BURGER'S MEDICINAL CHEMISTRY

Fourth Edition

Part I
The Basis of Medicinal Chemistry

Edited by

MANFRED E. WOLFF

BURGER'S MEDICINAL CHEMISTRY

Fourth Edition

Part I
The Basis of Medicinal Chemistry

Edited by

MANFRED E. WOLFF

School of Pharmacy
Department of Pharmaceutical Chemistry
University of California
San Francisco, California

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS, New York · Chichester · Brisbane · Toronto

Notice Concerning Trademark or Patent Rights.
The listing or discussion in this book of any drug in respect to which patent or trademark rights may exist shall not be deemed, and is not intended as, a grant of, or authority to exercise, or an infringement of, any right or privilege protected by such patent or trademark.

Library of Congress Cataloging in Publication Data (Revised)

Burger, Alfred, 1905– ed.
Burger's Medicinal Chemistry.

"A Wiley-Interscience publication."
Bibliography: p.
Includes index.
CONTENTS: pt. 1. The basis of medicinal chemistry.
1. Chemistry, Pharmaceutical. 2. Chemotherapy.
I. Wolff, Manfred E. II. Title. III. Title: Medicinal chemistry. [DNLM: 1. Chemistry, Pharmaceutical. QV744.3 B954]

RS403.B8 1979 615'.7 78-10791
ISBN 0-471-01570-9

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Preface

Did we know the mechanical affectations of the particles of rhubarb, opium, and a man, as a watchmaker does those of a watch, whereby it performs its operations, and of a file which by rubbing on them will alter the figure of any of the wheels; we should be able to tell beforehand that rhubarb will purge, hemlock kill, and opium make a man sleep.

John Locke, *Essay Concerning Human Understanding*, 1690.

All is well with us, except for the worry (another false alarm fortunately) about the blessing of too many children. One tries every conceivable trick to stem the tide of these little blessings, but without much confidence. One scrapes along, one might say, from one menstruation to the next. The life of civilized man certainly does have its quaint side.

Jung in a letter to Freud, May 18, 1911.

The effect of drugs on our daily existence is difficult to appreciate until one makes a comparison with the recent past. Jung and Freud, as medical scientists, lived lives that were not very different from those of the medicinal chemists who read these pages. They had the benefits of excellent homes, educational institutions, clothes, and food. They had the convenience of electricity, the telephone, the telegraph, fast trains, and steamships. And they had a lifestyle that included frequent vacations, music, theater, and literature. What they did not have were antibiotics, oral contraceptives, tranquilizers, or for that matter, most of the therapeutic classes that are indispensable to the treatment of disease. The result, as one can read in their letters, was a pervasive and unsettling dimension added to the human condition: an abiding threat of life-threatening illness, uncontrollable infection, or unwanted pregnancy. Almost at the time of Jung's letter, in 1910, Paul Ehrlich introduced arsphenamine, or 606, for the treatment of syphilis, thus making available the most potent weapon of the time against any infectious disease. In doing this Ehrlich founded the science of medicinal chemistry, a discipline that gave mankind the hope of power to design drugs as envisioned by Locke in his prophetic essay.

Early advances in medicinal chemistry were concerned principally with the estimation, isolation, structural determination, and synthesis of medicinal agents of natural origin. A second major area was the synthesis of simplified fragments of complex drug molecules. In this phase of its development medicinal chemistry was almost indistinguishable from organic chemistry. The golden age (1940–1960) in the discovery of medicinals by these empirical strategies came to an end concomitant with the thalidomide tragedy. An arid middle age marked by pessimism in drug synthesis in both industrial and academic quarters ensued because of the combined difficulties of toxicity, carcinogenicity, and teratogenicity, and the relatively low return from random synthesis. It is characteristic of historical trends, however, that transitions to a new era are obscured and difficult to identify. In medicinal chemistry the doldrums in new drug development are actually yesterday's news, even

though the renaissance that has begun is still not widely recognized. Underlying this new age is a foundation that includes the explosive development of molecular biology since 1960, the advances in physical chemistry and physical organic chemistry made possible by high-speed computers, and new, powerful analytic methods including various types of chromatography, radioimmunoassay, mass spectrometry, X-ray crystallography, and nuclear magnetic resonance spectroscopy.

