Color Atlas of Pharmacology

2nd edition, revised and expanded

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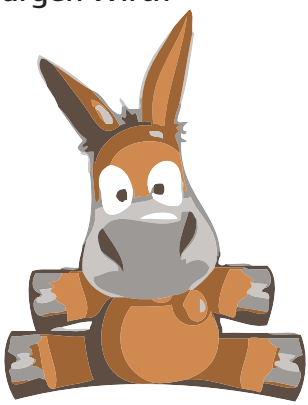

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Important Note: Medicine is an ever-changing science undergoing continual development. Research and clinical experience are continually expanding our knowledge, in particular our knowledge of proper treatment and drug therapy. Insofar as this book mentions any dosage or application, readers may rest assured that the authors, editors and publishers have made every effort to ensure that such references are in accordance **with the state of knowledge at the time of production of the book.**

Nevertheless this does not involve, imply, or express any guarantee or responsibility on the part of the publishers in respect of any dosage instructions and forms of application stated in the book. **Every user is requested to** examine carefully the manufacturers' leaflets accompanying each drug and to check, if necessary in consultation with a physician or specialist, whether the dosage schedules mentioned therein or the contraindications stated by the manufacturers differ from the statements made in the present book. Such examination is particularly important with drugs that are either rarely used or have been newly released on the market. **Every dosage schedule or every form of application used is entirely at the user's own risk and responsibility.** The authors and publishers request every user to report to the publishers any discrepancies or inaccuracies noticed.

Preface

The present second edition of the Color Atlas of Pharmacology goes to print six years after the first edition. Numerous revisions were needed, highlighting the dramatic continuing progress in the drug sciences. In particular, it appeared necessary to include novel therapeutic principles, such as the inhibitors of platelet aggregation from the group of integrin GPIIB/IIIA antagonists, the inhibitors of viral protease, or the non-nucleoside inhibitors of reverse transcriptase. Moreover, the re-evaluation and expanded use of conventional drugs, e.g., in congestive heart failure, bronchial asthma, or rheumatoid arthritis, had to be addressed. In each instance, the primary emphasis was placed on essential sites of action and basic pharmacological principles. Details and individual drug properties were deliberately omitted in the interest of making drug action more transparent and affording an overview of the pharmacological basis of drug therapy.

The authors wish to reiterate that the Color Atlas of Pharmacology cannot replace a textbook of pharmacology, nor does it aim to do so. Rather, this little book is designed to arouse the curiosity of the pharmacological novice; to help students of medicine and pharmacy gain an overview of the discipline and to review certain bits of information in a concise format; and, finally, to enable the experienced therapist to recall certain factual data, with perhaps some occasional amusement.

Our cordial thanks go to the many readers of the multilingual editions of the Color Atlas for their suggestions. We are indebted to Prof. Ulrike Holzgrabe, Würzburg, Doc. Achim Meißner, Kiel, Prof. Gert-Hinrich Reil, Oldenburg, Prof. Reza Tabrizchi, St. John's, Mr Christian Klein, Bonn, and Mr Christian Riedel, Kiel, for providing stimulating and helpful discussions and technical support, as well as to Dr. Liane Platt-Rohloff, Stuttgart, and Dr. David Frost, New York, for their editorial and stylistic guidance.

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Fall 1999

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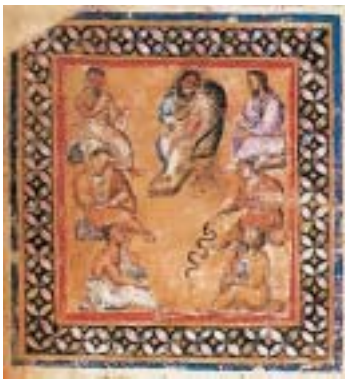
General Pharmacology

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 (129–200 A.D.) 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 observed and 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 A.D.), called Paracelsus, began to quesiton doctrines handed down from antiquity, demanding knowledge of the active ingredient(s) 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 isn't 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 judgement 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 relationship, drug receptor, and selective toxicity emerged from the work of, respectively, T. Frazer (1841–1921) in Scotland, J. Langley (1852–1925) in England, and P. Ehrlich (1854–1915) in Germany. Alexander J. Clark (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 since been published 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.

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 year-round, plants were preserved by drying or soaking them in vegetable oils or alcohol. Drying the plant or a 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**). Nowadays, the term is applied quite generally to a chemical substance that is used for pharmacotherapy.

