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Color Atlas of Pharmacology

Fifth Edition

Heinz Luellmann
Klaus Mohr
Lutz Hein

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At a glance

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Color Atlas of Pharmacology

Fifth Edition

Heinz Luellmann, MD †
Former Professor and Chairman
Department of Pharmacology
University of Kiel
Kiel, Germany

Klaus Mohr, MD
Professor
Institute of Pharmacy
Section of Pharmacology and Toxicology
University of Bonn
Bonn, Germany

Lutz Hein, MD
Professor
Institute of Experimental and Clinical Pharmacology and Toxicology
University of Freiburg
Freiburg, Germany

With 174 color plates by Juergen Wirth

Thieme
Stuttgart • New York • Delhi • Rio de Janeiro

Library of Congress Cataloging-in-Publication Data is available from the publisher.

This book is an authorized translation of the 7th German edition published and copyrighted 2015 by Georg Thieme Verlag, Stuttgart.
Title of the German edition: Taschenatlas Pharmakologie
Based on the original translation by Detlev Bieger, MD.
Revisions for the 5th Edition translated by Geraldine O'Sullivan, Dublin, Ireland
Illustrator: Prof. Juergen Wirth, Dreieich, Germany; Nora Wirth, Frankfurt, Germany

1st Albanian edition 2005
2nd Chinese edition 2015 (Taiwan)
4th Czech edition 2012
2nd Dutch edition 2009
5th French edition 2017
1st Greek edition 2005
1st Italian edition 2006
3rd Japanese edition 2012
2nd Polish edition 2009
4th Portuguese edition 2016 (Brazil)
1st Romanian edition 2012
2nd Russian edition 2016
3rd Spanish edition 2010
1st Turkish edition 2002

Thieme Publishers Stuttgart
Rüdigerstrasse 14, 70469 Stuttgart, Germany
+49 [0]711 8931 421, customerservice@thieme.de

Thieme Publishers New York
333 Seventh Avenue, New York, NY 10001 USA
+1 800 782 3488, customerservice@thieme.com

Thieme Publishers Delhi
A-12, Second Floor, Sector-2, Noida-201301
Uttar Pradesh, India
+91 120 45 566 00, customerservice@thieme.in

Thieme Publishers Rio de Janeiro,
Thieme Publicações Ltda.
Edifício Rodolpho de Paoli, 25º andar
Av. Nilo Peçanha, 50 – Sala 2508
Rio de Janeiro 20020-906 Brasil
+55 21 3172 2297 / +55 21 3172 1896

Cover design: Thieme Publishing Group
Typesetting by DiTech Process Solutions Pvt. Ltd., India

Printed in India by
Replika Press Pvt. Ltd., Haryana 5 4 3 2 1

ISBN 978-3-13-241065-7

Also available as an e-book:
eISBN 978-3-13-241143-2

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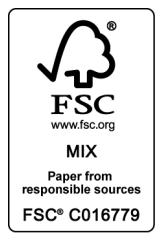

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Preface

In the European Union, about 25 new chemical preparations are approved annually for distribution as pharmaceutical products, approximately 10 of which are "innovative" drugs with a novel molecular mechanism of action. "New" is not always "better," thus new drugs undergo evaluation of their beneficial effects to establish whether new substances reflect an actual therapeutic improvement compared to existing structures, therefore justifying a possible increase in costs to the collective of insured persons.

The innovative strength of pharmaceutical manufacturers, licensing procedures, and the assessment of benefits, together form the basis for successful drug treatment, but the decisive factor is ultimately ensuring that individual patients have access to optimal "customized" treatment. This "therapeutic art" requires that pharmacological principles be understood, and not just memorized.

The *Color Atlas of Pharmacology* is intended to provide students of medicine, dental medicine, and pharmaceutics, as well as anyone with an interest in pharmaceuticals, with an overview of all the available information on pharmacological structures and their methods of action. Special emphasis is placed upon providing the information necessary to enable the reader to understand the principles of pharmacology. Purely factual information, for example, on dosages, can easily be found with an internet search. However, in order to make sense of the facts, connections are explained in graphics, mechanisms of action are clearly depicted, and new drug substances are listed together with existing ones. Many plates and text passages have been fundamentally revised in this new edition, and three completely new double-page spreads have been added. Modern specialized medications such as antibodies that fight malignant diseases and harmful infections, as well as kinase inhibitors, have been integrated into tabular overviews.

The concept of Luellmann's *Color Atlas of Pharmacology* recently celebrated its 25th anniversary. The Atlas was founded by Professor Heinz Luellmann in cooperation with Albrecht Ziegler, Klaus Mohr, and Juergen Wirth. Professor Luellmann passed away shortly before work on this new English edition was started. This edition is dedicated posthumously to his memory.

Klaus Mohr
Lutz Hein
Juergen Wirth

Disclosure: The authors of the *Color Atlas of Pharmacology* have no financial interests or other relationships that would influence the content of this book.

General Pharmacology

History of Pharmacology

Since time immemorial, medicaments have been used for treating disease in humans and animals. The herbals of antiquity describe the therapeutic powers of certain plants and minerals. Belief in the curative powers of plants and certain substances rested exclusively upon traditional knowledge, that is, empirical information not subjected to critical examination.

The Idea

Claudius Galen (AD 129–200) first attempted to consider the theoretical background of pharmacology. Both theory and practical experience were to contribute equally to the rational use of medicines through interpretation of the observed and the experienced results:

"The empiricists say that all is found by experience. We, however, maintain that it is found in part by experience, in part by theory. Neither experience nor theory alone is apt to discover all."

The Impetus

Theophrastus von Hohenheim (1493–1541), called Paracelsus, began to question doctrines handed down from antiquity, demanding knowledge of the active ingredients in prescribed remedies, while rejecting the irrational concoctions and mixtures of medieval medicine. He prescribed chemically defined substances with such success that professional enemies had him prosecuted as a poisoner. Against such accusations, he defended himself with the thesis that has become an axiom of pharmacology:

"If you want to explain any poison properly, what then is not a poison? All things are poison, nothing is without poison; the dose alone causes a thing not to be poison."

Early Beginnings

Johann Jakob Wepfer (1620–1695) was the first to verify by animal experimentation assertions about pharmacological or toxicological actions.

"I pondered at length. Finally I resolved to clarify the matter by experiments."

Foundation

Rudolf Buchheim (1820–1879) founded the first institute of pharmacology at the University of Dorpat (Tartu), Estonia in 1847, ushering in pharmacology as an independent scientific discipline. In addition to a description of effects, he strove to explain the chemical properties of drugs.

"The science of medicines is a theoretical, i.e., explanatory, one. It is to provide us with knowledge by which our judgment about the utility of medicines can be validated at the bedside."

Consolidation—General Recognition

Oswald Schmiedeberg (1838–1921), together with his many disciples (12 of whom were appointed to chairs of pharmacology), helped to establish the high reputation of pharmacology. Fundamental concepts such as structure–activity relationships, drug receptors, and selective toxicity emerged from the work of, respectively, T. Frazer (1840–1920) in Scotland, J. Langley (1852–1925) in England, and P. Ehrlich (1854–1915) in Germany. Alexander J. Clarke (1885–1941) in England first formalized receptor theory in the early 1920s by applying the Law of Mass Action to drug–receptor interactions. Together with the internist Bernhard Naunyn (1839–1925), Schmiedeberg founded the first journal of pharmacology, which has been published since without interruption. The "Father of American Pharmacology," John J. Abel (1857–1938) was among the first Americans to train in Schmiedeberg's laboratory and was founder of the *Journal of Pharmacology and Experimental Therapeutics* (published from 1909 until the present).

Status Quo

After 1920, pharmacological laboratories sprang up in the pharmaceutical industry outside established university institutes. After 1960, departments of clinical pharmacology were set up at many universities and in industry.

Important figures in the history of pharmacology

◀ The idea: Claudius Galen (129–200)

▲ Theophrastus von Hohenheim, known as Paracelsus (1493–1541)

◀ Johann Jakob Wepfer (1620–1695)

▲ Rudolf Buchheim (1820–1879)

◀ Oswald Schmiedeberg (1838–1921)

Fig. 1.1

Drug and Active Principle

Until the end of the 19th century, medicines were natural organic or inorganic products, mostly dried, but also fresh, plants or plant parts. These might contain substances possessing healing (therapeutic) properties, or substances exerting a toxic effect.

In order to secure a supply of medically useful products not merely at the time of harvest but all year round, plants were preserved by drying or soaking them in vegetable oils or alcohol. Drying the plant, vegetable, or animal product yielded a drug (from French "drogue" = dried herb). Colloquially, this term nowadays often refers to chemical substances with high potential for physical dependence and abuse. Used scientifically, this term implies nothing about the quality of action, if any. In its original, wider sense, *drug* could refer equally well to the dried leaves of peppermint, dried lime blossoms, dried flowers and leaves of the female cannabis plant (hashish, marijuana), or the dried milky exudate obtained by slashing the unripe seed capsules of *Papaver somniferum* (raw opium).

Soaking plants or plant parts in alcohol (ethanol) creates a *tincture*. In this process, pharmacologically active constituents of the plant are extracted by the alcohol. Tinctures do not contain the complete spectrum of substances that exist in the plant or crude drug, but only those that are soluble in alcohol. In the case of opium tincture, these ingredients are alkaloids (i.e., basic substances of plant origin) including morphine, codeine, narcotine = noscapine, papaverine, narceine, and others.

Using a natural product or extract to treat a disease thus usually entails the administration of a number of substances possibly possessing very different activities. Moreover, the dose of an individual constituent contained within a given amount of the natural product is subject to large variations, depending upon the product's geographical origin (biotope), time of harvesting, or conditions and length of storage. For the same reasons, the relative proportions of individual constituents may vary considerably. Starting with the extraction of morphine from opium in 1804 by F.W. Sertürner (1783–1841), the active principles of many other natural products were subsequently isolated in chemically pure form by pharmaceutical laboratories.

The Aims of Isolating Active Principles

1. Identification of the active ingredient(s).
2. Analysis of the biological effects (pharmacodynamics) of individual ingredients and of their fate in the body (pharmacokinetics).
3. Ensuring a precise and constant dosage in the therapeutic use of chemically pure constituents.
4. The possibility of chemical synthesis, which would afford independence from limited natural supplies and create conditions for the analysis of structure–activity relationships.

Finally, derivatives of the original constituent may be synthesized in an effort to optimize pharmacological properties. Thus, derivatives of the original constituent with improved therapeutic usefulness may be developed.

Modification of the chemical structure of natural substances has frequently led to pharmaceuticals with enhanced potency. An illustrative example is fentanyl, which acts like morphine but requires a dose 10 to 20 times less than that of the parent substance. Derivatives of fentanyl such as carfentanyl (employed in veterinary anesthesia of large animals) are actually 5000 times more potent than morphine.

