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JAYPEE

Catalyst for all PG Medical Examinations

PLATINUM NOTES

2015–16

Platinum Notes

Thoroughly Revised and Updated Edition Including Latest Exam Topics, Questions and Image-based Concept

Completely updated till 2016

Volume 1

Preclinical Sciences

Anatomy, Physiology, Biochemistry, Pharmacology, Pathology, Microbiology, Forensic Medicine, PSM

Important Topics Covered

AIPGMEE, AIIMS, PGI, Delhi PGMEE, Rajasthan PGMEE, UP PGMEE, Karnataka PGMEE, AP PGMEE, J&K BOPEE, Tamil Nadu PGMEE, Kolkata PGMEE, Bihar & Jharkhand PGMEE, Kerala PGMEE, MP PGMEE, DNB, Orissa PGMEE, and Maharashtra PGMEE

Latest Topics Covered from NBE 2015, DNB 2013, AIIMS 2015

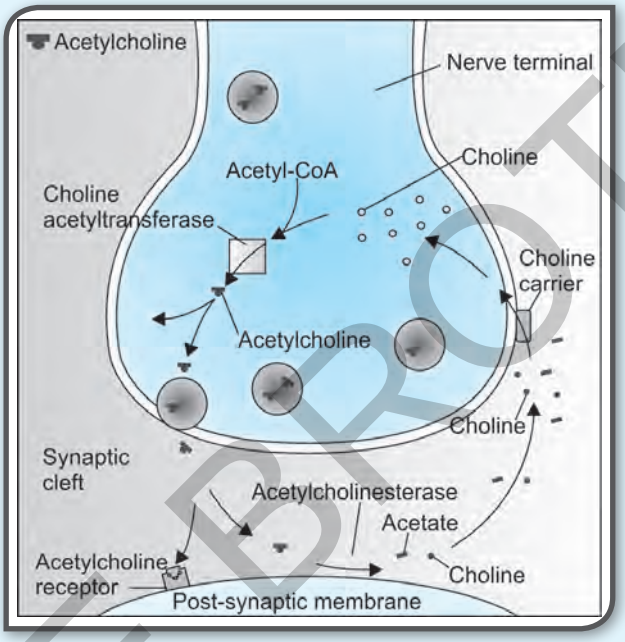
5th Edition

Ashfaq Ul Hassan

Contents

1.	Anatomy	1
2.	Physiology	117
3.	Biochemistry	201
4.	Pharmacology	265
5.	Pathology	367
6.	Microbiology	449
7.	Forensic Medicine	517
8.	Preventive and Social Medicine	553

Pharmacology



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4 Pharmacology

Pharmacokinetics: is quantitative **study of drug movement in through and out of the body.** ☛ **PGI 1995**
What the body does to a drug: ☛

- **Pharmacodynamics: is what the drug does to a body.** ☛
- **Pharmacogenetics:** study of **genetic basis for variability in drug response.** ☛
- **Pharmacogenomics: use of genetic information to guide choice of drug and dose on individual basis.** ☛
- **Pharmacovigilance: science and activities related to detection, assessment, understanding and prevention of adverse effects of drug or other drug related problems.** ☛

CLINICAL TRIALS (HIGH YIELD FOR AIIMS/AIPGME/DNB 2016)

- **Clinical trials:* Determine:**
- **Phase I: Human pharmacology and safety** ☛☛
- **Phase II: Therapeutic exploration and dose ranging** ☛☛**, Determines efficacy** **AI 2008**
- **Phase III: Therapeutic confirming** ☛☛
- **Phase IV: Postmarketing surveillance** ☛☛**. No ethical clearance required.** **AI 2004**
- **Good clinical practice is not needed for preclinical trials but is needed for phase I – IV** **AIIMS 2007**
- **Preclinical study is done in animals** ☛☛
- **Clinical trial is done in humans** ☛☛
- **Unwanted effect at therapeutic doses: Side effect** ☛ **PGI 1999**
- **Unwanted effect due to overdose Toxic dose** ☛