Such newly refined techniques will bring to us an understanding of drug metabolism and its relationship to drug toxicity, carcinogenicity, teratogenicity, and mutagenicity that will make it possible to minimize or eliminate these hazards. We already know that untoward reactions often are caused by reactive metabolites, and we are gaining an understanding of the chemical and biological factors involved in the production of such substances. In the study of receptors, the combined power of physical chemistry, physical organic chemistry, bioorganic chemistry, and the techniques of quantitative drug design have given such results as the histamine-H_2 blockers, a sophisticated antimetabolite and enzyme inhibitor theory, and a detailed understanding of structure-activity relationships in hormones. Again, the elucidation of the opiate receptor and the finding of endogenous opiatelike substances promise to revolutionize the development of analgetic agents. Work on immunostimulatory and immunosuppressive agents is dramatically altering our helplessness in the face of viral diseases and immune system disorders such as arthritis.

In preparing this new edition of these volumes founded through the vision of Alfred Burger, an attempt has been made to incorporate the new developments into the discussion in every place where it was possible. In this first volume we seek to present the underlying principles of medicinal chemistry. After an historical overview by Alfred Burger, the design of drugs is treated relative to both their therapeutic and toxic effects. The discussion includes the distribution and pharmacokinetics of drugs, the biological and chemical nature of drug metabolism, the basis of drug-receptor interactions, antimetabolite theory, drug allergy and its relationship to drug toxicity, carcinogenicity, and quantitative structure-analysis relationships (QSAR) and other methods of drug design.

This volume is intended, first of all, for practicing medicinal chemists as an aid in understanding the principles underlying their day-to-day activities. Second, it is hoped that it will be suitable for graduate students and others interested in learning about the principles of medicinal chemistry. Third, it is an attempt to aid those interested in other types of biological action of chemicals, such as the environmental toxicity of herbicides and pesticides.

Thus we hope that this volume will be a useful monograph for students and workers in the science of medicinal chemistry and related areas, and will also provide a suitable introduction and companion volume for the specialized chapters in the other two volumes of this series.

MANFRED E. WOLFF

San Francisco, California
January 1979

Contents

CHAPTER ONE

Introduction: History and Economics of Medicinal Chemistry

ALFRED BURGER

Department of Chemistry
University of Virginia
Charlottesville, Virginia 22901 USA

CONTENTS

1 INTRODUCTION

The roots of medicinal chemistry lie in many branches of chemistry and biology. The earlier name, pharmaceutical chemistry, reflected the fact that some nineteenth century pharmacists, working in their apothecary laboratories, were the first to extract and purify naturally occurring drugs. Some of the tasks of medicinal chemistry as we know them today were claimed by biological sciences. In 1876 the pharmacologist Buchheim wrote that "the mission of pharmacology was to establish the active substances within the *[natural]*

drugs, to find the chemical properties responsible for their action and to prepare synthetically drugs that were more effective" (1). When pharmacologists became preoccupied with other objectives, "to study the change brought about by the drug in the organism and then to explore the possible influence of such changes upon pathological conditions" (1), chemists took over the isolation and chemical identification of natural plant constituents with a background of medical folklore. They also embarked on the synthesis of structural analogs of such prototype compounds with potential therapeutic activity. Gradually this led to searches for new "lead" structures by screening synthetic organic compounds with or without relationships to naturally occurring drugs. As ever-increasing numbers of biologically active substances became known, it was found that synthetic chemicals often produced effects that were more useful medicinally than those attributed to natural materials, perhaps because plant metabolites are not usually intended by Nature to be of therapeutic value in animal systems.

Comparisons of chemical structures with trends in biological behavior stimulated the formulation of hypotheses on mechanisms of drug action at the turn of the present century. Some modern hypotheses have permitted improvements in the planned design of drugs, but systematic molecular modifications of prototype structures as well as serendipitous suggestions based on accidental biological observations have not yet been superseded in the search for new medications.

Drug design has also been aided by the increasing understanding of biochemical metabolism and biosynthesis, and by statistical analysis of some relationships of physical properties of chemicals and their biological performance. This progress has begun to erode the randomness of medicinal discovery and has elevated medicinal chemistry to a science in its own right.

2 FROM 3000 B.C. TO A.D. 1860

It is customary to credit ancient philosophers and scholars with being the forerunners of medicinal scientists, but in the context of current knowledge their experiments, observations, and interpretations must be regarded as purely heuristic, based on superstitions and misunderstanding of natural phenomena, and without much predictive value in therapy.