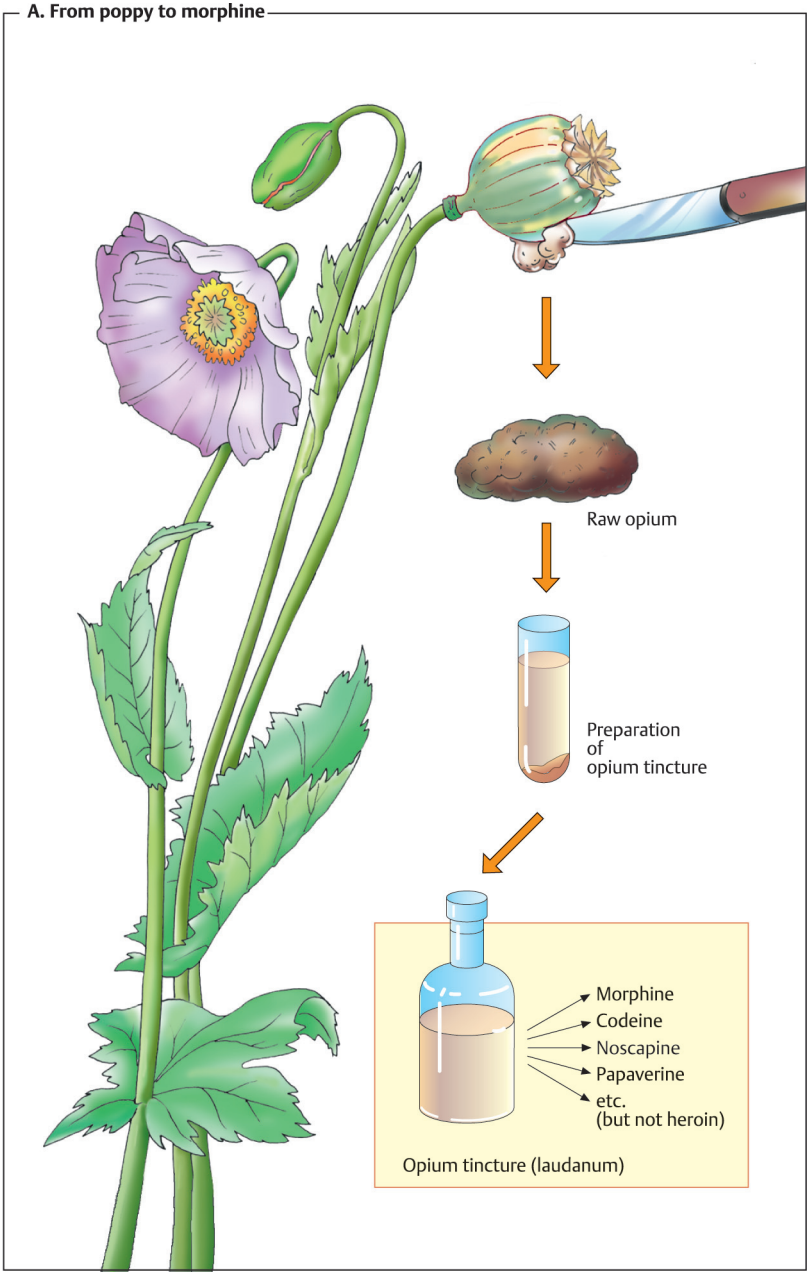

A. From poppy to morphine
Raw opium
Preparation
of
opium tincture
Morphine
Codeine
Noscapine
Papaverine
etc.
(but not heroin)
Opium tincture (laudanum)

Fig. 2.1

Plants as Sources of Effective Medicines

Since prehistoric times, humans have attempted to alleviate ailments or injuries with the aid of plant parts or herbal preparations. Ancient civilizations have recorded various prescriptions of this kind. In the herbal formularies of medieval times numerous plants were promoted as remedies. In modern medicine, where each drug is required to satisfy objective criteria of efficacy, few of the hundreds of reputedly curative plant species have survived as drugs with documented effectiveness. Presented below are some examples from local old-world floras that were already used in prescientific times and that contain substances that to this day are employed as important drugs.

a) A group of local plants used since the middle ages to treat "dropsy" comprises foxglove (digitalis sp.), lily of the valley *(Convallaria majalis),* Christmas rose *(Helleborus niger),* and spindletree *(Euonymus europaeus).* At the end of the 18th century the Scottish physician William Withering introduced **digitalis leaves** as a tea into the treatment of "cardiac dropsy" (edema of congestive heart failure) and described the result. The active principles in these plants are steroids with one or more sugar molecules attached at C3 (see p. 148). Proven clinically to be the most useful among all available cardiac glycosides, **digoxin** continues to be obtained from the plants *Digitalis purpurea* or *D. lanata* because its chemical synthesis is too difficult and expensive.

b) The **deadly nightshade** of Central Europe *(Atropa belladonna,* a solanaceous herb)[1] contains the alkaloids **atropine**, in all its parts, and **scopolamine**, in smaller amounts. The effects of this drug were already known in antiquity; e.g., pupillary dilation resulting from the cosmetic use of extracts as eye drops to enhance female attractiveness. In the 19th century, the alkaloids were isolated, their structures elucidated, and their specific mechanism of action recognized. Atropine is the prototype of a competitive antagonist at the acetylcholine receptor of the muscarinic type (cf. p. 124).

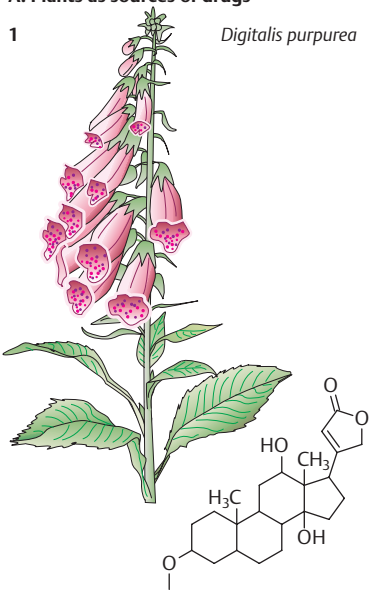
c) The **common white willow** and **basket willow** *(Salix alba, S. viminalis)* contain salicylic acid derivatives in their bark. Preparations of willow bark have been used since antiquity; in the 19th century, **salicylic acid** was isolated as the active principle of this folk remedy. This simple acid still enjoys use as an external agent (keratolytic action) but is no longer taken orally for the treatment of pain, fever, and inflammatory reactions. Acetylation of salicylic acid (introduced around 1900) to yield **acetylsalicylic acid** (ASA, Aspirin®) improved oral tolerability.

d) The **autumn crocus** *(Colchicum autumnale)* belongs to the lily family and flowers on meadows in late summer and fall; leaves and fruit capsules appear in the following spring. All parts of the plant contain the alkaloid **colchicine**. This substance inhibits the polymerization of tubulin to microtubules, which are responsible for intracellular movement processes. Thus, under the influence of colchicine, macrophages and neutrophils lose their capacity for intracellular transport of cell organelles. This action underlies the beneficial effect during an acute attack of gout (cf. p. 350). Furthermore, colchicine prevents mitosis, causing an arrest in metaphase (spindle poison).

[1] This name reflects the poisonous property of the plant: Atropos was the one of the three Fates (moirai) who cut the thread of life.

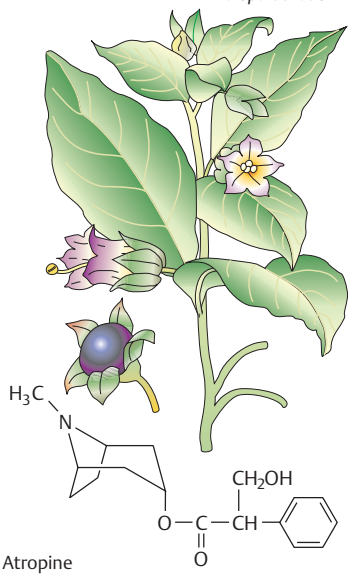
A. Plants as sources of drugs

1 *Digitalis purpurea*



Digoxin

2 *Atropa belladonna*



Atropine

3 *Salix alba*

Salicylic acid

4 *Colchicum autumnale*

Colchicine

Fig. 2.2

Human Proteins as Medicines

Proteins that are used as medicines should match the "human template" so as to avoid immune-mediated intolerability reactions. Producing human proteins by means of classic organic chemistry synthesis would be very complex: whereas only 20 atoms have to be joined correctly to form the low-molecular-weight analgesic acetaminophen (paracetamol), an antibody involves roughly 25 000 atoms.

Genetic Engineering

The protein-coding cDNA is integrated in an expression plasmid and this is inserted into suitable host cells (▶ Fig. 2.3**A**). The chosen *cellular expression system* and *cell culture conditions* have a major influence on the product.

- *Mammalian cells* such as CHO (Chinese hamster ovary) cells can link carbohydrate residues to proteins; *bacteria* such as E. coli are unsuitable for production of *glycoproteins* but do allow production of nonglycosylated proteins.
- The *spatial (3D) structure* of the product depends in part on whether disulfide bridges occur and if so, which ones.
- The *amino acid sequence* and *charge* can be altered by subsequent deamidation of the amino acids asparagine and glutamine to aspartate and glutamate.

Meticulous attention to every detail of the production process and sophisticated analytical tests are needed to ensure that the product's properties remain consistent.

Replacement Therapy

The number of human-identical or human-analogue proteins available for replacement therapy is increasing (▶ Fig. 2.3**B**). These include native or genetically modified human insulin (see p. 256) and *erythropoietin (epoetin),* which is used to treat severe anemia (see p. 154). When these proteins are injected, they readily reach their receptors in the cell membrane. Introduction of *polyethylene glycol* (PEG) chains to certain proteins can delay their elimination from the circulation, thereby prolonging their duration of action. Metabolic diseases resulting from a lysosomal enzyme deficiency require intracellular protein delivery. Genetically engineered enzymes with a *mannose-6-phosphate residue* are suitable. This acts as the "key" for getting into the cell by receptor-mediated endocytosis and then into the interior of the lysosomes.

▶ **Protein constructs to interrupt signaling pathways (▶ Fig. 2.3C).** This is possible on both the messenger compound (C1–C3) and on the receptor side (C4–C6). The inhibitors can be classified as different "types." The expression system is given in brackets.

▶ **C1–C3.** Vascular endothelial growth factor, VEGF (see p. 377) acts through its receptors to promote the proliferation of blood vessels in the wet form of macular degeneration (the macula is the part of the retina where visual acuity is maximal → risk of blindness).

VEGF can be inactivated by:

- bevacizumab, a complete artificial antibody (see p. 376); mab: monoclonal antibody (unlicensed indication)
- the Fab antibody fragment ranibizumab
- the fusion protein aflibercept, consisting of the binding area of the VEGF receptor and an antibody Fc segment.

▶ **C4–C6.** C4–C6 show ways of interrupting the signaling pathway by receptor blockade:

- complete antibody, e.g., basiliximab (see p. 304), which counteracts interleukin 2-mediated rejection of an organ transplant
- Fab antibody fragment, e.g., abciximab, which inhibits fibrinogen-mediated platelet aggregation (see p. 166)
- Genetically engineered replication of an endogenous inactivator, e.g., interleukin1 receptor antagonist, IL-1RA, in rheumatoid arthritis (see p. 360).

▶ **Analogue products.** Imitators of the "biologics" are also keen to share in the commercial success of a product. Unlike small organic drugs, however, an exact copy of the original substance is often not possible on account of the complexity of the genetically engineered production process (cell line, nutrient medium, temperature, pressure, etc.). A structurally similar imitation is called a "biosimilar." Its benefit and risk profile must be confirmed by separate clinical trials.

