A TEXTBOOK OF

FUNDAMENTAL MEDICAL PHARMACOLOGY

Chief Editors

Lin Yuan Li Shengnan

JILIN SCIENCE AND
TECHNOLOGY PUBLISHING HOUSE

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Lin Yuan 林原　　Li Shengnan 李胜男

Vice Chief Editors

Yan Zhongqun 严忠群　　Sui Dayuan 睢大员

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Yang Jingxian	杨静娴	Yao Jihong	姚继红	Cui Zheng	崔　征
Cai Jiqun	蔡际群				

Writers

Kaio Kitazato		Wang Kun	王　堃	Liu Xiaokang	刘小康
Li Yue	李　越	Chen Xiaohong	陈小红	Chen Xia	陈　霞
Yang Yunxia	杨云霞	Zhang Guiying	张桂英		

吉林科学技术出版社

JILIN SCIENCE AND TECHNOLOGY PUBLISHING HOUSE

图书在版编目(CIP)数据

药理学/林原,李胜男主编.—长春:吉林科学技术出版社,2004
ISBN 7-5384-2998-0

Ⅰ.药… Ⅱ.①林…②李… Ⅲ.药理学-医学院校-教材-英文 Ⅳ.R96

中国版本图书馆 CIP 数据核字(2004)第 071440 号

药 理 学(英文版)
林 原 李胜男 主编
责任编辑:吴文凯 封面设计:马继东
*
吉林科学技术出版社出版、发行
长春大学印刷厂印刷
*
880×1230 毫米 16 开本 26 印张 685 000 字
2004 年 9 月第 1 版 2004 年 9 月第 1 次印刷
定价:39.00 元
ISBN 7-5384-2998-0/R·756

社址 长春市人民大街 4646 号 邮编 130021
发行部电话 0431-5635177 5651759 5651628
邮购部 0431-5677817
电子信箱 JLKJCBS@public.cc.jl.cn
传真 0431-5635185 5677817
网址 www.jkcbs.com 实名 吉林科技出版社

Contributors

Cai Jiqun 蔡际群[15,17]
Dean of School of Pharmacy, Professor and vice Chair of Department of Pharmacology, China Medical University, Shenyang, PRC

Chen Xia 陈霞 [27)
Associate Professor, School of Basic Medical Sciences, Jilin University, Changchun, PRC

Chen Xiaohong 陈小红 [39]
Associate Professor, The Third Military Medical University, Chongqing, PRC

Cui Zheng(Zheng cui) 崔征, Ph. D [7]
Associate Professor, Department of Pathology, Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157, USA

Fan Jianglin 范江霖, Ph.D [6]
Professor of Department of Pathology, University of Tsukuba, Tsukuba, Japan

Kaio Kitazato., Ph.D [6]
Associate Professor of Department of Molecular Microbiology and Immunology, Nagasaki University, Nagasaki, Japan

Li Shengnan 李胜男, Ph.D [Preface, 4，11，23，48]
Professor and Chair, Department of Pharmacology, Nanjing Medical University, Nanjing, PRC

Lin Yuan 林原, Ph.D [Preface, 1，3，5，12，13，18，21，32，49, Review Exercises and Answers]
Professor and Chair, Department of Pharmacology, Dalian Medical University, Dalian, PRC

Li Yue 李越 [Index, Review Exercises and Answers]
Assistant, Dalian Medical University, Dalian, PRC

Liu Xiaokang Ph.D 刘小康 [43]
Associate professor of Department of Pharmacology, The School of Preclinical and Forensic Medicine, Sichuan University, Chengdu, PRC

Luo Jiandong 罗健东 [10]
Professor, Guangzhou Medical College, Guangzhou, PRC

Luo Xiaoxing 罗晓星 [24,47]
Professor and vice Chair, Department of Pharmacology, The Fourth Military Medical University, Xian, PRC

Lü Junhua 吕俊华 [30, 35]
Professor and Chair, Department of Pharmacology, School of Pharmacy, Jinan University, Guangzhou, PRC