Nevertheless, the accounts of those deeds of antiquity, the middle ages, and even the first 350 years of the "modern age" make fascinating anecdotal reading. A few arbitrarily selected references are included here to illuminate an otherwise defunct period that survives only as uncertain therapeutic folklore. Among the earliest materials discovered were *ch'ang shang* in China (2735 B.C.), later identified as the antimalarial plant *Dichroa febrifuga* (2), and *ma huang* as a stimulant and diaphoretic, now recognized as *Ephedra sinica* and other species (3). The Ebers Papyrus (Egypt, *ca.* 1500 B.C.) mentions the use of squill as a cardiac tonic, a precursor of digitalis therapy (4). Ipecac, from Brazilian *Cephaelis* species, was used as an antiamebic medication (5, 6), and *Chenopodium anthelminticum* was prescribed under different names by Hebrew, Mexican, and Roman physicians (7). One of the greatest chemotherapeutic discoveries was the use of the cinchona bark by South American Indians, as described first by the monk Calancha in 1633 and as reported by Herman van der Heyden as *Pulvus indicus* in 1643 (8). The antimalarial alkaloid, quinine, was isolated from this bark only 200 years later (9).

Inca mail runners and silver miners in the high Andean mountains chewed coca leaves as a stimulant and euphoric. During religious rites they also consumed various mushrooms containing psychotomimetic and hallucinogenic compounds. Poisonous vines furnished South American Indians resins containing curare [ourari, from *uria*

(bird) and *eor* (kill)] used to prime arrow tips for game hunting and tribal warfare.

In India courtesans poisoned the wine of their clients with *Datura stramonium* so that these men would not resist when robbed. *Datura* contains atropine and scopolamine. The same plant was burned under the tripod of the priestess at the oracular shrine of Apollo at the god's temple at Delphi; the priestess, intoxicated by the fumes, uttered incoherent cries that were interpreted in verse as oracles. The berries of the deadly nightshade, an alkaloidal plant called *Atropa belladonna* (Atropos, the oldest of the Three Fates, cut the thread of life), were the frequent source of accidental poisoning but also served to dilate the pupils of the sparkling eyes of Italian women (*bella donna*).

Another example of an ancient medicinal plant is the autumn crocus (meadow saffron, *Colchicum autumnale*), which had been recommended for the relief from pain of the joints by Alexander of Tralles in the sixth century A.D., and for acute gout by Baron Anton von Störck (1763). Benjamin Franklin heard of this treatment and reported it to American physicians. The alkaloid colchicine (10) was recognized later as the active antigout principle.

Poppy juice was mentioned as an analgetic by Theophrastus (third century B.C.) but must have been known before that. The Swiss alchemist Philippus Paracelsus (1943–1541) compounded laudanum, a somewhat purified opium concentrate. Opium smoking became prevalent in the eighteenth century but may have only surfaced at that time after many years of prior abuse.

Faith in the curative powers of plant extracts and botanical mixtures recommended by Galenus (A.D. 131–200) declined when Arabian alchemists of the thirteenth century conjured up the phantom idea of the philosopher's stone, which they hoped would prove to be a universal remedy or elixir of life. Basilius Valentinus (*ca.* 1460) and later Paracelsus also believed in inorganic drugs, the three "hypostatic principles", namely, salt, sulfur, and mercury. The latter element made its appearance in calomel, which survived in the form of Guy's Hospital Pill (calomel, digitalis, squill) and contributed to the diuretic action of this medication.

The development of the microscope, of anatomical dissection, and of physics combined to strengthen the conviction that such events as the circulation of the blood, respiration, and secretion were mechanical phenomena involving chemical reactions, albeit governed by an unfathomable vital force. The nature of the hormones had been anticipated by Aristotle, who claimed that humors were secreted at certain sites to act elsewhere in the body. It required the birth of chemistry and the liberation of organic chemistry from preconceived ideas of mysterious forces to classify natural products in the same way as inorganic chemicals.

Standards of purity and potency were established in compendia on materia medica that led to the first reference works, the pharmacopoeias, edited in Florence (1498), Nüremberg (1535), Augsburg (1564), Basel (1561), and London (1618). The terms antispasmodic, antiseptic, cathartic, and emetic appeared in a book by the Scottish physician William Cullen (1712–1790) (11). As new agents made their appearance, a glimmer of physiological understanding of their activities began to show. Thus Hoffmann's drops or anodyne, which contained ether, were used as analgetics (Friedrich Hoffmann, 1660–1742), and opium was studied by DeQuincey (1785–1859) "to tranquilize all irritations of the nervous system, to stimulate the capacity of enjoyment and · · · to sustain the else drooping animal energies" (12).

