molecule that are important for potency. 'Substituents and functions' deals with the rapid and systematic optimization of the lead compound. 'Spatial Organization, Receptor Mapping and Molecular Modelling' considers the three-dimensional aspects of drug-receptor interactions, giving particular emphasis to the design of peptidomimetic drugs and to the control of the agonist–antagonist transition. Parts VI and VII concentrate on the definition of satisfactory drug-delivery conditions, i.e. means to ensure that the molecule reaches its target organ. Pharmacokinetic properties are improved through adequate chemical modifications, notably prodrug design, obtaining suitable water solubility (of utmost importance in medical practice) and improving organoleptic properties (and thus rendering the drug administration acceptable to the patient). Part VIII, 'Development of New Drugs: Legal and Economic Aspects', constitutes an important area in which chemists are almost wholly self taught following their entry into industry.

This book fills a gap in the available bibliography of medicinal chemistry texts. There is not, to the author-editor's knowledge, any other current work in print which deals with the practical aspects of medicinal chemistry, from conception of molecules to their marketing. In this single volume, all the disparate bits of information which medicinal chemists gather over a career, and generally share by word-of-mouth with their colleagues, but which have never been organized and presented in coherent form in print, are brought together. Traditional approaches are not neglected and are illustrated by modern examples and, conversely, the most recent discovery and development technologies are presented and discussed by specialists. Therefore, *The Practice of Medicinal Chemistry* is exactly the type of book to be recommended as a text or as first reading to a synthetic chemist beginning a career in medicinal chemistry. And, even if primarily aimed at organic chemists entering into pharmaceutical research, all medicinal chemists will derive a great deal from reading the book.

The involvement of a large number of authors presents the risk of a certain lack of cohesiveness and of some overlaps, especially as each chapter is written as an autonomic piece of information. Such a situation was anticipated and accepted, especially for a first edition. It can be defended because each contributor is an expert in his/her field and many of them are 'heavyweights' in medicinal chemistry. In editing the book I have tried to ensure a balanced content and a more-or-less consistent style. However, the temptation to influence the personal views of the authors has been resisted. On the contrary, my objective was to combine a plurality of opinions, and to present and discuss a given topic from different angles. Such as it is, this first edition can still be improved and I am grateful in advance to all colleagues for comments and suggestions for future editions.

Special care has been taken to give complete references and, in general, each compound described has been identified by at least one reference. *For compounds for which no specific literature indication is given, the reader is referred to the Merck Index.*

The cover picture of the book is a reproduction of a copperplate engraving designed for me by the late Charles Gutknecht, who was my secondary school chemistry teacher in Mulhouse. It represents an extract of Brueghel's engraving *The alchemist ruining his family in pursuing his chimera*, surmounted by the aquarius symbol. Represented on the left-hand side is my lucky charm caster oil plant (*Ricinus communis* L., *Euphorbiaceae*), which was the starting point of the pyridazine chemistry in my laboratory. The historical cascade of events was as follows: cracking of caster oil produces n-heptanal and aldolization of n-heptanal – and, more generally, of any enolisable aldehyde or ketone – with pyruvic acid leads to a-hydroxy-γ-ketonic acids. Finally, the condensation of these keto acids with hydrazine yields pyrodazones. Thus, all our present research on pyridazine derivatives originates from my schoolboy chemistry, when I prepared in my home in Mulhouse n-heptanal and undecylenic acid by cracking caster oil!

Preparing this book was a collective adventure and I am most grateful to all authors for their cooperation and for the time and the effort they spent to write their respective contributions. I appreciate also their patience, especially as the editing process took much more time than initially expected.

I am very grateful to Brad Anderson (University of Utah, Salt Lake city), Jean-Jacques André (Marion Merrell Dow, Strasbourg), Richard Baker (Eli Lilly, Erl Wood, UK), Thomas C. Jones (Sandoz, Basle), Isabelle Morin (Servier, Paris), Bryan Reuben (South Bank University, London) and John Topliss (University of Michigan, Ann Arbor) for their invaluable assistance, comments and contributions.

My thanks go also to the editorial staff of Academic Press in London, Particularly to Susan Lord, Nicola Linton and Fran Kingston, to the two copy editors Len Cegielka and Peter Cross, and finally, to the two secretaries of our laboratory, François Herth and Marylse Wernert.

Last but not least, I want to thank my wife Renée for all her encouragement and for sacrificing evenings an Saturday family life over the past year and a half, to allow me to sit before my computer for about 2500 hours!

Camille G. Wermuth

Preface to the Second Edition

Like the first edition of *The Practice of Medicinal Chemistry* (nicknamed 'The Bible' by medicinal chemists) the second edition is intended primarily for organic chemists beginning a career in drug research. Furthermore, it is a valuable reference source for academic, as well as industrial, medicinal chemists. The general philosophy of the book is to complete the biological progress — Intellectualization at the level of function — using the chemical progress — Intellectualization at the level of structure (Professor Samuel J. Danishevsky, *Studies in the chemistry and biology of the epothilones and eleutherobins*, Conference given at the XXXIVémes Rencontres Internationales de Chimie Thérapeutique, Faculté de Pharmacie, Nantes, 8–10 July, 1998).

The recent results from genomic research have allowed for the identification of a great number of new targets, corresponding to hitherto unknown receptors or to new subtypes of already existing receptors. The massive use of combinatorial chemistry, associated with high throughput screening technologies, has identified thousands of hits for these targets. The present challenge is to develop these hits into usable and useful drug candidates. This book is, therefore, particularly timely as it covers abundantly the subject of drug optimization.

The new edition of the book has been updated, expanded and refocused to reflect developments over the nine years since the first edition was published. Experts in the field have provided personal accounts of both traditional methodologies, and the newest discovery and development technologies, giving us an insight into diverse aspects of medicinal chemistry, usually only gained from years of practical experience.

Like the previous edition, this edition includes a concise introduction covering the definition and history of medicinal chemistry, the measurement of biological activities and the three main phases of drug activity. This is followed by detailed discussions on the discovery of new lead compounds including automated, high throughput screening techniques, combinatorial chemistry and the use of the internet, all of which serve to reduce pre-clinical development times and, thus, the cost of drugs. Further chapters discuss the optimization of lead compounds in terms of potency, selectivity, and safety; the contribution of genomics; molecular biology and X-ray crystallization to drug discovery and development, including the design of peptidomimetic drugs; and the development of drug-delivery systems, including organ targeting and the preparation of pharmaceutically acceptable salts. The final section covers legal and economic aspects of drug discovery and production, including drug sources, good manufacturing practices, drug nomenclature, patent protection, social-economic implications and the future of the pharmaceutical industry.

I am deeply indebted to all co-authors for their cooperation, for the time they spent writing their respective contributions and for their patience during the editing process. I am very grateful to Didier Rognan, Paola Ciapetti, Bruno Giethlen, Annie Marcincal, Marie-Louise Jung, Jean-Marie Contreras and Patrick Bazzini for their helpful comments.
My thanks go also to the editorial staff of *Academic Press* in London, particularly to Margaret Macdonald and Jacqueline Read. Last but not least, I want to express my gratitude to my wife Renée for all her encouragements and for her comprehensiveness.

Camille G. Wermuth

1

A BRIEF HISTORY OF DRUGS: FROM PLANT EXTRACTS TO DNA TECHNOLOGY

François Chast*

Le médicament place l'organisme dans des conditions particulières qui en modifient heureusement les procédés physiques et chimiques lorsqu'ils ont été troublés. **Claude Bernard****

I	The ancient link between medicine and religion	3
II	Modern chemistry as the basis of the concept of modern drugs	5
III	The birth of organic chemistry	6
IV	The extraction of alkaloids from plants	7
V	Salicylates and aspirin: the first best-seller	8
VI	First drugs for the heart	9
VII	Treatment for hypertension as a disease	9
VIII	General and local anaesthesia	10
IX	Antiepileptic drugs	11
X	Fight against microbes	12
XI	Sulfonamides	13
XII	Antibiotics	14
XIII	Aids: an emerging disease	16
XIV	Drugs for endocrine disorders	17
XV	Drugs of the mind	18
XVI	Drugs for immunosuppression	20
XVII	Chemistry against cancer	20
XVIII	From genetics to DNA technology	23
XIX	Conclusion	23
References		23

I THE ANCIENT LINK BETWEEN MEDICINE AND RELIGION

The earliest written records of therapeutic practices are to be found in the Ebers Papyrus, dating from the sixteenth century BC. This is historically of value, since by itself, it represents a compilation of earlier works that contain a large number (877) of prescriptions and recipes. Many plants are mentioned, including opium, cannabis, myrrh, frankincense, fennel, cassia, senna, thyme, henna, juniper, linseed, aloe, castor oil and garlic.[1] Cloves of garlic have been found in Egyptian burials, including the tomb of Tutankhamun and in the sacred underground temple of the bulls at Saqqara.[2] The Ebers Papyrus describes several charms and invocations that were used to encourage healing. The Egyptians were also well known for other healing techniques: spiritual healing, massage and surgery, as well as the extensive use of therapeutic herbs and foods. The Egyptian Shaman physician had to discover the nature of the particular entity possessing the person and then attack, drive it out, or otherwise destroy it. This was done by some powerful magic for which rituals, spells, incantations, talismans and amulets were used.

The art of divination is first known to be used in Babylonian-Assyrian medicine along with the use of astrology to determine the influence of the stellar constellations on human welfare and medical ethics. Two others aspects were usually outlined: besides divination, exorcism and medical treatment were blended together to form a composite picture. Two hundred and fifty vegetable drugs and 120 mineral drugs were identified in the clay tablets from the library of King Assurbanipal. Excrements likewise played an important part in the therapy. They were supposed to throw out the evil spirit that had invaded the body of the patient.[3]

Ancient civilizations tended to borrow and adopt the skills and knowledge of medicine and healing of various cultures to their own. When Alexander the Great conquered and encompassed virtually the known world, he did so with the intention of extolling the humanizing Greek culture.

*Adresse de l'auteur: 1, place du Parvis Notre-Dame, F-75181, PARIS Cedex 04

** Leçons sur les Effets des Substances Toxiques et Médicamenteuses

ISBN 0-12-744481-5

All the nations brought under the wing of Greece, however, brought with them their own traditions and customs including their healing knowledge.[4]

Hippocrates (approximately 460–377 BC) is considered as the father of medicine through a major, but anonymous writing called *Corpus Hippocraticum*. The regulation of diet occupied the most important place in therapeutics. At his time, drugs were mainly from vegetal origin: juice of the poppy, henbane and mandrake are cited side by side with castor oil, fennel plant, linseed, juniper, saffron, etc. Aspects of the theoretical basis for their use and application were also adopted. Purgatives, sudorifics and emetics were frequently used in order to purify sick organisms. Just as the Greek universe was ordered according to the principles of four dynamic elements: fire, water, air and earth, Hippocrates saw the body as governed by four corresponding 'humors', consisting of: sanguine, melancholic, phlegmatic and choleric. Such theories, common to most ancient civilizations, outline essential differences between holistic objectives of traditional medicine in contrast to that of contemporary medicine.[5] These principles, formulated 2400 years ago, attempted to weed out various aspects of superstition which dominated people's minds at the time, in favour of applied logic and reason. Health and disease were seen as a question of humoral balance or imbalance with foods and herbs classified according to their ability to affect natural homeostasis. Of his many aphorisms the most memorable are: 'above all else, do no harm', or ' let your medicine be your food and your food, medicine'. The classification of herbs as 'hot, 'cold', 'wet', 'dry' for instance was not thought to represent absolutes in the scientific sense, but rather aspects to be utilized as part of the art of medicine.[6]

Ancient times were a period when poisoning was raised to a high art, and in turn spurred on dazzling efforts to discover or create effective antidotes. Thus the art of Greek pharmacy was strongly supported and encouraged by the wealthy. *Mithridaticum* was an antidote containing no less than 54 ingredients, developed for Mithridates, king of Pontus during the first century BC. The remedy consisted of small amounts of various poisons which taken over a period of time are supposed to make one immune to their fatal effects.[7] The Romans, famous for incorporating the best of their Greek forbears, attempted through the efforts of Andromachus, Nero's physician, to improve or at least enlarge upon Mithridatesshotgun anti-poison by increasing the number of toxic ingredients from 54 to 70. Under the name *Theriac*, it was described in pharmacopoeias for centuries, through the European Renaissance to the modern pharmacopoeias, at the end of the nineteenth century.

One of the most significant virtues of the Romans, responsible for the long-lasting success of their civilization, was their ability to adopt local customs, religions and cultural mores, along with incorporating the accumulated knowledge and wisdom of foreign cultures under Roman dominion.

The two most important medical figures of Rome, whose contributions remain the uncontested 'standard' for botany and medicine are Dioscorides and Galen.[8] Dioscorides was born in Turkey, in the first century. His most significant contribution was the five botanical books entitled *De Materia Medica*,[9] forming the basis for all subsequent *Materia Medica* for the next 1600 years throughout Europe.

Most of Dioscorides' *Materia Medica* consists of plant medicines, while the remainder is divided more or less 10% mineral and 10% animal. If we consider that many chemically synthesized drugs were once derived from plant products, the percentages of Dioscorides' work is remarkably similar to today's. Dioscorides sought to classify drugs according to broad physiological categories of action, including: warming, mollifying and softening, astringent, bitter, or binding, diuretics, drying, etc. He raised herbal medicine beyond the purely empirical principle of finding a specific herb for a specific disease and presupposed a corresponding system of diagnosis for which the above physiologic actions will be useful. His work became the primary source of future herbalists for over 1500 years.

Galen, born in Sicily, lived around 130 AD, learned anatomy at the Greek School in Alexandria, and was the last of the important Greek herbalists, writing over 400 works, of which 83 are extant. His major herbal, *De Simplicibus* represents the fruits of his extensive travel and research. Drugs supposed to have only one quality were classified as 'simples', while those with more qualities were considered 'composites'. He described 473 drugs from vegetable, animal and mineral origin. Galen, as a continuator of Hippocrates, kept the humoral pathology scheme, which was to rule western medicine throughout the Middle Ages.

Many other Roman medical authors may be cited: Celsus, with his book *De Medicina*, was very influential, as was Scribonius with *Compositiones* and Plinius with *Historia Naturalis*.

During the Middle Ages, which lasted from AD 400 to the 1500s, the Muslim Empire of Southwest and Central Asia made significant contributions to medicine. Rhazes, a Persian-born physician of the late 800s and early 900s wrote the first accurate descriptions of measles and smallpox, Avicenna, an Arab physician of the late 900s and early 1000s, wrote a vast medical encyclopedia called *Canon of Medicine*. It represented a summation of medical knowledge of the time and influenced medical education for more than 600 years.[10]

The primary medical advance of the Middle Ages was the founding of many hospitals and university medical schools. Christian religious groups maintained hundreds of charitable hospitals for victims of leprosy. In the 900s a medical school established in Salerno (Italy), became

the primary centre of medical learning in Europe during the 1000s and 1100s.

The *Leech Book*, the oldest known Anglo-Saxon herbarium, probably written in Winchester, circa AD 920, by Cyril Bald or at his special request, is the oldest book written in the vernacular and the first medical treatise of Western Europe.

During the twelfth century, pharmaceutical history was dominated by the high personality of Hildegard of Bingen (St. Hildegard). Through devotion and mysticism, she uses the Hippocratic four-humor system and integrated body-mind and spirit with specific descriptions of diet, herbs and gems. She recommended the use of various plants: psyllium, aloe, horehound, galangal, geranium, fennel, parsley, nettles and spices, and prepared wines, infusions, syrups, oils, salves, powders and smoking mixtures. Later, in the fifteenth century, the *Herbarius* and in 1491, *Hortus Sanitatis* both have some of the best woodcuts prior to the new period of botanical illustration beginning in 1530. In France, Le '*Grant Herbier*' was important because of its later English translation in 1526.[11]

Paracelsus (1493–1541), more properly Theophrastus Phillippus Aureolus Bombastus Von Hohenheim, was born in Einsiedeln (Switzerland), in 1493. He was a phenomenon in the history of medicine, who tried to substitute something better for what seemed to him antiquated and erroneous in therapeutics, thus falling into the mistake of other radical reformers, who, during the process of rebuilding, underestimated the work of their contemporaries. Like Hippocrates, he prescribed the observation of nature and dietetic directions, but attached too great a value to experience (empiricism). In nature, all substances have two kinds of influences, helpful (*essentia*) and harmful (*venena*), which were separated by means of alchemy. It required experience to recognize essences as such and to employ them at the proper moment. His aim was to discover a specific remedy (*arcanum*) for every disease. It was precisely here, however, that he fell into error, since not infrequently he drew conclusions as to the availability of certain remedies from purely external signs, e.g. when he taught that the pricking of thistles cured internal inflammation. This untrustworthy 'doctrine of signatures' was developed at a later date by Rademacher, and also to a certain extent also by Hahnemann.[12] Although the theories of Paracelsus, as contrasted with the Galeno-Arabic system, indicate no advance inasmuch as they ignore entirely the study of anatomy, his reputation as a reformer of therapeutics is still justified in that he broke new paths in the science. He may be taken as the founder of modern *Materia Medica*, and pioneer of scientific chemistry, since before his time medical science received no assistance from alchemy. To Paracelsus is due the use of mercury for syphilis as well as a number of other metallic remedies. He was the first to point out the value of mineral waters. He recognized the tincture of gallnut as a reagent for the iron properties of mineral water and showed a particular preference for native herbs, from which he obtained 'essences' and 'tinctures', the use of which was to replace the composite medicines so popular at the time.

Robert Boyle (1627–1691) is noted for his pioneer experiments on the properties of gases and his espousal of a corpuscular view of matter that was a forerunner of the modern theory of chemical elements and atomic theory. Boyle conducted pioneering experiments in which he demonstrated the physical characteristics of air and the necessity of air for combustion and respiration.[13] In 1661, he described, in the second edition of his work, *New Experiments Physio-Mechanical*, the relationship, known as Boyle's Law, of the volume of gases and pressure. Attacking the Aristotelian theory of the four elements (earth, air, fire, and water) and the three principles (salt, sulphur and mercury), proposed by Paracelsus, in *The Skeptical Chymist*, he can be considered as the founder of modern chemistry.[14]

In 1676, the British physician Thomas Sydenham published *Observationes Medicae* as a standard textbook for two centuries noted for its detailed observations and the accuracy of its records. His treatise on gout (1683) is considered his masterpiece. Sydenham was among the first to use iron to treat iron-deficiency anaemia and used laudanum (a solution of opium in alcohol) as a medication, and helped popularize the use of quinquina for malaria.

Despite these prestigious glories in medicine or pharmacotherapy, pharmacy remained an empiric science until the end of the eighteenth century, guided by ancient medicine, inherited from Hippocrates or Galen.

II MODERN CHEMISTRY AS THE BASIS OF THE CONCEPT OF MODERN DRUGS

The eighteenth century concluded its progress in chemistry with an enthusiastic environment. Joseph Priestley (1733–1804) in the United Kingdom, Carl Wilhelm Scheele (1742–1786) in Sweden, Antoine Augustin Lavoisier (1743–1794) in France,[15] pulled down alchemist practice by propounding a precise signification to the chemical reactivity and giving to a large number of substances the statute of chemical reagents. They overthrew the 'phlogiston' doctrine, which holds that a component of matter (phlogiston) is given off by a substance in the process of combustion. That theory had held sway for a century.

Scheele prepared and studied oxygen, but his account in *Chemical Observations and Experiments on Air and Fire* appeared after the publication of Joseph Priestley's studies: *Observations on the Different Kinds of Air*. He discovered nitrogen to be a constituent of air. His treatise on manganese

was influential, as well as the discovery of barium and chlorine. He also isolates glycerin and many acids, including tartaric, lactic, uric, prussic, citric, and gallic. Priestley is also considered the discoverer of nitrogen, carbon monoxide, ammonia, and several other gases, and in 1774 he became the first to identify oxygen. His report led Lavoisier to repeat the experiment, deduce oxygen's nature and role, and name it. Lavoisier is generally considered as the founder of modern chemistry. He should be known as one of the most astonishing eighteenth century 'men of the Enlightenment', the founder of modern scientific experimental methodology. As he worked on combustion, Lavoisier observed the oxidation caused by a gas contained in the air. He formulated the principle of the conservation of mass (the weights of the reactants must add up to the weights of the products) in chemical reactions, being the first to use quantitative procedures in chemical investigations. He gave a clear differentiation between elements and compounds, something so important for pharmaceutical chemistry. He devised the modern system of chemical nomenclature, naming oxygen, hydrogen and carbon. These preliminary works formed the basis of future preparations or synthesis.

The works performed by Antoine François de Fourcroy (1755–1809), Louis Nicolas Vauquelin (1763–1829), Joseph Louis Proust (1754–1826) and Jöns Jakob Berzelius (1779–1848) introduced new concepts in chemistry. Gay-Lussac published his *Law of Combining Volumes* in 1809, the year after John Dalton (1766–1844) had proposed his *Atomic Theory of Matter* around 1803. It was left to Amedeo Avogadro (1776–1856) to take the first major step in rationalizing Gay-Lussac's results two years later.