Mei Qibing 梅其柄 [31,46]
Professor and Chair, Department of Pharmacology, The Fourth Military Medical University, Xian'an, PRC

Peter T.-H. Wong Ph.D [8,14]
Associate Professor, Department of Pharmacology, Faculty of Medicine, National

University of Singapore, Singapore.
Qian Zhiyu 钱之玉 [2,33]
Professor and Dean, Department of Pharmacology, China Pharmaceutical University, Nanjing, PRC
Sun Huijun 孙慧君, Ph.D. [34]
Associate Professor, Dalian Medical University, Dalian, PRC
Sui Dayuan 睢大员 [25]
Professor and Chair of Department of Pharmacology, School of Pharmacy,Jilin University, Changchun, PRC
Wang Kun 王堃, Ph.D. [9]
Associate Professor,Dalian Medical University, Dalian, PRC
Wang Lei 王蕾,[16,37,45]
Associate Professor and vice chair, Department of Pharmacology, The Medical School of Qingdao University, Qingdao, PRC
Xu Yanfang 许彦芳 [20]
Professor, Department of Pharmacology, Hebei Medical University, Shijiazhuang, PRC
Yan Zhongqun 严忠群 [26]
Associate Professor, Center for Molecular medicine, Karolinska Institute, Sweden; Guest Professor, Dalian Medical University.
Yang Jingxian 杨静娴. Ph.D [28,29,44]
Associate Professor, Dalian Medical University, Dalian, PRC
Yang Yunxia 杨云霞 Ph.D [40]
Lecturer of Department of pharmacology, The School of Preclinical and Forensic Medicine, Sichuan University,Chengdu, PRC
Yao Jihong 姚继红, Ph.D[36]
Professor, Dalian Medical University, Dalian, PRC
Ye Chunling 叶春玲, Ph.D[30,35]
Professor, Jinan University Pharmacuetical, Guangzhou, PRC
Yue Wang 岳旺[16,37,45]
Professor and Chair, Department of Pharmacology, The Medical School of Qingdao University, Qingdao, PRC
Zhang Guiying 张桂英. [Spelling and grammar checking from chapter 1—chapter 49]
Associate Professor, Department of Foreign Language, Dalian Medical University, Dalian, PRC
Zhang Hailin 张海林[19,22]
Professor and vice Dean, School of Pharmacy, Hebei Medical University, Shijiazhuang, PRC
Zhou Hong 周红 [39,41,42]
Associate Professor and Chair, Department of Pharmacology, The Third Military Medical University, Chongqing, PRC
Zhou Liming 周黎明 Ph.D [38,40,43]
Associate Professor and Chair, Department of Pharmacology, The School of Preclinical and Forensic Medicine , Sichuan University, Chengdu, PRC

出 版 说 明

20 世纪 70 年代末，我国恢复了高考制度。一些高等医科院校开始尝试招收六年制外语医学班，采用了双语教学。1990 年由原白求恩医科大学等 10 余所医科院校共同编写，吉林科学技术出版社出版的《人体解剖学》（英文版）、《局部解剖学》（英文版）教材满足了英语医学班的教学需要。这两种英文版教材至今已出到了第三版。

近些年来，一些规模较大的医科院校开始招收七年制的本—硕连读学生，并逐年扩大招生规模。2004 年教育部又新批准了几所院校招收八年制本—硕—博连读学生。这些学生都将采用双语或英语教学。教学中迫切需要一套既适合中国国情又符合我国教学大纲要求的英文版医学教材。为满足这一需求，我社于 2003 年春夏组织全国 30 多所大学基础医学各相关学科教学第一线直接从事双语教学的教师编写了这套基础医学双语教学英文版系列教材。参编人员绝大多数都在国外学习工作多年，既有扎实的专业基础，又具有较雄厚的英文功底，还具有本专业丰富的教学经验。本系列教材有的学科邀请了新加坡、瑞典、日本、美国的相关专家参加了编写，有的全书或部分请外籍专家进行了审校。本套教材以国内医学教学大纲为基本框架，主要适合七年制、八年制医学、药学专业教学使用，亦可供留学生及外语基础较好的五年制教学使用。