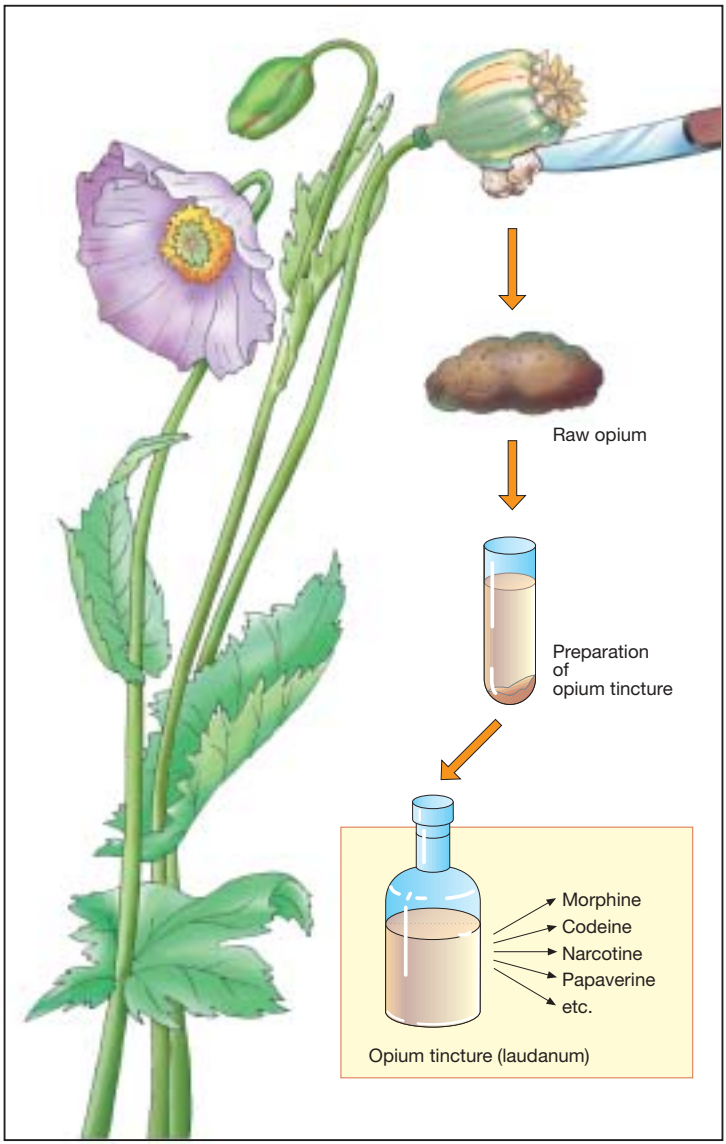
Soaking plants parts in alcohol (ethanol) creates a **tincture**. In this process, pharmacologically active constituents of the plant are extracted by the alcohol. Tinctures do not contain the complete spectrum of substances that exist in the plant or crude drug, only those that are soluble in alcohol. 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 proportion 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 are:

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.



A. From poppy to morphine

Drug Development

This 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 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.

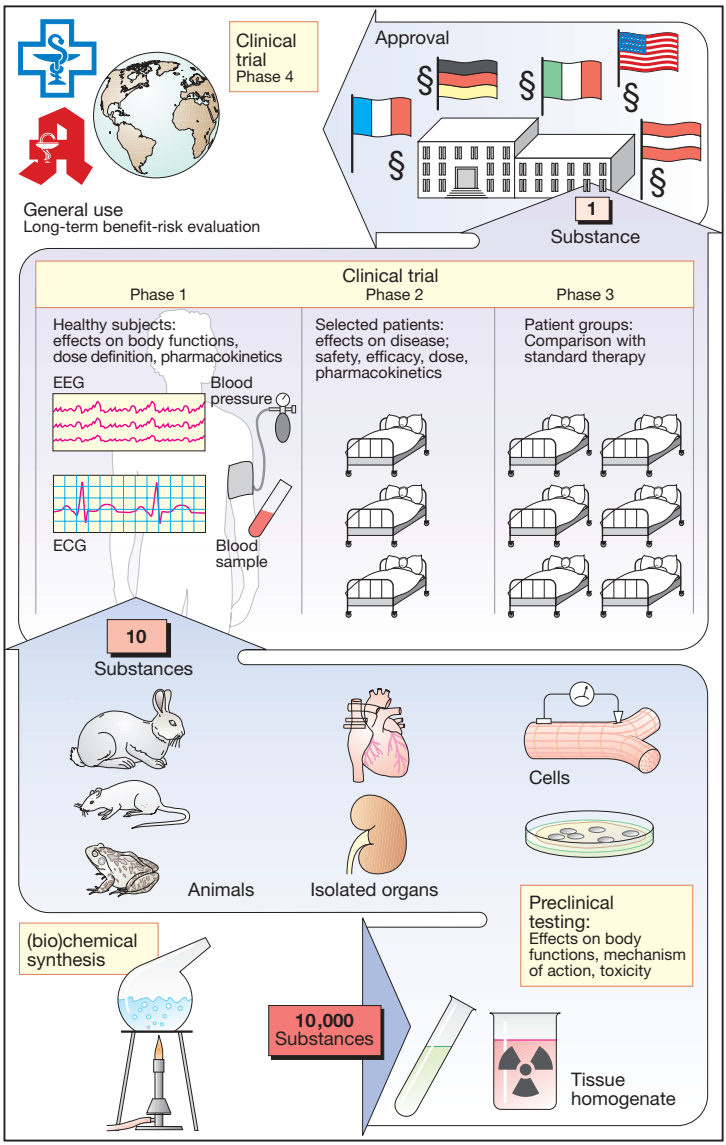
Preclinical testing yields information on the biological effects of new substances. Initial screening may employ *biochemical-pharmacological investigations* (e.g., receptor-binding assays p. 56) or experiments on cell cultures, isolated cells, and isolated organs. Since these models invariably fall 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 (onco- 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 fit for use in humans.

Pharmaceutical technology provides the methods for drug formulation.

Clinical testing starts with **Phase I** studies on healthy subjects and seeks to determine whether effects observed in animal experiments also occur in humans. Dose-response relationships are determined. In **Phase II**, potential drugs are first tested on selected patients for therapeutic efficacy in those disease states for which they are intended. Should a beneficial action be evident and the incidence of adverse effects be acceptably small, **Phase III** is entered, involving a larger group of patients in whom the new drug will be compared with standard 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 remains from approximately 10,000 newly synthesized substances.