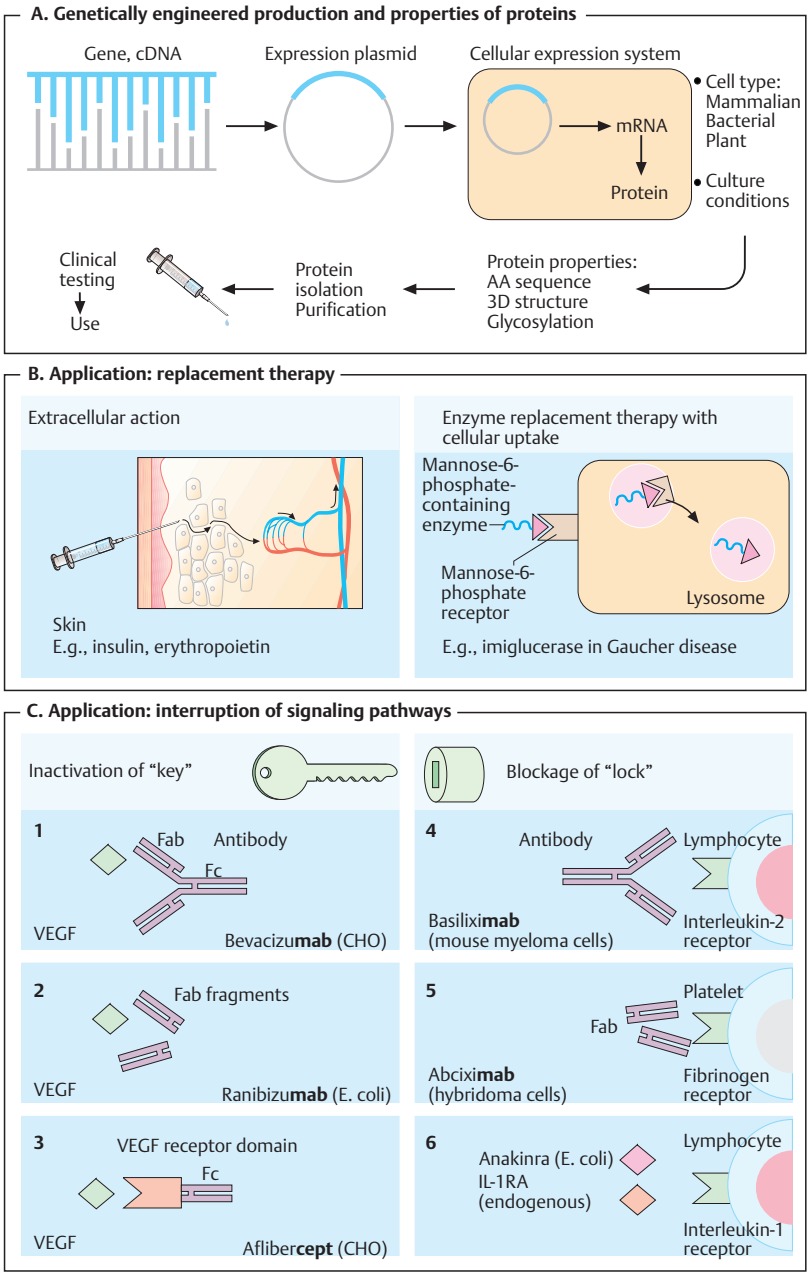

A. Genetically engineered production and properties of proteins
Gene, cDNA
Expression plasmid
Cellular expression system
mRNA
Protein
Cell type: Mammalian Bacterial Plant
Culture conditions
Protein properties: AA sequence 3D structure Glycosylation
Protein isolation Purification
Clinical testing
Use
B. Application: replacement therapy
Extracellular action
Skin
E.g., insulin, erythropoietin
Enzyme replacement therapy with cellular uptake
Mannose-6-phosphate-containing enzyme
Mannose-6-phosphate receptor
Lysosome
E.g., imiglucerase in Gaucher disease
C. Application: interruption of signaling pathways
Inactivation of "key"
Blockage of "lock"
1
Fab
Antibody
Fc
VEGF
Bevacizumab (CHO)
2
Fab fragments
VEGF
Ranibizumab (E. coli)
3
VEGF receptor domain
Fc
VEGF
Aflibercept (CHO)
4
Antibody
Lymphocyte
Basiliximab (mouse myeloma cells)
Interleukin-2 receptor
5
Platelet
Fab
Abciximab (hybridoma cells)
Fibrinogen receptor
6
Anakinra (E. coli)
IL-1RA (endogenous)
Lymphocyte
Interleukin-1 receptor

Fig. 2.3

Drug Development

The drug development process starts with the **synthesis** of novel chemical compounds. Substances with complex structures may be obtained from various sources, e.g., plants (cardiac glycosides), animal tissues (heparin), microbial cultures (penicillin G) or cultures of human cells (urokinase), or by means of gene technology (human insulin). As more insight is gained into structure–activity relationships, the search for new agents becomes more clearly focused.

Preclinical testing yields information on the biological effects of new substances. Initial screening may employ *biochemical–pharmacological investigations* (e.g., ▶ Fig. 8.3) or experiments on cell cultures, isolated cells, and isolated organs. Since these models invariably fall short of replicating complex biological processes in the intact organism, any potential drug must be tested in the whole animal. Only animal experiments can reveal whether the desired effects will actually occur at dosages that produce little or no toxicity. *Toxicological investigations* serve to evaluate the potential for: (1) toxicity associated with acute or chronic administration; (2) genetic damage (genotoxicity, mutagenicity); (3) production of tumors (oncogenicity or carcinogenicity); and (4) causation of birth defects (teratogenicity). In animals, compounds under investigation also have to be studied with respect to their absorption, distribution, metabolism, and elimination *(pharmacokinetics)*. Even at the level of preclinical testing, only a very small fraction of new compounds will prove potentially suitable for use in humans.

Pharmaceutical technology provides the methods for drug formulation.

Clinical testing starts with **Phase I** studies on healthy subjects to determine whether effects observed in animals also occur in humans. Dose–response relationships are determined. In **Phase II**, potential drugs are first tested on selected patients for therapeutic efficacy in the illness for which they are intended. If a beneficial action is evident, and the incidence of adverse effects is acceptably small, **Phase III** is entered, involving a larger group of patients in whom the new drug is compared with conventional treatments in terms of therapeutic outcome. As a form of human experimentation, these clinical trials are subject to review and approval by institutional ethics committees according to international codes of conduct (Declarations of Helsinki, Tokyo, and Venice). During clinical testing, many drugs are revealed to be unusable. Ultimately, only one new drug typically remains from some 10000 newly synthesized substances.

The decision to **approve a new drug** is made by a national regulatory body (Food and Drug Administration in the United States; the Health Protection Branch Drugs Directorate in Canada; the EU Commission in conjunction with the European Medicines Agency [EMA], London, United Kingdom) to which manufacturers are required to submit their applications. Applicants must document by means of appropriate test data (from preclinical and clinical trials) that the criteria of efficacy and safety have been met and that product forms (tablet, capsule, etc.) satisfy general standards of quality control.

Following approval, the new drug (p. 26) may be marketed under a trade name (p. 380) and so be available for prescription by physicians and dispensing by pharmacists. At this time regulatory surveillance continues in the form of postlicensing studies (**Phase IV** of clinical trials). **Pharmacovigilance** is the name given to activities intended to identify and guard against drug risks during clinical trials and subsequent marketing. This includes reporting of suspected cases of adverse drug effects (ADEs) to the national regulatory authorities. Only on the basis of long-term experience will the risk–benefit ratio be properly assessed and, thus, the therapeutic value of the new drug be determined. If the new drug offers hardly any advantage over existing ones, the cost–benefit relationship needs to be kept in mind.

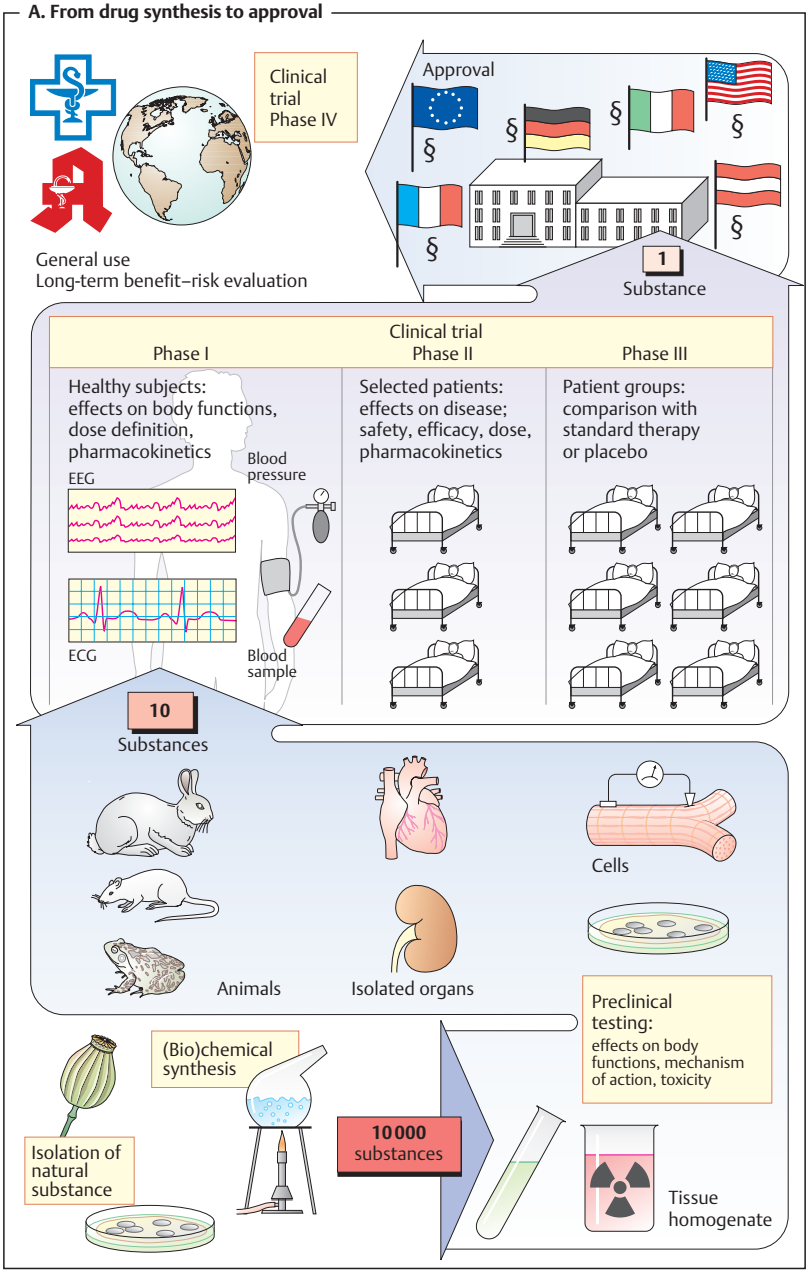

A. From drug synthesis to approval
Clinical trial Phase IV
General use
Long-term benefit–risk evaluation
Approval
§
1
Substance
Clinical trial
Phase I
Phase II
Phase III
Healthy subjects: effects on body functions, dose definition, pharmacokinetics
Selected patients: effects on disease; safety, efficacy, dose, pharmacokinetics
Patient groups: comparison with standard therapy or placebo
EEG
ECG
Blood pressure
Blood sample
10
Substances
Animals
Isolated organs
Cells
Preclinical testing:
effects on body functions, mechanism of action, toxicity
(Bio)chemical synthesis
Isolation of natural substance
10 000 substances
Tissue homogenate

Fig. 2.4

Drug Benefit Assessment

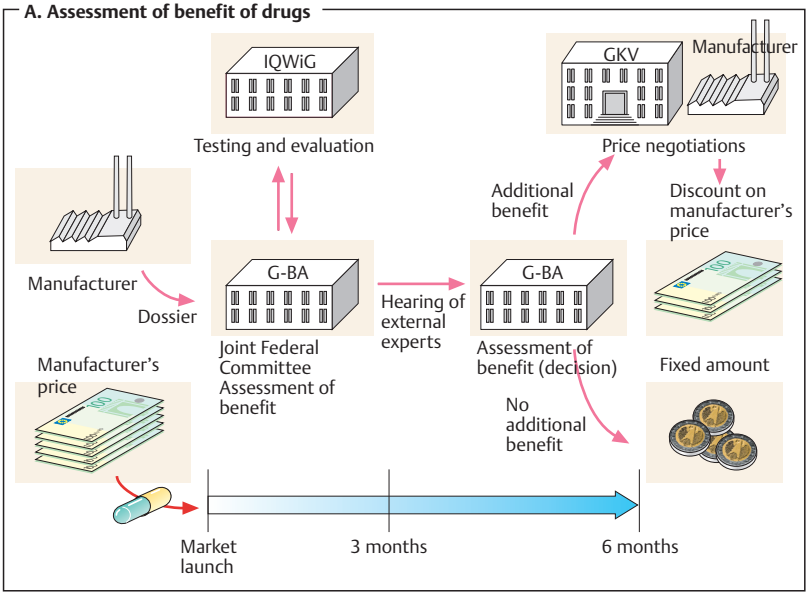
Legal Assessment of the Benefit of New Drugs

After marketing authorization for a new drug, countries have different procedures to assess the therapeutic benefit of the new compound and to adjust the drug prices accordingly. Unlike the (partially) harmonized procedures for drug approval in the US and in Europe (p. 22), the benefit assessment and price regulations differ from country to country. Due to the limited space here, we briefly illustrate the current regulations in Germany. A statutory procedure for assessing the benefit of new drugs was introduced in Germany in 2011 with a view to containing rising healthcare costs (▶ Fig. 2.5**A**). This procedure is specified in the Act for Restructuring the Pharmaceutical Market (German AMNOG). Immediately after the market launch of a new drug, the manufacturer must submit to the Joint Federal Committee (G-BA) documentation (the "dossier") showing the potential additional benefit compared with previous standard therapy. The Federal Committee receives expert advice from the Institute for Quality and Economy in Healthcare (IQWIG). Other organizations (e.g., the Medicines Committee of the German Medical Council) can comment on the submitted dossier. After three months, the G-BA decides whether the new medicine has any additional benefit and what this comprises. If there is an additional benefit compared with the previous comparative therapy, the manufacturer and National Association of Statutory Health Insurance Funds negotiate the price for the new medicine. A fixed price is specified for medicines without additional benefit.

Until December 2015, this assessment of benefit had been initiated or completed for 262 new drugs or drug combinations. No additional benefit was found in approximately 50% of the new medicines. A substantial additional benefit was confirmed for 10% and a small additional benefit for 22%. The latest information about the procedure and assessment results can be obtained on the internet on the website of the Joint Federal Committee: www.g-ba.de.