本套教材最大特点是适合我国教学体系，满足我国教学大纲要求，价格低廉，师生都易于接受。当然，本套教材除《人体解剖学》和《局部解剖学》已经过修订，出到了第三版外，《生物化学》、《药理学》、《病理学》、《生理学》、《医学微生物学》、《医学免疫学》等 6 种教材都是初版，在编辑出版过程中肯定会有这样那样的问题，会有一些不尽人意的地方。希望广大师生在使用这套教材的过程中及时将发现的问题反馈给我们，以便在修订过程中不断加以完善。我们的联系方式是：长春市人民大街 4646 号，吉林科学技术出版社；邮编：130021；电话：0431-5635173；E-mail:82001@sina.com。

吉林科学技术出版社

2004 年 8 月

Preface

One of the major reasons for the prevalence of bilingual education in Pharmacology is based upon the great difference between the pharmacology education and relevant life science home and abroad. Benefited from bilingual-education in Pharmacology, students will get information efficiently and get geared to the globalization in research related to Pharmacology in the future.

Selection of suitable textbook is of great importance in bilingual education. Integrating the strong points from some famous textbooks in life science, following the recent advance in Pharmacology, summarizing the experience in bilingual education, and understanding the way of Chinese students in learning English are the guidelines for editing our textbook. We have tried our best to make this textbook concise, systematic, illuminative, and with clear priority. This textbook is featured with the following characteristics in most chapters: Objectives, Discovery, Summary, Prospectus, Suggested Further Reading, Questions and Answers.

Pharmacologists in 12 domestic universities joined in the compiling; and most of them have overseas-study experience, and are familiar with the scientific research and teaching in Pharmacology. We have also invited scientists in relevant fields from Singapore, Sweden, Japan, and USA to contribute to the textbook. As the old saying goes "Judgment could be made only through comparison", we firmly believe that students will prefer our textbook after reading it. We do wish that we could get some valuable suggestions from readers and guidance from our colleagues. The email addresses to contact us are liny@dlmedu.edu.cn, Snli@njmu.edu.cn.

由于目前国内与药理学相关的生命科学的发展与国外存在相当大的差距，因此，用英语进行药理学的双语教学对于今后准确快速地掌握国外有关药理学方面的信息，从事与药理学有关的工作都是十分有益的。

搞好双语教学，教材的选择十分重要。通过总结国内外一些著名教材的编写方式、国内外药理学科的新进展、国内的双语教学经验以及我国学生学习的特点，我们尽力使本书简明扼要、重点突出、条理性强，尤其注重了内容的启发性。我们还在章节中安排了"学习要点"，与本章有关的"科学发现"、"总结"、"展望"、"建议阅读书籍目录"及"习题与答案"等内容。

参加本书编写的人员来自国内 12 所高等院校，其中大部分编者都有国外留学经历，有较丰富的教学与科研经验。此外，我们还邀请了新加坡、瑞典、日本及美国的相关专家编写了部分章节。有比较才有鉴别，我们坚信本书将受到同学们的欢迎，同时期望读者对本书提出宝贵的建议，希望有关专家不吝赐教。（E-mail:liny@dlmedu.edu.cn, Snli@njmu.edu.cn ）