The decision to **approve a new drug** is made by a national regulatory body (Food & Drug Administration in the U.S.A., the Health Protection Branch Drugs Directorate in Canada, UK, Europe, Australia) 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 may be marketed under a trade name (p. 333) and thus become available for prescription by physicians and dispensing by pharmacists. As the drug gains more widespread use, regulatory surveillance continues in the form of post-licensing studies (**Phase IV** of clinical trials). 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.



A. From drug synthesis to approval

Dosage Forms for Oral, Ocular, and Nasal Applications

A medicinal agent becomes a medication only after formulation suitable for therapeutic use (i.e., in an appropriate **dosage form**). The dosage form takes into account the intended mode of use and also ensures ease of handling (e.g., stability, precision of dosing) by patients and physicians. *Pharmaceutical technology* is concerned with the design of suitable product formulations and quality control.

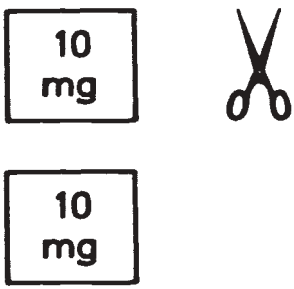
Liquid preparations (A) may take the form of **solutions, suspensions** (a sol or mixture consisting of small water-insoluble solid drug particles dispersed in water), or **emulsions** (dispersion of minute droplets of a liquid agent or a drug solution in another fluid, e.g., oil in water). Since storage will cause sedimentation of suspensions and separation of emulsions, solutions are generally preferred. In the case of poorly watersoluble substances, solution is often accomplished by adding ethanol (or other solvents); thus, there are both *aqueous* and *alcoholic solutions.* These solutions are made available to patients in specially designed drop bottles, enabling single doses to be measured exactly in terms of a defined number of drops, the size of which depends on the area of the drip opening at the bottle mouth and on the viscosity and surface tension of the solution. The advantage of a drop solution is that the dose, that is, the number of drops, can be precisely adjusted to the patient's need. Its disadvantage lies in the difficulty that some patients, disabled by disease or age, will experience in measuring a prescribed number of drops.

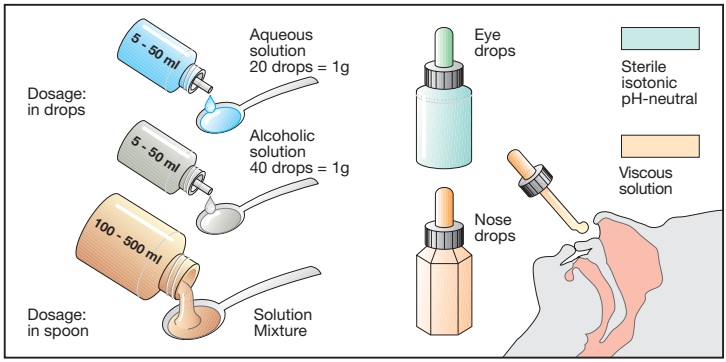
When the drugs are dissolved in a larger volume — as in the case of *syrups or mixtures* — the single dose is measured with a measuring spoon. Dosing may also be done with the aid of a tablespoon or teaspoon (approx. 15 and 5 ml, respectively). However, due to the wide variation in the size of commercially available spoons, dosing will not be very precise. (Standardized medicinal teaspoons and tablespoons are available.)

Eye drops and **nose drops** (A) are designed for application to the mucosal surfaces of the eye (conjunctival sac) and nasal cavity, respectively. In order to prolong contact time, nasal drops are formulated as solutions of increased viscosity.

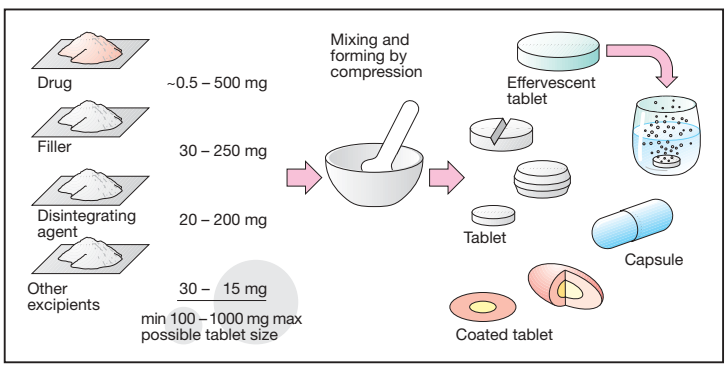
Solid dosage forms include **tablets**, **coated tablets**, and **capsules** (B). **Tablets** have a disk-like shape, produced by mechanical compression of active substance, filler (e.g., lactose, calcium sulfate), binder, and auxiliary material (excipients). The filler provides bulk enough to make the tablet easy to handle and swallow. It is important to consider that the individual dose of many drugs lies in the range of a few milligrams or less. In order to convey the idea of a 10-mg weight, two squares are marked below, the paper mass of each weighing 10 mg. Disintegration of the tablet can be hastened by the use of dried starch, which swells on contact with water, or of $NaHCO_3$, which releases CO_2 gas on contact with gastric acid. Auxiliary materials are important with regard to tablet production, shelf life, palatability, and identifiability (color).