At the same time, Louis-Joseph Gay-Lussac (1778–1850) made many less celebrated, but perhaps more important, contributions to chemistry. Along with his great rival, Humphrey Davy (1778–1829), Gay-Lussac established the elemental nature of chlorine, iodine and boron. He prepared pure sodium and potassium in large quantities. Within few years, those scientists integrated the practical advancements of a new generation of experimenters.

All these industrial innovations would have their own impact on other developments in industrial and then medicinal chemistry.[16] At the beginning of the nineteenth century, as the result of a scientific approach, drugs were becoming an industrial item. Claude Louis Berthollet (1748–1822) begins the industrial exploitation of chlorine (circa 1785). Nicolas Leblanc (1742–1806) prepared sodium hydroxide (circa 1789) and then bleach (circa 1796). Davy performed electrolysis and distinguished between acids and anhydrides. Louis Jacques Thénard (1777–1857) prepared hydrogen peroxide and Antoine Jérôme Balard (1802–1876) discovered bromide (1826).

The increase in therapeutic resources was mainly due to the mastery of chemical or physico-chemical principles proposed by Gay-Lussac, Justus Von Liebig (1803–1876),[17] and the new rules given to biology through the works of Claude Bernard (1813–1878),[18] Rudolph Virchow (1821–1902)[19] and Louis Pasteur (1822–1895).[20] Besides these fundamental sciences, physiology, biochemistry or microbiology were becoming natural tributaries of the outbreak of pharmacology. Thus, rational treatments were being designed, not on the Hippocratic basis of regulating humors, but on the purpose of new knowledge in various clinical or fundamental fields.

After a period of extraction and purification from nature (mainly plants), drugs were synthesized in factories or prepared through biotechnology (fermentation or gene technology) before being rationally designed in research laboratories. When the purpose was to isolate active molecules from plants during the first half of the nineteenth century, the birth of organic chemistry following the charcoal and oil industries, progressively lead pharmacists towards organic synthesis. It is precisely in the new concept of the laboratory that this research was performed.

Even when those laboratories host discoveries such as active principles extracted from plants, progress in drug compounding and packaging make the industrialization process irreversible. Gradually, this made the traditional apothecary less and less linked to the manufacture of drugs. Nevertheless, if chemical industries (dyes) gave birth to pharmaceutical companies in Great Britain or Germany, traditional pharmacies remain the origin of such companies in France or the United States. At the same time, the economic dimension of the growing pharmaceutical industry made drugs strategic items, mainly when they were involved with military processes.

During the first half of the nineteenth century, the study of drugs was included within the *Materia Medica*, the old traditional term through which pharmacists are considered the description of drugs and the way to obtain them. On the other hand, the 'modern' word *pharmacology* was more and more often used by physicians. Gradually a clear dichotomy took place between those two entities. *Materia Medica* was a static view of drugs, their production and the compounding of medicines, somewhere within the natural history of drugs, whereas pharmacology considers drugs from a more dynamic point of view. Pharmacology is the study of drugs considering their site or mechanism of action.

III THE BIRTH OF ORGANIC CHEMISTRY

A radical turn in the development of new chemicals occurred when coal, and then oil distillation offered so many opportunities. After the first chemical revolution, the birth of organic chemistry was also a leap forward in chemical industry developments. After the extract of

paraffin, carbon derivatives chemistry was developed with many industrial consequences during the second third of the century. Michael Faraday (1791–1867), the British physicist, discovered benzene in 1825, but the first organic molecules used for their therapeutic properties were acyclic. Chloroform was discovered in 1831 by three chemists, each working independently of the others: Eugene Soubeiran (1793–1858) in France (1831),[21] Justus Von Liebig (1803–1873) of Germany,[22] and Samuel Guthrie (1782–1848) in the United States (1832).[23] Sir James Simpson (1811–1870), in Scotland, publicly demonstrated chloroform as an anaesthetic in 1847.

Jean-Baptiste Dumas (1800–1884) proposed the ether theory, the theory of substitution with the 'radicals theory', the measurement of vapor densities, the determination of nitrogen in organic compounds, and the isolation of anthracene from tar, chloral, iodoform, bromoform and picric acid.

Von Liebig came to Paris to study with Louis-Jacques Thénard (1777–1857), Gay-Lussac, Michel-Eugène Chevreul (1783–1886) and Nicolas Vauquelin (1763–1829). Returning to the University of Giessen, in Germany, he became a university professor at the age of 21, something quite unique in history.

One of Liebig's greatest contributions to pure chemistry is his reformation of the methods for teaching the subject including teaching books like *Organic Chemistry and its Application to Agriculture and Physiology* (1840), and *Organic Chemistry in its Application to Physiology and Pathology* (1842).[24] From Giessen, he also edited the journal that was to become the pre-eminent publication in chemistry—*Annalen der Chemie und Pharmazie*. Friedrich Wöhler (1800–1882), after having studied at the University of Heidelberg went to Sweden to study with J.J. Berzelius before settling for nearly 50 years at the University of Göttingen.

In 1825, Liebig and Wöhler began various studies on two substances that apparently had the same composition—cyanic acid and fulminic acid—but very different characteristics. The silver compound of fulminic acid, investigated by Liebig is explosive, whereas silver cyanate, as Wöhler discovered, is not. These substances, called 'isomers' by Berzelius, lead chemists to suspect that substances are defined not simply by the number and kind of atoms in the molecule, but also by the arrangement of those atoms. The most famous creation of an isomeric compound is Wöhler's 'accidental' synthesis of urea (1828), when failing to prepare ammonium cyanate. For the first time someone prepared an organic compound by means of an inorganic one.[25] This 'incident' resulted in Wöhler saying: 'I can no longer, so to speak, hold my chemical water and must tell you that I can make urea without needing a kidney, whether of man or dog; the ammonium salt of cyanic acid is urea'.[26] Liebig and Wöhler discovered certain stable groupings of atoms in organic compounds that retain their identity, even when those compounds were transformed into others. The first to be identified is the 'benzoyl radical', found in 1832 during a study of oil of bitter almonds (benzaldehyde) and its derivatives. Their original objective was to interpret radicals as organic chemical equivalents of inorganic atoms. Their identification of radicals can be seen as an early step along the path to structural chemistry.

Those timid approaches took a precise shape when chemistry precipitously entered the medicinal arena in 1856 when William Perkin, in an unsuccessful attempt to synthesize quinine, stumbled upon mauvein, the first synthetic coal tar dye. This discovery led to the development of many synthetic dyes. The industrial world also understood that some of these dyes could have therapeutic effects. Synthetic dyes, and especially their medicinal 'side-effects,' helped put Germany and Switzerland in the forefront of both organic chemistry and synthesized drugs. The dye—drug connection began to be a very prolific way to discover drugs. Acetanilide was derived from aniline dye in 1886.

IV THE EXTRACTION OF ALKALOIDS FROM PLANTS

Besides this conceptual progress, another evolution in the concept of medicines formed the basis of another revolution. Many pharmacists, mainly in France and Germany, encouraged by an improved knowledge in extraction procedures, tried to isolate the substances responsible for drug action. The 'polypharmacy' was to be abolished. One of the theorists of this trend was the French pharmacist Charles Louis Cadet de Gassicourt.[27] In the inaugural issue of the *Bulletin de Pharmacie* (1809), he reported that the use of complex preparations must be withdrawn in favour of pure substances. It was necessary to study and classify them.[28] As Carl Von Linné did with plants when he published *Species plantarum* in 1753, which is still considered as the starting point for modern botanical nomenclature, pharmacist and physicians tried to classify drugs and their use. This trend was much more convenient with pure substances.

It was between the years 1815 and 1820 that the first active principles were isolated from plants. The French apothecary Jean François Derosne (1780–1846) probably isolated the alkaloid later known as narcotine in 1803, and the German apothecary Friedrich Serturner (1783–1841) further investigated opium and isolated a new compound, 'morphium' (1805), later named morphine. After administration to dogs, solutions of the white powder induced sedation and sleep in the dogs. His work was completed and published in 1817.[29]

This discovery was received with great perplexity: morphine has an alkaline reaction towards litmus paper. Up to that time, chemicals found in plants (in this case the poppy) had exhibited acidic reaction, and the scientific world was doubtful. Pierre Jean Robiquet (1780–1840) performed new experiments in Paris in order to check Serturner's results. Gay-Lussac accepted the revolutionary idea, following which alkaline drugs could be found in plants. All alkaline substances isolated in plants were to be given a name with the suffix '-ine' (Wilhelm Meissner, 1818) in order to recall the basic reaction of all these drugs. At that time, a whole new era in pharmaceutical chemistry was beginning.

Following Serturner's works, Pierre Joseph Pelletier (1788–1842) and François Magendie (1783–1855) found the first alkaloid ever isolated in the traditional ipecac. The pharmacist and the physician succeeded in the purification of emetine from *Ipecacuanha* (1817).[30] The same year, Joseph Pelletier and Joseph Bienaymé Caventou (1795–1877) extracted strychnine, a powerful neurostimulating agent, from *Strychnos*. Three years later (1820) the same extract quinine was derived from various *Cinchona* species.[31] Many attempts had previously been made to purify *Cinchona* bark. Pelletier and Caventou began the industrialization of quinine production, the drug being more and more popular as a tonic and anti-fever drug (before being recognized as a treatment of choice for malaria). No-one was aware of its parasiticide action, although its favourable effect on spleen congestion had already been described.

Other alkaloids were extracted soon after. Brucine (1819), piperine (1819), caffeine (1819), colchicine (1820) and coniine (1826), codeine (1832),[32] atropine (1833),[33] papaverine (1848),[34] were subsequently obtained. These first isolations were coincidental with the advent of the percolation process for the extraction of drugs. Coniine was the first alkaloid to have its structure established (Schiff, 1870) and to be synthesized,[35] but for others, such as colchicine, it was well over a century before the structures were finally elucidated.

Between the years 1817 and 1850, a new generation of scientists gave rise to a new relationship between medicine and new therapeutic tools. Drug formulation became more rational. Hereafter, drug activity would not depend on the concentrations of extracts or tinctures in active principles. The only variable would be the patient himself.

Nevertheless, in the first two-thirds of the nineteenth century, pure alkaloids were seldom used. For instance, even if recommended by a hospital physician, morphine was barely prescribed, as most physicians remained faithful to Sydenham's laudanum (opium tincture) to treat pain. There was greater curiosity from chemists than from physicians or pharmacists because it was impossible to find alkaline components in plants, where an alternative source for therapeutic strategies could be found.

The first medical textbook including alkaloids as a source of drugs was the *Formulaire des médicaments* by François Magendie (1822), where he tried to popularize the use of morphine, and fought against old formulas.[36]

V SALICYLATES AND ASPIRIN: THE FIRST BEST-SELLER

Another active principle soon extracted from plants was salicylic acid. Willow and salicin, in extensive competition with *Cinchona* bark and quinine, never became a very popular treatment for fever or rheumatic symptoms due to a Scottish physician, Thomas John MacLagan (1838–1934), who launched salicin in 1876.[37] His rationale was inspired by the Paracelse signature's theory: willow is growing in moisture along rivers and lakes, an ideal place to be crippled with rheumatism. Raffaele Piria (1815–1865), after isolation of salicylaldehyde (1839),[38] in *Spireae* species, prepared salicylic acid from salicin. This acid was easier to use and was an ideal step before future synthesis. His structure was closely related to that of benzoic acid, an effective preservative useful as an intestinal antiseptic, for instance in typhoid fever. Patients treated with salicylic acid were dying as frequently as untreated patients, but without fever.

Salol, a condensed product of salicylic acid and carbolic acid, described by Joseph Lister as a precious antibacterial drug, was more palatable and gained huge popularity.

Acetylsalicylic acid was first synthesized by Charles Frederic Gerhardt (1816–1856) in 1853[39] and then, in a purer form, by Johann Kraut (1869). Hermann Kolbe (1818–1884) improved acetylsalicylic acid synthesis with carbolic acid and carbonic anhydride, in 1874, but in fact nobody registered any pharmacological interest. It was almost a century later that Bayer began work on the topic. During the 1880s and 1890s, physicians became intensely interested in the possible adverse effects of fever on the human body and the use of antipyretics became one of the hottest fields in therapeutic medicine. The name of Arthur Eichengrün (1867–1949), who ran the research and development-based pharmaceutical division where Felix Hoffmann (1868–1946) worked, and Heinrich Dreser (1860–1924) who was in charge of testing the drug with Kurt Wotthauer and Julius Wohlgemuth should be remembered for this historical discovery (1897). It is likely that acetylsalicylic acid was synthesized under Arthur Eichengrün's direction and that it would not have been introduced in 1899 without his intervention.[40] Dreser carried out comparative studies of aspirin and other salicylates to

demonstrate that the former was less noxious and more beneficial than the latter.[41]

Bayer built his fortune upon this drug, which was given the name of 'aspirin', the most well-known and familiar drug name. Few groups of drugs have provided the manufacturers with such fortunes, physicians with such therapeutic resources, and the laity with so many semi-proprietary remedies, as have the so-called antipyretic or analgesic derivatives of coal tar. Nor is there any industrial group, which illustrates so well the close relationship between chemistry and practical therapeutics, and the relationship between chemical constitution and physiological action.

VI FIRST DRUGS FOR THE HEART

The fact that leaves from the foxglove contain a substance which increases the ability to pump blood round the weakened heart has been known by old wives, priests and botanical experts for several hundred years.

William Withering (1741–1799), an English doctor, learned that the local population was able to cure dropsy using a decoction of 20 different plants, one of which was the leaf from the foxglove. After having tested the various herbs on dropsy, the digitalis leaf remained the most active. In 1775, William Withering published a pamphlet in which he reported his discoveries about the way in which the foxglove can be used in medicine. He meticulously described his discovery, gave an account of how the extract of the digitalis should be prepared, and gave precise instructions on dosage including warnings about side-effects and overdose that he documented through the results obtained in 163 patients.[42] The only, but not least problem is a dreadful continuous vomiting and diarrhoea during the treatment. It is caused by the fact that the boundary between the therapeutic dose and poisoning is exceedingly fine. It was therefore evident and absolutely necessary to purify the active substance in order to fix the effective and non-toxic dosage.

Despite dropsy, caused by a deficiency in heart function, being one of the biggest scourges and the most common cause of death, Withering's discovery was forgotten at the beginning of the new century.

However, after decades of works, Augustin Eugène Homolle (1808–1875) and Théodore Quevenne (1806–1855) obtained an amorphous substance from foxglove leaves which they called 'digitaline', as they were sure that it was another alkaloid. In fact, it was a complex substance containing a specific sugar. It was not until 1867 that another French pharmacist, Claude Adolphe Nativelle was able to purify the leaves of the foxglove and produce the effective substance in the form of white crystals.[43] The Frenchman called the substance 'digitaline cristallisée'. A few years later the German, Oswald Schmiedberg (1838–1921), managed to produce digitoxin (1875),[44] and Alphonse Adrian (1832–1911) found a convenient way to prepare indictable digitalis preparations. In 1905, James Mackenzie (1853–1925) found a new justification for digitalis use: it was not only effective on cardiac load, facilitating the myocardial work, but it was also a drug for decreasing cardiac rate, making digitalis a drug of choice in atrial tachycardia or flutter.[45] Shortly thereafter, reports began to appear about other medicinal herbs which had the same effect on the heart as the foxglove products. Ethnopharmacology gave birth to ouabain, extracted by Albert Arnaud (1853–1915) from *Acocanthera* roots and bark, and strophantin, extracted from *Strophantus*. Arrow hunters in Equatorial Africa had previously used both of these drugs.

Antoine Jérôme Balard (1802–1876) synthesized nitroglycerine in 1844. He observed that when the drug was administered to animals they collapsed in a few minutes. Two years later, Ascani Sobrero (1812–1888) observed that a small quantity of the oily substance placed on the tongue elicited a severe headache. Konstantin Hering (1834–1918) in 1847 developed the sublingual dosage form of nitroglycerine, which he advocated for a number of diseases. Johann Friedrich Albers (1805–1867) had previously developed the cardiac properties of this yellow liquid, whose explosive property had been discovered by Alfred Nobel (1833–1896).[46] The English physician Thomas Lauder Brunton (1844–1916) was unable to relieve severe recurrent anginal pain, except when he bled his patient. He believed that phlebotomy provided relief by lowering arterial blood pressure.

The concept that reduced cardiac afterload and work are beneficial continues to the present day. In 1867, Brunton administered amyl nitrite, a potent vasodilator, by inhalation.[47] He notes that coronary pain was relieved within 30 to 60 seconds after administration. However, the action of amyl nitrite was transitory. The dosage was difficult to adjust. In 1879, William Murrell (1853–1912), proved that the action of nitroglycerine mimicked that of amyl nitrite, and he establishes the use of sublingual nitroglycerin for relief of acute angina attacks and as a prophylactic agent to be taken prior to physical exercise. The empirical observation that organic nitrates could be used safely for the rapid, dramatic alleviation of the symptoms of angina pectoris led to their widespread acceptance by the medical profession.

VII TREATMENT FOR HYPERTENSION AS A DISEASE

In the 1930s and 1940s, only few antihypertensive treatments were available: sympathectomy,[48] very-low-sodium

diets,[49] thiocyanates,[50] and pyrogen therapy.[51] Sympathectomy, which involved cutting nerves to blood vessels, lowered blood pressure in some patients, but it required more than ordinary surgical skill, often produced life-threatening complications, and has unpleasant side effects.[52] Rigid low sodium diets were also unpleasant because they limited food choice, but they were effective in lowering blood pressure. Pyrogen therapy (intravenous infusion of bacterial products) was based on the observation that fever lowered blood pressure.

The first successful drug treatments for hypertension were introduced after World War II. By that time, researchers had learnt that blocking the sympathetic nervous system could lower blood pressure. In 1946, tetraethylammonium, a drug known for 30 years to block nerve impulses, was introduced as a treatment for hypertension. Hexamethonium, an improved version of tetraethylammonium, was available for use by 1951.[53] Another effective blood pressure-lowering drug, hydralazine,[54] resulting from the search for antimalarial compounds, was diverted to the treatment of hypertension when it was found to have no antimalarial activity, but to lower blood pressure and increase kidney blood flow.

For a few years, hexamethonium and hydralazine were mainstays in the treatment of severe hypertension. They were reasonably effective in lowering blood pressure, but often caused severe side-effects. The final drug developed in those early days, reserpine,[55] was the product of more than two decades of research into compounds derived from *Rauwolfia serpentina*, a plant used for centuries by physicians and herbalists on the Indian subcontinent.[56] The quality of the result obtained with the various drugs used in mono- or combined therapy to treat hypertension proved clearly that fatal outcomes associated with this disease are caused by high blood pressure.[57]

Relevant clinical trials were conducted, using the three drugs then available: hydrochlorothiazide, hydralazine and reserpine. In one of them, males with elevated blood pressure were randomly divided into two groups. One group received antihypertensive drugs; the other group received a placebo. The study was planned to last for approximately 5 years, but was stopped after 18 months. The men with severe hypertension and receiving the placebo were dying at a greater rate than those receiving the antihypertensive drugs.[58] The clinical interest of treating hypertension was definitively proven.

Among recent discoveries, the research pointing out the role of converting enzyme is crucial. Advances leading to recognition of the relationship of the renin-angiotensin system to aldosterone includes the measurement of aldosterone plasma levels, the discovery of an aldosterone-stimulating factor in plasma, the finding that a potent aldosterone-stimulating factor is secreted by the kidney, and the evidence that synthetic angiotensin II increases aldosterone secretion. The fractionation of crude kidney extracts allowed Robert Tigerstedt (1853–1923) to find that aldosterone-stimulating factor was a peptide: renin.[59] The renin-angiotensin-aldosterone system plays an important role in congestive heart failure and in renovascular and malignant hypertension. The early use of blocking agents for the renin-angiotensin system had been proposed because arterial pressure decreased in experimental renovascular hypertension.[60] Major steps in the initial development of angiotensin I conversion inhibitors include the discovery of the *Bothrops* peptides (bradykinin potentiating factor) and the demonstration of its therapeutic potential. It is a history where chance, serendipity and clear scientific reasoning weave together the work of several scientists. It is also a classical example of drug development for which the initial basic research was made at university level, but the useful product is achieved by industry.[61]

The renin-angiotensin system was a key element in blood pressure regulation and fluid volume homeostasis. Since angiotensin II (AII) is the effector molecule of the RAS, the most direct approach to block this system was to antagonize AII at the level of its receptor. Therefore, at Du Pont Merck, the working hypothesis was that the identification of metabolically stable and orally effective AII-receptor antagonists would constitute a new and superior class of agents, useful in treating hypertension and congestive heart failure. The program began with a detailed pharmacological evaluation of some simple *N*-benzylimidazoles, originally described by Takeda Chemical Industries in Osaka, Japan. Potent and orally effective nonpeptide antagonists were found. The first major breakthrough, to increase the potency of the compounds, came with the development of a series of *N*-benzylimidazole phthalamic acid derivatives and the discovery of losartan, a highly potent angiotensin type 1 (AT_1) selective receptor antagonist with a long duration of action.[62]

VIII GENERAL AND LOCAL ANAESTHESIA

One of the greatest therapeutic revolutions during the nineteenth century was the introduction of general anaesthesia in the practice of surgery. As early as 1776, Joseph Priestley discovered laughing gas (nitrous oxide), but analgesia seemed to be beyond reach. Priestley and Humphrey Davy commented in 1796: ‘it may probably be used with advantage during surgical operations in which no great effusion of blood takes place’. Michael Faraday (1791–1867) proposed the use of diethyl ether to induce similar action. However, their inhalation was proposed during exhibitions for shows named ‘ether frolics’. Neither diethyl ether nor nitrous oxide was clinically used before 1846. Surgery was so difficult before that it was very

uncommon until the middle of the century: the pain and the infection risk resulting from the surgical procedure were very discouraging.