Ling Yuan 林原　　Li Shengnan 李胜男

Contents

Chapter 1 Introduction to General Pharmacology

Upon opening the textbook first time, the students might inquire, "What does **pharmacology** mean?" "Why drugs can be used to treat diseases?" "What kind of drug should be used if one is suffering from diseases?". There is no doubt that students may get the answers to these questions after learning **Pharmacology**. However, it should be noted that previous experience showed that in almost every academic year, many students complained the difficulties to memorize the incredible amount of information in **Pharmacology**. To deal with such a big burden in learning P**harmacology**, we suggest that students pay attention particularly to the following important information: (a) the general principles described in the chapters of **Pharmacodynamics** and **Pharmacokinetics**; (b) the major pharmacological effects, mechanisms of action, clinical applications, and adverse effects of a drug class; especially rare and severe adverse effects of some drugs, e.g., allergic reaction caused by **penicillin**, ototoxicity caused by **aminoglycoside**; (c) the special feature of drug(s) in a drug class, e.g., **thiazide diuretics** reducing urine volume by up to 50% for nephrogenic diabetes insipidus; (d) the drug of choice in the treatment of disease, e.g., **penicillin G** is of choice for infections caused by sensitive strains of S. *pneumoniae*; (e) some important **pharmacokinetic** features, e.g., half-life of mainly described drugs, the unique way of administration of some drug, active metabolite which will influence drug effects; (f) the drug interaction if co-administered two drugs or more; (g) structure-activity relationship which is well established for a class of drugs, e.g., **opioids**, **glucocoticoids**.

Students not only should keep in mind the important guideline described in the above section, but also should firmly believe that it is unnecessary to memorize the huge amount of trifle details of each individual drugs. The achievements of students in learning P**harmacology** is not to memorize the detailed facts of each drug, but master the basic rule of **Pharmacology**, e.g., if students master the common characterization of beta adrenergic receptor antagonists, they can implicate the framework of a new drug in the same class if introduced into clinics.

Understanding of the pharmacological effects of drugs does not mean mastering **Pharmacology**. It should be noted that the pharmacological effects of drugs are not always constant, and they are influenced by drug interaction, genetic difference, health/age states, previous experience of the drug and the personal attitude to the drug.

The relationship between health, disease and drugs

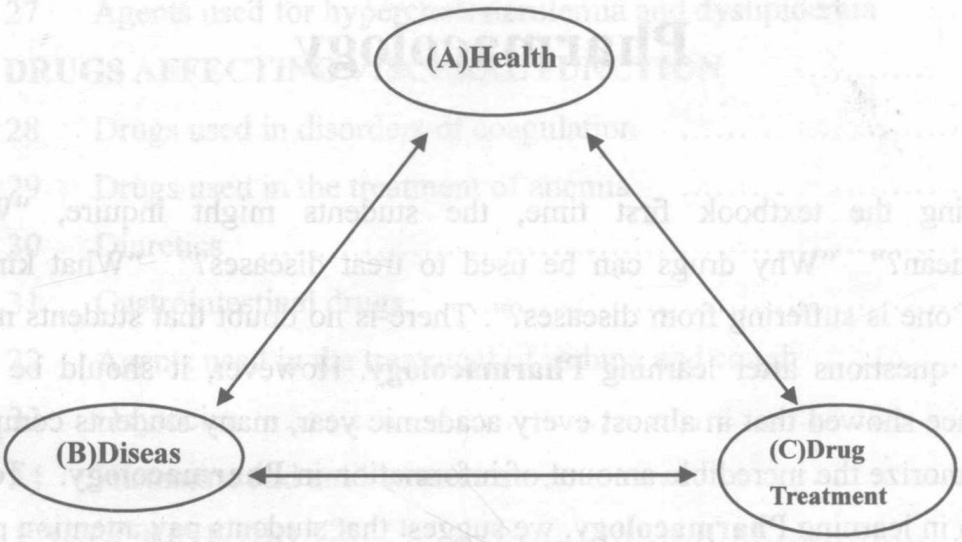

Fig. 1-1 The relationship between health, disease, and drug treatment

Firstly, it should be noted that health not only includes physiological health, but also psychological health, and society health. Social environment, psychological state of a person will affect physiological health. Secondly, diseases can be caused by exterior factors, e.g., microorganism invasion, and interior factors, e.g., weakness of the body, genetic disease. Thirdly, diseases can be treated with drugs, by which health returns. We should stress that drug treatment is bilateral: returning to health and/or bringing about toxicity.