3 DRUG RESEARCH IN THE LAST CENTURY

In this series each chapter on drugs with a major therapeutic action is introduced with

a history of early agents and the discovery of the specific structural types that exert such activity. These historical surveys are not duplicated here. There have been changing fashions in the search for drugs, each time period emphasizing certain types of agent. This was often dictated by contemporary medical, economic, sociologic, and even political considerations. The wave of antiprotozoal chemotherapy set in motion around 1890 and the early synthetic antimalarials intermingled with the development of hypnotics, anti-inflammatory drugs, and adrenergic and cholinergic hormones and drugs. Then followed the feverish discovery of antibacterials and antibiotics, while in the pharmacodynamic area the potent analgetics, antihistaminics, vitamins, and new hormones moved to the fore. The post–World War II period featured three major breakthroughs in drug research: the antituberculous agents, the steroid hormones and contraceptives, and the antipsychotic, anxiolytic, and antidepressant psychopharmacological drugs.

The application of increasingly sophisticated methods of structural analysis by spectroscopy, isotopic labeling, automated quantitative analysis, and separation by chromatography and other partition procedures opened avenues of study of minute amounts of biochemicals. Improved biological monitoring of many complex activities added to these advances, which began to lay biochemical foundations to immunology and intricate modes of biochemical actions of many drugs. The increased attention to molecular biology and metabolite antagonism in medicine led to an upsurge in the chemotherapy of cancers and mental diseases. Table 1.1 lists some of the more significant advances in medicinal therapy, in approximate chronological order.

Although experimental biochemical methodology has moved ahead explosively during the last four decades, the intellectual thought processes of predictive drug design have developed with more hesitation.

S. C. F. Hahnemann (1755–1843), the founder of homeopathy, believed that "*similia similibus curantur*"—that is, drugs must be the opposite of the disease, and only symptoms can be treated, not the causes of a disease. Drug solutions should be diluted to the point of practically omitting their content of active components because high concentrations of drugs produce toxic reactions, that is, reactions similar to those of the disease. Hahnemann's contemporary Samuel Thomson (1769–1843) stated that "all diseases are the effects of one general cause and may be removed by one general remedy" (13). These ideas became obsolete as soon as the causes of at least some diseases become known. One of these counterproposals was that of Louis Pasteur (1822–1895), whose discovery of pathogenic parasites as the causes of infectious diseases prepared the way for the healing of such diseases with chemicals (chemotherapy). But echoes of Thomson's general remedy are still heard in Ehrlich's ambition to find a *materia magna sterilans*, a cureall for all infections, and in Hans Selye's general stress theory of functional disorders.

The reactivity of chemicals changes if their chemical structure is altered. By the same token, a change in structure brings about a change in biological properties. The British pharmacologist Fraser and the Scottish chemist Crum-Brown proposed that biological response is a function of chemical structure (14). Their attempts to express this relationship mathematically failed but were taken up again by the French physiologist Charles Richet (1893), and the pharmacologists Hans Horst Meyer (15) and Charles Overton (16), who ranked the action of narcotics according to ratios of their solubility in blood and lipids (i.e., water and organic solvents).

Paul Ehrlich (1854–1915), a German physician and immunologist turned chemist, was the first true exponent of drug research as we know it today (17). He

defined many of the intellectual tools of medicinal science, such as the existence and apparent function of receptors for drugs and metabolites. Drug molecules were classified into "pharmacophoric" groups, a term borrowed from the chromophores of dyestuffs. Dyestuffs fascinated Ehrlich, because their staining properties provided a convenient analytical tool in biological studies, and because they held out hope of staining selectively some cells and not others. Since it had become possible to produce animal models of clinical infections by inoculation with pathogens, dyestuffs appeared to be particularly promising as chemotherapeutic agents in infectious diseases.