Terms Frequently Asked in Examinations

• **Affinity:** ☛	**ability of a drug to combine with receptor.**	
• **Intrinsic activity (efficacy):** ☛	**ability of drug to activate receptor.**	
• **Agonist:** ☛	**have affinity and maximal efficacy**	**Delhi 1987**
• **Antagonist:** ☛	**have affinity and no maximal efficacy**	**Delhi 1990**
• **partial agonist:** ☛	**have affinity and submaximal efficacy**	
• **inverse agonist:** ☛	**have affinity and opposite efficacy**	

Important Terminology * (AIIMS/AIPGME/DNB 2016)

- **Clearance**, a measure of the **body's ability to eliminate drug**; Clearance is a measure of the rate at which the organs that eliminate drug from the body remove drug from the blood. ☛ **KAR 2006**
- **Volume of distribution**, an indication of the **extent to which the drug is distributed outside of the blood compartment;** ☛☛

Contd…

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Contd...

- **Bioavailability**, the **fraction of the administered dose that reaches the systemic circulation**. ☛
- **Steady state** is achieved when the **rate of drug elimination equals the rate of drug delivery into the systemic circulation,** which, if bioavailability is complete, corresponds to the rate at which the drug dose is administered. ☛
- **Therapeutic index: the ratio of the toxic dose to the therapeutic dose. LD_{50}/ED_{50}** **AI 2008, UP 2007**
- If absorption is too rapid, then the resulting high concentration may cause adverse effects not observed with a more slowly available formulation. At the other extreme, slow absorption is deliberately designed into 'slow-release' or 'sustained-release' drug formulations in order to maintain plasma concentrations essentially constant during the dosage interval, because the drug's rate of elimination is offset by an equivalent rate of absorption controlled by formulation factors. ☛☛ **JK 2005**
- **Half-Life:** Half-life ($t_{1/2}$) is the time that it takes for the plasma concentration or amount of drug in the body to decline by 50%. ☛☛**. Time taken for a drug to reach plateau level in plasma after repeated doses also depends on its plasma half life.** **JKBOPEE 2012**
- **Drug Potency:** Relative concentrations of two or more drugs that elicit same effect. **Refers to amount of drug needed to produce a certain response**. ☛☛
- **Drug Efficacy**: **Maximal effect** that a particular drug may elicit. ☛☛ **PGI 1998**
- **More important than potency in determining choice of drug**. ☛
- **Therapeutic window phenomenon:** Optimal therapeutic response of drug is exerted only over a narrow range of plasma drug concentration, e.g. TCA, clonidine, glipize. **PGI 1995**

$t_{1/2}$ can determine: ☛☛ **AIIMS 1992**

- elimination time☛
- steady state plasma concentration☛
- dosing rate☛
- maintainance dose☛

- First pass metabolism is seen with oral route and rectal route. ☛ **AI 1994**
- **More first pass metabolism is seen with oral route.** ☛
- Bioavailability by **IV route** is 100%.☛
- **Sublingual route bypasses** first pass metabolism.☛

Drug Metabolism Occurs in Two Phases: **(AIIMS/AIPGME/DNB 2016)

- **Phase I:** ☛☛
  - **Oxidation**☛
  - **Reduction**☛
  - **Hydrolysis**☛
  - **Cyclization, Decyclization** ☛

MFO (Mixed Function Oxidases) in Liver participate.☛

- **Phase II:** ☛☛ Conjugation with
  - **Glucronide** ☛
  - **Sulfate**☛
  - **Glutathione, Acetylation, Methylation**☛ **PGI 2002**
  - Conjugation **does not** occur in metabolism of xenobiotics. ☛ **AIIMS 2008**

Drugs with High First Pass Metabolism: *

- **beta blockers (propranolol),** ☛ **PGI 2003**
- **lignocaine** ☛ **PGI 2003**
- **salbutamol** ☛ **PGI 2003**
- **verapamil** ☛

Contd...