Drug

Ⅰ. The meaning of a drug

Drugs here mean therapeutic **drugs** or medicines, and can be defined as any substances (exogenous or endogenous substances e.g., synthetic **drugs**, hormones, antibiotics, peptide, DNA fragment, etc), when introduced into body, interact with specific molecular in the biologic system, resulting in a biological change to elevate or lower body's function according to their own chemical and physical properties. **Drugs** may also be used to kill the invading pathogen without harming the body. **Drugs** are used to prevent, diagnose and treat diseases.

Ⅱ. Drug nomenclature

Many **drugs** have a variety of names. Chemical name gives the information by which the chemist understands exactly the chemical constitution of the **drug**. Official name is given by government and is used in pharmacopoeias. Propriety name is manufacture's name. An example is given as the following.

Chemical name: ortho-acetoxybenzoic acid.

Official name: **acetylsalicyclic acid** (British pharmacopoeias), **aspirin** (U.S.P. = united states pharmacopiea)

Proprietary names: **Acetophen**, **Empirin**

Ⅲ. The properties of an ideal drug

No **drug** confers new function to organism, instead, it serves to increase or decrease the existing physiological or biochemical functions of organism. An ideal **drug** should have high selective biological action (e.g., **acetylcholine** is an M and N receptor agonist, **pilocarpine** is an M receptor agonist), little untoward reactions, low toxicity, and is easily administered. However, high selectivity is not considered as an advantage for antibiotics.

Pharmacology

Ⅰ. The meaning of Pharmacology

Pharmacology can be broadly defined as a science dealing with the study of the rule and mechanism of mutual interaction between drugs and living systems, which include human species, animal, and organism. **Pharmacology** comprises mainly **Pharmacokinetics** and **Pharmacodynemics**, which provides the base for drugs in preventing, diagnosing, and treating diseases. **Pharmacology** is also concerned with history, physical and chemical properties of drugs.

Ⅱ. The main subdivisions of Pharmacology

There are 6 subdivisions of **Pharmacology**. They are: **Pharmacodynamics, pharmacokinetics, Toxicology, Pharmacotherapeutics, chrono-Pharmacology, and Pharmacognosy**. The first four subdivisions are of most importance.

Ⅲ. The relationship between drug disposition and effects

Though **drug** disposition and effects are described in the separated chapter, what should be stressed on is that the absorption, distribution, biotransformation, and elimination, the pharmacological effects, and the adverse effects of a **drug** happen almost simultaneously; factors which influence **drug** disposition will also affect the **drug** effects.

(*Lin Yuan*)

Chapter 2 Pharmacokinetics

Objectives

The study purpose of **pharmacokinetics** is to reveal the regularity of dynamic changes of drugs in the body, that is, the process of **absorption, distribution, metabolism** and **excretion** of drugs in the body (Fig. 2-1).