How could the toxicity of a dyestuff for a pathogen be increased? One answer was to prepare derivatives or analogs containing a toxic element. Arsenic, which had just been shown to possess antitrypanosomal properties when attached to an aromatic nucleus, appeared as a logical candidate, and in arsphenamine, a pale-yellow azo dyestuff-like compound in which nitrogen had been replaced by arsenic, the first clinically useful antispirochetal drug was created. Continued study revealed that a metabolite of arsphenamine was the active form of the drug, and this opened the door to the study of drug metabolism as it is known now.

4 THE MODERN PERIOD

The idea that dyestuffs might be useful against the hitherto intractable bacterial infections persisted for another 20 years and culminated in the selection of the red dye Prontosil as an antibacterial agent (18). Again, the bacteriostatically active drug was a metabolite of the dyestuff, namely, sulfanilamide (19). This compound taught medicinal biochemistry a number of lessons. First, it had been synthesized 29 years before the discovery of its antibacterial activity (20). Similar cases have been encountered with some other drugs such as the tuberculostatic 4-aminosalicylic acid (666). This called attention to the need of the early interpretation of the biological potential of known substances based on relationships to biochemical metabolites, steric analogs, and compounds of similar localized electron densities that are of interest in a given structural type.

The second observation made with sulfanilamide was its antagonism to *p*-aminobenzoic acid (21). This study heralded the understanding of the biochemical action of many different drugs, namely, that drugs often exert a competitive or noncompetitive antagonism to biochemical substrates, especially those involved in biosynthetic processes. The effect of drugs is not usually on the substrate but on enzymes that catalyze the chemical reactions of the latter. Thousands of such cases have become known. Drugs active against essential enzymes of foreign or neoplastic invasive cells concerned with the biosynthesis of nucleic acids, proteins, enzymes, and other constituents of subcellular organelles have scored the greatest practical successes. Their specificity is enhanced in such cases by the emerging minor differences between isozymes of the more susceptible parasitic and the less susceptible communal cells (22). Such divergencies may also contribute to the relatively specific actions of functional drugs in disorders of different organs and various animal species.

For the medicinal chemist, the concept of interference of drugs with the bioconversions of substrates in enzymic reactions has had a profound didactic effect. It has enabled chemical drug design to be based on the structure of known substrates (i.e., amino acids, carbohydrates, hormones, nucleotide bases, vitamins, other biocatalysts, biogenic amines and other modulators of neurotransmission, constituents of lipids, steroids, prostaglandins, etc.). Molecular modification of these structures often results in "anti" agents. If an active drug does

not resemble any enzymic substrate, the assumption is made that it changes the conformation of the substrate site by allosteric modification of the enzyme. If a long-lasting drug effect is desired, one can take one's chances with near-irreversible enzyme inhibitors (23); such compounds are most often alkylating agents that establish covalent links between drug and macromolecular biocatalysts, but hydrogen- or hydrophobically bonded intercalation compounds can also serve this purpose.

The sulfanilamide and antihistaminic agents of the 1940s provided the first practical test of the validity of the rules of bioisosterism in drug design. To modify the structure of a "lead" compound that is biologically interesting but inadequate for therapeutic purposes, a chemist is faced with a multitude of options for such molecular analogs. As Marcelin Berthelot stated many years ago, chemistry resembles the arts; the potential of its creativity is terrifying (24). In Aldous Huxley's words "science is the reduction of the bewildering diversity of unique events to manageable uniformity within one of a number of symbol systems, and technology is the art of using these symbol systems so as to control and organize unique events" (24). The concept of isosterism (25) attempts to explain similarities between molecular options, thus to control their diversity. It was applied to medicinal research by Hans Erlenmeyer (26), and its limits have been extended gradually (27). Combined with intuition and acquired experience, thinking along the lines of bioisosterism has enabled two generations of medicinal chemists to curb the number of analogs to be studied in the course of molecular modification.

The same rules that guide medicinal chemists in singling out promising variants of "lead" compounds governed the development of other selectively toxic materials. These include insecticides, insect attractants and repellants, pesticides, herbicides, fungicides, flavorants, odorants, and toxic industrial chemicals that must be replaced by less toxic ones without losing those properties that make them of value to the industry and to environmental conditions (xenobiotics).

Since about 1964 Hansch (28), Free and Wilson (29), and others (30, 31) have tried to take some—although by no means all—of the intuitive educated guess work out of molecular modification. They started with Hammett's experimentally confirmed substituent constants for atoms and groups and with an equation that had enabled Hammett to calculate values for other substituents that had not been determined previously. By comparing values of such constants to partition coefficients of a compound between water and organic solvents, Hansch showed that the intensity of certain biological activities parallels trends in partition coefficients. Thus maximum potency in certain series of structurally related medicinal agents can be pinpointed, and this can be correlated to the roles of electronic, steric, and hydrophobic factors when drugs interact with receptors.