Dentists set the pace in the field of analgesia. They became familiar with both diethyl ether (sulphuric ether) and nitrous oxide. They were in permanent contact with pain in complaining patients. They also produced pain through unfair or badly controlled operations. Horace Wells (1815–1848), a dentist, asked a colleague to extract his own teeth while under the influence of nitrous oxide.[63] This trial, held in 1844, was successful and painless. Shortly thereafter, in 1845, he attempted to demonstrate his discovery at the Massachusetts General Hospital in Boston. His first attempt was a total failure. Another Bostonian dentist, William T.G. Morton (1819–1868), familiar with the use of nitrous oxide from his friendship with Wells, asked the surgeons of the Massachusetts General Hospital to demonstrate his technique after many attempts on animals, himself and friends. The first patient, Gilbert Abbott was to be operated on by the chief surgeon Dr. John Collins Warren (1778–1856). Morton arrived with special apparatus with which to administer the ether and only a few minutes of ether inhalation were necessary to make the patient unconscious.[64] According to the eminent surgeon, Henry J. Bigelow (1818–1890), who noted 'I have seen something today that will go around the world', a new era in the history of medicine had begun.[65]

Techniques and safety of anaesthesia will continue to improve. Even though ether was an interesting agent, other drugs were rapidly being tested, among which was chloroform, introduced into the surgery by the Scottish obstetrician James Simpson (1811–1870) in 1847. As ether is flammable, chloroform is safer from this point of view.[66] Unfortunately, chloroform is a severe hepatotoxic drug and cardiovascular depressant. Despite the relatively high incidence of deaths associated with the use of chloroform, it was the anaesthetic of choice for nearly 100 years. Many other halogenoalcanes had been synthesized, among which ethylene chloride and more recently halothane, a non-flammable anaesthetic, was introduced into clinical practice in 1956, after its preparation at Imperial Chemical Industries. It revolutionized anaesthesia.

In the 1860s, the introduction of the hypodermic syringe presented new opportunities for the use of drugs for anaesthesia. Injectable anaesthetics were introduced after the works of Eugene Baumann (1846–1896) and Alfred Kast (1856–1903) who, in 1887, introduced a major advance with sulfones, mainly Sulfonal®, a long-acting sedative drug.[67]

Prepared by Adolf Von Baeyer (1835–1917) as early as 1864, barbituric acid was not used before 1903, at that time Emil Fischer (1852–1919) had already prepared the first derivative of barbituric acid, one of which, diethylmalonylurea, would be marketed under the trade name Veronal, also known as Barbital.[68] Barbiturates, mainly used as sleep inducers, are also very useful in the operating room, especially when Thiopental, a very rapid and short-acting derivative was launched in 1935, after the work of the American anaesthetist John S. Lundy (born 1894). Thiopental had been enthusiastically accepted as an agent for the rapid induction of general anaesthesia. Barbiturates enabled the patient to go to sleep quickly, smoothly and pleasantly contrary to inhaled agents.

In the 1940s and early 1950s, muscle relaxants were introduced, firstly with curare (derived from the original South American Indian poison studied by Claude Bernard 100 years before) and then over subsequent decades a whole series of other agents.[69] Curare, in the form of tubocurarine, was first used in clinical anaesthesia in Montreal in 1943 by Harold Griffith (born 1894) and Enid Johnson.[70] In 1946, T.C. Gray first used Curare in Liverpool in the UK: 'The road lies open before us and ... we venture to say we have passed yet another milestone, and the distance to our goal is considerably shortened'.[71]

Local anaesthesia began in Vienna (1884) when Carl Koller (1857–1944)[72] and Sigmund Freud (1856–1939)[73] administered cocaine locally over the cornea, in order to anaesthetize the eye before cataract surgery. They noticed that the drug was able to prevent the oculomotor reflex in frogs. Cocaine had been previously isolated from coca leaves by Albert Niemann (1834–1861) in 1860.[74] Before this founding step, local sensitivity could be abolished by the dermal administration of organic derivatives like diethyl ether or ethylene chloride on the skin. A few years later, William Halsted (1852–1922) in the United States used cocaine to block nerves. Paul Reclus (1847–1914) in France and August Bier (1861–1949) used it for locoregional anaesthesia.[75] Unfortunately, cocaine is an addictive drug and between the years 1890s to 1910s, it became a pillar of drug addiction.[76] Cocaine was to be completely eradicated from clinical use in the years 1914–1916 with restrictive law in the USA, as well as in Europe. Fortunately, synthetic local anaesthetics would appear, thanks to the works of Alfred Einhorn (1856–1939)[77] and Wilhem Filehne (1844–1927),[78] in Germany, and Ernest Fourneau (1872–1949)[79] in France.

IX ANTIEPILEPTIC DRUGS

Soon after its introduction as a hypnotic drug, phenobarbital was found to be an excellent antiepileptic drug. Historically, agents introduced for the treatment of epilepsy are also turned to for psychiatric indications. The original 'first generation' antiepileptic drug, a bromide salt, which appears in 1857,[80] was also known for its tranquilizing

properties. After phenobarbital came into use for epilepsy in 1912, reports of its psychopharmacologic application soon followed. Tracy J. Putnam (born 1894) and Houston H. Merritt[81] (1902–1979) introduced phenytoin as an antiepileptic drug in 1938 and immediately described its psychotropic advantages. This is generally considered as the beginning of the modern psycho-pharmacological usage of antiepileptic drugs (1942), although relatively few psychiatric uses for antiepileptic drugs were reported over the next decade.

Major events preceding this work are the fortuitous discovery of phenobarbital as an anticonvulsant agent, structure/hypnotic activity studies with barbiturates and hydantoins in the early 1920s by A.W. Dox in the Parke Davis laboratories, and the development of anticonvulsivant assay techniques in animals, by a number of laboratories. Phenytoin was the first item on the list of compounds sent to Putnam by Dox and W.G. Bywater in April 1936. It was found to have anticonvulsivants properties in animals late in 1936, but no public reports were issued until the following year. Clinical efficacy was established in 1937, but again no public reports were issued until 1938. Dilantin® sodium capsules were prepared by Parke, Davis & Co. and were ready for marketing the same year.[82]

In the early 1960s, there was a near-simultaneous introduction of carbamazepine and valproic acid and its derivatives, as new treatments for epilepsy. Although in 1882 Beverly S. Burton, an American working in Europe, had prepared valproic acid,[83] its antiepileptic utility was not appreciated until this was serendipitously discovered 65 years later by Meunier in France.[84] Carbamazepine was first synthesized in 1960, in the United States by Schindler — who, a decade earlier, had patented the structurally closely related imipramine and it was found to have antiepileptic properties.[85] When concurrent remedial effects on mood and behaviour were noted with both carbamazepine and valproic acid in the very early epilepsy trials, both drugs were soon appropriated by psychiatrists, first by Lambert[86] in France (1966), using the amide derivative of valproic acid.

It has only been since the mid-1990s that a series of novel antiepileptic drug has been approved. There are currently five of these agents available, which might then be termed the 'third generation'. These are felbamate, lamotrigine,[87] gabapentin,[88] topiramate and tiagabine.[89]

X FIGHT AGAINST MICROBES

After the initial developments in organic chemistry during the first half of the twentieth century, the question of the chemical basis of life was clearly put in the forefront of the scientific debate. Since Wöhler's works, it was clear that chemistry is a unique science, with the same rules governing reactions, kinetics and atomic, radical or molecular arrangements. The advent of scientific cooperation using multidisciplinary approaches led to a greater understanding of natural and experimental phenomena. A typical example of this approach is Louis Pasteur. This leading physicist began his career as a specialist in crystallography. He studied the impact of bacteria on stereochemical properties of tartaric acid crystals. Later, his interest remained fixed on alcoholic and acetic fermentations. Afterwards, he pulled the concept of spontaneous generation to pieces. As microorganisms reacted on organic substances, he presumed that they could also be active on living beings, which is why he began his research on animal epidemics, culminating in the discovery of the rabies vaccine.

Carl Wilhelm Scheele inaugurated the practical use of disinfectant fumigation. It preceded 'Guytonian's fumigations', which was based on chlorine activity. As early as in 1785, a solution of chlorine gas in water was used to bleach textiles. Potassium hypochlorite (Eau de Javel) was prepared by Berthollet in 1789. After its first use as a means of discolouration, bleach was revealed to be a really good antibacterial activity, used by Antoine Germain Labarraque (1777–1850).[90] In 1820, he replaced potash liquor by the cheaper caustic soda liquor, and thus sodium hypochlorite was invented. At the end of the 1820s, Robert Collins, followed by Oliver Wendell Holmes (1809–1894), showed that puerperal fever frequency decreased when midwives washed their hands in chlorinated water.[91] A few decades later (1861) Ignaz Philip Semmelweis (1818–1865) published his research on the transmissible nature of puerperal (childbed) fever.[92] But he failed to convince physicians either in Vienna or in Budapest that this was the cause of infection in pregnant women.

Thomas Alcock published his *Essay on the Use of Chlorites of Oxide of Sodium and Lime* in 1827 (sodium and calcium hypochlorites). Recommended for disinfecting and deodorizing a wide range of environments, e.g. hospitals, workshops, stables, toilets, reservoirs, sewers and areas contaminated with blood or other body fluids. At about the same time a health commission in Marseilles recommended hypochlorite for disinfecting hands, clothes and drinking water. In 1881, Robert Koch (1843–1910) demonstrated the lethal effect of hypochlorites on pure cultures of bacteria. A few years later, Isidore Traube (1860–1943) established the purifying and disinfecting properties of hypochlorites in water treatment.[93] During the First World War, much progress was made: Dakin's solution (0.5% sodium hypochlorite) for disinfection of open and infected wounds was widely used in 1915. Milton fluid (containing 1% sodium hypochlorite and 16.5% sodium chloride) was marketed in the UK in 1916 used as a general disinfectant and antiseptic in paediatrics and childcare. In 1917, Halazone® tablets were

introduced and provided a dose-controlled method of disinfecting small volumes of drinking water.

In 1881, Bernard Courtois (1777–1838) introduced another halogen, iodine, extracting the element from wracks at the seashore. William Wallace proposed iodine tincture in 1835 to disinfect wounds. It was superseded by iodoform, which was less of an irritant, invented by Georges Simon Serullas (1774–1832). Structurally, it was very comparable to chloroform, the chlorine atom being substituted by an iodine one. Aqueous iodine solutions were proposed by Casimir Davaine (Lugol's solution) as antiseptics.

Joseph Lister (1827–1912) instituted a revolutionary change in hospital hygiene[94] by introducing carbolic acid, prepared by distillation of coal tar.[95] The disinfectant was used for surgical ligatures and dressings. Sprays of carbolic acid, improved by the French surgeon, Just Lucas-Championnière (1843–1913) were used in operating rooms around 1860.[96] All these procedures were deeply contested, but the final proof was obtained from the works of prestigious biologists, like Robert Koch. He performed laboratory tests demonstrating the bactericidal activity of carbolic acid.[97] Increasingly, the experimental proof confirmed empirical behaviour.

In this environment, the microbial theory many diseases constituted the hallmark of nineteenth-century medicine. The theory that infectious diseases were caused by invisible agents provided an opportunity for much progress. The laboratory took its rightful place when microscopes, staining of preparations and sterilization became available for new discoveries. For example, *Escherichia coli*, discovered in 1879, became the perfect example of an easily grown, 'safe' bacteria for laboratory practice. Working with pure cultures of the diphtheria bacillus in the Pasteur Institute, in Paris, Emile Roux (1853–1933) and Alexandre Yersin (1863–1943) first isolated, in 1888, the deadly toxin that causes most of diphtheria's lethal effects.[98] One by one over the next several decades, various diseases revealed their microbial origins.

XI SULFONAMIDES

Up to the advent of the twentieth century, the fight against microbes was devoted to disinfecting external wounds and to sanitizing drinking water. Since Pasteur's works, the objective was to treat infectious diseases: cholera, tuberculosis, diphtheria, etc. Some vaccines were already available, but only for smallpox and rabies.

The breakthrough came from an unexpected side of the scientific field: the dye industry. In 1865, Friedrich Engelhorn (1821–1902) founded Badische Anilin und Soda-Fabrik AG (BASF). The company produced coal tar dyes and precursors, gaining a leading position in the world dye market within only a few decades. The demand for dyes was strong, reflecting soaring population growth, matched by the textile industry. BASF's first products included aniline dyes. In 1871, the company marketed the red dye alizarin, and other new dyestuffs follow: eosin, auramine and methylene blue, together with the azo dyes, which were eventually developed into the largest group of synthetic dyestuffs.

Around the 1880s, German chemists, following in Paul Ehrlich's wake, discovered the fact that living cells absorb dyes in a different way to dead cells.[99] If a microorganism could be coloured, vital properties of the bacteria or the parasite could also be transformed.[100] What conclusions can be drawn from this new information on the viability of coloured microorganisms? Ehrlich refined the use of methylene blue in bacteriological staining and used it to stain the tubercle bacillus, showing that the dye binds to the bacterium and resists discolouration with an acid alcohol wash.[101] Following this hypothesis, Paul Ehrlich (1854–1915) administered methylene blue to patients suffering from malaria.[102]

Ehrlich is looking for a cure or treatment for 'sleeping sickness', a disease caused by a microbe.[103] He found that a chemical called Atoxyl® worked well, but was a fairly strong poisonous arsenic compound. Ehrlich began an exhaustive search for an arsenic compound that would be a 'magic bullet', capable of killing the microbe but not the patient. In 1909, after testing over 900 different compounds on mice, Ehrlich's new colleague Sahachiro Hata went back to No. 606: doxydiaminoarsenobenzol, dihydrochloride. Although unsuccessful against the sleeping sickness microbe, it seemed to kill another (recently discovered) trypanosoma, which caused syphilis. At that time, syphilis was a disabling and prevalent disease. Ehrlich and Hata tested No. 606 repeatedly on mice, guinea pigs, and then rabbits contaminated with syphilis. They achieved complete cures within three weeks, with no mortalities.[104] Production of the first batch of Salvarsan® at Hoechst started in July 1910. It was an almost immediate success, being sold all over the world. It spurred Germany to become a leader in chemical and drug production, and made syphilis a curable disease. The concept of the 'magic bullet' was born simultaneously with the concept of chemotherapy.

The following year, Julius Morgenroth (1871–1924) worked on experimental trypanosomiasis. He had just discovered that not only was quinine the drug of choice for malaria, but that it was also very active against the parasites *Trypanosoma* spp. In the same laboratory, other work was performed on *Pneumococcus* and particularly on the nature of the external capsule of the microorganism. The bacterium *Streptococcus pneumoniae* is the most common cause of severe pneumonia. Morgenroth noticed that biliary salts could dissolve *Trypanosomia* structures as well as *Pneumococcus* ones. Another concept concerning unspecific targets for drugs in infectious diseases was founded,

which also explained the activity of various isoquinolines derivatives for treating different infectious diseases.[105]

The influenza pandemic of 1918–1920 clearly demonstrated the inability of medical science to stand up to disease. More than 20 million people worldwide were killed by flu that attacked not the old and frail, but the young and strong. This was a disease that no magic bullet could cure and no government could stamp out. Chemotherapy research had to be improved and continued.

In 1927, Gerhardt Domagk (1895–1964), who had been promoted in Bayer's research department, aimed to find a drug capable of destroying microorganisms after oral administration. The internal route is imperative to treat most infectious diseases. The experimental model he used was the streptococci infection of mice. This model allowed the study of the effect of a large number of drugs. Among a large number of candidates, Domagk turned his attention to azo dyes, so-called because the two major parts of the molecule are linked by a double bond between two nitrogen atoms. Some of these dyes attach strongly to protein in fibres or leather, so that they hold fast against fading or cleaning. Domagk reasoned that they might also attach themselves to the protein in bacteria, inhibiting if not killing microorganisms.

Chrysoidine, which was a deep-red dye, had to be grafted to a sulfonylurea derivative (sulfamidochrysoidine) in order to be active. In 1932, it was studied by two chemists, Fritz Mietzsch and Josef Klarer. Testing the new dye on laboratory rats and rabbits infected with streptococci bacteria, Domagk found that it was highly antibacterial but not toxic. It was called Streptozan®, but its name soon changed to Prontosil®.

It gave birth to the new era of antimicrobial chemotherapy. The first cure occurred in 1932. At least two versions of the same story coexist. It is still not clear whether it was administered in an act of desperation, to a 10-month-old boy who was dying of staphylococcal septicaemia; the baby made an unexpectedly rapid recovery. Another account is that Domagk himself used Prontosil® to treat his own daughter, who was deathly ill from a streptococcal infection following a pin prick.

Domagk did not immediately publish his remarkable results. His landmark paper of February 1935 was edited shortly after having taken a patent on the product and won wide acclaim in Europe.[106] Domagk was awarded the Nobel Prize in Physiology or Medicine in 1939, but due to the Nazi veto, did not receive his medal until 1947, after World War II. However, although Domagk discovered sulfonamides, he did not discover the way in which they were active.

A French research team with Ernest Fourneau (1872–1949), Jacques Trefouel (1897–1977) and Thérèse Trefouel (born 1892), Federico Nitti (1905–1947) and Daniel Bovet (1907–1992) at the Pasteur Institute in Paris did the work. Prontosil® was inactive on bacilli cultures because it needed the presence of an esterase to split the molecule. The active part was the sulfonamide (amino-4-benzene sulfonamide) itself and not the dye.[107]

Doctors in Europe in 1936 had excellent results using the new drug to treat childbed fever and meningitis. Tests in the USA in 1936, initially at Johns Hopkins Hospital in Baltimore and Western Pennsylvania Hospital in Pittsburgh, showed that it was also effective against various streptococci infections and pneumonia. Prontosil® won wide publicity in the USA in 1936 when it was used to treat President Franklin D. Roosevelt's son, Franklin, Jr., who was severely ill from a streptococcal infection.

More than 5000 sulphur drugs were prepared in the late 1930s and early 1940s. Among them, sulfapyridine was used against pneumonia (it was used to treat Winston Churchill when he came down with pneumonia in 1943 just before the Casablanca Conference). Sulfathiazole was used against both pneumonia and staphylococci infections; sulfadiazine was used against pneumonococci, streptococci and staphylococci; and sulfaguanadine against dysentery.

XII ANTIBIOTICS

The 1930s were also the beginning of another chapter of this new era: the birth of antibiotic treatments.[108] The first antibiotic ever used was Gramicidin, the first natural antibiotic extracted from soil bacteria. It was prepared By René Dubos (1901–1982),[109] in 1939, and showed an interesting capacity to arrest the growth of staphylococcus, limited by its high toxicity. The works led by Alexander Fleming (1881–1955) are symbolic of the history of twentieth century's drug development. It was the desire to find an internal antiseptic that drove Scottish-born doctor Alexander Fleming in his pioneering work in London in the 1920s. In 1922 Fleming made the amazing observation that the human teardrop contains a chemical capable of destroying bacteria—and at an alarming rate. However, the excitement at this discovery was soon dashed. While the new discovery, which Fleming called lysozyme, was effective at dissolving harmless microbes it proved ineffective at negating those that cause disease.

Fleming, however, did not give up. In 1928 his diligence was rewarded. In his laboratory Fleming was in the process of developing staphylococci. Removing the lid from one of these cultures, Fleming was surprised to see that around the mould of *Penicillium*, the colonies of staphylococci had been dissolved. Something produced by the mould has dissolved the bacteria. After further testing, Fleming was able to isolate the essence of the mould and it was this that he named penicillin.[110] Bacteria which cause diseases such as gonorrhea, meningitis, diphtheria and pneumonia were about to be dramatically affected by this new breakthrough.

Best of all, although very toxic for microorganisms, it was not poisonous to humans. At the time, the medical community reacted coldly to this new discovery, however: everyone thought that once a bacteria entered the body, nothing could be done, and penicillin was seen as a non-event.