Effervescent tablets (compressed effervescent powders) do not represent a solid dosage form, because they are dissolved in water immediately prior to ingestion and are, thus, actually, liquid preparations.

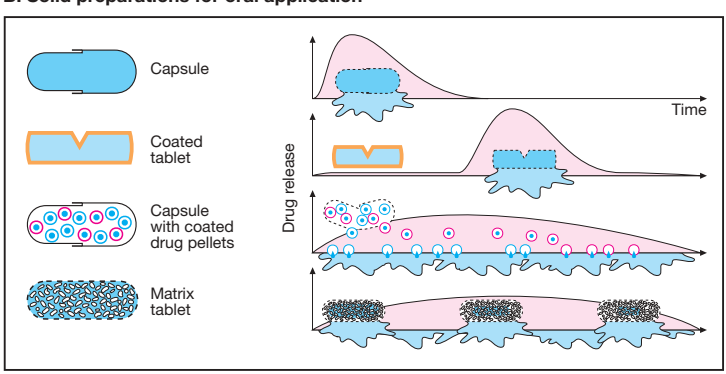




A. Liquid preparations



B. Solid preparations for oral application



C. Dosage forms controlling rate of drug dissolution

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

Capsules usually consist of an oblong casing — generally made of gelatin — that contains the drug in powder or granulated form (See. p. 9, C).

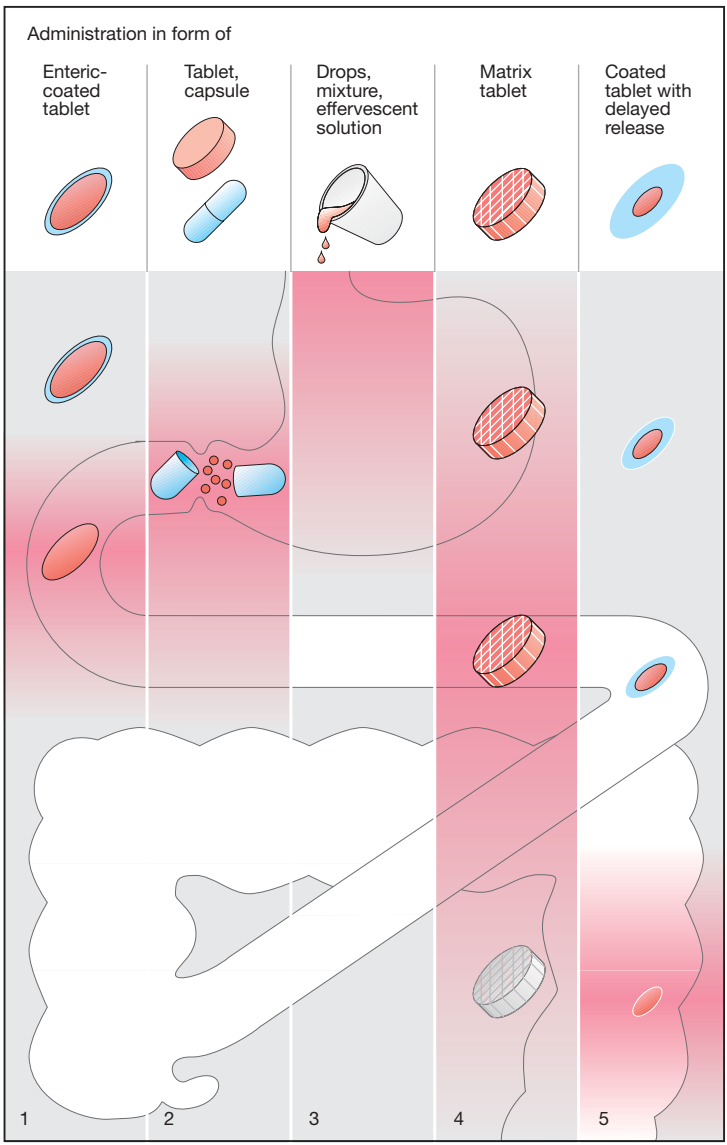
In the case of the **matrix-type** tablet, the drug is embedded in an inert meshwork from which it is released by diffusion upon being moistened. In contrast to *solutions,* which permit direct absorption of drug (**A**, track 3), the use of solid dosage forms initially requires *tablets* to break up 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 (**A**, track 2). In the case of a solution, absorption starts in the stomach (**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 speed (**A**, track 1) and drug liberation *per se* is not retarded.

The **liberation of drug**, 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, the drug is incorporated 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 (**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 (**A**, track 1) or distal (**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 a granulate 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.* Contrary to timed-release capsules (Spansules®), *slow-release tablets* have the advantage of being dividable *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 level 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

Dosage Forms for Parenteral (1), Pulmonary (2), Rectal or Vaginal (3), and Cutaneous Application

Drugs need not always be administered **orally** (i.e., by swallowing), but may also be given **parenterally**. This route usually refers to an injection, although enteral absorption is also bypassed when drugs are inhaled or applied to the skin.