The role of physical-organic chemistry in drug design is still in flux. This discipline provides the best solutions in the inhibition of enzymes by candidate drugs of related structure *in vitro* and becomes less satisfactory as the complexity of the biological environment is increased and such unrelated factors as loss of drug by premature adsorption, incomplete absorption, and by metabolism and excretion, are aggravated.

Table 1.1 Historical Survey of Medicinal Observations and Discoveries[a]

Year(s) of Research or Publication	Discovery or Observation
1785	Digitalis, mentioned by Welsh physicians in 1250, and described and named by Fuchsius in 1542, is used in congestive heart failure (4).
1820–1945	Isolation of quinine (9); structure (42); synthesis (43).
1820–1947	Colchicine is isolated (10); structure (44–46).
1805–1968	Morphine is isolated from opium by F. W. A. Sertürner (47); named by Gay-Lussac (48); codeine, isolated by Robiquet in 1832, is made from morphine (49). Structure of morphine (50); synthesis (51); absolute configuration (52).
1812–1884	Picrotoxin, from *Anamirta cocculus*, is toxic (53); purification (54); cleavage into picrotin (inactive) and picrotoxinin (active) (55).
1820	First U.S. Pharmacopoeia is published.
1824	Summary of chemical study of plant and animal products is published (56).
1833–1901	Atropine is isolated (57); early pharmacology (58); synthesis (59).
1839	Iodine is used as topical antiseptic by the French surgeon Chatin (60).
1842–1847	General anesthesia in surgery: ether, Crawford W. Long, 1842; William T. G. Morton, 1846; nitrous oxide, Horace Wells and Colton, 1844; chloroform, J. Y. Simpson, 1847 (61).
1848–1913	Papaverine is isolated from opium (62); structure (63); syntheses (64, 65). Antispasmodic and vasodilator actions (66), clinical use (67).
1848–1918	Quinidine is described by van Heyningen in 1848; named by Pasteur, 1853. Use of *Cinchona* in auricular fibrillation, Jean-Baptiste de Sénac, 1749 (68, 69); controlled study (70).
1855–1951	*Veratrum* alkaloids: extraction (71); antihypertensive activity (72); partial syntheses (73, 74). Reviews (75, 76).
1856–1958	Curare (77), known since von Humboldt in 1805, is tested as neuromuscular blocking agent (78–80).
1860–1867	Phenol is recommended as a disinfectant (81) and as an antibacterial agent in surgery (82).
1860–1877	Salicin is found in bark of *Salix alba*, hydrolyzed to glucose and salicyl alcohol by Leroux, 1827; salicylic acid from salicin (Piria, 1838), from oil of Gaultheria in 1844. Synthesis (116); recommended as antipyretic (117), for rheumatic fever (118).
1864–1900	Caffeine is identified as a diuretic in coffee (83); clinical use (84); synthesis (85, 86).
1859–1884	Cocaine is isolated (87, 88). It numbs the tongue (89); local anesthetic action (90, 91); clinical use (92, 93).
1867–1926	Acetylcholine: synthesis (94); vasodepressor action (95); occurrence in ergot (96); pharmacology (97, 98); identified as neurotransmitter (99, 100).
1867	Glyceryl trinitrate is recommended as coronary vasodilator (101).
1868	Curariform action of tetraethylammonium is recognized (14, 103).
	Membrane hypothesis of neurotransmission (104).
1869	Hypnotic activity of alcohols is a function of their molecular weight (105).
	Chloral is a hypnotic (106).
1869–1881	Mercuric chloride is used as an antiseptic (107, 108); use against anthrax infections (109).