Twelve years later, the overwhelming casualties on the battlefield during the Second World War led two medical researchers, Howard Florey (1898–1968) and Boris Ernst Chain (1906–1979), to look into resurrecting Fleming's work with penicillin. After much refinement they were able to develop a powdered form of penicillin and experimented with mice.[111] In 1941 the first human was successfully treated. Before long, penicillin was in full production. Fleming, Florey and Chain were awarded the Nobel Prize for Medicine in 1945.[112]

As early as 1945, in an interview with The New York Times, Fleming warned that the misuse of penicillin might lead to resistant forms of bacteria.[113] In fact, Fleming had already experimentally derived such strains by varying the dosage and conditions upon which he added the antibiotic to bacterial cultures. As a result, Fleming warned that the drug carried great potential for misuse, especially with patients taking it orally at home, and that inadequate treatments would likely lead to mutant forms. Fleming stated that resistance to penicillin can be conferred in two ways—either through the strengthening of the bacterial cell wall, which the drug destroyed, or through the selection of bacteria expressing mutant proteins capable of degrading penicillin. The study was performed by B.E. Chain and coworkers.[114] Nevertheless, until the mid-1950s, penicillin is available orally to the public without prescription. During this period, the drug was indeed sometimes used inappropriately.

In 1942, full-scale production for therapeutic use in World War II began. Many factors were responsible for the delay between Fleming's discovery and the industrial step. A scientific explanation of Fleming's 'phenomenon' was needed, the finding of a classification of the fungus secreting the active substance, source of the mould, difficulties of bacteriologists in reproducing Fleming's discovery, identifying the chemical make-up of penicillin, search for other penicillin-producing organisms to enhance production of penicillin, purification and crystallization of penicillin, experiments on animals (chiefly mice) to determine toxicity, hesitancy to administer the drug to humans, standardization of an effective dosage for humans, and search for equipment and financial resources to enhance full-scale production. The adjunctive role of serendipity (chance, happenstance, improbability and luck) in overcoming these obstacles and in contributing to the successful, scientific conclusion of the penicillin project is an unusual story.[115]

By 1946, one hospital reported that 14% of the strains of *Staphylococcus* isolated from sick patients were penicillin resistant. By the end of the decade, the same hospital reported that resistance had been conferred to 59% of the strains *Staphylococcus* studied.

In 1940, Selman Waksman (1888–1973) isolated and purified actinomycin from *Actinomyces griseus* (later named *Streptomyces griseus*), which led to the discovery of many other antibiotics from that same group of microorganisms. Actinomycin attacks Gram-negative bacteria responsible for diseases like typhoid, dysentery, cholera and undulant fever and was the first antibiotic purified from an actinomycete. Considered too toxic for the treatment of diseases in animals or humans, actinomycin is primarily used as an investigative tool in cell biology. Waksman, with Albert Schatz (born 1920) and Elizabeth Bugie isolated the first aminoglycoside, streptomycin, from *S. griseus.*[116] Like penicillin, aminoglycosides decrease protein synthesis in bacterial cells, except that streptomycin targets Gram-positive organisms instead of Gram-negative ones. Waksman studied the value of streptomycin in treating bacterial infections, especially tuberculosis. In 1942, several hundred thousand deaths resulted from tuberculosis in Europe and another 5 to 10 million people suffered from the disease.

Merck immediately started manufacturing streptomycin. Simultaneously, studies by William H. Feldman (born 1892) and H. Corwin Hinshaw (1902–2000) at the Mayo Clinic confirm streptomycin's efficacy and relatively low toxicity against tuberculosis in guinea pigs.[117] On 20 November 1944, doctors administered streptomycin for the first time to a seriously ill tuberculosis patient and observed a rapid and impressive recovery.[118] His advanced disease was visibly arrested, the bacteria disappeared from his sputum, and he made a rapid recovery. The only problem was that the new drug made the patient deaf. Streptomycin was particularly toxic on the inner ear. No longer unconquerable, tuberculosis could be tamed and beaten into retreat. In 1952, Waksman was awarded the Nobel Prize in Physiology or Medicine for his discovery of streptomycin. During the following years, a succession of tuberculicid drugs appeared. These were important because with streptomycin monotherapy, resistant mutants began to appear within a few years, *p*-aminosalicylic acid (1949), isoniazid (1952),[119] pyrazinamide (1954), cycloserine (1955), ethambutol (1962),[120] ethionamid (1959)[121] were introduced as anti-tuberculosis drugs.

The discovery of rifampicin in 1967 is considered one of the greatest achievements in the history of chemotherapy against tuberculosis. Rifampin was developed in the Lepetit Research Laboratories (Italy) as part of an extensive program of chemical modification of the rifamycins, the natural metabolites of *Nocardia mediterranei*. All of the studies leading to highly active derivatives were performed on a molecule (rifamycin B) that was itself practically inactive. Systematic structural modifications of most of the functional groups of the rifamycin molecule were

performed with the objective of finding a derivative that was active when administered orally. The understanding of structure–activity relations in the rifamycins led to the synthesis of several hydrazones of 3-formylrifamycin SV. Among them, the hydrazone with *N*-amino-*N′*-methylpiperazine (rifampin) was found to be the most active in the oral treatment of infections in animals and, after successful clinical trials, was introduced into therapeutic use in 1968.[122]

Aminoglycosides such as capreomycin, viomycin, kanamycin and amikacin and the newer quinolones (e.g. pefloxacin, ofloxacin and ciprofloxacin) were only used in drug resistance situations. Tuberculosis in particular experienced a resurgence. In the mid-1980s, the worldwide decline in tuberculosis cases levelled off and then began to rise.

In 1948, Benjamin M. Duggar (1872–1956), a professor at the University of Wisconsin and a consultant to Lederle, isolated chlortetracycline from *Streptomyces aureofaciens*. Chlortetracycline, also called aureomycin, was the first tetracycline antibiotic and the first broad-spectrum antibiotic. Active against various organisms, aureomycin works by inhibiting protein synthesis. The discovery of the tetracycline ring system also enabled further development of other important antibiotics.[123] Since that time more than a hundred molecules active against a wide range of bacteria have been discovered.

XIII AIDS: AN EMERGING DISEASE

The first published reports of the new disease seemed at first to be no more than medical curiosities. On 5 June 1981, the Atlanta-based Centers for Disease Control and Prevention (CDC), the US agency charged with keeping tabs on disease, published an unusual notice in its *Morbidity and Mortality Weekly Report*: the occurrence of *Pneumocystis carinii* pneumonia among gay men.[124] In New York, a dermatologist encountered cases of a rare cancer, Kaposi's sarcoma,[125] a disease so obscure he recognized it only from descriptions in old textbooks.[126]

By the end of 1981, those symptoms were recognized as harbingers of a new and deadly disease.[127] The disease is initially called 'Gay Related Immune Deficiency'. Within a year, similar symptoms appeared in other demographic groups, primarily haemophiliacs and users of intravenous drugs. The CDC renamed the disease Acquired Immune Deficiency Syndrome (AIDS). By the end of 1983, the CDC had recorded some 3000 cases of this new plague. The prospects for AIDS patients were not good: almost half had already died. Twenty years after, more than 30 million cases are estimated worldwide.

In 1984, Luc Montagnier (born 1932) of the Pasteur Institute[128] and Robert Gallo (born 1937) of the National Cancer Institute (NCI)[129] proved that AIDS was caused by a retrovirus (whose replication is linked to a key enzyme, reverse transcriptase). There is still a controversy over priority of discovery. A number of therapeutic strategies can now be used in the treatment of AIDS. Many of these are suitable for immediate application in clinical trials and have already yielded positive results in many patients.[130]

The first drug introduced to treat the disease was AZT (azidothymidine, zidovudine), a thymidine analogue. AZT had been developed in 1964 as an anticancer drug by Jerome Horowitz of the Michigan Cancer Foundation (Detroit). Because AZT was ineffective against cancer, Horowitz never filed a patent. Nevertheless, *in vitro* studies showed some activity of this supposed anticancer drug against the AIDS virus.[131] In a six-week clinical trial 4 dose regimens of 3′-azido-3′-deoxythymidine, with potent anti-viral activity against HTLV-III *in vitro*, were examined in 19 patients with the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC). Fifteen of the 19 patients had increases in their numbers of circulating helper-inducer T lymphocytes during therapy. Six who were anergic at entry showed positive delayed-type hypersensitivity skin test reactions during treatment, two had clearance of chronic fungal nailbed infections without specific antifungal therapy, six had other evidence of clinical improvement, and the group as a whole had a weight gain of 2.2 kg. This was the first clinical trial for an anti-HIV drug.[132]

The Delta trial was a major clinical trial of combination antiretroviral therapy. In September 1995 the results of this trial showed that combining AZT with ddI (didanosine) or ddC (zalcitabine), provided a major improvement in treatment compared with AZT on its own.[133] Of the different steps of the HIV replicative cycle, the reverse transcription step has received most attention as a target for chemotherapeutic intervention. Reverse transcriptase (RT) can be blocked by both nucleoside (nucleotide) and non-nucleoside types of inhibitors. Whereas the former act as competitive inhibitors with respect to the natural substrates or alternative substrates (chain terminators), the latter act allosterically with a nonsubstrate binding site of the enzyme.[134] Other nucleotide analogues including stavudine, lamivudine, abacavir and tenofovir, began to be used in 1994 while non-nucleoside reverse transcriptase inhibitors, nevirapine, delavirdine, efavirenz came to the market in 1996. The third subclass of antiretroviral drugs was introduced at the same time: protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir and lopinavir. Highly active antiretroviral therapies usually consisting of two nucleoside reverse transcriptase inhibitors plus an HIV protease inhibitor, have been widely used since 1996. They produce durable suppression of viral replication with undetectable plasma levels of HIV-RNA in more than half of patients. Immunity recovers, and morbidity and mortality fall by more than 80%. Treatment was thought to

be particularly effective when started early. Despite these successes, however, antiretroviral therapies also produce numerous side-effects.

The use of chemotherapy to suppress replication of the human immunodeficiency virus (HIV) has transformed the face of AIDS in the developed world. Pronounced reductions in illness and death have been achieved and healthcare utilization has diminished. HIV therapy has also provided many new insights into the pathogenesis and the viral and cellular dynamics of HIV infection. However, challenges remain. Treatment does not suppress HIV replication in all patients, and the emergence of drug-resistant virus hinders subsequent treatment. Highly active antiretroviral therapy has revolutionized the treatment of human immunodeficiency virus (HIV) infection, which can now be viewed as a chronic and manageable disease. However, HIV infection differs from other chronic diseases in that early treatment decisions can irrevocably alter the patient's response to future therapy.[135] Chronic therapy can also result in toxicity. These challenges prompt the search for new drugs and new therapeutic strategies to control chronic viral replication.[136] The preparation of an effective vaccine is probably the only way to eradicate the disease.[137]

XIV DRUGS FOR ENDOCRINE DISORDERS

The flowering of biochemistry in the early part of the new century is key, especially as it relates to human nutrition, anatomy and disease. Some critical breakthroughs in metabolic medicine were made in the 1890s, but these were exceptions rather than regular occurrences. In 1891, myxedema was treated with sheep thyroid injections. This event is the first proof that animal gland solutions could benefit humans. In 1896, Addison's disease was treated with minced adrenal glands from a pig. These test treatments provide the starting point for all hormone research. From the 1920s to the 1940s, new treatments for physiological disorders were discovered, among them insulin for diabetes mellitus and cortisone for inflammatory diseases. Throughout human history, the condition diabetes mellitus meant certain death. Since the late nineteenth century, scientists have attempted to isolate the essential hormone and inject it into the body to control this disorder. Using dogs, numerous researchers had tried and failed, but in 1921, Canadian physician Frederick Banting (1891–1941) realized that if he tied off the duct to the pancreas of a living dog to atrophy the gland before removing it, there would be no digestive juices left to dissolve the hormone. It was first called 'iletin'.

Beginning in the late spring of 1921, Banting worked on his project in Toronto with his assistant, medical student Charles Best (1899–1978). After many failures, one of the dogs whose pancreas had been tied off showed signs of diabetes. Banting and Best removed the pancreas, ground it up, and dissolved it in a salt solution to create the long-sought extract. They injected the extract into the diabetic dog, and within a few hours the canine's blood sugar returned to normal. The scientists had created the first effective treatment for diabetes.[138] John Macleod (1876–1935), physiologist at the University of Toronto provided facilities for Banting's work, biochemists James Collip (1892–1965) and E.C. Noble joined the research team to help purify and standardize the hormone, which was renamed insulin.[139] It was Connaught and Lilly in Northern America and Novo in Europe (Denmark) who performed the technical developments that enabled large-scale collection of raw material, extraction and purification of insulin, and supplied the drug in a state suitable for clinical use. Only after proper bulk production and/or synthesis techniques were established did insulin and many other hormones discovered in the 1920s and 1930s become useful and readily available to the public. This would continue to be the case with most pharmaceutical breakthroughs throughout the century. During the 1960s new developments in peptide engineering led to synthetic insulin and in the 1970s, with biotechnology developments genetically manufactured insulin.

If insulin revolutionized diabetes mellitus treatment, cortisone discovery was another revolution in inflammatory and arthritis management. The discovery of corticosteroids as a therapeutic can be linked to Thomas Addison (1793–1860), who made the connection between the adrenal glands and the rare Addison's disease in 1855.[140] Edward C. Kendall (1886–1972)[141] at the Mayo Clinic (Rochester, USA) and Tadeus Reichstein (1897–1996)[142] at the University of Basel (Switzerland) independently isolated several hormones from the adrenal cortex. In 1948, Kendall and Philip S. Hench (1896–1965) demonstrated the successful treatment of patients with rheumatoid arthritis using cortisone.[143] Kendall, Reichstein, and Hench were awarded the 1950 Nobel Prize in Physiology or Medicine for determining the structure and biological effects of adrenal cortex hormones.

The birth of steroid chemistry meant that the female hormonal cycle was being controllable.[144] The modern knowledge of the menstrual cycle began when Edgar Allen (1892–1943) and Edward Doisy (1893–1986) showed that uterine bleeding occurs as a withdrawal effect when estrogen ceases to act on the endometrium.[145] At the same time, the chemistry of steroids becomes clearer with the works of Adolf Butenandt (1903–1995),[146] John Browne,[147] Leopold Ruzicka (1887–1976),[148] etc. Perhaps no contribution of chemistry in the second half of the twentieth century has a greater impact on social customs than the development of oral contraceptives. Several people were important in its development — among them Margaret Sanger (1879–1966), Katherine MacCormick (1875–1967), advocates of birth control as a means of solving the world's overpopulation,[149] Russell Marker (1903–1995), Gregory Pincus (1903–1967),

and Carl Djerassi (born 1923). Pincus agreed with the project when he was asked by the feminist leaders to produce a physiological contraceptive. The key to the problem was the use of a female sex hormone, such as progesterone. This hormone prevents physiological ovulation and could be considered as a pregnancy-preventing hormone. The first difficulty to be overcome was to find a suitable, inexpensive source of the scarce compound to do the necessary research.[150]

The chemist Russell Marker who converted sapogenin steroids, extracted from dioscoreas, into progesterone has performed the task. Until 1970, his source for the sapogenins was a yam grown in Mexico. Marker created a new company, Syntex, in Mexico to produce progesterone. In 1949, he left the company to a young scientist hired that same year by Syntex and who ultimately figured prominently in the further development of 'the Pill'. The period from late 1949 through 1951 is an extraordinarily productive one in steroid chemistry and especially so at Syntex in Mexico City.[151] Two of the most important Syntex contributions — the synthesis of 19-nor,17-alpha-ethynyltestosterone (norethindrone) and of cortisone from diosgenin. Djerassi first worked on the synthesis of cortisone from diosgenin. He later turned his attention to synthesizing an 'improved' progesterone, one to be taken orally. Progesterone is able to be absorbed by the oral route after a minimal change in the carbone 19 of the steroid, the withdrawal of a methyl group. Those derivatives are called '19-nor'. In 1951, his group developed a progesterone-like compound called norethindrone.

Shortly thereafter, G.D. Searle & Co. initiated a major effort in steroid research, the objective of which was to discover better steroid drugs than those available at that time or steroids that could be used for conditions for which no compounds were previously available. This effort was remarkably successful and resulted in the introduction of several important pioneering drugs. These included norethandrolone, marketed in 1956 as Nilevar®, the first anabolic agent with a favourable separation between protein building and virilization, and spironolactone, introduced in 1959 as Aldactone®, the first steroid antialdosterone antihypertensive agent. Of special importance was the research that culminated in the discovery of Enovid®. This substance, a combination of the progestin norethynodrel and the estrogen mestranol is first approved in 1957 for the treatment of a variety of disorders associated with the menstrual cycle. The era of oral contraception began in May 1960, when Enovid® was approved by the Food and Drug Administration for ovulation inhibition.[152]

XV DRUGS OF THE MIND

The field of psychiatry is so complex that until the middle of the twentieth century, it is clear that the only a behaviourist approach could represent a means to explore and treat mental disorders. This idea proved more popular than 'biological' explanations, which stressed that the cause of schizophrenia, depression or other mental illnesses was an imbalance in the chemicals of the brain. Severe mental illness had been increasing since the beginning of the century. In 1904, 0.2% of people were hospitalized in mental hospitals; by 1955, the number had doubled. Psychiatrists argued whether it was the result of biology or of experience, but there was nothing to help the chronically mentally ill. They were usually housed in state institutions.

If psychoanalysis was extremely popular across Europe and in the USA, science lagged behind. Early treatments for depression at the beginning of the twentieth century involved dosing patients with barbiturates, keeping them unconscious for several days, in the hope that sleep would restore them to a healthier frame of mind.[153]

It was then discovered that, in certain cases, patients who experienced epileptic fits also experienced less severe symptoms of mental illness. By causing a person to have a controlled fit (first by dosing the patients with camphor then, in 1938, by the use of electricity), doctors found they could lessen the effects of depression. Nowadays, electroconvulsive therapy (ECT) is still used as a treatment for severe depression.

The understanding of depression depends on the understanding of the brain itself. This took a leap forward in 1928, when Austrian scientist Otto Loewi (1873–1961) discovered the first neurotransmitter in the brain, acetylcholine.[154] He concluded that this substance was necessary to help electrical messages pass through the brain, from one nerve ending (neuron) to the next. It was to be another 24 years before scientists would discover the presence of other neurotransmitter substances in the brain, such as serotonin, norepinephrine and dopamine. By the 1980s, scientists isolated 40 different neurotransmitter substances in the brain.[155]

Modern psychiatric treatments were introduced in 1948, when lithium carbonate was discovered as a treatment for mania by Australian psychiatrist John F. Cade.[156] After Cade's initial report, lithium treatment was principally developed in Denmark by Mogens Schou (1918–), beginning in 1954.[157] After a decade of trials by these and other groups in the USA and abroad, the Psychiatric Association and the Lithium Task Force recommended lithium to the Food and Drug Administration for therapy of mania in 1969, 20 years after its discovery by Cade. In 1970, the FDA approved the prescription drug. A breakthrough had finally been achieved in the treatment and prevention of one of the world's major mental health problems in the form of manic depression, and the genetically related forms of recurrent depression.

In 1952, reserpine had been isolated from *Rauwolfia* and eventually was used for treating essential hypertension,

and a year later, reserpine, a *Rauwolfia* alkaloid is used as a first tranquillizer drug.[158] The source plant comes from India, where it has long been used as a folk medicine.