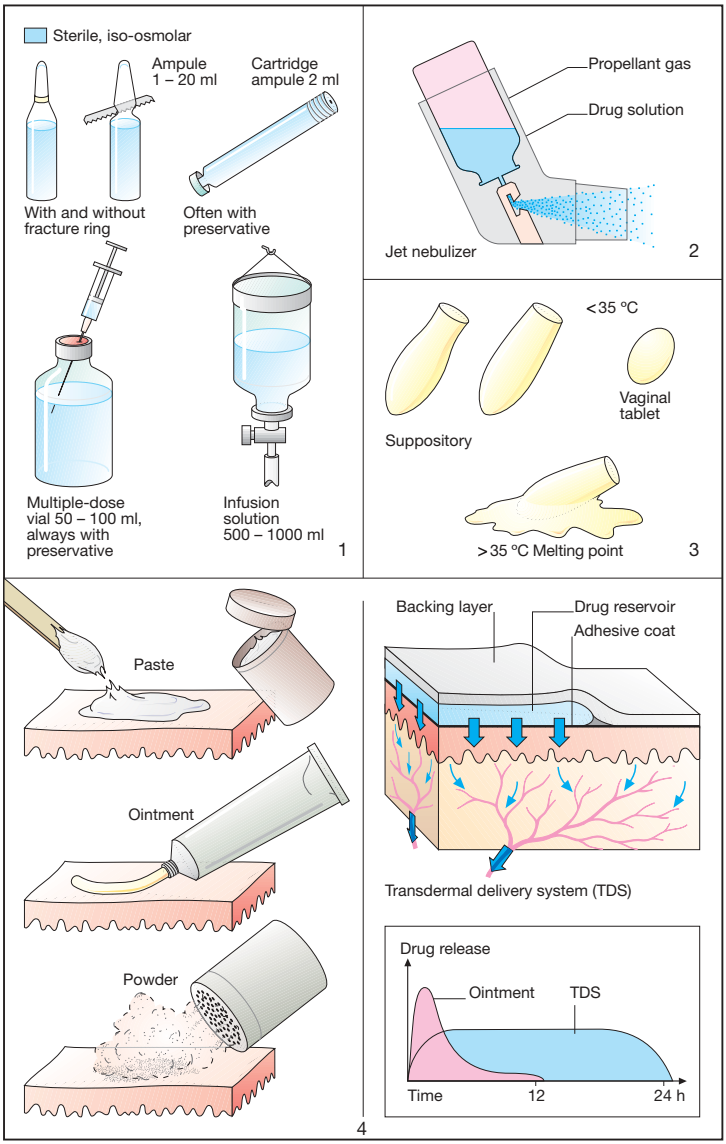
For intravenous, intramuscular, or subcutaneous injections, drugs are often given as solutions and, less frequently, in crystalline suspension for intramuscular, subcutaneous, or intraarticular injection. An **injectable solution** must be free of infectious agents, pyrogens, or suspended matter. It should have the same osmotic pressure and pH as body fluids in order to avoid tissue damage at the site of injection. Solutions for injection are preserved in airtight glass or plastic sealed containers. From **ampules for multiple or single use**, the solution is aspirated via a needle into a syringe. The **cartridge ampule** is fitted into a special injector that enables its contents to be emptied via a needle. An infusion refers to a solution being administered over an extended period of time. **Solutions for infusion** must meet the same standards as solutions for injection.

Drugs can be sprayed in **aerosol** form onto mucosal surfaces of body cavities accessible from the outside (e.g., the respiratory tract [p. 14]). An aerosol is a dispersion of liquid or solid particles in a gas, such as air. An aerosol results when a drug solution or micronized powder is reduced to a spray on being driven through the nozzle of a pressurized container.

Mucosal application of drug via the rectal or vaginal route is achieved by means of **suppositories** and **vaginal tablets,** respectively. On rectal application, absorption into the systemic circulation may be intended. With vaginal tablets, the effect is generally confined to the site of application. Usually the drug is incorporated into a fat that solidifies at room temperature, but melts in the rectum or vagina. The resulting oily film spreads over the mucosa and enables the drug to pass into the mucosa.

Powders, ointments, and **pastes** (p. 16) are applied to the skin surface. In many cases, these do not contain drugs but are used for skin protection or care. However, drugs may be added if a topical action on the outer skin or, more rarely, a systemic effect is intended.

Transdermal drug delivery systems are pasted to the epidermis. They contain a reservoir from which drugs may diffuse and be absorbed through the skin. They offer the advantage that a drug depot is attached noninvasively to the body, enabling the drug to be administered in a manner similar to an infusion. Drugs amenable to this type of delivery must: (1) be capable of penetrating the cutaneous barrier; (2) be effective in very small doses (restricted capacity of reservoir); and (3) possess a wide therapeutic margin (dosage not adjustable).