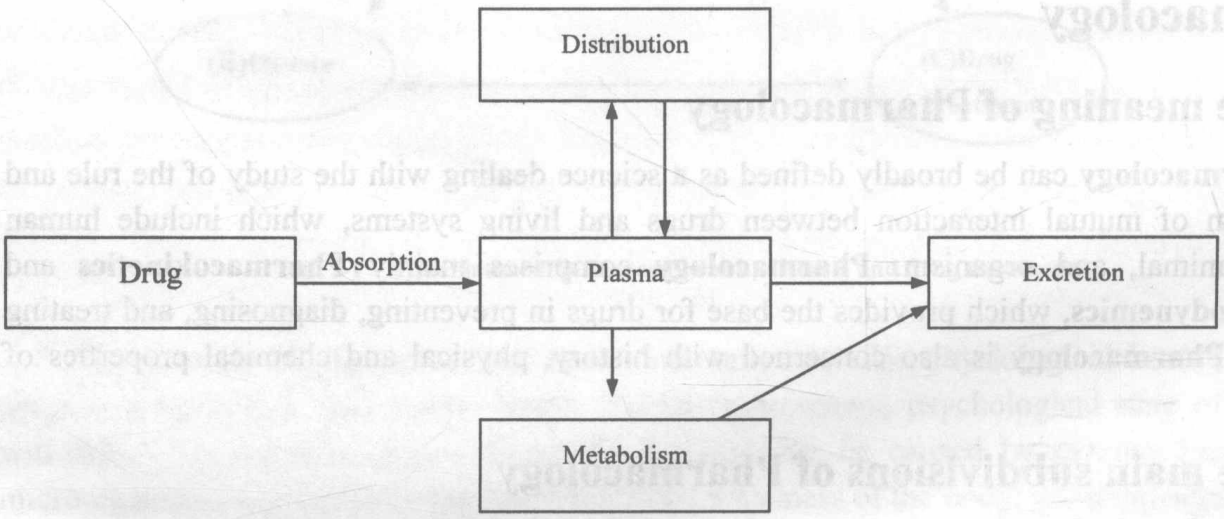

Fig.2-1 Process of dynamic change of drugs in the body

As is shown in the above figure, drugs are in the state of dynamic change all the time in the body, and the process of drug disposition in the body is complicated due to the influence of numerous factors. To reveal the regularity of dynamic change of drugs in the body, mathematical methods are frequently adopted to clarify the regularity of change of in vivo drug quantity versus time. According to the value of in vivo drug quantity and time, an appropriate mathematical model is established to calculate corresponding **pharmacokinetic** parameters from which the regularity of dynamic change of drugs in the body is described. Understanding of the regularity, on one hand, helps us to know the regularity of drug action and thus directs us to establish rational medication project to enhance the security and rationality of medication; on the other hand, it can provide guideline to the development, research and evaluation of new drugs.

Drug transport

Drugs must first arrive at the action site to produce corresponding effects after entering the

body. In the process, drugs need to cross various biological membranes with lipoid properties. This is called transmembrane transport of drugs. The transport of drugs may be chiefly divided into two patterns, passive transport and carrier-mediated transport.

Ⅰ. Passive transport of drugs

Passive transport is defined as a kind of transport process in which drugs transport from a region of higher concentration to one of lower concentration. The primary drive force is the concentration gradient of drug across the membrane, so the transport process achieves homeostasis when the concentrations of both sides are equal. This kind of transport needs no energy, and no saturation phenomenon exists in the process. The majority of drugs are transported in the body by passive transport. Passive transport may be further divided into simple **diffusion** and **filtration**.

A. Simple diffusion

The **diffusion** rate of simple **diffusion** is not only associated with the physicochemical properties of drugs such as molecular weight, polarity, lipid-solubility and dissociation, but also the property and the area of plasma membrane and the concentration gradient across the membrane. Because most drugs are weak electrolytes, they exist in the body fluid in two species, namely the unionized and ionized species. The polarity of drugs in the ionized form is stronger than that of drugs in the unionized form, while the lipid-solubility of the latter is greater than that of the former. Therefore, drugs in the unionized form are easier to diffuse across the membrane due to the lipoid characteristics of the biological membrane. The extent of the dissociation of a drug is determined by its own dissociation constant (pKa) and the pH of its environment. Their relationships can be explained according to the Handerson-Hasselbalch equation, where Ka is the dissociation constant and pKa is its negative logarithm.

weak acidic drug	**weak basic drug**
$HA \longleftrightarrow H^+ + A^-$	$BH^+ \longleftrightarrow H^+ + B$
$Ka = \frac{[H^+][A^-]}{[HA]}$	$Ka = \frac{[H^+][B]}{[BH^+]}$
$pKa = pH - \log \frac{[A^-]}{[HA]}$	$pKa = pH - \log \frac{[B]}{[BH^+]}$
$pH - pKa = \log \frac{[A^-]}{[HA]}$	$pKa - pH = \log \frac{[BH^+]}{[B]}$
$10^{pH-pKa} = \frac{[A^-]}{[HA]}$	$10^{pKa-pH} = \frac{[BH^+]}{[B]}$

Where $[A^-]$ and $[BH^+]$ are ionic form; [HA] and [B] are un-ionic form.