A potent type of antidepressant, monoamine oxidase inhibitor (MAOI), was developed in the 1950s. This works by blocking the action of certain enzymes in the brain (oxidases) which break down neurotransmitters.[159] The brain thus remains 'bathed' in extra quantities of neurotransmitters, and is able to fight off the depression. Though an effective remedy, this drug could have unpleasant reactions when taken alongside certain foods and drink. Patients taking MAOIs have to observe quite strict dietary rules because the side-effects could be fatal. Iproniazid, the first modern antidepressant, was originally developed as a drug for the chemotherapy of tuberculosis in the early 1950s. Nathan Kline (1916–1984) observed that iproniazid, in addition to its ability to treat tuberculosis, could elevate mood and stimulate activity in many patients.[160] These effects led researchers to investigate the ability of iproniazid to treat the symptoms of depression. After promising preliminary findings reported in 1957, iproniazid was widely prescribed to patients with major depression.[161]

The first tricyclic antidepressant, imipramine, was originally developed in the search for drugs useful in the treatment of schizophrenia. Although clinical trials demonstrate a lack of effect in treating schizophrenia, an astute clinician decided to examine its effectiveness in depressed patients. Early studies in 1958, performed by Roland Kuhn (born 1912), published in the *American Journal of Psychiatry*, led to the first antidepressant to be introduced. Imipramine is reported to significantly alleviate symptoms in patients with major depression.[162] Interestingly, although imipramine elevated mood and increased energy in depressed patients, the drug proved to be sedating in individuals without major depression. These effects led to the idea that imipramine selectively reversed the depression, rather than simply producing a general activating effect. Subsequent biochemical studies on imipramine demonstrate that this drug increases the activity of the monoamine neurotransmitters, norepinephrine and serotonin, by inhibiting their reuptake into neurons.[163]

Most of the early antidepressants work by affecting several different neurotransmitter chemicals at the same time. Scientists began to work on drugs that would target one specific neurotransmitter, while leaving others unaffected. In 1968, a Swedish scientist Arvid Carlsson (born 1923), made discoveries that would eventually lead to the creation of the drug Prozac. He found that when an electrical impulse passed from one neuron to another, serotonin was released into the space between the neurons—the synapse—to help the 'message' be transmitted. Once the job was done, the serotonin was reabsorbed by the neuron. But antidepressants prevented the neurons from taking the serotonin. It remained in the synapse, where its presence seemed to help the patient recover from depression. Carlsson was the 2000 Nobel Laureate in Physiology or Medicine. By 1974, American scientists were testing a drug which prevented the neurons from reabsorbing serotonin, while not preventing the absorption of other brain chemicals, such as noradrenaline. They called this drug a specific serotonin re-uptake inhibitor (SSRI). Its name is fluoxetine. In tests, they discover that it provided rapid relief from the symptoms of depression, without any of the unpleasant side-effects associated with the older, tricyclic antidepressants or the dietary restrictions that were necessary with MAOI drugs. By 1987, the drug was marketed as Prozac®. By 1994, it was the number two best-selling drug in the world.[164]

In 1952, Henri Laborit (1914–1995), a naval surgeon in Paris, was looking for a way to reduce surgical shock in his patients. Much of the shock came from the anaesthesia, and if he would find a way to use less, his patients could recover quicker. He knew that shock was the result of certain brain chemicals and looked for a chemical that might counteract these. He tried antihistamines, usually used to fight allergies. He noticed when he gave a strong dose to his patients, their mental state changed. They did not seem anxious about their forthcoming surgery, in fact, they were rather indifferent. Laborit was able to operate using much lower doses of anaesthetic. He was so struck by the effect on his patients, especially with a drug called chlorpromazine (Largactil® in Europe; Thorazine® in the USA), he thought the drug must have some use in psychiatry.[165] A chemistry team at Rhône-Poulenc had prepared this new drug.[166] The French psychiatrist Pierre Deniker (1907–1987) was interested in these results and ordered some chlorpromazine to try on his most agitated, uncontrollable patients. The results were stunning. Patients who had stood in one spot without moving for weeks and patients who had to be restrained because of violent behaviour, could now make contact with others and be left without supervision.[167] Another psychiatrist reported, 'For the first time we could see that they were sick individuals to whom we could now talk'.

Meanwhile, Smith Kline purchased the rights to chlorpromazine from Rhône-Poulenc in 1952. Smith Kline put it on the market as an anti-vomiting treatment but tried to convince American medical schools and hospitals to test the drug as an antipsychotic drug. Unfortunately, the academics saw it as just another sedative and were more interested in psychoanalysis and behaviourism. Smith Kline invited Pierre Deniker to help them convince US practitioners to try the drug. Their success came by way of the state institutions seeing the drug as a money saver. Testing began at these institutions, where the most hopeless cases were housed. The results are convincing, even miraculous. In 1954 the US Food and Drug Administration approved

chlorpromazine. By 1964, some 50 million people around the world had taken the drug.

The demand for sedatives was profound, and the drug marketplace responded rapidly. Although meprobamate, the first of the major tranche, discovered by Frank M. Berger is called the Wonder Drug of 1954,[168] sedatives were not widely used until 1961, when Librium® (chlordiazepoxide) was discovered by Leo Sternbach (born 1908) and marketed as a treatment for tension. Librium® was a phenomenal success. Then Valium® (diazepam), discovered in 1960, was marketed by Roche in 1963 and rapidly become the most widely prescribed drug in history. These drugs were touted to the general population, mass-marketed and prescribed by doctors with what many claimed was blithe abandon. While the youth of occidental world were smoking joints and tripping on 'acid', their parents' generation of businessmen and housewives were downing an unprecedented number of sedatives. For many, physical and psychological addiction followed.

XVI DRUGS FOR IMMUNOSUPPRESSION

Over the past 50 years, many immunosuppressive drugs have been described. Often their mechanisms of action were established long after their discovery. Eventually these mechanisms were found to fall into five groups: regulators of gene expression; alkylating agents; inhibitors of purine synthesis; inhibitors of pyrimidine synthesis and inhibitors of kinases or phosphatases. Glucocorticoids exert immunosuppressive and anti-inflammatory activity mainly by inhibiting the expression of genes for interleukin-2 and other mediators. After the 1950s and 1960s when corticosteroids were proposed to prevent organ rejection in renal transplantation, surgery enters a new era of optimism, characterized by improving allograft survival rates when tissue typing and new immunosuppressive drugs such as cyclosporin A were introduced. Revolutionary methods of rejection treatment have been responsible for this new era,[169] and a few years later in 1967, the first heart transplant was performed in Capetown by Christiaan Barnard.[170]

A few determined individuals in the medical and research community spent the next two decades attempting to solve the organ rejection puzzle. One of these scientists was Jean-François Borel (1933–), who worked in Switzerland for Sandoz Pharmaceuticals. He discovered the immunosuppressant agent that ultimately moved transplantation from the realm of curiosity into routine therapy. Both J. Borel and Hartmann Stahelin markedly contributed to the discovery and characterization of the biological profile of the drug.[171] In its subsequent exploitation, Borel played a leading role.[172] He chose to examine a weak compound that was isolated from the soil fungus *Tolypocladium inflatum* Gams (subsequently renamed *Beauveria nivea*). The compound was thought to have little practical value, yet Sandoz chemists continued to study and purify the compound because of its 'interesting' chemical properties. Borel discovered that this compound selectively suppressed the T-cells of the immune system. Excited by these characteristics, Borel continued his study and, in 1973, purified a compound called cyclosporine A.[173] Cyclosporine acts in two ways. First, it impedes the production and release of interleukin-2 by T-helper white blood cells. Secondly, it inhibits interleukin-2 receptor expression on both T-helper and T-cytotoxic white blood cells.

Other immunosuppressants are available. Cyclophosphamide, a nitrogen mustard,[174] alkylates DNA bases and preferentially suppresses immune responses mediated by B-lymphocytes. Methotrexate and its polyglutamate derivatives suppress inflammatory response through release of adenosine; they suppress immune response by inducing the apoptosis of activated T-lymphocytes and inhibiting the synthesis of both purines and pyrimidines.[175] Azathioprine metabolites, studied by Roy Calne (1930–), inhibit several enzymes of purine synthesis.[176] Mycophenolic acid inhibits inosine monophosphate dehydrogenase, thereby depleting guanosine nucleotides and induces apoptosis of activated T-lymphocytes.[177] Like cyclosporine, tacrolimus suppresses the production of IL-2 and other cytokines. In addition, these compounds have recently been found to block signalling pathways triggered by antigen recognition in T-cells.[178] In contrast, rapamycin inhibits kinases required for cell cycling and responses to IL-2. Rapamycin also induces apoptosis of activated T-lymphocytes. Immunosuppressive and anti-inflammatory compounds in development include inhibitors of p38 kinase and of the type IV isoform of cyclic AMP phosphodiesterase, which is expressed in lymphocytes and monocytes. A promising future application of immunosuppressive drugs is their use in a regime to induce tolerance to allografts.[179]

XVII CHEMISTRY AGAINST CANCER

Many anticancer drugs are extracted from plants.[180] Galen proposed the juice expressed from woody nightshade (*Solanum dulcamara*) to treat tumours and warts, which has been demonstrated to exert anti-inflammatory properties.[181] More than 1600 genera have been examined in recent decades.[182]

Since the use of *Podophyllum* in ancient China, many vegetal derivatives from this plant are being used in cancer chemotherapy. Two glycosides were extracted from *Podophyllum* to prepare semisynthetic derivatives of podophyllotoxin, etoposide and teniposide.[183] In folklore medicine, extracts of the leaves of the subtropical plant *Catharanthus*

roseus (L.) (Madagascar periwinkle) were reputed to be useful in the treatment of diabetes. The attempt to verify the antidiabetic properties of the extracts led instead to the discovery and isolation of two complex indole alkaloids, vinblastine and vincristine, which are used in the clinical treatment of a variety of lymphomas, leukaemias and various cancers such as small cell lung or cervical and breast cancer. The two alkaloids, although structurally almost identical, nevertheless differ markedly in the type of tumours that they affect and in their toxic properties.

As the 1970s opened, new chemistries and the war on cancer seized centre stage. US President Richard Nixon established the National Cancer Program, popularly known as the war on cancer, with an initial half-billion dollars of new funding. This explains why in the recent years, many new compounds with antineoplastic properties were isolated in plants. Among them, the pyridocarbazole alkaloids ellipticine and 9-methoxyellipticine from *Ochrosia elliptica*, that intercalate between the base pairs of DNA.[184] Camptothecin and its derivatives, alkaloids from Chinese tree *Camptotheca acuminata*, showed a broad-spectrum activity. 10-Hydroxycamptothecin and moreover, 9-aminocamptothecin which was more active, gave birth to topotecan and irinotecan.[185] New alkaloid esters from *Cephalotoaxus* species are currently being isolated for experimental and clinical studies. If the parent alkaloid is inactive, but the esters harringtonine and homoharringtonine form *Cephalotaxus harringtonia*, give new hopes in the cure of solid tumours or leukaemias.

The most enthusiastic reports concern the diterpenoids Taxol® and Taxotere® having unique tri- or tetracyclic 20-carbon skeletons. Taxol has been extracted from the bark of the Pacific yew (*Taxus brevifolia*), a slow-growing tree found in the virgin rain forests of the Pacific Northwest United States. Yew was known as a toxic plant for animals and humans for centuries.[186] Monroe E. Wall (1917–2002) and Mansukh C. Wani at Research Triangle Park, identified the active principle of the yew tree in 1971.[187] In 1979, Susan Horwitz of the Department of Molecular Pharmacology, Albert Einstein College of Medicine, New York, suggested that Taxol's® mechanism of action is different from that of any previously known cytotoxic agent. She observed an increase in the mitotic index of P388 cells and an inhibition of human HeLa and mouse fibroblast cells in the G2 and M phases of the cell cycle.[188] It was suggested that Taxol® exerted its activity by preventing depolymerization of the microtubule skeleton.

Clinical use of Taxol® included many solid tumours with best results in ovarian and breast cancers. Extraction of Taxol® (paclitaxel) from the yew bark is quite difficult: three trees were needed for 1 gram of drug (one cycle of chemotherapy). This difficulty has encouraged the pursuit of semisynthetic production. The strategy included immediately increasing the amount of Taxol® derived from yew bark and establishing a broad research program to evaluate alternative sourcing options and their commercial feasibility.[189] Taxol® introduced into the marketplace in January 1993 by Bristol-Myers Squibb reached worldwide sales of $1.2 billion in 1998. The prospects for finding a solution to the Taxol® supply problem through semisynthesis using a naturally occurring taxane as a starting material were considerable. This approach was pioneered by Pierre Potier (born 1935) in Gif-sur-Yvette (France). He found in the early 1980s that a naturally occurring taxane containing the Taxol® core, 10-deacetyl baccatin III, was twenty times more abundant than Taxol® and was primarily contained in the needles of the abundant English Yew (*Taxus baccata*). Potier succeeded in the difficult conversion of 10-DAB into Taxol®, in 1988 using only four steps with an overall yield being only 35%.[190] Pierre Potier and coworkers discovered a paclitaxel semisynthetic analogue, docetaxel (Taxotere®), which represented a significant advance in the treatment of various malignancies. Although paclitaxel and docetaxel have a similar chemical root, extensive research and clinical experience indicate that important biological and clinical differences exist between the two compounds. Although the mechanism by which they disrupt mitosis and cell replication is novel and unique to this class of compounds, there are small but important differences in the formation of the stable, nonfunctional microtubule bundles and in the affinity of the two compounds for binding sites.[191] These differences may explain the lack of complete cross-resistance observed between docetaxel and paclitaxel in clinical studies.[192]

Besides natural products, synthetic anticancer drugs flourished in various directions. The first agents were nitrogen mustards (halogenated alkyl amine hydrochlorides) among which 2-2′-2′-trichlotriethylamine was the prototype first studied by two prestigious pharmacologists from Yale University, Louis Goodman (1906–2000) and Alfred Gilman (1908–1984).

Louis Sanford Goodman, Maxwell M. Wintrobe, William Dameshek, Morton Goodman, Alfred Gilman and Margaret MacLennan[193] performed studies in 1943, but only presented the salutary results obtained in patients treated for Hodgkin's disease, lymphosarcoma and leukaemia in 1946. Indeed, in the first two disorders dramatic improvement was observed in an impressive proportion of terminal and so-called radiation-resistant cases.[193] First constant successes in haematological malignancies were obtained in 1970 with the 'MOPP' therapy (mechlorethamine, vincristine, procarbazine, prednisone). This protocol was superior to that previously reported with the use of single drugs with 35 of 43, or 81% of the patients achieving a complete remission, defined as the complete disappearance of all tumour and return to normal performance status.[194]

Antimetabolites in cancer treatment was discovered by George Hitchings (1905–1998) and Gertrude Elion

(1918–1999), utilizing what today is termed 'rational drug design'. They methodically investigated areas where they could see cellular and molecular targets for the development of useful drugs.[195] During their long collaboration, they produced a number of effective drugs to treat a variety of illnesses including leukaemia, malaria, herpes, and gout.

Hitchings and Elion began examining the nucleic acids, particularly purines, including adenine and guanine, two of DNA's building blocks at Wellcome Research Laboratories. They discovered that bacteria could not produce nucleic acids without the presence of certain purines, and set to work on antimetabolite compounds, which locked up the enzymes necessary for the incorporation of these purines into nucleic acids. They synthesized two substances: diaminopurine and thioguanine, which the enzymes apparently latched on to, instead of adenine and guanine. These new substances proved to be effective treatments for leukaemia. Elion later substituted an oxygen atom with a sulphur atom on a purine molecule, thereby creating 6-mercaptopurine used to treat leukaemia.[196] After this success, Elion and Hitchings developed a number of additional drugs using the same principle. Later, these related drugs were found to not only interfere with the multiplication of white blood cells, but also suppress the immune system. This latter discovery led to a new drug, Imuran® (azathioprine), and a new application—organ transplants. Imuran suppresses the immune system that would otherwise reject newly transplanted organs. For the first time, patients can receive organ transplants without their bodies rejecting the new organs. The team also develops allopurinol, a drug successful in reducing the body's production of uric acid, thereby treating gout. They discovered pyrimethamine, used to treat malaria, and trimethoprim used to treat meningitis, septicaemia, and bacterial infections of the urinary and respiratory tracts. With Howard Schaeffer, Elion is also at the origin of acyclovir, marketed as Zovirax®, which interferes with the replication process of the herpes virus.[197]

Anthracyclines may be listed among the main anticancer drugs. Daunomycin (also called daunorubicin) was isolated from *Streptomyces peucetius* in 1962 by Aurelio Di Marco (Farmitalia, Milano).[198] With Adriamycin, it is the prototypical member in the anthracycline antitumour antibiotic family. Adriamycin, a 14-hydroxy derivative of daunorubicin, was isolated from the same microorganism, in 1967. Despite their severe cardiotoxicity and other side-effects, these drugs have been widely used as dose-limited chemotherapeutic agents for the treatment of human solid cancers or leukaemias since their discovery.[199] These antibiotics contain a quinone-containing chromophore and an aminoglycoside sugar. The antineoplastic activity of these drugs has been mainly attributed to their strong interactions with DNA in the target cells. While anthracyclines can be very effective against breast and other cancers, they pose a risk of cardiotoxicity and therefore, they are typically used in limited doses. Doxorubicin and epirubicin are examples of anthracyclines used to treat breast cancer, commonly used in combination with other chemotherapy drugs to help decrease the risk of side-effects.[200]

Cisplatin was discovered serendipitously in 1965 while Rosenberg's team was studying the effect of an electric current on *E. coli* cultures. It was found that cell division was inhibited by the production of *cis*-diamminedichloroplatinum from the platinum electrodes rather than by the method expected.[201] Further studies on the drug indicated that it possessed antitumour activity. In 1972 the National Cancer Institute introduced cisplatin into clinical trials. It now has a major role in the treatment of several human malignancies, including testicular, ovarian, head and neck, bladder, esophageal and small cell lung cancers. Cisplatin is a square planer compound containing a central platinum atom surrounded by two chloride atoms and two molecules of ammonia moieties. The antitumour activity has been shown to be much greater when the chloride and ammonia moieties are in the *cis* configuration as opposed to the *trans* configuration. The cytotoxicity of cisplatin is due to its ability to form DNA adducts which include DNA–protein cross-links, DNA monoadducts, and inter/intra DNA cross-links.[202] The drug is able to enter the cell freely in its neutral form, yet once in the cell the chloride ions are displaced to allow the formation of a more reactive, aquated compound. In 1975, Memorial Sloan-Kettering Cancer Center initiated trials of cisplatin alone and later in combination with cyclophosphamide and/or adriamycin in patients with urothelial tract cancer. The results were not as positive as those seen in the testicular cancer studies, but they were favourable. Combination of cisplatin and adriamycin also showed noteworthy improvements in tumour cells. Studies by Holland using cisplatin alone and in combination with adriamycin to fight ovarian cancer gave substantial improvements.[203]

Due to the extreme toxicity of cisplatin, as well as resistance against it, there has been a need for the development of analogues which are just as potent, but not as toxic. One of the most widely known analogues of cisplatin is carboplatin.[204] Carboplatin has the same two amine groups that cisplatin does, but rather than chloride it contains two cyclobutanedicarboxylated groups. These groups are much less labile, thus the reactions in water to activate it are much slower. Thus, carboplatin is more stable and less reactive than cisplatin. There has been less testing and fewer trials with carboplatin than with cisplatin, but it has been shown that the neurotoxicity is no longer a limiting side-effect. This does not mean it does not occur, simply it means that the effects are not as drastic. It has been suggested however, that in higher doses carboplatin may have similar effects, although no studies have been performed as yet.

XVIII FROM GENETICS TO DNA TECHNOLOGY

As chemists and pharmacists joined together in finding new drugs, a second revolution in biology (the first came from Claude Bernard's and Louis Pasteur's generation) took place when advances in experimental genetics, biology, and virology happened in the middle of the century.

In 1935, George W. Beadle (1903–1989), before collaborating with Edward L. Tatum (1909–1975), began studying the development of eye pigment in *Drosophila* with Boris Ephrussi (1901–1979). After producing mutants of *Neurospora crassa*, a bread mould by irradiation and searching for interesting phenotypes, they concluded in a 1940 report that each gene produced a single enzyme, also called the 'single gene–single enzyme' concept. The two scientists shared the Nobel Prize in Physiology or Medicine in 1958 for discovering that genes regulate the function of enzymes and that each gene controls a specific enzyme.[205]

Eminent scientific research was carried out by Joshua Lederberg (born 1925) on plasmid concept, John F. Enders (1897–1985), Thomas H. Weller (born 1915), and Frederick C. Robbins (born 1916) on virus cultures, Salvador Luria (1912–1991), and Alfred D. Hershey (1908–1997) on the bacteriophage role. James Watson (born 1928) and Francis Crick (born 1916) determined the structure of genetic material in 1953.[206] In 1955, Severo Ochoa (1905–1993) at New York University School of Medicine discovered polynucleotide phosphorylase, an RNA-degrading enzyme. In 1956, Arthur Kornberg (born 1918) at Washington University Medical School (St. Louis, MO) discovered DNA polymerase. In 1960, François Jacob (born 1920) and Jacques Monod (1910–1976) and André Lwoff (1902–1994) proposed their operon model. It was the birth of gene regulation models which launched a continuing quest for gene promoters and triggering agents. In 1964, Bruce Merrifield (born 1921) invented a simplified technique for protein and nucleic acid synthesis. These discoveries were made outside the pharmaceutical industry, but gave enormous contributions to the understanding of the mechanisms of diseases and on the discovery of new drugs.

The next following step was the manufacture of therapeutic proteins. In 1970, two years before the birth of recombinant DNA (rDNA) technology, cytogeneticist Robert J. Harris coined the term 'genetic engineering'. However, DNA recombinant technology needed the discovery by Werner Arber, in 1970, of restriction enzymes which cut DNA in the middle of a specific symmetrical sequence. Modern genetic engineering began in 1973 when Herbert Boyer (born 1928) and Stanley Cohen (born 1922) used enzymes to cut a bacteria plasmid and insert another strand of DNA in the gap. The invention of recombinant DNA technology offered a window into the previously impossible: the mixing of traits between totally dissimilar organisms. To prove it was possible, Cohen and Boyer used the same process to put frog DNA into a bacteria. Since 1973, this technology has been made more controllable by the discovery of new enzymes to cut the DNA differently and by mapping the genetic code of different organisms.

The year 1975 heralded DNA sequencing. Walter Gilbert (born 1932) and Allan Maxam and Frederick Sanger (born 1918) simultaneously develop different methods for determining the sequence of bases in DNA with relative ease and efficiency.