Assessment of Benefit—Number Needed to Treat

Many medicines are given to prevent later disease. Treatment of high blood pressure is an example: in itself, high blood pressure usually does not cause any symptoms, but it increases the risk for serious conditions such as myocardial infarction and stroke. Preventive drug treatment in turn is associated with a risk of adverse drug effects. The "number needed to treat" is used to quantify the expected level of benefit of a preventive measure. This states the number of persons that must be treated prophylactically for one person to derive benefit. The calculation is based on the results of clinical studies. This parameter must be strictly distinguished from the percentage risk reduction. ▶ Fig. 2.5**B** illustrates the results of a study of vertebral fracture prevention. Treatment over a number of years reduced the relative fracture risk by about 70% relative to the fracture risk in the placebo-treated control group. This ratio, however, does not identify the benefit that an individual patient can expect in statistical terms. Since the fracture event itself is relatively rare (only about one person in ten is affected in the observation period), the NNT result is 13. The remaining 12 treated persons would derive no benefit statistically—either because they would not have suffered a vertebral fracture anyway or because the medicine would not have been beneficial in the individual case. The pharmaco-economist can now calculate how much one prevented event (a fracture in this case) would cost the community of insured persons.


A. Assessment of benefit of drugs
IQWiG
Testing and evaluation
GKV
Manufacturer
Price negotiations
Additional benefit
Discount on manufacturer's price
Manufacturer
Dossier
G-BA
Joint Federal Committee Assessment of benefit
Hearing of external experts
G-BA
Assessment of benefit (decision)
Manufacturer's price
Fixed amount
No additional benefit
Market launch
3 months
6 months

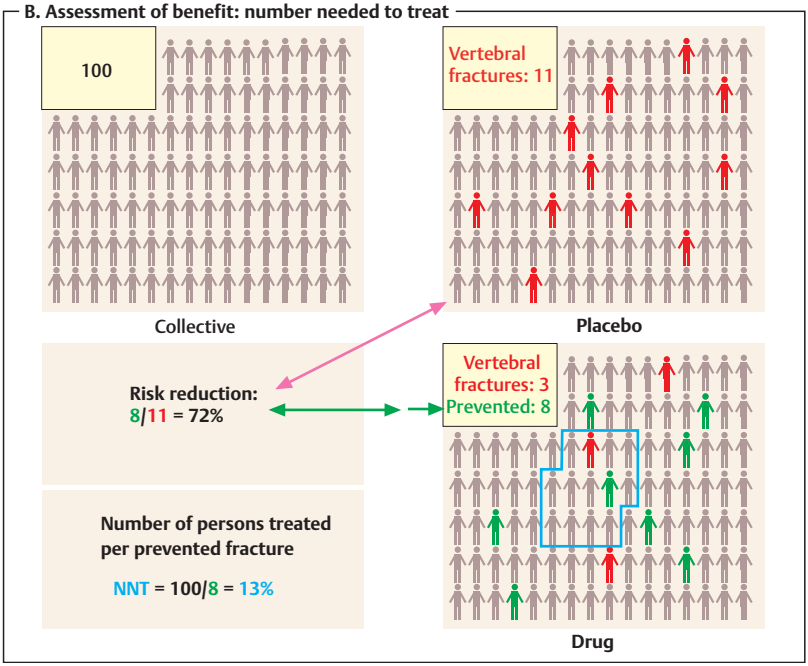

B. Assessment of benefit: number needed to treat
100
Collective
Vertebral fractures: 11
Placebo
Risk reduction:
8/11 = 72%
Vertebral fractures: 3
Prevented: 8
Number of persons treated per prevented fracture
NNT = 100/8 = 13%
Drug

Fig. 2.5

Congeneric Drugs and Name Diversity

The preceding pages outline the route leading to approval of a new drug. The pharmaceutical receives an **International Nonproprietary Name** (INN) and a brand or trade name chosen by the pharmaceutical company. Patent protection enables the patent holder to market the new substance for a specified period of time. As soon as the patent protection expires, the drug concerned can be put on the market as a generic under a nonproprietary name or as a successor preparation under other brand names. When successor preparations of biopharmaceuticals (such as epoetin or somatotropin) are put on the market, they are called **biosimilars**. These products must meet particularly high requirements with regard to bioequivalence and side effects. Since patent protection is generally already sought during the development phase, sale of the drug may be protected only for a few years.

The value of a **new drug** depends on whether it involves a novel active principle or merely an analogue (or congeneric) preparation with a slightly changed chemical structure. It is of course much more arduous to develop a substance that possesses a novel mechanism of action and thereby expands therapeutic possibilities. Examples of such fundamental innovations from recent years include the kinase inhibitors (e.g., imatinib, p. 300), HIV adsorption and integrase inhibitors (p. 288), and incretin mimetics (p. 262).

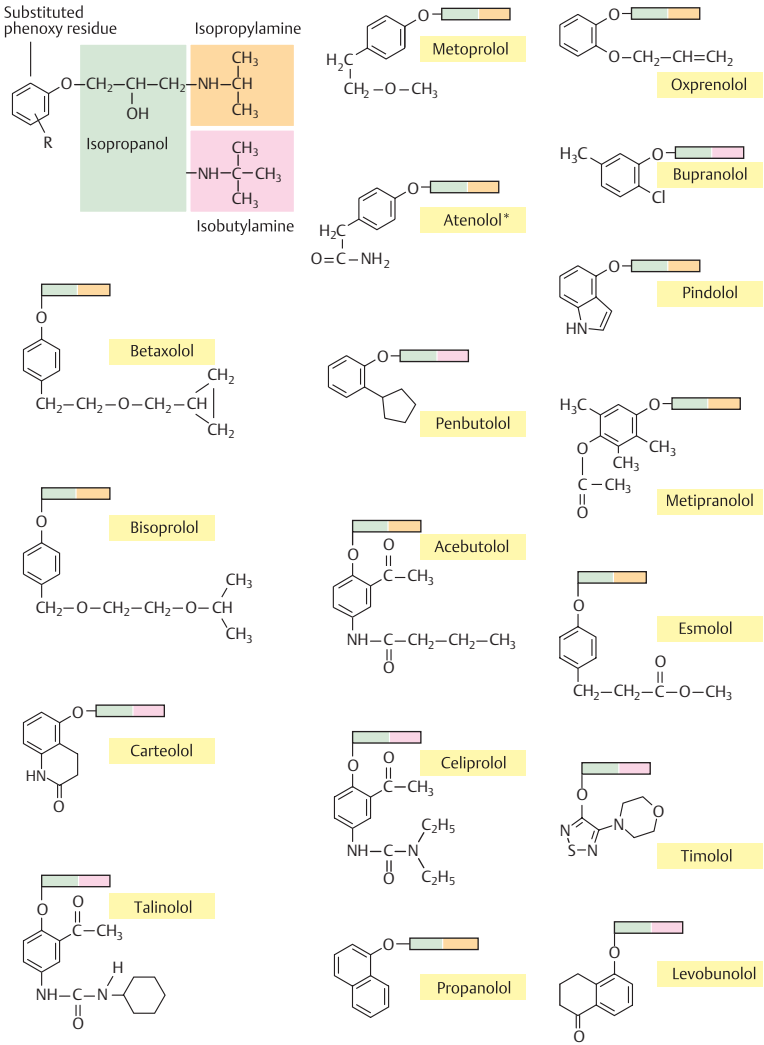
Much more frequently, "new drugs" are analogue substances that imitate the chemical structure of a successful pharmaceutical. These compounds contain the requisite features in their molecule but differ from the parent molecule by structural alterations that are biologically irrelevant. Such **analogue substances**, or "me-too" products, do not add anything new regarding the mechanism of action. The β-blockers are an example of the overabundance of analogue substances: about 20 individual substances with the same pharmacophoric groups differing only in the substituents at the phenoxy residue. This entails small differences in pharmacokinetic behavior and relative affinity for β-receptor subtypes (examples shown in **A**). A small fraction of these substances would suffice for therapeutic use. The WHO Model List of Essential Medicines names only three β-blockers (bisoprolol, propranolol, timolol) from the existing profusion (▶ Fig. 2.6**A**). The corresponding phenomenon is evident among various other drug groups (e.g., benzodiazepines, nonsteroidal anti-inflammatory agents, and cephalosporins). Most analogue substances can be neglected.

After patent protection expires, competing drug companies will at once market successful (i.e., profitable) pharmaceuticals as second-submission **successor** (or "follow-on") **preparations**. Since no research expenses are involved at this point, successor drugs can be offered at a cheaper price, either as **generics** (INN + pharmaceutical company name) or under new fancy names. Thus some common drugs circulate under many different trade names. An extreme example is presented in **B** for the analgesic ibuprofen.

The excess of analogue preparations and the unnecessary diversity of trade names for one and the same drug make the pharmaceutical markets of some countries (e.g., Germany) rather perplexing. A critical listing of **essential drugs** is a prerequisite for optimal pharmacotherapy and would be of great value for medical practice.

Another sales strategy of the pharmaceutical industry can complicate matters for the prescribing physician, by combining a necessary drug with an indifferent or low-dose second substance. For instance, analgesics are combined with a little caffeine (about as much as in a cup of coffee) or vitamin C (as much as in one tomato), a new trade name is invented, and the price is raised.

A. β-Blockers of similar basic structure



The nebivolol and carvedilol molecules are more complicated.

B. Successor preparations for a pharmaceutical (2014)

Ibuprofen under different trade names, introduced as Brufen® (no longer available in some countries): 259 products from 36 companies (in Germany)

Fig. 2.6

Oral Dosage Forms

The **coated tablet** contains a drug within a core that is covered by a shell, e.g., wax coating, that serves (1) to protect perishable drugs from decomposing, (2) to mask a disagreeable taste or odor, (3) to facilitate passage on swallowing, or (4) to permit color coding.

Capsules usually consist of an oblong casing —generally made of gelatin—that contains the drug in powder or granulated form.

In the **matrix-type tablet**, the drug is embedded in an inert meshwork, from which it is released by diffusion upon being moistened. In contrast to *solutions*, which permit direct absorption of drug (▶ Fig. 3.1**A**, track 3), the use of solid dosage forms initially requires *tablets* to break up and *capsules* to open (**disintegration**), before the drug can be dissolved (**dissolution**) and pass through the gastrointestinal mucosal lining (**absorption**). Because disintegration of the tablet and dissolution of the drug take time, absorption will occur mainly in the intestine (▶ Fig. 3.1**A**, track 2). In the case of a solution, absorption already starts in the stomach (▶ Fig. 3.1**A**, track 3).

For acid-labile drugs, a coating of wax or of a cellulose acetate polymer is used to prevent disintegration of solid dosage forms in the stomach. Accordingly, disintegration and dissolution will take place in the duodenum at normal rate (▶ Fig. 3.1**A**, track 1) and drug liberation per se is not retarded.

The **liberation** of drug, and hence the site and time-course of absorption, are subject to modification by appropriate production methods for matrix-type tablets, coated tablets, and capsules. In the case of the matrix tablet, this is done by incorporating the drug into a lattice from which it can be slowly leached out by gastrointestinal fluids. As the matrix tablet undergoes enteral transit, drug liberation and absorption proceed en route (▶ Fig. 3.1**A**, track 4). In the case of coated tablets, coat thickness can be designed such that release and absorption of drug occur either in the proximal (▶ Fig. 3.1**A**, track 1) or distal (▶ Fig. 3.1**A**, track 5) bowel. Thus, by matching dissolution time with small-bowel transit time, drug release can be timed to occur in the colon.

Drug liberation and, hence, absorption can also be spread out when the drug is presented in the form of granules consisting of pellets coated with a waxy film of graded thickness. Depending on film thickness, gradual dissolution occurs during enteral transit, releasing drug at variable rates for absorption. The principle illustrated for a *capsule* can also be applied to tablets. In this case, either drug pellets coated with films of various thicknesses are compressed into a tablet or the drug is incorporated into a *matrix-type* tablet. In contrast to timed-release capsules *slow-release tablets* have the advantage of being divisible ad libitum; thus fractions of the dose contained within the entire tablet may be administered.

This kind of **retarded drug release** is employed when a rapid rise in blood levels of drug is undesirable, or when absorption is being slowed in order to prolong the action of drugs that have a short sojourn in the body.