The above equations indicate that pKa is the pH value when 50% of the drug dissociate in solution regardless of weak acidic or weak basic drugs. If pH = pKa, [HA] = [A^-]; if pH=pKa, [B] = [BH^+]. The pKa value of drugs does not relate to weak acidity or weak basicity of drugs themselves. The pKa value of weak acidic drugs may be more than 7, and the value of weak basic ones may be less than 7. The alteration of the pH of solutions can affect the transmembrane transport of weak acidic or weak basic drugs. The extent of ionization of weak acidic drugs is low in low-pH solution, and thus they are easy to transport across the membrane. So this kind of drugs can be absorbed in gastric fluid and reabsorbed easily in acidified urine by the renal tubule, whereas basifying urine can accelerate their renal excretion. Weak basic drugs are difficult to dissociate in basic intestinal fluid. Consequently these drugs are mostly absorbed in the intestine, and basifying urine can increase their **reabsorption** in the renal tubule so as to slower renal **excretion** while acidifying urine can accelerate their renal **excretion**.

B. Filtration

Filtration is defined as the transport process in which drugs whose particle size is less than the membrane gap in diameter move from the side of higher pressure to that of lower pressure by dint of liquid static pressure or osmotic pressure disparity. For example, drugs filtrate across the renal tubule.

Ⅱ. Carrier-mediated transport of drugs

A. Active transport

Active transport refers to the transmembrane movement of drugs with the aid of special carriers and the requirement of energy consumption. This kind of transport does not depend on the concentration gradient across the membrane. Drugs can transport from a region of lower concentration to one of higher concentration. The process needs special carriers and energy consumption with situation of saturation and competitive inhibition. For instance, the secretory **excretion** of drugs from the renal tubule belongs to **active transport**. The competitive inhibition of **ethacrynic acid** and uric acid on the renal tubular secretion may cause adverse reactions including gout when **ethacrynic acid** is administered.

B. Facilitated diffusion

Facilitated diffusion is a kind of transport process with the help of special **carriers** inside the membrane. The process needs no energy, has relatively high selectivity with competitive inhibition, but drugs are not capable of transporting against the concentration gradient. For example, glucose and amino acids are transported by **facilitated diffusion**.

In vivo process of drugs

Ⅰ. Drug absorption

Absorption may be defined as the process in which drugs transport from the site of administration to the blood circulation after extra-vascular administration. The rate and extent of

absorption can affect the latent period and action intensity of drugs. Generally speaking, the rate and extent of **absorption** are chiefly determined by their own physicochemical properties such as lipid-solubility, the extent of dissociation and molecular weight. However, drug **absorption** is also affected by many other factors, which can be summarized into two categories, the drug factors and the body factors. Drug factors include the physicochemical properties of drugs, formulations (solubility and dissociation rate) and the route of administration. Different routes of clinical administration exert great influence on drug **absorption**, obviously affecting the effects and toxicity of drugs.

A. Gastrointestinal administration

Oral administration is the most frequently-used route of gastrointestinal administration with the features of safety, convenience and economy. Nevertheless, the **absorption** is slow and various factors may influence it, altering the rate and extent of **absorption**. Drugs are absorbed into the systemic circulation via the capillary vessels in the gastrointestinal mucous membrane. The intestinal tract is the major site for drug **absorption** because of the largeness of **absorption** area of intestinal mucous membrane, rapid intestinal motility, ample intestinal fluid in which drugs show great solubility, and abundant blood flow. Absorbed by the gastrointestinal tract, drugs first enter the liver via the portal vein along with the blood flow, and then enter into the systemic circulation. Some drugs are inactivated, i.e. metabolized, in the gastrointestinal tract and liver before entering into the systemic circulation. The process, called **first pass elimination**, decreases actual drug quantity entering into the systemic circulation. Clinically some common-used drugs such as **glonoin**, **propranolol, lidocaine**, **imipramine** and **chlorpromazine** have distinct **first pass elimination**. Adoption of sublingual and rectal administration without passing the portal vein can avoid the **first pass elimination** of the liver. Oral administration is unsuitable to be adopted under the following situations: (a)Drugs exert violent stimuli on the gastrointestinal tract or bear strong **first pass elimination**; (b) The patient is unconscious or unable to swallow; (c)Some drugs are difficult to be absorbed in he gastrointestinal tract or easily destroyed under the acidic and basic circumstances of the gastrointestinal tract; (d)Some drugs must be administered by **injection** to achieve expectant effects. For instance, oral administration of **magnesium sulfate** can only cause diarrhea, and anticonvulsive and sedative effects can be obtained only by **injection**.