Genentech's goal of cloning human insulin in *Escherichia coli* was achieved in 1978, and the technology was licensed to Eli Lilly. The recombinant DNA era grew from these beginnings and have a major impact on pharmaceutical production and research in the 1980s and 1990s. Since that time, dozens of protein drugs, have been marketed: growth hormone, colony-stimulating factors, erythropoietin, tissue plasminogen activator, antihaemophilic factors, interferons, etc.

XIX CONCLUSION

Modern medicinal chemistry is more and more focused on the interactions of small molecules with proteins than with genes, which code for the synthesis of those proteins. Many of the medically relevant proteins have already been identified and will continue to be important targets for modern therapies even after the human genome is fully sequenced. The human genome sequence may help scientists finish the task of identifying these proteins. It looks likely that protein drugs may be a prominent part of the pharmaceutical library of the future.

Pharmaceuticals will be more personalized, thanks to a growing field known as pharmacogenomics, which focuses on polymorphism in drug-metabolizing enzymes and the resulting differences in drug effects. Due to slight genetic differences between humans in drug absorption, metabolism and excretion, pharmacogenomics will identify the patient population most likely to benefit from a given medication. Greater integration of chemistry into biological research will allow biology to be studied in a less reductionist way. This seems vital, given that tissue engineering taking cells (stem cells) to restructure or rebuild damaged or congenitally defective tissues will probably be the next step towards an effective cure.

REFERENCES

1. Nunn, J.F. (1996) *Ancient Egypt Medicine*. University of Oklahoma Press, Norman, Oklahoma.
2. Frey, E.F. (1985–86) The earliest medical texts. *Clio. Med.* **20**: 79–90.

3. Sigerist, H. (1951) *History of Medicine*, vol. 1, Primitive and archaic medicine. Oxford University Press, New York.
4. Sabbah, G., Corsetti, P.P. and Fischer, K.D. (1987) *Bibliographie des Textes Médicaux Latins, Antiquité et Haut Moyen Age*. Saint Etienne.
5. Grmek, M.D. (1995) *Histoire de la Pensée Médicale en Occident*, vol. 1. Antiquité et Moyen Age, Le Seuil, Paris. Especially following chapters: Introduction by Mirko D. Grmek; La naissance de l'art médical occidental, by Jacques Jouanna; Entre le savoir et la pratique: la médecine hellénistique, by Mario Vegetti; Les voies de la connaissance: la médecine dans le monde romain by Danielle Gourevitch; Le concept de maladie, by Mirko D. Grmek; Stratégies thérapeutiques: les médicaments, by Alain Touwaide.
6. Bariety, M. and Coury, C. (1963) *Histoire de la Médecine*. Fayard, Paris.
7. Griffin, J.P. (1995) Famous names in toxicology. Mithridates VI of Pontus, the first experimental toxicologist. *Adverse Drug React. Toxicol. Rev.* **14**: 1–6.
8. Hankinson, R.J. (1991) *Galen: On the Therapeutic Method*, I and II. Oxford.
9. Dioscorides, P.A. (1906–14) *De Materia Medica*. Berolini, Weidmann.
10. Nurhussein, M.A. (1989) Rhazes and Avicenna. *Ann. Intern. Med.* **111**: 691–692.
11. Nyverd, G. (1520) *Le Grant Herbier en Francoys, Contenant les Qualitez, Vertus et Proprietez des Herbes, Arbres, Gommes et Semences*. Paris.
12. Court, W.E. (1999) The ancient doctrine of signatures or similitudes. *Pharm. Hist (Lond.)*, **29**: 41–48.
13. Oster, M. (1993) Biography, culture, and science: the formative years of Robert Boyle. *Hist. Sci.* **31**: 177–226.
14. Reti, L. and Gibson, W.C. (1968) *Some Aspects of Seventeenth-Century Medicine and Science*. University of California Press, Los Angeles.
15. Lavoisier, A.A. (1789) *Traité Elémentaire de Chimie Présenté dans un Ordre Nouveau et d'Après les Découvertes Récentes, Avec Figures*, Cuchet, Paris.
16. Aftalion, F. (1988) *Histoire de la Chimie*, Masson, Paris.
17. Bensaude-Vincent, B. and Stengers, I. (1993) *Histoire de la Chimie*, La Découverte, Paris.
18. Bernard, C. (1855–56) *Leçons de Physiologie Expérimentale Appliquée à la Médecine*. 2 vols. J.-B. Baillière, Paris.
19. Virchow, R.L. (1858) *Die Cellularpathologie in ihrer Begründung auf Physiologische und Pathologische Gewebelehre*. A. Hirschwald, Berlin.
20. Pasteur, L. (1922–39) Œuvres complètes réunies par Pasteur Vallery-Radot, 7 vols., Masson, Paris.
21. Soubeiran, E. (1831) Recherches sur quelques combinaisons du chlore. *Ann. Chim. (Paris)*, **48**: 113–157.
22. Von Liebig, J. (1832) Ueber die Verbindungen, welche durch die Einwirkung des Chlors auf Alkohol, Aether, ölbildenes Gas und Essiggeist entstehen. *Ann. Pharm.* **1**: 182–230.
23. Guthrie, S. (1832) New mode of preparing a spirituous solution of chloric ether. *Am J. Sci. Arts* **21**: 64–65 and **22**: 105–106.
24. Von Liebig, J. (1842) *Die organische Chemie in ihrer Anwendung auf Physiologie und Pathologie*. Braunschweig, F. Vieweg.
25. Wohler, F. (1828) Ueber kunstliche Bildung des Harnstoffs. *Ann. Phys. Chem.* (Leipzig). (French translation of this article appears in *Ann. Chim (Pans)* **37**: 33–34.)
26. Müller-Jahncke, W.D. and Friedrich, C. (1996) *Geschichte der Arzneimitteltherapie*, Deutscher Apotheker Verlag, Stuttgart.
27. Cadetde Gassicourt, C.L. (1809) Considérations sur l'etat actuel de la pharmacie. *Bull. Pharm.* **1**: 5–12.
28. Chast, F. (1995) *Histoire Contemporaine des Médicaments*, La Découverte Ed., Paris.
29. Sertürner, F. (1805) Auszuge aus briefen an den Herausgeber. (a) Säure im opium. (b) Ein deres Schreiben von Ebendenselben. Nachtrag zur Charakteristik der Saüre im Opium. *J. Pharmazie für Artze, Apotheker, und Chemisten von D.J.B. Trommsdorff* **13**: 29–30.
30. Pelletier, P.J. and Magendie, F. (1817) Recherches chimiques et physiologiques sur l'ipecacuanha. *Ann. Chim. Phys.* **4**: 172–185.
31. Pelletier, P.J. and Caventou, J.-B. (1820) Recherches chimiques sur les quinquinas. *Ann. Chim. Phys.* **15**: 289–318, 337–365.
32. Robiquet, P.J. (1832) Nouvelles observations sur les principaux produits de l'opium. *Ann. Chim.* **51**: 225–267.
33. Mein, H.F. (1833) Ueber die Darstellung des Atropins in weissen Krystallen. *Ann. Chem. Pharm.* **6**: 67–72.
34. Merck, G.F. (1848) Vorläufige Notiz über eine neue organische Base im Opium. *Ann. Phys. Chem. (Lpz.)* **66**: 125–128.
35. Ladenburg, A. (1881) Die Natürlich vorkommenden mydriatische wirkenden Alkaloïde. *Ann. Chem. Pharm.* **206**: 274–307.
36. Magendie, F. (1822) *Formulaire pour la préparation et l'emploi de plusieurs nouveaux médicamens, tels que la noix vomique, la morphine, etc.* Méquignon-Marvis, Paris.
37. McLagan, T.J. (1876) The treatment of acute rheumatism with salicin. *Lancet*, **1**: 342–343, 383–384.
38. Piria, R. (1839) Recherches sur la salicine et les produits qui en dérivent. *CR Acad. Sci. (Paris)*, **8**: 479–485.
39. Gerhardt, C.F. (1853) Untersuchungen über die wasserfrei organischen Saüren. *Ann. Chem. Pharm.* **87**: 149–179.
40. Sneader, W. (2000) The discovery of aspirin: a reappraisal. *Br. Med. J.* **321**: 1591–1594.
41. Dreser, H. (1899) Pharmakologisches über Aspirin (Acetylsalicylsaüre). *Pflüg. Arch. Ges. Physiol.* **76**: 306–318.
42. Withering, W. (1785) *An account of the foxglove, and some of its medical uses*, G.G.J. & J. Robinson, Birmingham.
43. Nativelle, C.A. (1872) De la digitaline et de la digitale. *Bull. Acad. Méd.* Paris i: 201.
44. Schmiedeberg, J.E.O. (1875) Untersuchungen uber die pharmakologische wirksamen Bestandteile der *Digitalis purpurea*. *L. Arch. Exp. Path. Pharmak.* **3**: 16–43.
45. Mackenzie, J. (1905) New methods of studying affections of the heart. *Br. Med. J.* **1**: 519–521, 587–589, 702–505, 759–562, 812–515.
46. Albers, J.F.H. (1864) Die Physiologische und Therapeutische wirkung. *Dtsch. Klin.* **42**: 405.
47. Brunton, T.L. (1867) On the use of nitrite of amyl in angina pectoris. *Lancet* **2**: 97–98.
48. Smithwick, R.H. (1947) Surgery of the autonomic nervous system. *N. Engl. J. Med.* **236**: 662–669.
49. Kempner, W. (1948) Treatment of hypertensive vascular disease with rice diet. *Am. J. Med.* **4**: 545–577.
50. Barker, M.H. (1936) Blood cyanates in the treatment of hypertension. *J. Am. Med. Ass.* **106**: 762–767.
51. Page, I.H. and Corcoran, A.C. (1949) *Arterial Hypertension: Its Diagnosis and Treatment*. Year Book Medical Publishers, Chicago.
52. Dustan, H.P., Rocella, E.J. and Garrison, H.H. (1996) Controlling hypertension: a research success story. *Arch. Intern. Med.* **17**: 1926–1935.
53. Freis, E.D., Finnerty, F.A., Schnaper, H.W. and Johnson, R.L. (1952) The treatment of hypertension with hexamethonium. *Circulation* **5**: 20–27.
54. Schroeder, H.A. (1952) The effect of 1-hydrazinophthalazine in hypertension. *Circulation* **5**: 28–37.
55. Wilkins, R.W. and Judson, W.E. (1953) Use of *Rauwolfia serpentina* in hypertensive patients. *N. Engl. J. Med.* **248**: 48–53.
56. Vakil, R.J. (1949) A clinical trial of *Rauwolfia serpentina* in essential hypertension. *Br. Heart J.* **11**: 350–355.

57. Perry, H.M. and Schroeder, H.A. (1958) The effect of treatment on mortality ratio in severe hypertension. *Arch. Intern. Med.* **102**: 418–425.
58. Veterans Administration Cooperative Study Group on Antihypertensive Agents (1967) Effects of treatment on morbidity in hypertension, I: results in patients. with diastolic blood pressure averaging 115 through 129 mm Hg. *J. Am. Med. Assoc.* **202**: 1028–1034.
59. Tigerstedt, R.A. and Bergman, P.G. (1898) Niere und Kreislauf. *Skand. Arch. Physiol.* **8**: 223–271.
60. Davis, J.O. and Freeman, R.H. (1982) Historical perspectives on the renin-angiotensin-aldosterone system and angiotensin blockade. *Am. J. Cardiol.* **49**: 1385–1389.
61. Ferreira, S.H. (1985) History of the development of inhibitors of angiotensin I conversion. *Drugs* **30** (Suppl. 1): 1–5.
62. Wexler, R.R., Carini, D.J., Duncia, J.V., Johnson, A.L., Wells, G.J., Chiu, A.T., Wong, P.C. and Timmermans, P.B. (1992) Rationale for the chemical development of angiotensin II receptor antagonists. *Am. J. Hypertens* **5**: 209S–220S.
63. Wells, J. G. (1847) *A History of the Discovery of the Applications of Nitrous Oxyde Gas, Ether and Other Vapours to Surgical Operations*. Hartford.
64. Morton, W.T.G. (1847) *Remarks on the Proper Mode of Administering Sulfuric Ether by Inhalation*. Dutton & Wentworth, Boston.
65. Bigelow, H. J. (1846) Insensibility during surgical operations produced by inhalation. *Boston Med. Surg. J.* **35**: 309–317, 379–382.
66. Snow, J. (1848) On the inhalation of chloroform and ether. With description of an apparatus. *Lancet* **1**: 177–180.
67. Baumann, E. (1886) Ueber Disulfone. *Ber. Dtsch. Chem. Ges.* **19**: 2806–2814.
68. Fischer, E. and Mering, J. Von (1903) Ueber eine neue Klasse von Schlafmitteln. *Ther. Gegenw.* **44**: 97–101.
69. Bernard, C. (1883) Cours de Médecine du Collège de France. Première leçon (29 Février 1856), In *Leçons sur les Effets des Substances Toxiques et Médicamenteuses*. J.-B. Baillière, Paris.
70. Grifith, H.R. and Johnson, E. (1942) The use of curare in general anaesthesia. *Anesthesiology* **3**: 418–420.
71. Gray, T.C. and Halton, J. (1946) Technique for the use of d-tubocurarine chloride with balanced anaesthesia. *Br. Med. J.* **2**: 29329–29335.
72. Koller, C. (1884) Vorlaüfige Mittheilung über locale Anästhesirung am Auge. *Klin. Mbl. Augenheilk.* **22**: 60–63.
73. Freud, S. (1885) *Über Coca*. Verlag Von Moritz Perles, Wien.
74. Niemann, A. (1860) *Ueber eine neue organische Base in den Cocablättern*. E.A. Huth, Göttingen.
75. Bier, A. K. G. (1899) Versuche über Cocainisirung des Rückenmarkes. *Dtsch. Z. Chir.* **51**: 361–369.
76. Musto, D.F. (1992) Cocaine's history, especially the American experience. *Ciba Found. Symp.*, **166**: 7–14; discussion, 14–19.
77. Einhorn, A. (1899) Ueber die Chemie der localen Anesthaestica. *Munch. Med. Wschr.* **46**: 1218–1220, 1254–1256.
78. Filehne, W. (1887) Die local Anästhesirende Wirkung von Benzoylderivaten. *Berliner Klinische Wochenschrift* **24**: 107–108.
79. Fourneau, E. (1904) Stovaine, anesthésique local. *Bull. Soc. Pharmacol.* **10**: 141–148.
80. Dreifuss, F.E. (1995) Other antiepileptic drugs. In Levy, R., Mattson, R.H. and Meldrum, B.S. (eds). *Antiepileptic Drugs*, 4th edn., pp. 949–962. Raven Press, New York.
81. Merritt, H.H. and Putnam, T.J. (1938) Sodium diphenylhydantoinate in the treatment of convulsive disorders. *J. Am. Med. Ass.* **111**: 1068.
82. Glazko, A.J. (1986) Discovery of phenytoin. *Ther. Drug Monit.* **4**: 490–497.
83. Burton, B.S. (1882) On the propyl derivatives and decomposition products of ethyl acetoacetate. *Am. Chem. J.* **3**: 385–395.
84. McElroy, S.L. and Keck, P.E. (1995) Antiepileptic drugs. In Schatzberg, A. and Nemeroff, C.B. (eds). *Textbook of Psychopharmacology*, Vol. 17, pp. 351–375. American Psychiatric Press, Washington, DC.
85. Schindler, W. (1960) 5H-Dibenz[b,f]azepines, US patent 2,948, 718 (1960 to Geigy). *Chem. Abstr.* **55**: 1671c.
86. Lambert, P.A., Carraz, G. and Carbel, S. (1966) Action neuropsychotrope d'un nouvel anti-épileptique: le dépamide. *Ann. Méd. Psychol.* **124**: 707–710.
87. Cohen, A.F., Ashby, L., Crowley, D., Land, G., Peck, A.W. and Miller, A.A. (1985) Lamotrigine (BW 430C), a potential anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam. *Br. J. Clin. Pharmacol.* **6**: 619–629.
88. Saletu, B., Grunberger, J. and Linzmayer, L. (1986) Evaluation of encephalotropic and psychotropic properties of gabapentin in man by pharmaco-EEG and psychometry. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **24**: 362–373.
89. Pierce, M.W., Suzdak, P.D., Gustavson, L.E., Mengel, H.B., McKelvy, J.F. and Mant, T. (1991) Tiagabine. *Epilepsy Res. Suppl.* **3**: 157–160.
90. Labarraque, A.G. (1825) *De l'Emploi des Chlorures d'Oxide de Sodium et de Chaux*. Mme Hazard, Paris.
91. Holmes, O.W. (1855) *Puerperal Fever, as a Private Pestilence*. Ticknor & Fields, Boston.
92. Semmelweis, I.P. (1861) *Die Aetiologie, der Begriff und die Prophylaxis des Kindbettfiebers*. C. A. Hartleben, Vienna.
93. Traube, I. (1910, 1911) Die Theorie des Haftdrucks (Oberflächendrucks) und ihre Bedeutung fur die Physiologie. *Pfldg. Arch. Ges. Physiol.* **132**: 511–538; **140**: 109–134.
94. Lister, J. (1867) On a new method of treating compound fracture, abscess, etc., with observations on the conditions of suppuration. *Lancet* **1**: 326–329, 357–359, 387–389, 507–509; **2**: 95–96.
95. Runge, F. F. (1834) Ueber einige Producte den Steinkohlendestillation. *Ann. Phys. Chem. (Lpz.)* **31**: 65–77, 308–332, 513–532.
96. Lucas-Championnière, J.M.M (1876) *Chirurgie Antiseptique*. J. B. Baillière, Paris.
97. Koch, R. (1881) Ueber Desinfection. *Mitt. k. GesandhAmte* **1**: 234–282.
98. Roux, P.P.E. and Yersin, A.E.J. (1888, 1889, 1890) Contribution à l'étude de la diphtérie. *Ann. Inst. Pasteur* **2**: 629–661; **3**: 273–288; **4**: 385–426.
99. Ehrlich, P. (1881) Ueber das Methylenblau und seine klinisch-bakterioskopische Verwerthung. *Z. Klin. Med.* **2**: 710–713.
100. Ehrlich, P. (1877) Beitrag zur Kenntnis der Anilinfärbungen und ihrer Verwendung in der mikroskopischen Technik. *Arch. Mikr. Anat.* **13**: 263–277.
101. Ehrlich, P. (1881) Ueber das Methyleneblau und seine klinisch-bakterioskopische Verwerthung. *Ztschr. F. Klin. Med.* **ii**: 710–713.
102. Guttmann, P. and Ehrlich, P. (1891) Ueber die Wirkung des Methylenblau bei Malaria. *Berl. Klin. Wschr.* **28**: 953–956.
103. Ehrlich, P. (1907) Chemotherapeutische Trypanosomen-Studien. *Berl. Klin. Wschr.* **44**: 233–236, 280–283, 310–314, 341–344.
104. Ehrlich, P. (1912) Ueber Laboratoriumsversuche und Klinische Erprobung von Heistoffen. *Chem. Ztg.* **36**: 637–638.
105. Parascandola, J. (1997) Alkaloids to arsenicals: systematic drug discovery before the First World War. *Publ. Am. Inst. Hist. Pharm.* **16**: 77–91.
106. Domagk, G. (1935) Ein Beitrag zur Chemotherapie der bakteriellen Infektionen. *Dtsch. Med. Wschr.* **C1**: 250–253.
107. Tréfouël, J., Tréfouël, T., Nitti, F. and Bovet, D. (1935) Activité du p-aminophénylsulfamide sur les infections streptococciques expérimentales de la souris et du lapin. *CR Soc. Biol. (Paris)* **120**: 756–758.
108. *The Pharmaceutical Century. Ten Decades of Drug Discoveries*. The American Chemical Society Web Site.