Table 1.1 (*continued*)

Year(s) of Research or Publication	Discovery or Observation
1869–1916	Muscarine is isolated from *Amanita muscaria* (110); chemistry (111, 112).
1874	Heroin is prepared from morphine (113, 114); use as analgetic (115).
1875	Pilocarpine is isolated from *Pilocarpus* sp. (119, 120).
1877	Anthrax bacillus is inhibited by other bacteria; this was the first suggestion of action of antibiotics (137).
1878	The term "enzyme" is coined (121); the term "receptive substance" is used (122); side chain theory of receptors to explain drug action (123).
1880–1953	Scopolamine is isolated (124); synthesis (125, 126).
1882	Hypnotics are introduced: paraldehyde (127); barbital, synthesis (128), action (129).
1883	Mescaline is suggested for production of experimental psychoses (130); psychological effects (131); chemistry (132); review (133).
	Pyrazolones are used as antipyretics (134); aminopyrine (135, 136).
1884	Bacteria are classified by staining (138).
1885	Bacterial enzymes and toxins are studied (139, 140).
	Mercurous chloride has diuretic activity (141).
1886	Salol is used for rheumatism (142).
	Acetanilide is antipyretic (143) but toxic; acetophenetidine is introduced (144).
1887	Ephedrine is isolated from *Ephedra sinica* (145, 146); syntheses (147–151); pharmacology (152); introduction (475).
1888	National Formulary of Unofficial Preparations is established; N.F. followed in 1906.
1890	Local anesthetics are developed: orthoform (153, 154), benzocaine (155–157).
1891	Homogentisic acid (158) is not biooxidized in alcaptonuria, "an inborn error of metabolism" (A. B. Garrod, 1900).
	The term "chemotherapy" is coined (published later) (159).
	Synthetic organic dyestuffs are used as topical and systemic antiseptics: methylene blue (160, 161); gentian violet (162); acriflavine (163); merbromin (164).
1891–1964	Thyroid extract is used in myxedema (165); thyroxine is isolated later (166); structure (167); synthesis (168); triiodothyronine (169, 170), congeners (171–173).
1893	Silver salts are bacteriostatic (174), used in prophylaxis of gonorrheal ophthalmia (175).
1894–1904	Dialkylaminoalkyl esters appear in local anesthetics: holocain (176), eucaines (177), stovaine (178), procaine (179–180). The alleged rejuvenating activity of procaine is disproved (181).
1895–1949	Adrenal extract causes pressor effect (182). Epinephrine: name (183), isolation (184–186), structure (187), synthesis (188, 189), resolution (190), configuration (191), biosynthesis (192, 193). Norepinephrine: synthesis (194), isolation (195–197, 308); recognized as neurotransmitter (198, 309).
1897	Rice polishings added to the diet prevent beriberi (199). Term "vitamin" coined later (200).
	Zymase, the first cell-free enzyme, is extracted from yeast (201).
1898–1940	Renin is found in kidney extracts (202); identification as an enzyme (203) that liberates angiotensin (204).

Table 1.1 *(continued)*

Year(s) of Research or Publication	Discovery or Observation
1899	Aspirin is introduced (205).
1899–1961	Theories of anesthesia are proposed: colloid theory (206); lipid theory (15, 16); clathrate theory (207); others (208–210).
1900	Phenolphthalein is found to be cathartic (211).
1902	Theophylline is tested as a diuretic (212).
1904–1950	Aromatic arsenicals are used in chemotherapy (161): atoxyl in experimental trypanosomiasis (213); arsphenamine, synthesis (214), action (215); neoarsphenamine (216); oxophenarsine (217); tryparsamide (218, 219); butarsen (220); melarsopol (221); carbarsone: amebicidal action (222), synthesis (223); glycobiarsol (224, 225), etc.
1906	Ergot alkaloids are α-adrenergic blocking agents (226); isolation (227, 228).
	U.S. Pure Food and Drug Act; 1938 amendments to the Food, Drug, and Cosmetics Act; 1952 Durham-Humphrey amendment; 1962 Kefauver-Harris amendments.
	Based on trypanocidal action of afridol violet (229), trypan red (230), and trypan blue (231), the "colorless dye" suramin is developed (232); synthesis (233, 234).
1907	Histamine is synthesized (235) before isolation from ergot (236, 237) or animal tissues (238). Pharmacology (239).
1908	Sulfanilamide is synthesized (20). Sulfanilamidochrysoidines were said to be degradable to sulfanilamide (240).
	Local anesthetics are used in spinal anesthesia (241).
1910	Structure–activity relationships of sympathomimetic amines are recorded (242); mode of action (243).
	α-Glyceryl phenyl ether shows CNS effects (244); later (1946) used in muscle relaxation.
1911	Stable analogs of acetylcholine are used as parasympathomimetics (245): methacholine (246–248); carbachol (249, 250); bethanechol (251).
	Phenobarbital, the first 5,5-unsymmetrically substituted barbiturate, is synthesized (252, 253); used as anticonvulsant (254), as hypnotic (255, 256). Other unsymmetrical barbiturates (257) (e.g., amobarbital, secobarbital).
1912	Emetine is located from ipecac (258); structure (259, 260); synthesis (261, 262). (−)2-Dehydroemetine is preferred as antiamebic analog (263, 264).
1913	Deficiency in artificial diets (265, 266) leads to isolation of vitamin A (267), present in pigmented vegetables (268). Provitamin A is carotene (269, 270). Structure of vitamin A_1 (271), synthesis (272, 273); role in vision (274).
	Methenamine, used as a urinary antiseptic since 1894, is promoted as the mandelate (275). Other bactericidal mandelates (276).
1914	Phenazopyridine, a urinary antiseptic, is synthesized (277).
	N-Allylnorcodeine antagonizes morphine-induced respiratory depression (278).
1916	Hypochlorite, *N*-chloramines are topical antiseptics (279); synthesis (280).
	Heparin is found as natural anticoagulant (281); purification (282), chemistry (283), clinical use (284).
1918	Benzyl alcohol is used as a topical local anesthetic (285).