A. Preparations for parenteral (1), inhalational (2), rectal or vaginal (3), and percutaneous (4) application

Drug Administration by Inhalation

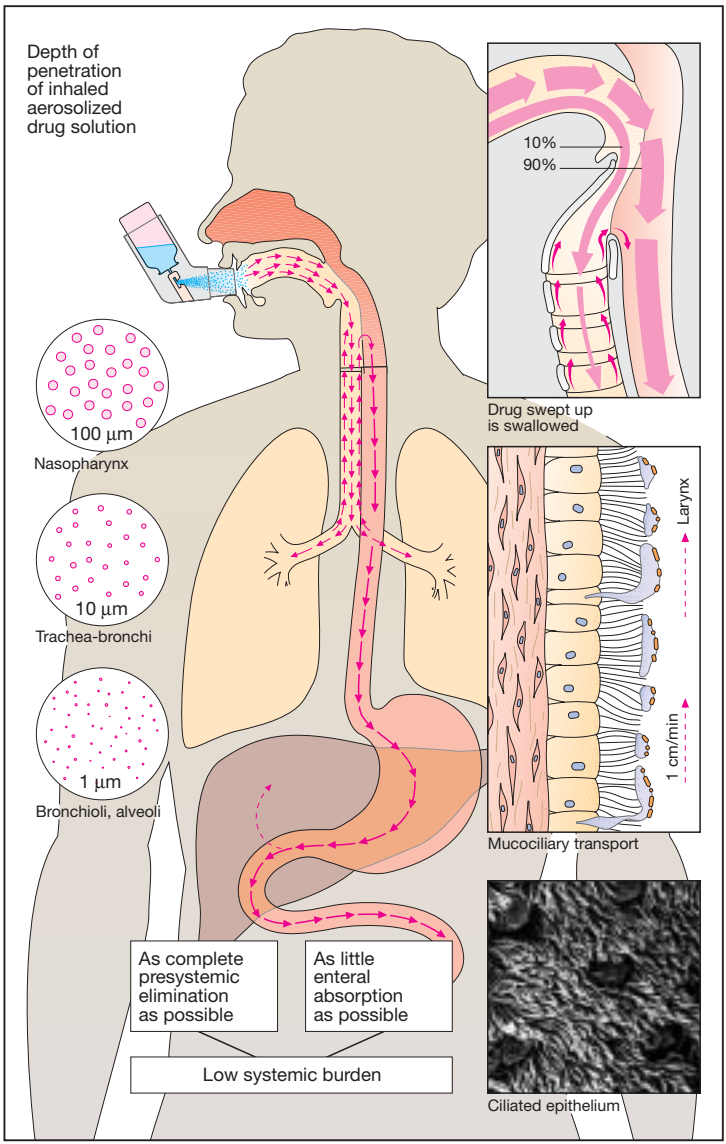
Inhalation in the form of an aerosol (p. 12), a gas, or a mist permits drugs to be applied to the bronchial mucosa and, to a lesser extent, to the alveolar membranes. This route is chosen for drugs intended to affect bronchial smooth muscle or the consistency of bronchial mucus. Furthermore, gaseous 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 blast required for 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 aerosol particles, and the coordination between opening of the spray valve and inspiration. The size of aerosol particles determines the speed at which they are swept along by inhaled air, 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 largely exhaled because of their low tendency to impact on the alveolar epithelium.

Drug deposited on the mucous lining of the bronchial epithelium is partly absorbed and partly transported with bronchial mucus towards the larynx. Bronchial mucus travels upwards due 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 application) is fully exploited by using drugs that are poorly absorbed from the intestine (isoproterenol, ipratropium, cromolyn) or are subject to first-pass elimination (p. 42; beclomethasone dipropionate, budesonide, flunisolide, fluticasone dipropionate).

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., in smoker's cough, bronchitis) or can be adversely affected by drugs (atropine, antihistamines).



A. Application by inhalation

Dermatologic Agents

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

Skin Protection (A)

Protective agents 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 [p. 290], intense solar irradiation).

Distinctions among protective agents are based upon consistency, physicochemical properties (lipophilic, hydrophilic), and the presence of additives.

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) consists of a lipophilic base (paraffin oil, petroleum jelly, wool fat [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) is an ointment containing more than 10% pulverized constituents.

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

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

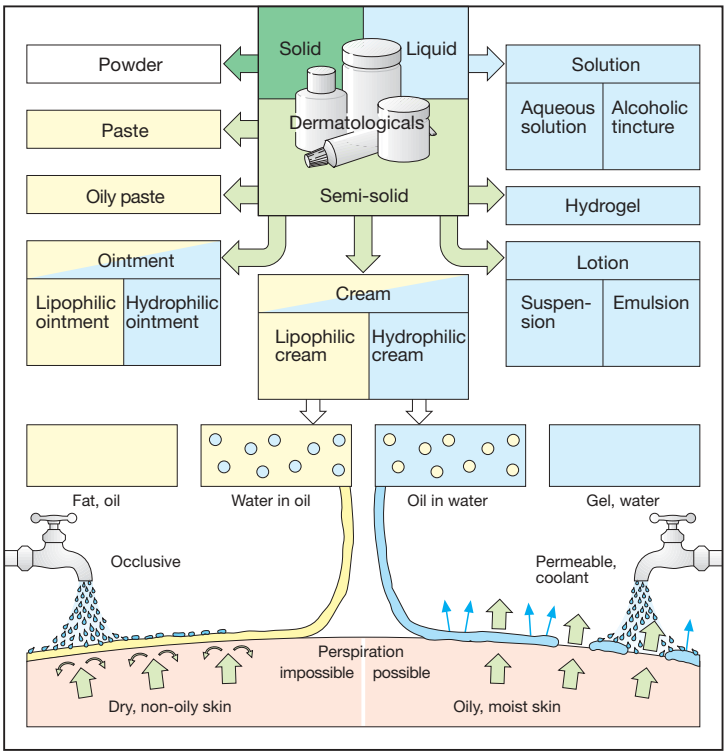
Hydrophilic (aqueous) cream is an emulsion of an oil in water formed with the aid of an emulsifier; it may also be considered an oil-in-water emulsion of an emulsifying ointment.