B. Injection

Injection is also one of common clinical routes of administration, through which drugs directly reach the systemic circulation without the process of **absorption** after intravenous administration. Following intramuscular and subcutaneous **injection**, drugs entering into the blood circulation via capillary vessels, and the rate of **absorption** is usually quicker than that via oral administration. But some drugs are unsuitable for **injection** due to their intensive local irritation. The rate of **absorption** is associated with the water-solubility of drugs and local blood flow at the site of **injection**.

Inhalation The lung possesses alveolus with large surface area and abundant blood flow, hence some volatile drugs such as ether and **halothan** can be rapidly absorbed via the lung after **inhalation**. Rapid **absorption** features this route of administration, but the dosage is difficult to

control. The aerosol particle of some solid and liquid drugs is small (diameter < 5μm), and they can produce systemic action through the **absorption** of the lung after **inhalation**. Larger aerosol particle can only be applied to local therapy, such as antibacterial and anti-inflammatory therapy of nasopharynx, and snuffle. **Inhalation** is suitable for volatile or gas drugs, e.g. **inhalation** anesthetics.

Transdermal administration

Aside from a few drugs with high lipid solubility, most drugs can not be absorbed via intact derma. This route of administration is featured by slow and irregular **absorption**; hence the dosage is hard to control.

Ⅱ. Drug distribution

The **distribution** of drugs refers to the process in which drugs absorbed in the blood transport from the blood to tissues, intercellular fluid and cellular fluid across various physiological barriers; and most drugs are transported by passive transport. The drug transport between the plasma and tissue fluid is bi-directional and reversible. Consequently, when the **distribution** reaches homeostasis, the ratio of the drug concentration between tissues and plasma remains constant, called **tissue partition coefficient** of drugs, but the drug concentration of tissues and that of plasma are not always equal. The transport rate of a drug towards a certain tissue is primarily determined by its physicochemical properties (such as lipid-solubility of drugs), the blood flow of the tissue and permeability of membrane. The **distribution** concentration of drugs in tissues lies on the **tissue partition coefficient** of drugs, the pH of the body fluid, plasma protein binding rate and the volume of tissues. Among the aforementioned factors, the physicochemical properties, the pH of body fluid, plasma protein binding rate and the permeability of membrane are main factors affecting **distribution**.

A. The influence of the pH of body fluid on drug distribution

The pH of body fluid may influences the extent of dissociation of drugs and thus affect the **distribution** and transport of drugs in the body. The pH of cellular fluid is 7.0 and that of extra-cellular fluid is 7.4 under physiological circumstances, so the concentration of weak acidic drugs in extra-cellular fluid is higher than that in cellular fluid. Reducing the pH of the blood can transfer weak acidic drugs into cells, while increasing the pH of blood can cause rightabout transfer of those drugs. The situation for weak basic drugs is opposite.

B. The influence of plasma protein binding on drug distribution

Drugs can bind proteins to form bound drug in plasma and tissues, and residual uncombined drugs are called free drug. Drugs mostly bind **albumin** in plasma, and they can also link to plasma β-globin and acidic glucoprotein. The extent of combination of drugs with plasma protein differs, which is usually expressed by the ratio of the concentration of bound drug over total drug, i.e. plasma protein binding rate. Because the combination of drug with plasma protein influences the transport and pharmacological activities of drugs, the bound drug is incapable of crossing the biological membrane to transfer and thus loses pharmacological activities. Obviously, the plasma protein binding rate of drugs is one of the important **pharmacokinetic** parameters. However, due