109. Dubos, R.J. (1939) Bactericidal effect of an extract of a soil bacillus on gram-positive cocci. *Proc. Soc. Exp. Biol.* (NY) **40**: 311–312.
110. Fleming, A. (1929) On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzae*. *Br. J. Exp. Path.* **10**: 226–236.
111. Chain, E.B., Florey, H.W., Gardner, A.D., Heatley, N.G., Jennings, M.A., Orr-Ewing, J. and Sanders, A.G. (1940) Penicillin as a chemotherapeutic agent. *Lancet* **2**: 226–228.
112. Wainwright, M. (1990) *Miracle Cure: The Story of Penicillin and the Golden Age of Antibiotics*. Basil Blackwell, Oxford.
113. Levy, S.B. (1992) *The Antibiotic Paradox*. Plenum Press, New York.
114. Abraham, E.P. and Chain, E.B. (1940) An enzyme from bacteria able to destroy penicillin. *Nature (Lond.)* **146**: 837.
115. Henderson, J.W. (1997) The yellow brick road to penicillin: a story of serendipity. *Mayo Clin. Proc.* **7**: 683–687.
116. Schatz, A., Bugie, E. and Waksman, S.A. (1944) Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. *Proc. Soc. Exptl. Biol. Med.* **55**: 66–69.
117. Hinshaw, H.C. and Feldman, W.H. (1945) Streptomycin in treatment of clinical tuberculosis: a preliminary report. *Proc. Mayo Clin.* **20**: 313–318.
118. Hinshaw, H.C., Feldman, W.H. and Pfuetze, K.H. (1946) Streptomycin in treatment of clinical tuberculosis. *Am. Rev. Tuberc.* **54**: 191–203.
119. Robitzek, E.H., Selikoff, J. and Ornstein, G.G. (1952) Chemotherapy of human tuberculosis with hydrazine derivatives of isonicotinic acid, (preliminary report of representative cases). *Quart. Bull. Sea View Hosp.* **13**: 27–51.
120. Thomas, J.P., Baughn, C.O., Wilkinson, R.G. and Shepherd, R.G. (1961) A new synthetic compound with antituberculous activity in mice: ethambutol (dextro-2,2′-(ethylenediimino)-di-l-butanol). *Am. Rev. Resp. Dis.* **83**: 891–893.
121. Rist, N., Grumbach, F. and Liberman, D. (1959) Experiments on the antituberculous activity of alpha-ethyl-thioisonicotinamide. *Am. Rev. Tuberc.* **79**: 1–5.
122. Sensi, P. (1983) History of the development of rifampin. *Rev. Infect. Dis.* **5**(Suppl. 3): S402–S406.
123. Finland, M. (1974) Twenty-fifth anniversary of the discovery of Aureomycin: the place of the tetracyclines in antimicrobial therapy. *Clin. Pharmacol. Ther.* **1**: 3–8.
124. Anonymous (1981) *Pneumocystis* pneumonia — Los Angeles. *MMWR Morb. Mortal. Wkly. Rep.* **21**: 250–252.
125. Anonymous (1981) Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men —- New York City and California. *MMWR Morb. Mortal. Wkly. Rep.* **30**: 305–308.
126. Hymes, K.B., Cheung, T., Greene, J.B., Prose, N.S., Marcus, A., Ballard, H., William, D.C. and Laubenstein, L.J. (1981) Kaposi's sarcoma in homosexual men — a report of eight cases. *Lancet* **2**: 598–600.
127. Gottlieb, M.S., Schroff, R., Schanker, H.M., Weisman, J.D., Fan, P.T., Wolf, R.A. and Saxon, A. (1981) *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N. Engl. J. Med.* **305**: 1425–1431.
128. Barre-Sinoussi, F., Chermann, J.C., Rey, F., Nugeyre, M.T., Chamaret, S., Gruest, J., Dauguet, C., Axler-Blin, C., Vezinet-Brun, F., Rouzioux, C., Rozenbaum, W. and Montagnier, L. (1983) Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* **4599**: 868–871.
129. Gallo, R.C., Sarin, P.S., Gelmann, E.P., Robert-Guroff, M., Richardson, E., Kalyanaraman, V.S., Mann, D., Sidhu, G.D., Stahl, R.E., Zolla-Pazner, S., Leibowitch, J. and Popovic, M. (1983) Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). *Science* **4599**: 865–867.
130. Mitsuya, H. and Broder, S. (1987) Strategies for antiviral therapy in AIDS. *Nature* **6107**: 773–778.
131. Mitsuya, H., Weinhold, K.J., Furman, P.A., St. Clair, M.H., Lehrman, S.N., Gallo, R.C., Bolognesi, D., Barry, D.W. and Broder, S. (1985) 3′-Azido-3′-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus *in vitro*. *Proc. Natl. Acad. Sci. USA* **82**: 7096–7100.
132. Yarchoan, R., Klecker, R.W., Weinhold, K.J., Markham, P.D., Lyerly, H.K., Durack, D.T., Gelmann, E., Lehrman, S.N., Blum, R.M. and Barry, D.W. (1986) Administration of 3′-azido-3′-deoxythymidine, an inhibitor of HTLV-III/LAV replication, to patients with AIDS or AIDS-related complex. *Lancet* **8481**: 575–580.
133. Delta Coordinating Committee. (1996) Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* **348**: 283–291.
134. De Clercq, E. (1994) New developments in the chemotherapy of lentivirus (human immunodeficiency virus) infections: sensitivity/resistance of HIV-1 to non-nucleoside HIV-1-specific inhibitors. *Ann. NY Acad. Sci.* **724**: 438–456.
135. Gallant, J.E. (2000) Strategies for long-term success in the treatment of HIV infection. *J. Am. Med. Assoc.* **283**: 1329–1334.
136. Richman, D.D. (2001) HIV chemotherapy. *Nature* **6831**: 995–1001.
137. Moore, J.P. (2002) AIDS vaccines: on the trail of two trials. *Nature* **6870**: 365–366.
138. Banting, F.G., Best, C.H. and MacLeod, J.J.R. (1922) The internal secretion of the pancreas. *Am. J. Physiol.* **59**: 479.
139. Banting, F.G., Best, C.H., Collip, J.B., Campbell, W.R. and Fletcher, A.A. (1922) Pancreatic extracts in the treatment of diabetes mellitus. *J. Can. Med. Assoc. J.* **12**: 141–146.
140. Addison, T. (1855) *On the Constitutional and Local Effects of Disease of the Suprarenal Capsules*. S. Highley, London.
141. Kendall, E.C., Mason, H.L., Mackenzie, B.F., Myers, C.S. and Koelsche, G.A. (1934) Isolation in crystalline form of the hormone essential to life from the suprarenal cortex; its chemical nature and physiologic properties. *Proc. Mayo Clin.* **9**: 245–250.
142. Reichstein, T. (1936) Über Bestandteile der Nebennieren-Rinde VI. Trennungsmethoden sowie Isolierung der Substanzen Fa, H, und J. *Helv. Chim. Acta* **19**: 1107–1126.
143. Hench, P.S., Kendall, E.C., Slocumb, C.H. and Polley, H.F. (1949) The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. *Proc. Mayo Clin.* **24**: 181–197.
144. Medvei, V.C. (1993) *The History of Clinical Endocrinology*. Parthenon, New York.
145. Allen, E. and Doisy, E.A. (1927) The menstrual cycle of the monkey, *Macacus rhesus*: Observations on normal animals, the effects of removal of the ovaries and the effects of injection of ovarian and placental extracts into the spayed animals. *Contr. Embryol. Carneg. Instn* **19**: 1–44.
146. Butenandt, A.F.J. (1931) Ueber die chemische Untersuchung der Sexualhormone. *Z. Angew. Chem.* **44**: 905–908.
147. Browne, J.S.L. (1933) Chemical and physiological properties of crystalline oestrogenic hormones. *Canad. J. Res.* **8**: 180–197.
148. Ruzicka, L., Goldberg, M.W., Meyer, J., Brüngger, H. and Eichenberger, E. (1934) Über die Synthese des Testikelhormons (Androsteron) und Stereoisomerer desselben durch Abbau hydrierter Sterine. *Helv. Chim. Acta* **17**: 1395–1406.
149. Chast, F. (1997) Histoire de la Contraception. *Pour la Science* **233**: 14–17.

150. Pincus, G.G. and Chang, M.C. (1953) The effects of progesterone and related compounds on ovulation early development in the rabbit. *Acta Physiol. Latinoamer.* **3**: 177–183.
151. Djerassi, C. (1992) Steroid research at Syntex: 'the pill' and cortisone. *Steroids* **12**: 631–641.
152. Colton, F.B. (1992) Steroids and 'the pill': early steroid research at Searle. *Steroids* **12**: 624–630.
153. Persidis, A. and Copen, R.M. (1999) Mental disorder drug discovery. *Nat. Biotechnol.* **17**: 307–309.
154. Loewi, O. (1921, 1922, 1924) Ueber humorale Uebertragbarkeit der Herznervenwirkung. *Pflüg. Arch. Ges. Physiol.* **189**: 239–242; **193**: 201–213; **203**: 408–412.
155. Triggle, D.J. (2000) Pharmacological receptors: a century of discovery — and more. *Pharm. Acta Helv.* **74**: 79–84.
156. Cade, J.F.J. (1949) Lithium salts in the treatment of psychotic excitement. *Med. J. Aust.* **36**: 349–352.
157. Schou, M. (1993) *Lithium Treatment of Manic Depressive Illness*. Karger, Basel.
158. Muller, J.M., Schlittler, E. and Bein, H.J. (1952) Reserpin, der sedative Wirkstoff aus *Rauwolfia serpentina* Benth. *Experientia (Basel)* **8**: 338.
159. Youdim, M.B. (1975) Monoamine oxidase. Its inhibition. *Mod. Probl. Pharmacopsyc.* **10**: 65–88.
160. Kline, N.S. (1958) Clinical experience with iproniazid (Marsilid). *J. Clin. Exp. Psychopathol.* **19** (Suppl.): 72–78.
161. Healy, D. (1998) Pioneers in psychopharmacology. *Int. J. Neuropsychopharmcol.* **1**: 191–194.
162. Kuhn, R. (1958) The treatment of depressive states with G22355 (Imipramine hydrochloride). *Am. J. Psych.* **115**: 459–464.
163. Iversen, L.L. (1999) The discovery of monoamine transporters and their role in CNS drug discovery. *Brain Res. Bull.* **50**: 379.
164. Shorter, E. (1997) *A History of Psychiatry — From the Era of the Asylum to the Age of Prozac*. John Wiley FRSC, University of Toronto.
165. Laborit, H., Huguenard, P. and Alluaume, R. (1952) Un nouveau stabilisateur végétatif, le 4560 RP. *Presse Méd.* **60**: 206–208.
166. Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M. and Koetschet, P. (1953) Propriétés pharmacodynamiques du chlorhydrate de chloro 3-(diméthylamino-3′propyl) 10-phénothiazine (4560 RP). *Arch. Int. Pharmacodyn.* **92**: 305–361.
167. Delay, J. and Deniker, P. (1952) Trente-huit cas de psychoses traitées par la cure prolongée et continue de 4560 RP. *Le Congrès des Aliénistes et Neurologues de Langue Française.* In *Compte Rendu du Congrès*. Masson et Cie, Paris.
168. Berger, F.M. (1954) The pharmacological properties of 2-methyl 2 *m*-propyl-1,3-propane-diol dicarbamate (Miltown), a new interneuronal blocking agent. *J. Pharmacol.* **112**: 413–423.
169. Helderman, J.H. and Gailiunas, P., Jr. (1983) Transplantation. *Am. J. Kidney Dis.* **3**: 194–198.
170. Barnard, C.N. (1967) The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. *S. Afr. Med. J.* **48**: 1271–1274.
171. Stahelin, H.F. (1996) The history of cyclosporin A (Sandimmune) revisited: another point of view. *Experientia* **52**: 5–13.
172. Heusler, K. and Pletscher, A. (2001) The controversial early history of cyclosporin. *Swiss Med. Wkly.* **131**: 299–302.
173. Borel, J.F. and Kis, Z.L. (1991) The discovery and development of cyclosporine (Sandimmune). *Transplant. Proc.* **23**: 1867–1874.
174. Gilman, A. and Philips, F.S. (1946) The biological actions and therapeutic applications of the chlorethylamines and sulfides. *Science* **103**: 409–415.
175. Jukes, T.H. (1978) The history of methotrexate. *Cutis* **3**: 396–398.
176. Calne, R.Y., Alexander, G. P. J. and Murray, J.E. (1962) A study of drugs in prolonging survival of homologous renal transplant in dogs. *Ann. NY Acad. Sci.* **99**: 743–761.
177. Taylor, D.O., Ensley, R.D., Olsen, S.L., Dunn, D. and Renlund, D.G. (1994) Mycophenolate mofetil (RS-61443): preclinical, clinical, and three-year experience in heart transplantation. *J. Heart Lung Transplant.* **13**: 571–582.
178. Borel, J.F., Feurer, C., Gubler, H.U. and Stahelin, H. (1976) Biological effects of cyclosporin A: a new antilymphocytic agent. *Agents Actions* **6**: 478–475.
179. Allison, A.C. (2000) Immunosuppressive drugs: the first 50 years and a glance forward. *Immunopharmacology* **47**: 63–83.
180. Abelson, P.H. (1990) Medicine from plants. *Science* **4942**: 513.
181. Tunon, H., Olavsdotter, C. and Bohlin, L. (1995) Evaluation of anti-inflammatory activity of some Swedish medicinal plants. Inhibition of prostaglandin biosynthesis and PAF-induced exocytosis. *J. Ethnopharmacol.* **2**: 61–76.
182. Dewick, P.M. (1996) Tumor inhibitors from plants. In Evans, W.C. (ed.). *Trease and Evans' Pharmacognosy*, 14th edn. Saunders, London.
183. Stahelin, H.F. and Von Wartburg, A. (1991) The chemical and biological route from podophyllotoxin glucoside to etoposide: Ninth Cain Memorial Award Lecture. *Cancer Res.* **1**: 5–15.
184. Kouadio, K., Chenieux, J.C., Rideau, M. and Viel, C. (1984) Antitumor alkaloids in callus cultures of *Ochrosia elliptica*. *J. Nat. Prod.* **47**: 872–874.
185. Wall, M.E. and Wani, M.C. (1996) Camptothecin. Discovery to clinic. *Ann. NY Acad. Sci.* **803**: 1–12.
186. Langreth, R. (1991) Whom do yew trust? *Science* **5014**: 1780.
187. Wani, M.C., Taylor, H.L., Wall, M.E., Coggon, P. and MacPhail, A.T. (1971) Plant antitumor agents. VI. The isolation and structure of Taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. *J. Am. Chem. Soc.* **93**: 2325–2327.
188. Schiff, P.B., Fant, J. and Horwitz, S.B. (1979) Promotion of microtubule assembly *in vitro* by Taxol. *Nature* **5698**: 665–667.
189. Defuria, M.D. and Horovitz, Z. (1993) Taxol commercial supply strategy. *J. Natl Cancer Inst. Monogr.* **15**: 195–198.
190. Gueritte-Voegelein, F., Guenard, D., Lavelle, F., Le Goff, M.T., Mangatal, L. and Potier, P. (1991) Relationships between the structure of Taxol analogues and their antimitotic activity. *J. Med. Chem.* **34**: 992–998.
191. Guenard, D., Gueritte-Voegelein, F., Dubois, J. and Potier, P. (1993) Structure–activity relationships of Taxol and Taxotere analogues. *J. Natl. Cancer Inst. Monogr.* **15**: 79–82.
192. Von Hoff, D.D. (1997) The taxoids: same roots, different drugs. *Semin. Oncol.* **24** (Suppl. 13): S13-3–S13-10.
193. Goodman, L.S., Wintrobe, M.M., Dameshek, W., Goodman, M.J., Gilman, A. and McLennan, M.T. (1946) Nitrogen mustard therapy. Use of methyl-*bis*(beta-chlorethylamine hydrochloride and *tris*(beta-chlorcethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied miscellaneous disorders. *J. Am. Med. Assoc.* **132**: 126–132.
194. Devita, V.T., Serpick, A.A. and Carbone, P.P. (1970) Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann. Intern. Med.* **73**: 881–895.
195. Elion, G.B. and Hitchings, G.H. (1965) Metabolic basis for the actions of analogs of purines and pyrimidines. *Adv. Chemother.* **2**: 91–177.
196. Elion, G.B. (1969) Actions of purine analogs: enzyme specificity studies as a basis for interpretation and design. *Cancer Res.* **12**: 2448–2453.
197. Bowden, M.E. (2001) *Pharmaceutical Achievers*. Chemical Heritage Foundation, Philadelphia.

198. Di Marco, A., Cassinelli, G. and Arcamone, F. (1981) The discovery of daunorubicin. *Cancer Treat. Rep.* **65** (Suppl. 4): 3–8.
199. Weiss, R.B., Sarosy, G., Clagett-Carr, K., Russo, M. and Leyland-Jones, B. (1986) Anthracycline analogs: the past, present, and future. *Cancer Chemother. Pharmacol.* **18**: 185.
200. Weiss, R.B. (1992) The anthracyclines: will we ever find a better doxorubicin? *Semin. Oncol.* **19**: 670–686.
201. Rosenberg, B., Van Camp, L. and Krigas, T. (1965) Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode. *Nature* **205**: 698–699.
202. Bellon, S.F., Coleman, J.H. and Lippard, S.J. (1991) DNA unwinding produced by site-specific intrastrand cross-links of the antitumor drug *cis*-diammine-dichloroplatinum(II). *Biochemistry* **30**: 8026–8035.
203. Bruckner, H.W., Ratner, L.H., Cohen, C.J., Wallach, R., Kabakow, B., Greenspan, E.M. and Holland, J.F. (1978) Combination chemotherapy for ovarian carcinoma with cyclophosphamide, adriamycin, and cis-dichlorodiammineplatinum (II) after failure of initial chemotherapy. *Cancer Treat. Rep.* **62**: 1021–1023.
204. Knox, R., Friedlos, F., Lydall, D. and Roberts, J. (1986) Mechanism of cytotoxicity of anticancer platinum drugs: evidence that *cis*-diammine-dichloroplatinum (II) and *cis*-diammine-(1,1-cyclobutane-dicarboxylato)platinum (II) differ only in the kinetics of their interaction with DNA. *Cancer Res.* **46**: 1972–1979.
205. Raju, T.N. (1999) The Nobel chronicles, 1958: George Wells Beadle, Edward Lawrie Tatum and Joshua Lederberg. *Lancet* **353**: 2082.
206. Watson, J.D. and Crick, F. (1953) Molecular structure of nucleic acids a structure for deoxyribose nucleic acid. *Nature* **171**: 724–738.

2

MEDICINAL CHEMISTRY: DEFINITION AND OBJECTIVES, THE THREE MAIN PHASES OF DRUG ACTIVITY, DRUG AND DISEASE CLASSIFICATIONS

Camille G. Wermuth

Medicinal chemistry remains a challenging science, which provides profound satisfaction to its practitioners. It intrigues those of us who like to solve problems posed by nature. It verges increasingly on biochemistry and on all the physical, genetic and chemical riddles in animal physiology which bear on medicine. Medicinal chemists have a chance to participate in the fundamentals of prevention, therapy and understanding of diseases and thereby to contribute to a healthier and happier life. **A. Burger**[1]

I	Definition and objectives	29
	A Medicinal chemistry	29
	B Molecular and cellular pharmacology	30
	C Systemic pharmacology	30
	D Clinical pharmacology	31
II	The three main phases of drug activity	31
	A The pharmaceutical phase	31
	B The pharmacokinetic phase	33
	C The pharmacodynamic phase	34
	D Medicinal chemistry approaches as a function of the therapeutic classes	35
III	Drug classifications	36
	A Classification systems	36
	B Practical classifications	37
IV	Conclusion	38
References		38

I DEFINITION AND OBJECTIVES

A Medicinal chemistry

Taken in the *prospective sense* the objective of medicinal chemistry is the design and the production of compounds that can be used in medicine for the prevention, treatment and cure of human or animal diseases. Thus medicinal chemistry is a part of pharmacology, this latter being taken in its etymological sense ('pharmakon' + 'logos': study of drugs; Fig. 2.1).

Taken in the *retrospective sense*, medicinal chemistry also includes the study of already existing drugs, of their pharmacological properties, and their structure–activity relationships. An official definition of medicinal chemistry was given by an IUPAC specialized commission.[2]

> *Medicinal chemistry concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level. Emphasis is put on drugs, but the interest of the medicinal chemistry is also concerned with the study, identification, and synthesis of the metabolic products of drugs and related compounds.*

The main activities of medicinal chemists appear clearly from the analysis of their most important scientific journals (*Journal of Medicinal Chemistry*, *European Journal of Medicinal Chemistry*, *Bioorg MedChem*, *Il Farmaco*, *Archiv der Pharmazie*, *Arzneimittelforschung*, *Chemical and Pharmaceutical Bulletin*, etc.). Thus, medicinal chemistry covers three critical steps:[3]

- A **discovery step**, consisting of the *choice of the therapeutic target* (receptor, enzyme, transport group, cellular or *in vivo* model) and the *identification* (or *discovery*) *and production* of new active substances interacting with the selected target. Such compounds are usually called lead compounds, they can originate from

ISBN 0-12-744481-5

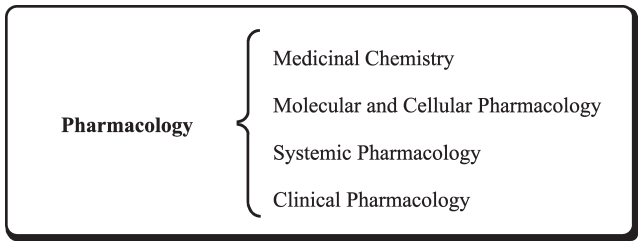

Fig. 2.1 The domains of pharmacology.

synthetic organic chemistry, from natural sources, or from biotechnological processes.