All dermatologic 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.

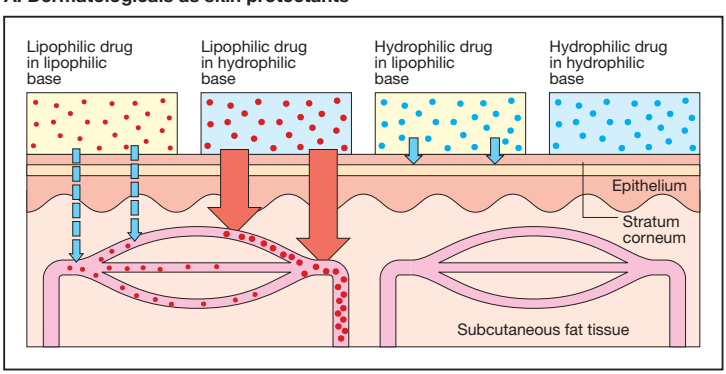
Diminished evaporation of water results in warming of the occluded skin area. Hydrophilic agents wash off easily and do not impede transcutaneous output of water. Evaporation of water is felt as a cooling effect.

Dermatologic Agents as Vehicles (B)

In order to reach its site of action, a drug (D) must leave its pharmaceutical preparation 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. 120). The tendency for the drug to leave the drug vehicle (V) is higher the more the drug and vehicle differ in lipophilicity (high tendency: hydrophilic D and lipophilic V, and vice versa). Because the skin represents a closed lipophilic barrier (p. 22), only lipophilic drugs are absorbed. Hydrophilic drugs fail even to penetrate the outer skin when applied in a lipophilic vehicle. This formulation can be meaningful when high drug concentrations are required at the skin surface (e.g., neomycin ointment for bacterial skin infections).



A. Dermatologicals as skin protectants



B. Dermatologicals as drug vehicles

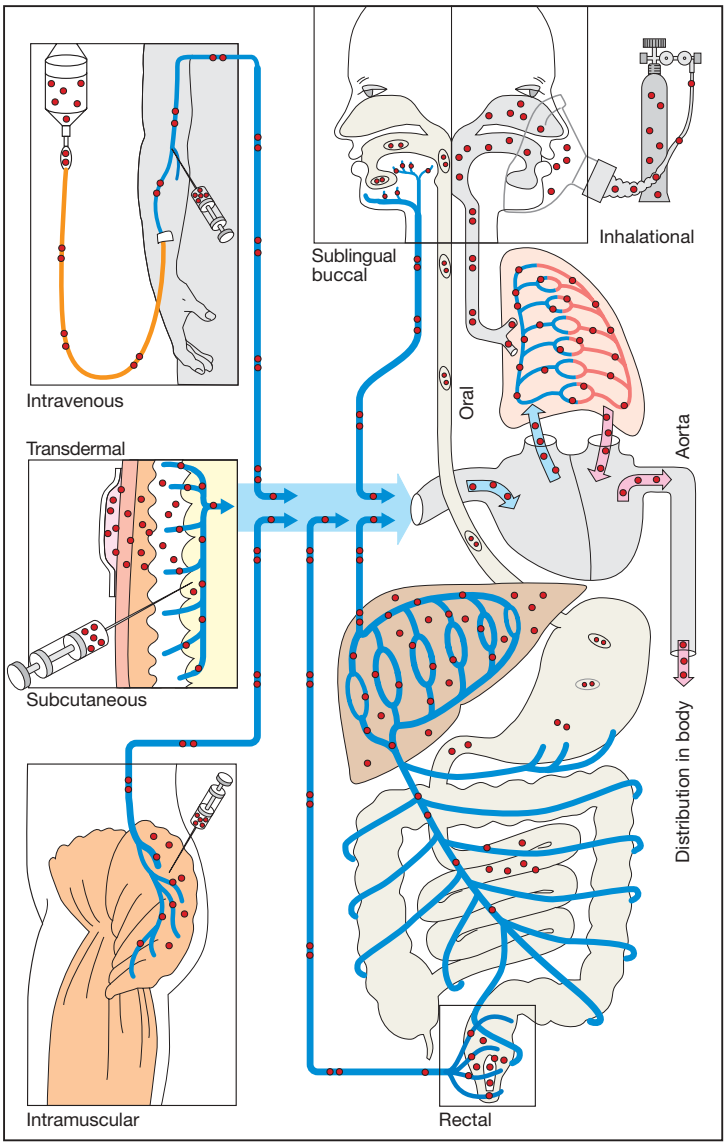
From Application to Distribution in the Body

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

The drug may be injected or infused **intravenously,** in which case the drug is introduced directly into the bloodstream. In **subcutaneous** or **intramuscular** injection, the drug has to diffuse from its site of application into the blood. Because these procedures entail injury to the outer skin, strict requirements must be met concerning technique. For that reason, the **oral** route (i.e., simple application 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. This fact assumes practical significance with any drug that may be rapidly transformed or possibly inactivated in the liver (first-pass hepatic elimination; p. 42). Even with **rectal** administration, at least a fraction of the drug enters the general circulation via the portal vein, because only veins draining the short terminal segment of the rectum communicate directly with the inferior vena cava. Hepatic passage is circumvented when absorption occurs buccally or sublingually, because venous blood from the oral cavity drains directly into the superior vena cava. The same would apply to administration by **inhalation** (p. 14). However, with this route, a local effect is usually intended; 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 (p. 12). In this case, drug is slowly released from the reservoir, 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 application. It is fastest with **intravenous** injection, less fast which **intramuscular** injection, and slowest with **subcutaneous** injection. When the drug is applied to the oral mucosa (**buccal, sublingual** route), 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. The same does not hold true 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.