A. Oral administration: drug release and absorption

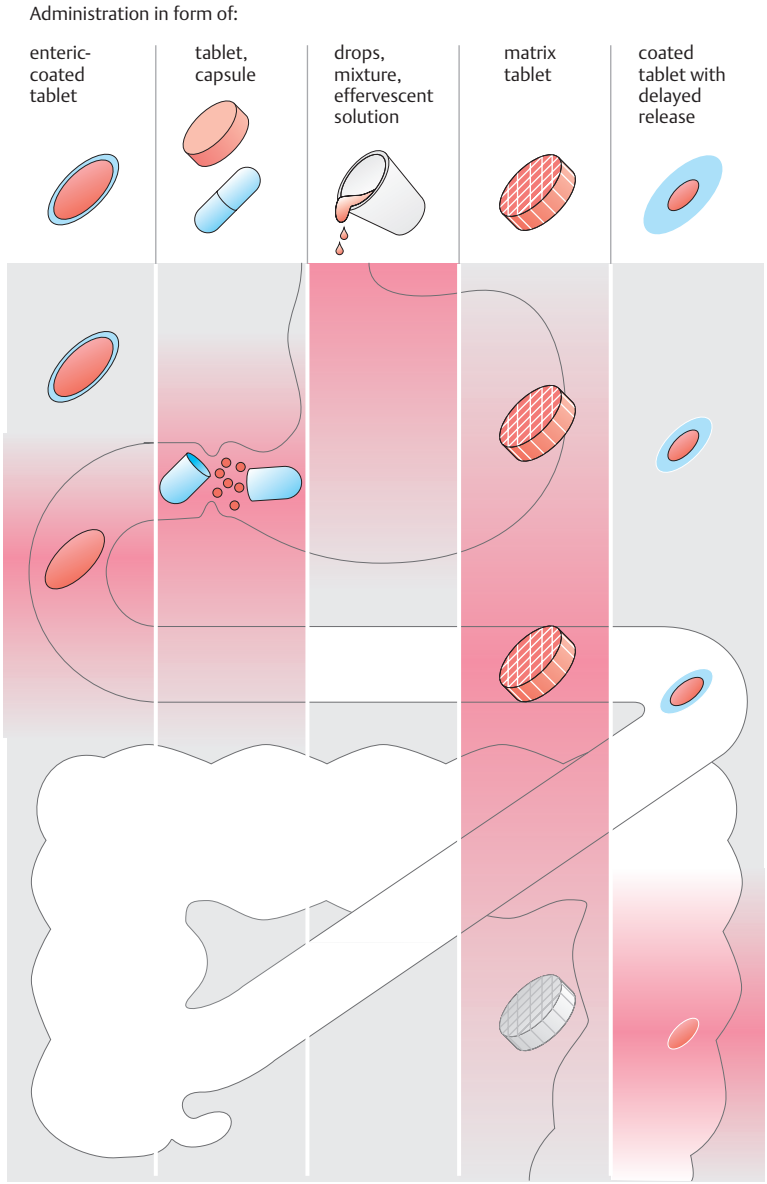


Fig. 3.1

Drug Administration by Inhalation

Inhalation in the form of an aerosol, a gas, or a mist permits drugs to be delivered to the bronchial mucosa and, to a lesser extent, to the alveolar membranes. This route is chosen for drugs intended to affect bronchial smooth muscle or the consistency of bronchial mucus. Furthermore, gaseous or volatile agents can be administered by inhalation with the goal of alveolar absorption and systemic effects (e.g., inhalational anesthetics, p. 218). **Aerosols** are formed when a drug solution or micronized powder is converted into a mist or dust, respectively.

In conventional sprays (e.g., nebulizer), the air jet required for the aerosol formation is generated by the stroke of a pump. Alternatively, the drug is delivered from a solution or powder packaged in a pressurized canister equipped with a valve through which a metered dose is discharged. During use, the inhaler (spray dispenser) is held directly in front of the mouth and actuated at the start of inspiration. The effectiveness of delivery depends on the position of the device in front of the mouth, the size of the aerosol particles, and the coordination between opening the spray valve and inspiration. The size of the aerosol particles determines the speed at which they are swept along by inhaled air, and hence the **depth of penetration into the respiratory tract**. Particles >100 µm in diameter are trapped in the oropharyngeal cavity; those having diameters between 10 and 60 µm will be deposited on the epithelium of the bronchial tract. Particles <2 µm in diameter can reach the alveoli, but they will be exhaled again unless they settle out.

Drug deposited on the mucous lining of the bronchial epithelium is partly absorbed and partly transported with bronchial mucus toward the larynx. Bronchial mucus travels upward owing to the orally directed undulatory beat of the epithelial cilia. Physiologically, this mucociliary transport functions to remove inspired dust particles.

Thus, only a portion of the drug aerosol (~10%) gains access to the respiratory tract and just a fraction of this amount penetrates the mucosa, whereas the remainder of the aerosol undergoes mucociliary transport to the laryngopharynx and is swallowed. The advantage of inhalation (i.e., localized administration without systemic load) is fully exploited by using drugs that are poorly absorbed from the intestine (tiotropium, cromolyn) or are subject to first-pass elimination (p. 60); for example, glucocorticoids such as beclomethasone dipropionate, budesonide, flunisolide, and fluticasone dipropionate or β-agonists such as salbutamol and fenoterol.

Even when the swallowed portion of an inhaled drug is absorbed in unchanged form, administration by this route has the advantage that drug concentrations at the bronchi will be higher than in other organs.

The efficiency of mucociliary transport depends on the force of kinociliary motion and the viscosity of bronchial mucus. Both factors can be altered pathologically (e.g., by smoker's cough or chronic bronchitis).

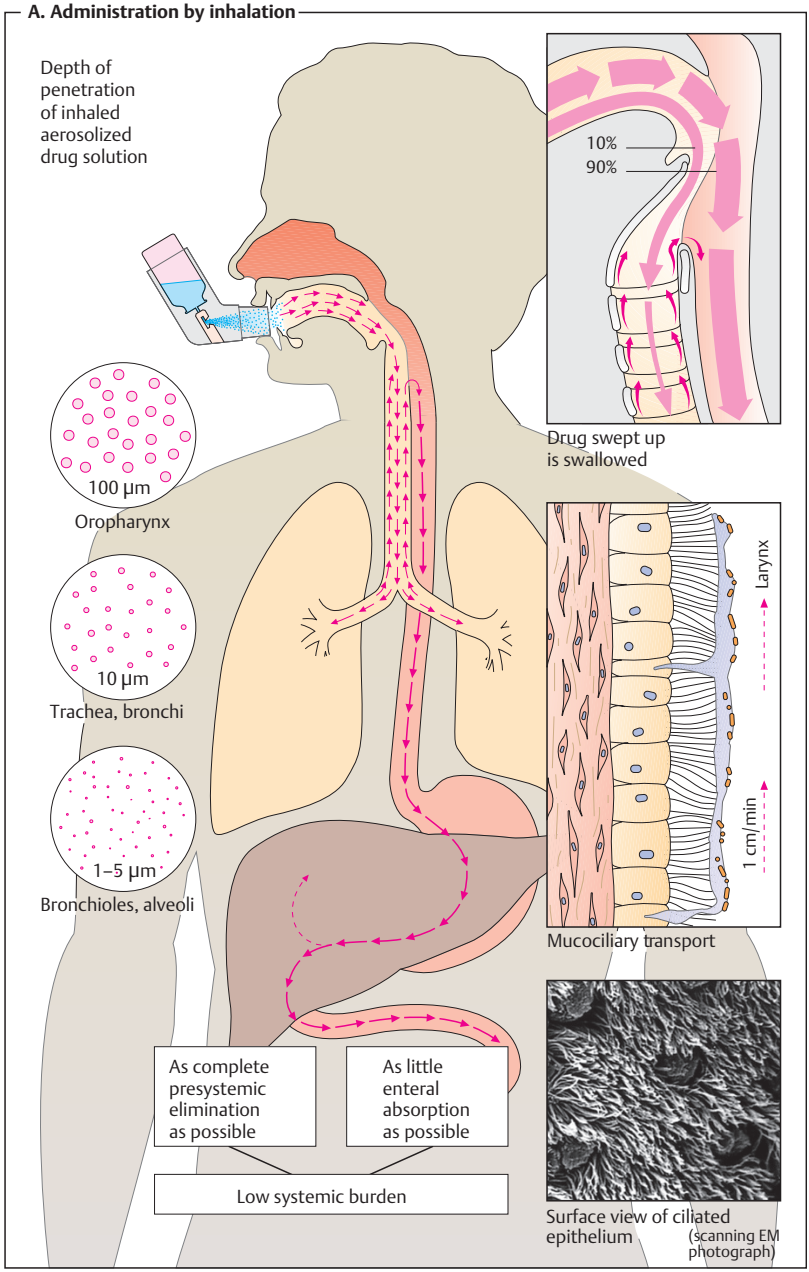

A. Administration by inhalation
Depth of penetration of inhaled aerosolized drug solution
100 µm
Oropharynx
10 µm
Trachea, bronchi
1–5 µm
Bronchioles, alveoli
10%
90%
Drug swept up is swallowed
Larynx
1 cm/min
Mucociliary transport
Surface view of ciliated epithelium
(scanning EM photograph)
As complete presystemic elimination as possible
As little enteral absorption as possible
Low systemic burden

Fig. 3.2

Dermatological Agents

Pharmaceutical preparations applied to the outer skin are intended either to provide skin care and protection from noxious influences (▶ Fig. 3.3**A**) or to serve as a vehicle for drugs that are to be absorbed into the skin or, if appropriate, into the general circulation (▶ Fig. 3.3**B**).

Skin Protection

Protective agents (▶ Fig. 3.3**A**) are of several kinds to meet different requirements according to skin condition (dry, low in oil, chapped vs. moist, oily, elastic), and the type of noxious stimuli (prolonged exposure to water, regular use of alcohol-containing disinfectants, intense solar irradiation). Distinctions among protective agents are based upon consistency, physicochemical properties (lipophilic, hydrophilic), and the presence of additives.

▶ **Dusting powders.** Dusting powders are sprinkled onto the intact skin and consist of talc, magnesium stearate, silicon dioxide (silica), or starch. They adhere to the skin, forming a low-friction film that attenuates mechanical irritation. Powders exert a drying (evaporative) effect.

▶ **Lipophilic ointment (oil ointment).** Lipophilic ointment consists of a lipophilic base (paraffin oil, petroleum jelly, lanolin) and may contain up to 10% powder materials, such as zinc oxide, titanium oxide, starch, or a mixture of these. Emulsifying ointments are made of paraffins and an emulsifying wax, and are miscible with water.

▶ **Paste (oil paste).** Paste is an ointment containing more than 10% pulverized constituents.

▶ **Lipophilic (oily) cream.** Lipophilic cream is an emulsion of water in oil, easier to spread than oil paste or oil ointment.

▶ **Hydrogel and water-soluble ointment.** These substances achieve their consistency by means of different gel-forming agents (gelatin, methylcellulose, polyethylene glycol). **Lotions** are aqueous suspensions of water-insoluble and solid constituents.

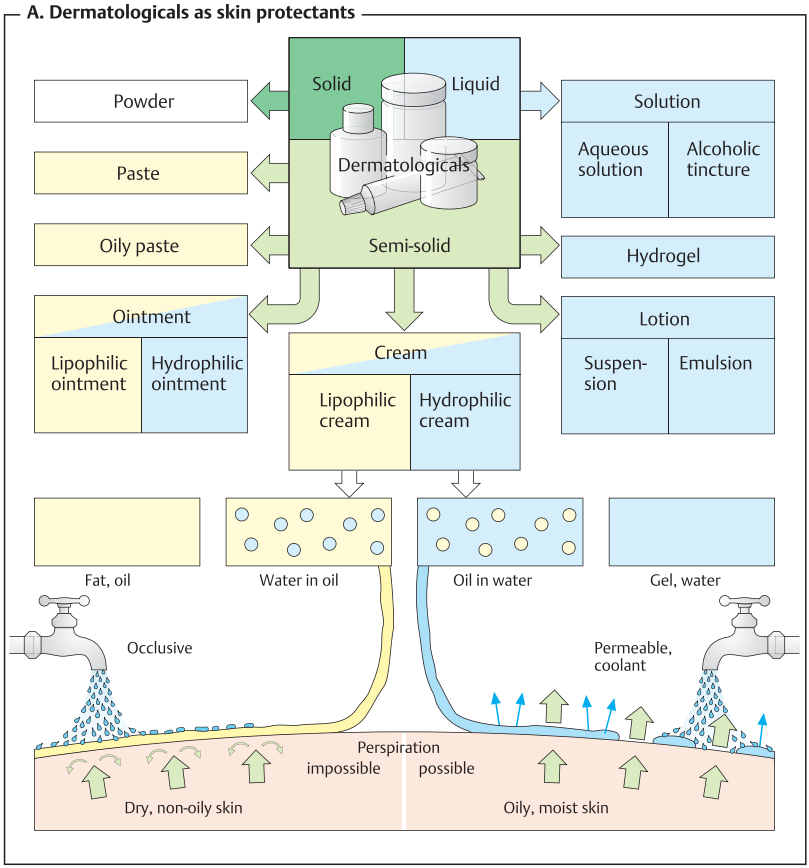
▶ **Hydrophilic (aqueous) cream.** Hydrophilic cream is an oil-in-water emulsion formed with the aid of an emulsifier; it may also be considered an oil-in-water emulsion of an emulsifying ointment.