Table 1.1 (*continued*)

Year(s) of Research or Publication	Discovery or Observation
	Antimony compounds are schistosomicidal: tartar emetic (286); stibophen (287); antimony dimercaptosuccinate (288). Sodium stibogluconate is useful in leishmaniasis (289).
	Rauwolfia plant (290) is used in hypertensive (291) and in psychotic patients (292). Alkaloid content (293). Isolation of reserpine (294, 295), structure (296), synthesis (297).
1919	Merbromin is first mercurial antiseptic (298).
	Mercurial diuretics are discovered (299); prototype organomercurial diuretics prepared in 1922 (300, 301).
	Physostigmine (eserine) is isolated from Calabar bean in 1864 (302); structure (303), synthesis (304); anticholinesterase action (305), used in glaucoma.
	8-Aminoquinolines are recognized as antimalarials (306, 307).
1921	Iodinated quinolines are amebicidal: chiniofon (310), synthesis (311); iodochlorhydroxyquin (312, 313); diiodohydroxyquin (314).
1922	Synthetic anticholinergics are considered as mydriatics, cycloplegics, antispasmodics, antiulcer drugs. Homatropine (315); adiphenine (316, 317); oxyphenonium (318); methantheline and propantheline (319); cyclopentolate (320, 321).
	Insulin: isolation (322, 323); purification, crystallization (324); chemistry (325), synthesis (326).
	Vitamin D from cod liver oil (327) cures rickets (328); this is also achieved by irradiation (329). Ergocalciferol (330, 331); vitamin D_3 (332), synthesis (333, 334).
	Diet and fertility of rats are connected (335); vitamin E from wheat germ oil (336); α-tocopherol, structure (337), synthesis (338), antioxidant action (339).
	Sweet clover disease of cattle (340) is a prothrombin deficiency caused by decomposition of coumarin (341) to bishydroxycoumarin; synthesis (342), clinical use as anticoagulant (343, 344). Congeners include warfarin, ethyl biscoumacetate, phenprocoumon, acenocoumarin, phenindione, diphenadione, anisindione. Reviews (345, 346).
	Nikethamide (347) is a respiratory stimulant (348, 349).
1923	Ethylene, first noted as an anesthetic in 1865, is rediscovered (350).
1924	Pentylenetetrazole (351) is used as a convulsant and in regressed geriatric patients (352).
1925	Parathyroid hormone is discovered (353–355).
	Niacin, known as nicotinic acid since 1867 (356), is a pellagra-preventing factor from yeast (357, 358). Niacinamide is part of cozymase (359, 360) or NAD and NADP (361); useful in pellagra (362).
	Oxyphenisatin acetate (acetphenolisatin) is used as cathartic (363); other laxatives: bisacodyl (364), bisoxatin (365).
1926	Hexylresorcinol is a urinary antiseptic (366), anthelmintic (367); hexachlorophene followed in 1932 (368; review 369).
	ACTH is isolated from anterior pituitary (370); structure (371), synthesis (372, 373).
1927	Amphetamine, synthesized in 1887 (374), is recognized as a CNS stimulant (375); clinical use (376).