Bioavailability is defined as the fraction of a given drug dose that reaches the circulation in unchanged form and becomes available for systemic distribution. The larger the presystemic elimination, the smaller is the bioavailability of an orally administered drug.



A. From application to distribution

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. 130), carriers (e.g., for Na/glucose-cotransport, p. 178), and ion channels e.g., for sodium (p. 136) or calcium (p. 122) (**1**).

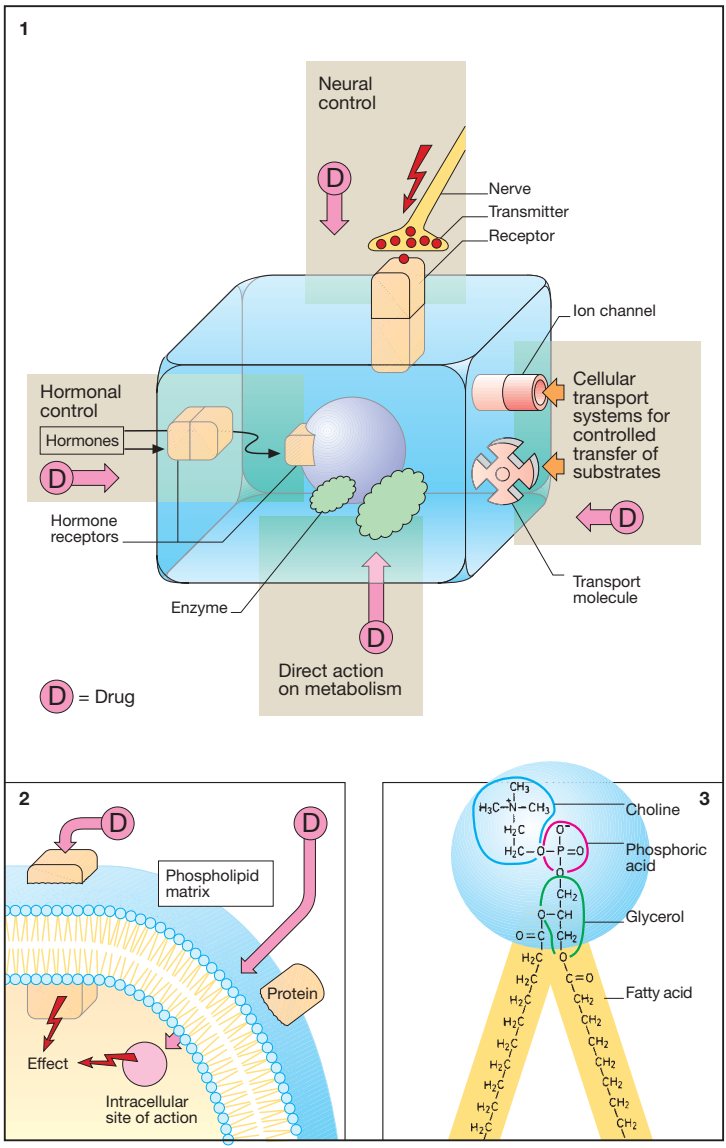
Functional coordination between single cells is a prerequisite for viability of the organism, hence also for the survival of individual cells. Cell functions are regulated by means of messenger substances for the transfer of information. Included among these are "transmitters" released from nerves, which 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, signalling substances can originate from neighboring cells, e.g., prostaglandins (p. 196) 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. 60). Altered activity of transport systems affects cell function (e.g., cardiac glycosides, p. 130; loop diuretics, p. 162; calcium-antagonists, p. 122). Drugs may also directly interfere with intracellular metabolic processes, for instance by inhibiting (phosphodiesterase inhibitors, p. 132) or activating (organic nitrates, p. 120) an enzyme (**2**).

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** (80Å = 8 nm in thickness) in which are embedded 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 directed outwards into the aqueous medium, the fatty acid chains facing each other and projecting into the inside of the membrane (**3**).

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



A. Sites at which drugs act to modify cell function

External Barriers of the Body

Prior to its uptake into the blood (i.e., during absorption), a drug has to overcome barriers that demarcate the body from its surroundings, i.e., separate the internal milieu 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 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, so 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 the 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 (ion pumps, ion channels) that occupy specific areas of the cell membrane.

This phospholipid bilayer represents the intestinal mucosa-blood barrier that a drug must cross during its enteral absorption. Eligible drugs are those whose physicochemical properties allow permeation through the lipophilic membrane interior (yellow) or that are subject to a special carrier transport mechanism. Absorption of such drugs proceeds rapidly, because the absorbing surface is greatly enlarged due 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 application, a drug encounters the non-keratinized, 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 phospholipid-containing membrane fragments 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 outer **skin**. The presence of a continuous phospholipid layer means that squamous epithelia will permit passage of lipophilic drugs only, i.e., agents capable of diffusing through phospholipid membranes, with the epithelial thickness determining the extent and speed of absorption. In addition, cutaneous absorption is impeded by the keratin layer, the stratum corneum, which is very unevenly developed in various areas of the skin.