All dermatological agents having a lipophilic base adhere to the skin as a water-repellent coating. They do not wash off and they also prevent (**occlude**) outward passage of water from the skin. The skin is protected from drying, and its hydration and elasticity increase.

Diminished evaporation of water results in warming of the occluded skin. Hydrophilic agents wash off easily and do not impede transcutaneous output of water. Evaporation of water is felt as a cooling effect.

Dermatological Agents as Vehicles

In order to reach its site of action, a drug must leave its pharmaceutical preparation (▶ Fig. 3.3**B**) and enter the skin if a local effect is desired (e.g., glucocorticoid ointment), or be able to penetrate it if a systemic action is intended (transdermal delivery system, e.g., nitroglycerin patch, p. 138). The tendency for the drug to leave the drug vehicle is higher the more the drug and vehicle differ in lipophilicity (high tendency: hydrophilic drug and lipophilic vehicle; and vice versa). Because the skin represents a closed lipophilic barrier (p. 38), only lipophilic drugs are absorbed. Hydrophilic drugs fail to penetrate the outer skin even when applied in a lipophilic vehicle. This formulation can be useful when high drug concentrations are required at the skin surface (e.g., neomycin ointment for bacterial skin infections).


A. Dermatologicals as skin protectants
Powder
Paste
Oily paste
Solid
Liquid
Dermatologicals
Semi-solid
Solution
Aqueous solution
Alcoholic tincture
Hydrogel
Ointment
Lipophilic ointment
Hydrophilic ointment
Cream
Lipophilic cream
Hydrophilic cream
Lotion
Suspen-sion
Emulsion
Fat, oil
Water in oil
Oil in water
Gel, water
Occlusive
Permeable, coolant
Perspiration
impossible
possible
Dry, non-oily skin
Oily, moist skin

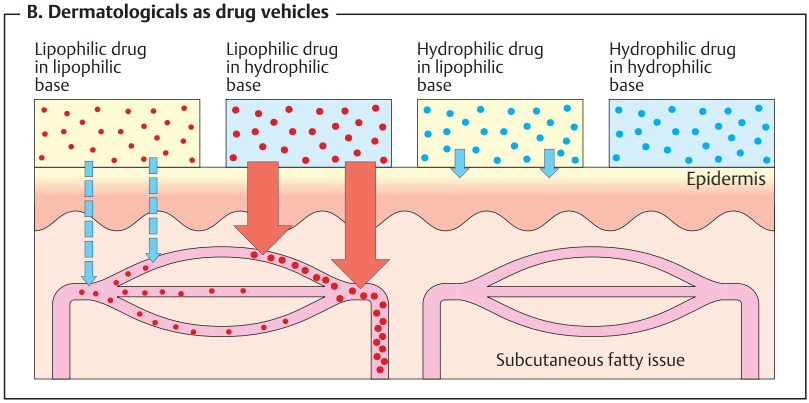

B. Dermatologicals as drug vehicles
Lipophilic drug in lipophilic base
Lipophilic drug in hydrophilic base
Hydrophilic drug in lipophilic base
Hydrophilic drug in hydrophilic base
Epidermis
Subcutaneous fatty issue

Fig. 3.3

From Administration to Distribution in the Body

As a rule, drugs reach their target organs via the blood. Therefore, they must first enter the blood, usually in the venous limb of the circulation. There are several possible sites of entry.

The drug may be injected or infused **intravenously**, in which case it is introduced directly into the bloodstream. In **subcutaneous** or **intramuscular** injection, the drug has to diffuse from its site of administration into the blood. Because these procedures entail injury to the outer skin, strict requirements must be met concerning technique. For this reason, the **oral** route (i.e., simple administration by mouth) involving subsequent uptake of drug across the gastrointestinal mucosa into the blood is chosen much more frequently. The disadvantage of this route is that the drug must pass through the liver on its way into the general circulation. In all of the above modes of administration, this fact assumes practical significance for any drug that may be rapidly transformed or possibly inactivated in the liver (first-pass effect, presystemic elimination, p. 60; bioavailability). Furthermore, a drug has to traverse the lungs before entering the general circulation. Pulmonary tissues may trap hydrophobic substances. The lungs may then act as a buffer and thus prevent a rapid rise in drug levels in peripheral blood after i.v. injection (important, for example, with i.v. anesthetics). Even with rectal administration, at least a fraction of the drug enters the general circulation via the portal vein, because only blood from the short terminal segment of the rectum drains directly into the inferior vena cava. Hepatic passage is circumvented when absorption occurs buccally or sublingually, because venous blood from the oral cavity drains into the superior vena cava. The same would apply to administration by **inhalation** (p. 30). However, with this route, a local effect is usually intended, and a systemic action is intended only in exceptional cases. Under certain conditions, drug can also be applied percutaneously in the form of a **transdermal** delivery system. In this case, drug is released from the reservoir at constant rate over many hours, and then penetrates the epidermis and subepidermal connective tissue where it enters blood capillaries. Only a very few drugs can be applied transdermally. The feasibility of this route is determined by both the physicochemical properties of the drug and the therapeutic requirements (acute vs. long-term effect).

Speed of absorption is determined by the route and method of administration. It is *fastest* with *intravenous injection, less fast* with *intramuscular injection,* and *slowest* with *subcutaneous injection.* When the drug is applied to the oral mucosa (**buccal**, **sublingual** routes), plasma levels rise faster than with conventional oral administration because the drug preparation is deposited at its actual site of absorption and very high concentrations in saliva occur upon the dissolution of a single dose. Thus, uptake across the oral epithelium is accelerated. Furthermore, drug absorption from the oral mucosa avoids passage through the liver and, hence, presystemic elimination. The buccal or sublingual route is not suitable for poorly water-soluble or poorly absorbable drugs. Such agents should be given orally because both the volume of fluid for dissolution and the absorbing surface are much larger in the small intestine than in the oral cavity.

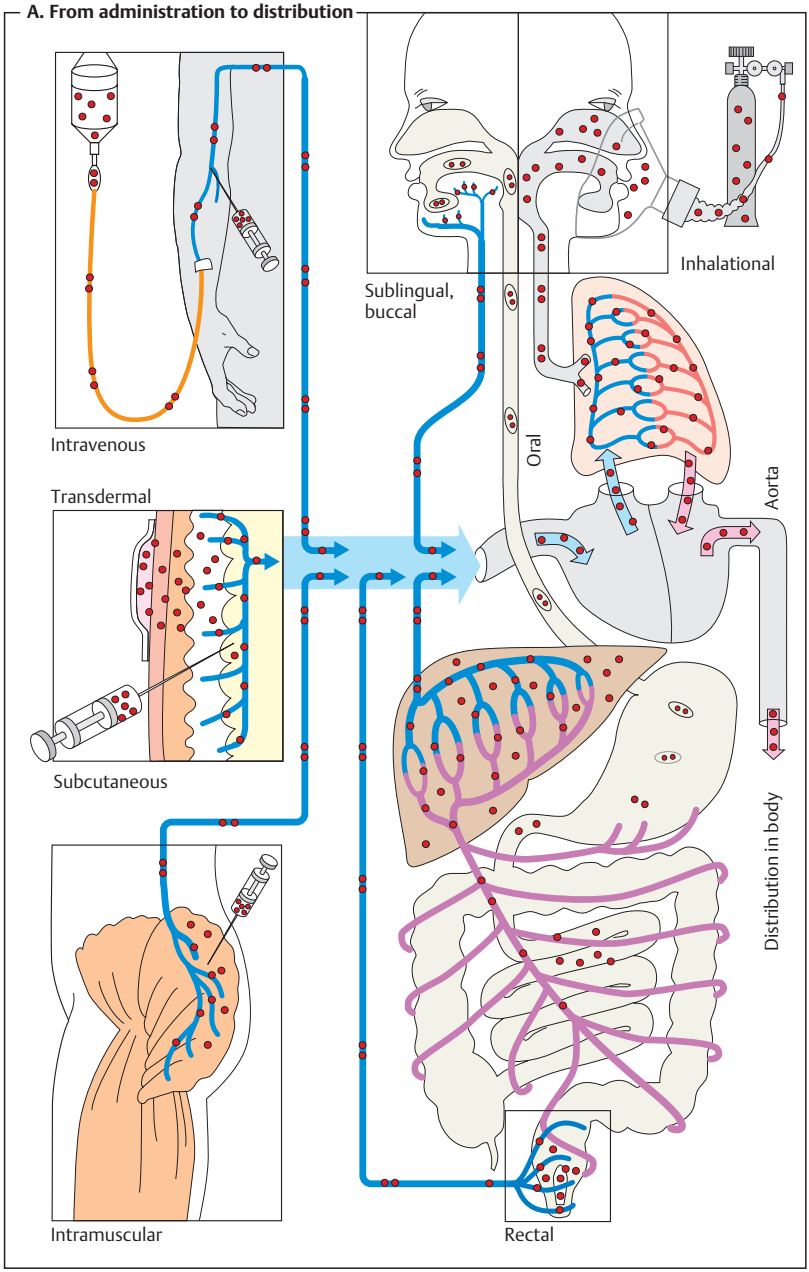

A. From administration to distribution
Intravenous
Transdermal
Subcutaneous
Intramuscular
Sublingual, buccal
Inhalational
Oral
Aorta
Distribution in body
Rectal

Fig. 3.4

Potential Targets of Drug Action

Drugs are designed to exert a selective influence on vital processes in order to alleviate or eliminate symptoms of disease. The smallest basic unit of an organism is the **cell**. The outer cell membrane, or plasmalemma, effectively demarcates the cell from its surroundings, thus permitting a large degree of internal autonomy. Embedded in the plasmalemma are **transport proteins** that serve to mediate *controlled metabolic exchange with the cellular environment*. These include energy-consuming pumps (e.g., Na^+/K^+-ATPase, p. 148), carriers (e.g., for Na^+/glucose cotransport), and ion channels (e.g., for sodium [p. 150] or calcium [p. 140]) (▶ Fig. 4.1**A** 1).

Functional coordination between single cells is a prerequisite for the viability of the organism, hence also the survival of individual cells. Cell functions are coordinated by means of cytosolic contacts between neighboring cells (gap junctions, e.g., in the myocardium) and messenger substances for the transfer of information. Included among these are transmitters released from nerves, which the cell is able to recognize with the help of specialized membrane binding sites or **receptors**. Hormones secreted by endocrine glands into the blood, then into the extracellular fluid, represent another class of chemical signals. Finally, signaling substances can originate from neighboring cells: paracrine regulation, for instance by the prostaglandins (p. 198) and cytokines.

The **effect of a drug** frequently results from interference with cellular function. Receptors for the recognition of endogenous transmitters are obvious sites of drug action (receptor agonists and antagonists, p. 78). Altered activity of membrane transport systems affects cell function (e.g., cardiac glycosides, p. 148; loop diuretics, p. 178; calcium antagonists, p. 140). Drugs may also directly interfere with intracellular metabolic processes, for instance by inhibiting (phosphodiesterase inhibitors, p. 136) or activating (organic nitrates, p. 138) an enzyme (▶ Fig. 4.1**A** 2); even processes in the cell nucleus can be affected (e.g., DNA damage by certain cytostatics).

In contrast to drugs acting from the outside on cell membrane constituents, agents acting in the cell's interior need to penetrate the cell membrane.