- An **optimization step**, that deals with the improvement of the lead structure. The optimization process takes primarily into account the increase in potency, selectivity and toxicity. Its characteristics are the establishment and analysis of *structure–activity relationships*, in an ideal context to enable the understanding of the molecular mode of action. However, an assessment of the pharmacokinetic parameters such as absorption, distribution, metabolism, excretion and oral bioavailability is almost systematically practised at an early stage of the development in order to eliminate unsatisfactory candidates.
- A **development step**, whose purpose is the continuation of the improvement of the pharmacokinetic properties and the fine tuning of the pharmaceutic properties (*chemical formulation*) of the active substances in order to render them suitable for clinical use. This chemical formulation process can consist in the preparation of better absorbed compounds, of sustained release formulations, of water-soluble derivatives or in the elimination of properties related to the patient's compliance (causticity, irritation, painful injections, undesirable organoleptic properties).

Medicinal chemistry is an interdisciplinary science covering a particularly wide domain situated at the interface of organic chemistry with life sciences, such as biochemistry, pharmacology, molecular biology, immunology, pharmacokinetics and toxicology on one side, and chemistry-based disciplines such as physical chemistry, crystallography, spectroscopy and computer-based information technologies on the other.

The knowledge of the molecular targets (enzymes, receptors, nucleic acids), has benefitted from the progress made in molecular biology, genetic engineering and structural biology. For an increasing number of targets the three-dimensional structure and the precise location of the active site are known. The design of new active substances is therefore more and more based on results obtained from ligand–receptor modelling studies. One can actually consider the existence of a molecular pharmaco*chemistry* making a pair with molecular pharmaco*logy*.

If the main objective is the discovery of new drug candidates, medicinal chemistry is also concerned with the fate of drugs in living organisms ('ADME' studies: absorption, distribution, metabolism, excretion), and with the study of bioactive compounds not related to medicine (agrochemicals, food additives, etc.).

A certain number of terms more or less synonymous with medicinal chemistry are used: pharmacochemistry, molecular pharmacochemistry, drug design, selective toxicity. The French equivalent to medicinal chemistry is 'Chimie Thérapeutique' and the German one is 'Arzneimittelforschung'.

B Molecular and cellular pharmacology

This is the study of the pharmacological action of drug at the molecular or at the cellular level. The first objective is to identify the cellular levels of action. Three levels, important for drug activity can be distinguished: (1) the plastic membrane which is very rich in potential targets, notably in receptors; (2) the cytosol with its enzymatic equipment and the organelle membranes with their particular ion transporters; and (3) the nucleus which notably responds to the steroid hormones, to anticancer drugs and to gene therapy. The second objective is to elucidate the precise biochemical and biophysical sequence of events that result from the drug–target interaction. All these studies are performed *in vitro*, therefore they yield generally rather reliable quantitative data. They are also free from pharmacokinetic factors such as the peregrination and the metabolism of the drug between the site of administration and the site of action. Finally they save animals and are thus better accepted by the animal protection leagues.

C Systemic pharmacology

The systemic pharmacology considers the effects of biologically active substances in integrated systems (cardiovascular, skeletal, central nervous, gastrointestinal, pulmonary, etc.). The experimentation is performed in intact animals or in isolated organs (isolated heart, isolated arteria, perfused kidney, etc.). The main difficulty resides in the design of animal experimental models that are predictive of an activity in a human disease. As many pharmacological experiments are still performed on healthy animals or on disease-simulating paradigms, their extrapolation to clinical situations is questionable. The availability of transgenic mice, in which the genes of a human disease were introduced, represent an interesting progress. However in all animal models, intra- and interspecific physiological variations account for rather imprecise results the margins being often as elevated as $\pm 50\%$.

D Clinical pharmacology

Clinical pharmacology deals with the examination in humans of the effects of a new drug candidate. The tests are performed under the responsibility of the clinical pharmacologist who is generally a medical doctor and who has to report to an ethical committee. Phase I tests take place in healthy volunteers. They aim to assess the level of dosing and the tolerance ('dose ranging') and to initiate metabolic studies in humans. Once the safety margin has been determined, phase II, III and IV studies examine successively the beneficial effects in patients, the possible side-effects, the comparison of the drug with reference drugs and the emergence of new therapeutic indications.

II THE THREE MAIN PHASES OF DRUG ACTIVITY

The activity of a given drug depends on a sequence of physico-chemical events that begin when the active molecule penetrates into the living organism and which culminates when the active molecule reaches its target and elicits the appropriate biological response. Classically it is admitted that three characteristic phases govern the biological activity of a drug in a living organism[4,5] the *pharmaceutical phase*, the *pharmacokinetic phase*, and the *pharmacodynamic phase* (Table 2.1).

A The pharmaceutical phase

The *pharmaceutical phase*, sometimes also called *biopharmaceutical phase*, deals with the choice of the appropriate *route of administration* and with the choice of the *pharmaceutical formulation* most suited to the desired medical treatment.

Routes of administration

Possible routes of administration are divided into two major classes: *enteral*, whereby drugs are absorbed from the alimentary canal and *parenteral*, in which drugs enter the bloodstream directly (intravenous injection) or by some other non-enteral absorptive route (intramuscular or subcutaneous injections, transdermal delivery systems, nasal sprays, etc.). Below we describe in brief the intravenous and the oral route; other routes of administration are considered in Chapter 30.

Intravenous injections. The *intravenous injection* is the route of administration leading to the fastest effects. The drug preparation is directly injected into the bloodstream and from there the active principle is carried along to its site of action. The intravenous route shunts the natural barriers of the body to absorption, and therapeutic blood levels are reached almost instantaneously. The drug solution must be completely clear with no particulate matter present. On the other hand, injection solutions should be sterile to avoid any infections, also isotonic and at pH values close to that of the plasma ($pH = 7.4$) to avoid local pain and tissue necrosis.[6–8] Once arrived at the target, the drug can trigger its receptor mechanism and induce the awaited biological response. Actually the situation is not so simple and many additional and sometimes unwanted events can occur (Fig. 2.2):

(1) In the bloodstream the drug can bind to the plasmatic proteins or to the blood cells or the platelets and never reach the target organs with a sufficient concentration.
(2) Due to its ionized character or to its inadequate partition coefficient, the drug may be unable to cross the lipidic biomembranes.
(3) Instead of being carried to the biophase, the drug can be concentrated in the fat storage compartment.
(4) The drug can also be rapidly altered by metabolic processes. Drug metabolism usually yields more water-soluble, less active and much less toxic derivatives of the parent drug. However, sometimes metabolic processes can generate active or toxic molecules.

Table 2.1 *The three phases that govern the activity of a drug*

Phase	Concerned events	Objectives
Pharmaceutical phase	Selection of the administration route Preparation of the most appropriate pharmaceutical formulation	Optimize the distribution Facilitate the absorption Eliminate unwanted organoleptic properties
Pharmacokinetic phase	Fate of the drug in the organism: absorption, distribution, metabolism, excretion ('ADME')	Control the bioavailability, i.e. the ratio of the administered dose over the concentration at the site of action, in function of the time
Pharmacodynamic phase	Quality of the drug–receptor interaction Nature and intensity of the biological response	Maximal activity Maximal selectivity Minimal toxicity

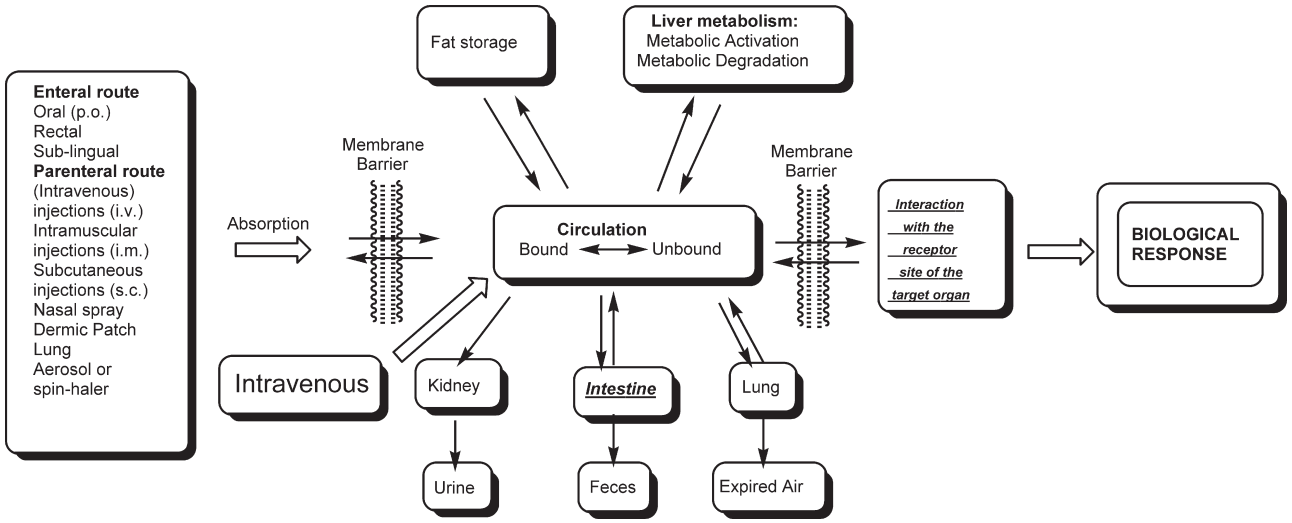

Fig. 2.2 Schematic diagram of *in vivo* events and compartments (after Kier[9] and Ariëns[10]).

(5) Due to exchanges with the intestine, the kidneys and the lungs, the parent drug or its metabolites can be too quickly removed from the organism.
(6) On a practical side, only water-soluble drugs can easily be administrated by the intravenous route and the injections have to be done very slowly to avoid excessively high concentrations (as much as 400 times the final blood level) of the drug in the heart tissue.

Oral route. The most common route of administration is the *oral route*. In this case additional peregrinations of the drug are involved to ensure its passage from the gastrointestinal tract to the bloodstream. The drug preparation is swallowed and the active principle is absorbed through the mucous membrane of the small intestine or, to a limited extent, from the stomach. As absorption is maximal for unionized drugs, acidic drugs are rather well absorbed through the stomachal epithelium (pH of the stomachal juice = 2–3) and weakly basic drugs through the small intestine epithelium (pH varying progressively from 5 to 7). Once absorbed, drugs do not directly reach the sites of action, but are carried to the portal vein and from there into the liver where they are subjected to chemical attacks (oxidations, reductions, hydrolyses, coupling with solubilizing moieties) before being released into the bloodstream. These metabolic attacks, taking place before the drug reach the general circulation, are called 'first pass effects'. They are avoided when using intravenous injections and thus represent the major difference between the intravenous and the oral route.

For oral administration, the active compound is usually integrated in tablets, soft or hard gelatine capsules or coated tablets. As a rule, a tablet is a compressed preparation that contains approximately 5–10% of the active principle, 80% of various excipients (fillers, disintegrants, lubricants, glidants and binders) and about 10% of compounds ensuring an easy disintegration, deaggregation and dissolution of the tablet in the stomach or the intestine. Tablets are relatively simple to manufacture and to use. They represent the most current presentation.

Thanks to appropriate *pharmaceutical formulation techniques,* the disintegration time can be modified so that a fast effect or a sustained release is achieved. Special coatings can also render the tablet gastro-resistant, the disintegration taking place only in the duodenum, under the combined action of the intestinal enzymes and of the pH change. In the family of tablets one finds equally the dragées. These are tablets covered with a colored sugar layer and a fine layer of varnish or wax. Recently films have replaced the sugar and the dyestuffs.

Capsules are constituted of a gelatinous envelope that contains the active substance in the form of powder or granules. The most used form are capsules in hard or tender gelatine, capsules to chew and capsules for rectal use.

Other pharmaceutical preparations (see also Chapter 30). *Suppositories* are composed from an excipient that melts at body temperature. It can be a natural fat (cocoa butter) or a polyethylene-glycol (Carbowax). They are exclusively destined to be introduced in the anus. They allow a rapid action because the rectum is richly irrigated, moreover, they avoid loading the digestive system.

Ovules are destined to be introduced in the vagina, so as to exert a local action. They are usually constituted of a dissolution of the active principle in a soft gelatine. *Ointments* are coatings that one spreads on the skin or on mucus. They are generally used for the treatment of cutaneous or subcutaneous lesions. *Aerosols* are sprays for

local applications. Their therapeutic advantages are as follows: possibility to process large surfaces, good resorption, simple and easy utilization. Aerosols are of particular importance for inhalation therapies of the respiratory system. *Liquid medicines*, sterile for most, are composed of active substances in solution. Besides the intravenous injection, other liquid medicines are perfusions destined for parenteral nutrition after a surgical intervention or a traumatic coma, or solutions for stomach washings after an intoxication. Finally drinkable ampoules also belong to the group of liquid medicines.

The bioequivalence problem. A given formulation procedure of an active principle ensures the corresponding bioavailability in patients (bioavailability = the fractional part of a drug that reaches the general circulation in a given time span). A slight modification in the galenic procedure (change of one excipient, changes in the granulation process before tabletting, changes in the drying process, modification of the aging or storage conditions) can sometimes dramatically influence the drug release of the final product. The same is true for changes in the final purification process of the active principle. Thus re-crystallization from another solvent system or under other temperature and/or concentration conditions can produce mesomorphic crystalline forms, presenting other solubilities and as a consequence a change in bioavailability (see Chapter 39). As quoted by Kellaway:[11] 'When a patient is successfully treated or stabilized on a branded product, it is therefore undesirable to change to a chemically equivalent product from an alternative manufacturer unless bioequivalence has been proven. Economic pressures advocating change of product should be resisted, at least until bioequivalence data are presented'.

When the pharmaceutical formulation of an active compound is ineffective, slight chemical modifications or formation of bioreversible derivatives (esters, amides, peptides) can improve its physico-chemical properties (lipophilicity, pK, polarity) and optimize the dissolution rates in the biological fluids and the passage through the very first biological membranes (cutaneous, intestinal, etc.). The global result is better penetration into the organism. Compared with the pharmaceutical formulation mentioned above, this process can be considered as a chemical formulation and will be considered in Chapter 39.

B The pharmacokinetic phase

The *pharmacokinetic phase* controls the different parameters that govern the random walk of the drug between its application point and its final site of action and which ensure the destruction and/or the elimination once the effect is produced. The site of action is often separated in space and time from the administration or penetration place. In a chronological order the events of the pharmacokinetic phase are as follows: *Absorption:* The absorption processes through the different biological membranes and compartments, they are highly dependent on the physico-chemical properties of the drug (ionized or unionized state, partition coefficient, size) and can proceed simply through passive diffusion or to more sophisticated physiological transport mechanisms (Chapter 30). *Distribution:* The distribution of the drug substance into the various compartments is ensured by the blood, and to a minor extent by the lymphatic circulation. Blood plasma, contains the suspended blood cells and platelets and is essentially a solution of 70 g per litre of proteins (albumin and globulins), of 9 g‰ of mineral salts (essentially sodium chloride) and of ~1 g‰ of glucose (exact composition see Table 2.2, from Rettig[12]). The proteins, especially albumin, are able to bind to various drugs and thus to temporarily subtract them from their pharmacological destination. Albumin has a molecular weight of 69 000 and is mainly negatively charged at the physiological pH of the blood (pH = 7.4). At pH = 5, its isoelectric point, it has 100 negative and 100 positive charges, which explains its important role also as physiological buffer molecule. *Metabolism:* The apparent finality of metabolism is to chemically transform drugs or any other substances that are foreign to the organism (xenobiotics) into water-soluble derivatives to facilitate their urinary elimination. This change normally produces a diminution, or even suppression, of the pharmacological activity and of the eventual toxicity. However it can happen that the metabolism activates the parent molecule (see Chapters 31 and 32) or even generates highly reactive intermediates (mostly electrophiles) that induce toxicity mechanisms (see Chapter 32). If metabolic activation is implied, drugs inactive *in vitro* may be found to be active *in vivo*.

Table 2.2 *Constitution of blood*[12]

Constituent	%	% of the total
Blood cells (hematocrit)		45
Erythrocytes	44.6	
Leukocytes	0.15	
Thrombocytes	0.25	
Plasma		55
Fibrinogen	0.3	
Serum	54.7	
Proteins	3.5	
Electrolytes	~0.4	
Carbohydrates	~0.05	
Hormones	Trace	
Enzymes	Trace	
Vitamins	Trace	
Antibodies, gases, dyestuffs	Trace	

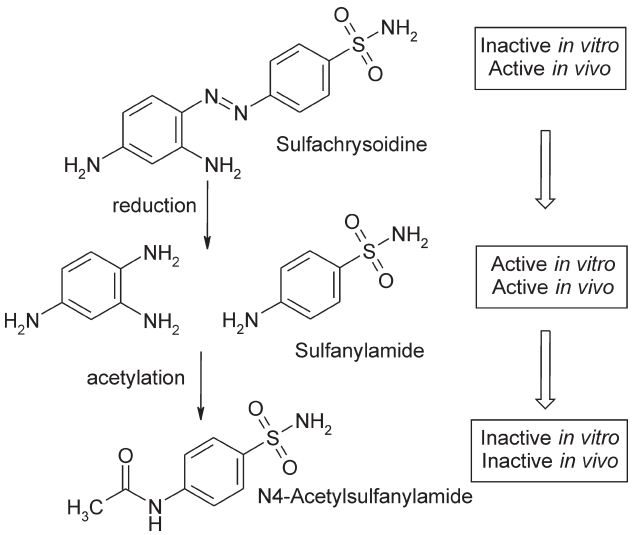

Fig. 2.3 Metabolic activation and inactivation.

Sulfamidochrysoidine ('Prontosil rubrum'), converted *in vivo* to the anti-infectious agent sulphanilamide, is the historical example. In its turn, the active metabolite sulphonamide is inactivated through acetylation (Fig. 2.3). Metabolic reactions take place in majority in the liver, but other organs such as the kidneys, the lungs or the brain can also ensure drug transformations. *Elimination:* Once the awaited pharmacological effect is produced, drugs and metabolites have to be eliminated from the organism with adequate kinetics. A too slow elimination process produces a progressive accumulation of the drug and appearance of toxic effects. Conversely too fast elimination leads to repeated daily administrations and low patient acceptance. The main elimination routes are renal (urine) and rectal (faeces). They can occasionally be pulmonary (expired air), oral (salivary) and cutaneous (sweat). The elimination kinetics are very seldom of order zero (Fig. 2.4a). One of the best known examples is the linear elimination of ethanol (which allows the calculation of the ethanol blood level at the moment of a car accident even when the blood sample was taken some time after the accident).

The usual elimination kinetic of a drug from the circulating blood is of first order (Fig. 2.4b). In this case

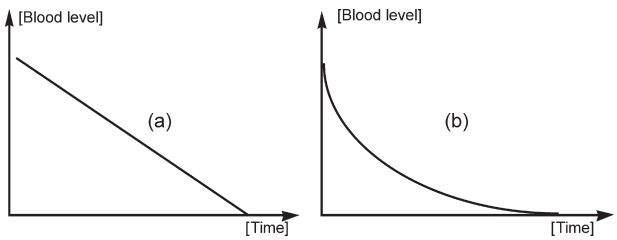

Fig. 2.4 Elimination kinetics of order zero (a) and of order 1 (b).

Table 2.3 *Examples of drugs possessing very different elimination half-times (taken from references 13–15)*

Compound	$t_{\frac{1}{2}}$ (hours)
Pyridostigmine	0.1
Fentanyl	0.2
Morphine	2–3
Clonidine	8
Adamantane	10
Griseofulvin	20
Phenobarbital	35–96
Chloroquine	48
Reserpine	150
Sulfamethoxine	200
Bromide ion	280–340

the time at which the drug is completely cleared from the blood is relatively difficult to determine, since the curve does not intersect with the x axis, but only approaches it in an asymptotic way. Much easier is the determination of the biological half-time ($Et_{\frac{1}{2}}$), i.e. the time after which the blood level has reached half of the original level. Table 2.3 gives some examples of elimination half-times.

The four above-mentioned pharmacokinetic processes ('ADME': absorption, distribution, metabolism, excretion) account for the bioavailability of a given drug. As the bioavailability expresses the percentage of a given drug that reaches the general circulation in a given time span, an intravenous administration represents therefore, by definition, a 100% bioavailability. After an oral dosage, a 100% bioavailability would imply a complete absorption and no first pass destruction; such a situation is rather improbable.

C The pharmacodynamic phase

The *pharmacodynamic phase* is the phase of the greatest interest to the medicinal chemist as it deals directly with the nature and the quality of the interaction of the drug with its biological target. Starting often with a relatively weak and non-selective compound, the challenge is to maximize the potency and to minimize the deleterious or undesired effects of the molecule. The biological response obtained is maximal when the active principle shows the precise stereoelectronic complementarity with the target structure. Ideally the medicinal chemist, from the knowledge of the characteristics of the target tissue (enzyme, receptor, transport protein, nucleic acid), tries to design drugs with the optimal size, shape, hydrophilic–lipophilic ratio, disposition of functional groups. The sharper is the obtained fit between the receptor site and the molecule, the more selective will be the drug in eliciting only the expected biological response.