The **cell membrane** basically consists of a **phospholipid bilayer** (50 Å = 5 nm in thickness), embedded in which are proteins (integral membrane proteins, such as receptors and transport molecules). Phospholipid molecules contain two long-chain *fatty acids* in ester linkage with two of the three hydroxyl groups of *glycerol.* Bound to the third hydroxyl group is *phosphoric acid,* which, in turn, carries a further *residue,* e.g., choline (phosphatidylcholine = lecithin), the amino acid serine (phosphatidylserine), or the cyclic polyhydric alcohol inositol (phosphatidylinositol). In terms of solubility, phospholipids are amphiphilic: the tail region containing the apolar fatty acid chains is lipophilic; the remainder—the polar head—is hydrophilic. By virtue of these properties, phospholipids aggregate spontaneously into a bilayer in an aqueous medium, their polar heads being directed outward into the aqueous medium, the fatty acid chains facing each other and projecting into the inside of the membrane (▶ Fig. 4.1**A** 3).

The **hydrophobic interior** of the phospholipid membrane constitutes a diffusion barrier virtually impermeable to charged particles. Apolar particles, however, are better able to penetrate the membrane. This is of major importance with respect to the absorption, distribution, and elimination of drugs.

A. Site at which drugs act to modify cell function

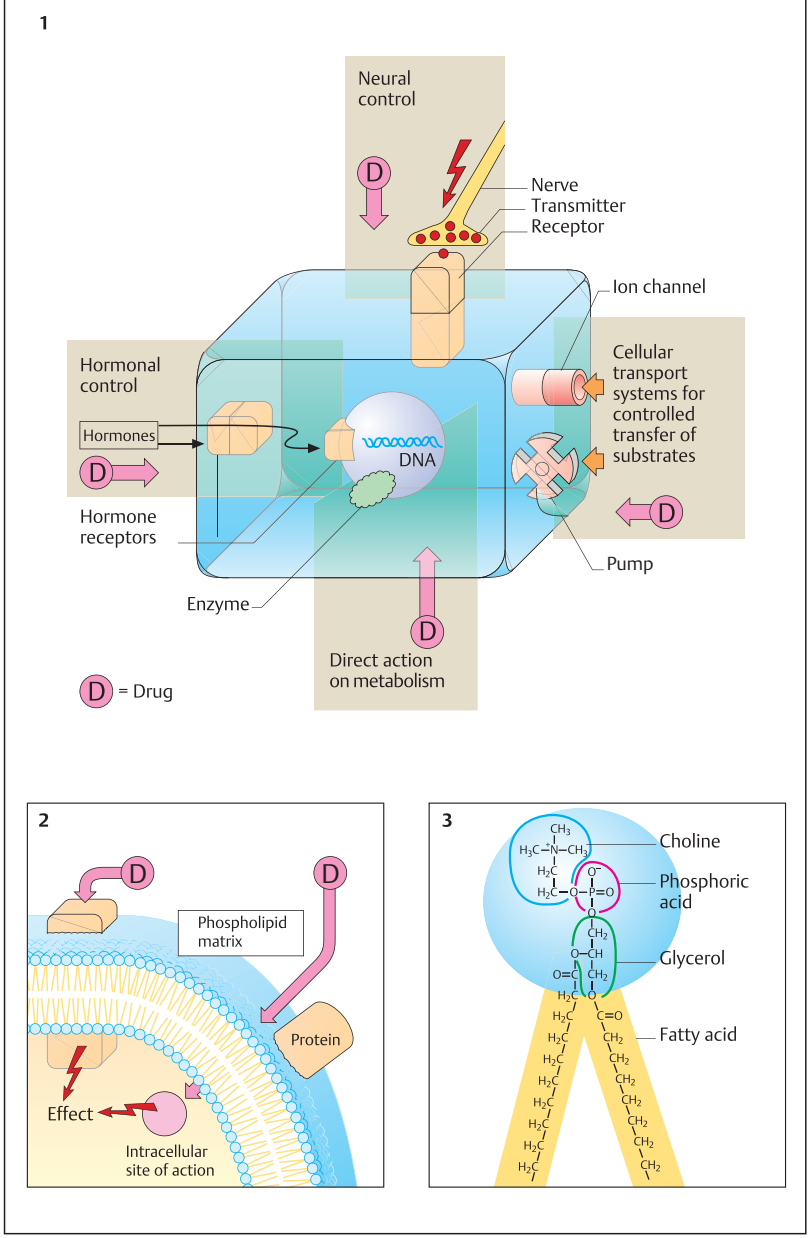


Fig. 4.1

External Barriers of the Body

Prior to its uptake into the blood (i.e., during absorption), the drug has to overcome barriers that demarcate the body from its surroundings, that is, that separate the internal from the external milieu. These boundaries are formed by the skin and mucous membranes.

When absorption takes place in the **gut** (enteral absorption), the intestinal epithelium is the barrier. This single-layered epithelium is made up of enterocytes, with a brush border (microvilli) to increase surface area, and mucus-producing goblet cells. On their luminal side, these cells are joined together by *zonulae occludentes* (indicated by black dots in the inset, bottom left). A *zonula occludens*, or tight junction, is a region in which the phospholipid membranes of two cells establish close contact and become joined via integral membrane proteins (semicircular inset, left center). The region of fusion surrounds each cell like a ring such that neighboring cells are welded together in a continuous belt. In this manner, an unbroken phospholipid layer is formed (yellow area in the schematic drawing, bottom left) and acts as a continuous barrier between the two spaces separated by the cell layer—in the case of the gut—the intestinal lumen (dark blue) and interstitial space (light blue). The efficiency with which such a barrier restricts exchange of substances can be increased by arranging these occluding junctions in multiple arrays, as for instance in the endothelium of cerebral blood vessels. The connecting proteins (connexins) furthermore serve to restrict mixing of other functional membrane proteins (carrier molecules, ion pumps, ion channels) that occupy specific apical or basolateral areas of the cell membrane.

This phospholipid bilayer represents the intestinal mucosa–blood barrier that a drug must cross during enteral absorption. Eligible drugs are those whose physicochemical properties allow permeation through the lipophilic membrane interior (yellow) or that are subject to a special inwardly directed carrier transport mechanism. Conversely, drugs can undergo backtransport into the gut by means of efflux pumps (P-glycoprotein) located in the luminal membrane of the intestinal epithelium. Absorption of such drugs proceeds rapidly because the absorbing surface is greatly enlarged owing to the formation of the epithelial brush border (submicroscopic foldings of the plasmalemma). The absorbability of a drug is characterized by the *absorption quotient*, that is, the amount absorbed divided by the amount in the gut available for absorption.

In the **respiratory tract**, cilia-bearing epithelial cells are also joined on the luminal side by zonulae occludentes, so that the bronchial space and the interstitium are separated by a continuous phospholipid barrier.

With sublingual or buccal administration, the drug encounters the nonkeratinized, multilayered squamous epithelium of the **oral mucosa**. Here, the cells establish punctate contacts with each other in the form of desmosomes (not shown); however, these do not seal the intercellular clefts. Instead, the cells have the property of sequestering polar lipids that assemble into layers within the extracellular space (semicircular inset, center right). In this manner, a continuous phospholipid barrier arises also inside squamous epithelia, although at an extracellular location, unlike that of intestinal epithelia. A similar barrier principle operates in the multilayered keratinized squamous epithelium of the **skin**.

The presence of a continuous phospholipid layer again means that only lipophilic drugs can enter the body via squamous epithelia. Epithelial thickness, which in turn depends on the depth of the stratum corneum, determines the extent and speed of absorption. Examples of drugs that can be conveyed via the skin into the blood include scopolamine (p. 126), nitroglycerin (p. 138), fentanyl (p. 214), and the gonadal hormones (p. 246). Toxic substances that are sufficiently lipophilic can also be absorbed through the skin to cause percutaneous poisoning. Examples include benzene, chlorinated dibenzodioxins, and organophosphates.

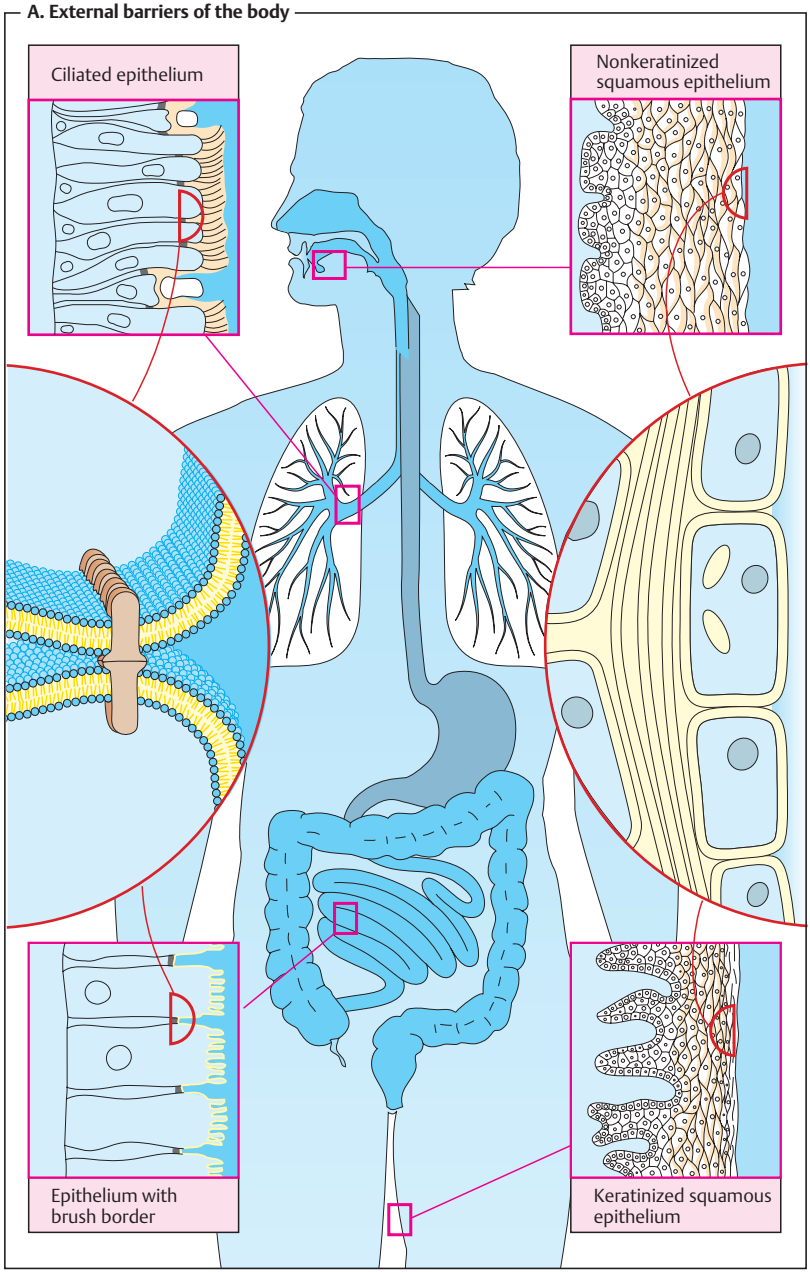

A. External barriers of the body
Ciliated epithelium
Nonkeratinized squamous epithelium
Epithelium with brush border
Keratinized squamous epithelium

Fig. 5.1

Blood–Tissue Barriers

Drugs are transported in the blood to different tissues of the body. In order to reach their sites of action, they must leave the bloodstream. Drug permeation occurs largely in the capillary bed, where both surface area and time available for exchange are maximal (extensive vascular branching, low velocity of flow). The capillary wall forms the blood–tissue barrier. Basically, this consists of an endothelial cell layer and a basement membrane enveloping the latter (solid black line in the schematic drawings). The endothelial cells are "riveted" to each other by tight junctions or occluding zonulae (labeled Z in the electron micrograph, upper left) such that no clefts, gaps, or pores remain that would permit drugs to pass unimpeded from the blood into the interstitial fluid.

The blood–tissue barrier is developed differently in the various capillary beds. Permeability of the capillary wall to drugs is determined by the structural and functional characteristics of the endothelial cells. In many capillary beds, e.g., those of **cardiac muscle**, endothelial cells are characterized by pronounced **endocytotic** and **transcytotic** activity, as evidenced by numerous invaginations and vesicles (arrows in the electron micrograph, upper right). Transcytotic activity entails transport of fluid or macromolecules from the blood into the interstitium and vice versa. Any solutes trapped in the fluid, including drugs, may traverse the blood–tissue barrier. In this form of transport, the physicochemical properties of drugs are of little importance.

In some capillary beds (e.g., in the **pancreas**), endothelial cells exhibit **fenestrations**. Although the cells are tightly connected by continuous junctions, they possess pores (arrows in electron micrograph, lower left) that are closed only by diaphragms. Both the diaphragm and basement membrane can be readily penetrated by substances of low molecular weight—the majority of drugs—but less so by macromolecules, e.g., proteins such as insulin (G: insulin storage granule). Penetrability of macromolecules is determined by molecular size and electric charge. Fenestrated endothelia are found in the capillaries of the *gut* and *endocrine glands*.

In the central nervous system (**brain** and **spinal cord**), capillary endothelia lack pores and there is little transcytotic activity. In order to cross the **blood–brain barrier**, drugs must diffuse transcellularly, i.e., penetrate the luminal and basal membrane of endothelial cells. Drug movement along this path (p. 42) requires specific physicochemical properties or the presence of a transport mechanism, e.g., L-dopa (p. 334). Thus, the blood–brain barrier is permeable only to certain types of drugs.

Drugs exchange freely between blood and interstitium in the liver, where endothelial cells exhibit large fenestrations (100 nm in diameter) facing Disse spaces (D) and where neither diaphragms nor basement membranes impede drug movement.

Diffusion barriers are also present beyond the capillary wall; e.g., *placental barrier* of fused syncytiotrophoblast cells; *blood–testicle barrier,* junctions interconnecting Sertoli cells; brain *choroid plexus–blood barrier,* occluding junctions between ependymal cells.

(Vertical bars in the electron micrographs represent 1 µm; E, cross-sectioned erythrocyte; AM, actomyosin; G, insulin-containing granules.)

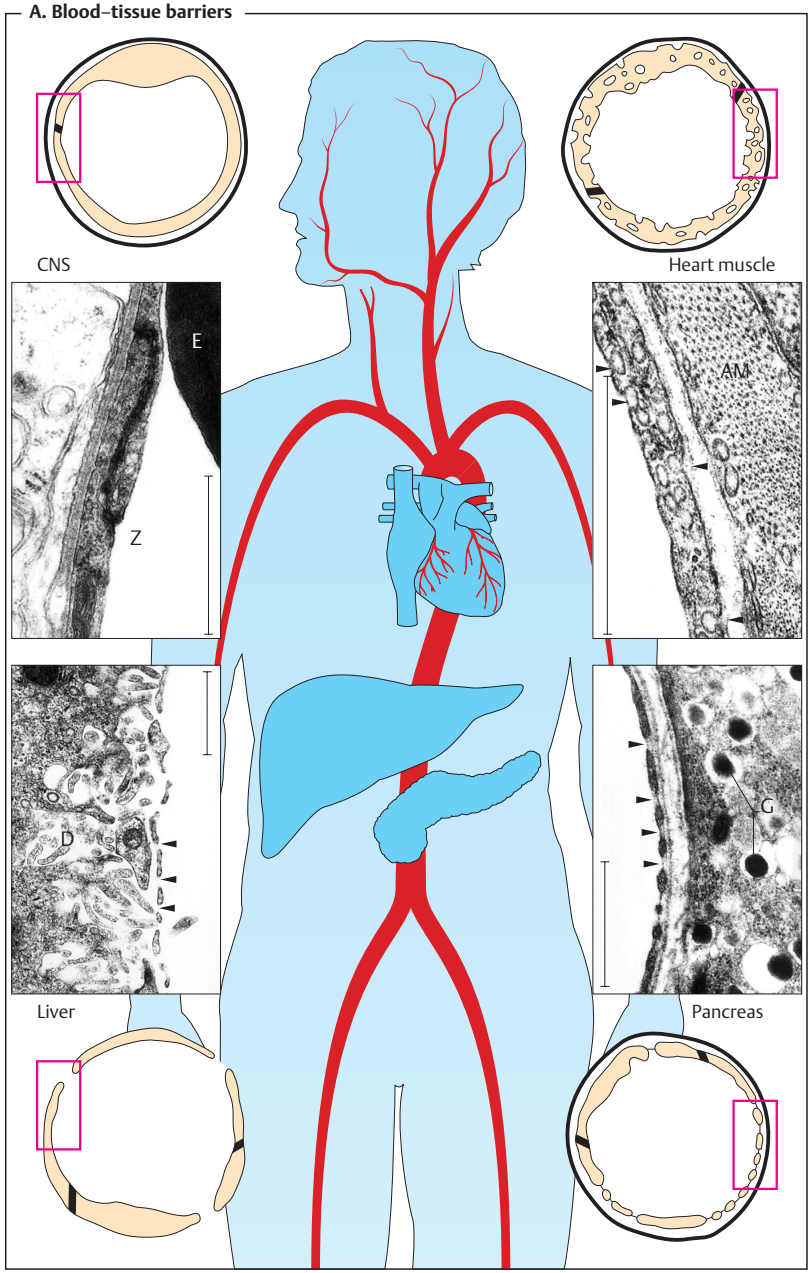

A. Blood–tissue barriers
CNS
Heart muscle
E
Z
AM
D
G
Liver
Pancreas

Fig. 5.2

Membrane Permeation

The ability to penetrate lipid bilayers is a prerequisite for the absorption of drugs, their entry into cells or cellular organelles, and passage across the blood–brain and placental barriers. Owing to their amphiphilic nature, phospholipids form bilayers possessing a hydrophilic surface and a hydrophobic interior (p. 36). Substances may traverse this membrane in three different ways.

► **Diffusion (► Fig. 5.3A).** Depending on how lipophilic they are, substances can diffuse directly through the lipid bilayer down the concentration gradient across the membrane (red dots). However, the membrane represents an almost insuperable barrier for highly hydrophilic substances (e.g., norepinephrine).

► **Passive transport (► Fig. 5.3A).** Many tissues possess transport systems to enable substances that cannot pass through the membrane to enter the cells and cell compartments where they are required. These transport systems are located in the membranes and are more or less specific for a particular group of substances. No energy is required for passive transport across the membrane. Channels or carrier proteins enable hydrophilic substances to pass through membranes. Examples include voltage- or ligand-controlled ion channels (p. 150), e.g., voltage-gated Na^+ channels and Ca^{2+} channels (p. 204), and aquaporins. **Aquaporins** (p. 176) are specialized transport proteins that enable water to pass through the hydrophobic cell membrane in numerous tissues of the body.

► **Active transport (► Fig. 5.3A).** Numerous transport processes in the body use energy in the form of ATP directly or indirectly. This applies particularly when the substances to be transported have to be transported through the cell membrane against a concentration gradient, i.e., "uphill." **Primary active transport** involves proteins that can themselves hydrolyze ATP (ATPase) and thus transport substances. Na^+/K^+-ATPase or H^+/K^+-ATPase in the gastric parietal cells are examples. Some primary active transport proteins act as targets for drugs: digitalis glycosides inhibit Na^+/K^+-ATPases (p. 148). Proton pump inhibitors reduce acid production in the stomach by inhibiting H^+/K^+-ATPase (p. 184).

Secondary active transport processes require functional coupling of a cotransporter to a primary ATP-dependent transporter (► Fig. 5.3**A**). In this case, the energy needed for the transport of the substance is obtained from a downhill shift of ions. The Na^+ gradient (► Fig. 5.3**A**, yellow triangles) is usually the energy donor. To maintain this ion gradient, a Na^+/K^+-ATPase may in turn be responsible. Many neurotransmitter and anion or cation transporters use cellular Na^+ gradients as an energy source (see SLC transporters, p. 44).

► **Transcytosis (vesicular transport, ► Fig. 5.3B).** When new vesicles are pinched off, substances dissolved in the extracellular fluid are engulfed and then ferried through the cytoplasm, unless the vesicles (phagosomes) undergo fusion with lysosomes to form phagolysosomes and the transported substance is metabolized.

► **Receptor-mediated endocytosis (► Fig. 5.3B).** The drug first binds to membrane surface receptors (**1**, **2**) whose cytosolic domains contact special proteins (adaptins, **3**). Drug-receptor complexes migrate laterally in the membrane and aggregate with other complexes by a clathrin-dependent process to form coated pits (**4**). The affected membrane region invaginates and eventually pinches off to form a detached vesicle (**5**). The clathrin and adaptin coats are shed (**6**), resulting in formation of the "early" endosome (**7**). Inside this, proton concentration rises and causes the drug-receptor complex to dissociate. Next, the receptor-bearing membrane portions separate from the endosome (**8**). These membrane sections recirculate to the plasmalemma (**9**), while the endosome is delivered to the target organelles (**10**).

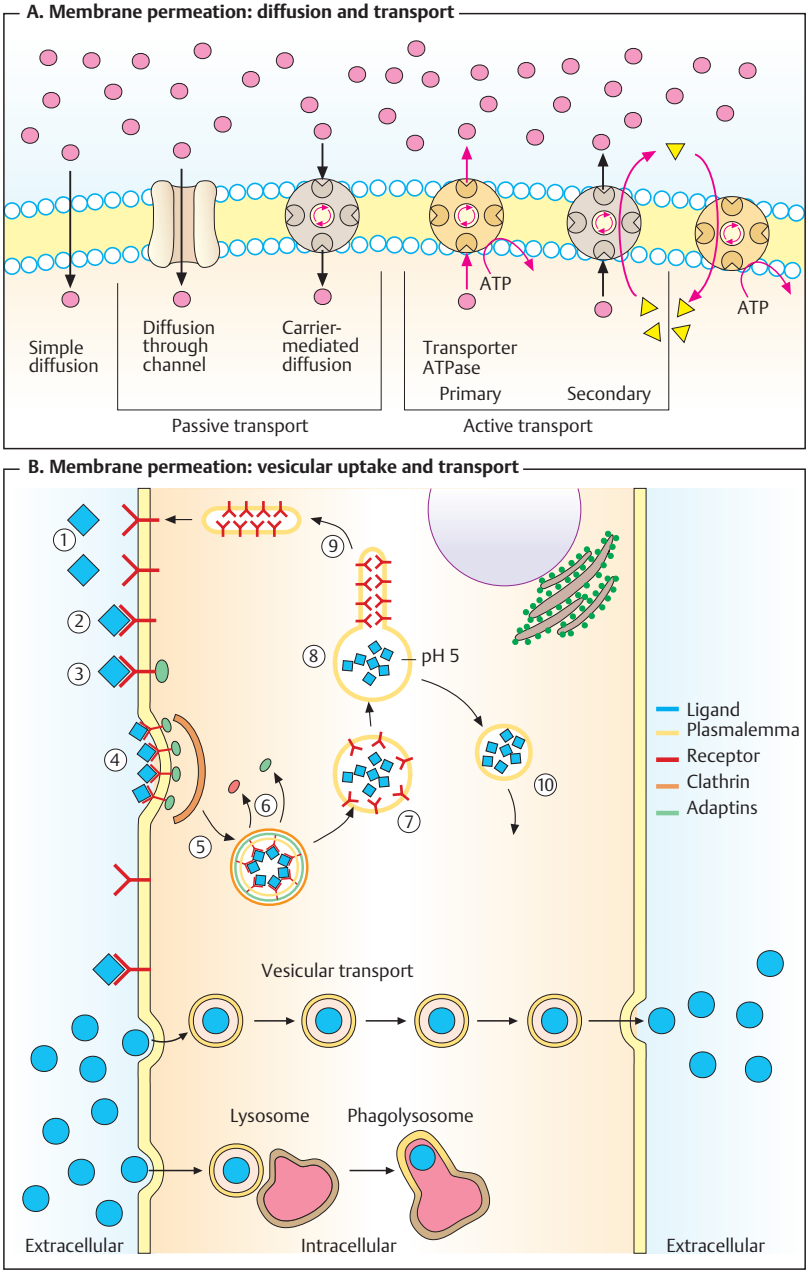

A. Membrane permeation: diffusion and transport
Simple diffusion
Diffusion through channel
Carrier-mediated diffusion
ATP
ATP
Transporter ATPase
Primary
Secondary
Passive transport
Active transport
B. Membrane permeation: vesicular uptake and transport
pH 5
Ligand
Plasmalemma
Receptor
Clathrin
Adaptins
Vesicular transport
Lysosome
Phagolysosome
Extracellular
Intracellular
Extracellular

Fig. 5.3