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Contd…

- **nitroglycerine** ☛
- **testosterone** ☛
- **morphine** ☛
- **hydrocortisone** ☛

Drug Monitoring is useful in drugs with low safety margin:

1. lithium — **AIIMS 2014**
2. digoxin
3. antiepileptics
4. antiarrhythmics
5. theophylline
6. aminoglycosides.

Serum levels of Lithium should be: 0.8–1.2 mEq/L. — **AIIMS 2014**
Levels greater than 2.0 indicate Toxicity — **PGI 2013**

Drug deposited in retina: chloroquine — **UP 2007**

Drug deposited in muscle: digoxin. — **UP 2007**

Factors governing volume of distribution of a drug are: **

- **Lipid: water coefficient** of drug. ☛ — **UP 2007**
- **pKa:** value of a drug. ☛
- Degree of **Plasma protein binding** ☛ — **UP 2007**
- Degree of **blood flow**. ☛
- **Affinity** for different tissues. ☛ — **UP 2007**
- **Fat: Lean body** mass ratio ☛
- **Diseases** like CHF, Uremia, Cirrhosis ☛
- **Pregnancy** ☛

Cytochrome P450 Superfamily (CYP): (AIIMS/AIPGME/DNB 2016)

- is a **large and diverse group of enzymes**.
- The function of most CYP enzymes is to **catalyze the oxidation of organic substances.**
- The substrates of CYP enzymes include metabolic intermediates such as **lipids and steroidal hormones, as well as xenobiotic substances such as drugs and other toxic chemicals.**
- CYPs are the major enzymes involved in drug metabolism and bioactivation, accounting for ~75% of the total metabolism.
- The most common reaction catalyzed by cytochromes P450 is a monooxygenase reaction.
- Cytochromes P450 (CYPs) belong to the superfamily of proteins containing a heme cofactor and, therefore, are hemoproteins.
- CYPs use a variety of small and large molecules as substrates in enzymatic reactions.
- Often, they form part of multi-component electron transfer chains, called P450-containing systems.
- Cytochromes P450 have been named on the basis of their cellular location and spectrophotometric characteristics (chrome): when the reduced heme iron forms an adduct with CO, **P450 enzymes absorb light at wavelengths near 450 nm, identifiable as a characteristic Soret peak.**
- CYP enzymes have been identified **in all kingdoms of life**, i.e. in animals, plants, fungi, protists, bacteria, archaea, and viruses.

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Never Forget: (High Yield for AIIMS/AIPGME/DNB 2016)

- **Plasma protein binding occurs with many drugs.** ☛
- **Highly plasma protein bound drugs are restricted mainly to vascular compartment.** ☛
- **Displacement of protein bound drug↑ plasma levels of drug.** **PGI 2000**
- **Have lower volumes of distribution.** ☛
- **Bound fraction is not available for action.**
- **In hypoalbumenemia binding may be reduced and high concentration of free drug may be available** ☛
- **Binding sites are non specific and one drug can displace other.** **AI 2000**

Drugs Bound to Albumin are: ☛☛

- barbiturates☛
- benzodiazepenes☛
- phenytoin☛ **PGI 1986**
- penicillins☛
- sulfonamides☛
- tetracycline☛
- tolbutamide☛
- warfarin☛ **PGI 1986**

Drugs Bound to α Acid Glycoprotein are: ☛☛ (JKBOPEE)

- Prazosin☛
- Methadone☛
- Lidocaine☛
- Imipramine☛
- Verapamil☛
- Bupivicaine☛
- Disopyramide☛
- Quinidine☛

List of 'Prodrugs': ☛ (High Yield for AIIMS/AIPGME/DNB 2016)

- Enalapril: Enalaprilate☛☛ **AIIMS 2006, NIMHANS 2001**
- **All ACE inhibitors are Prodrugs except Captopril and Lisnopril.** **AIIMS 2014**
- Sulfasalazine: 5 Aminosalisylic acid☛☛
- Flourouracil: Flourouracil monophosphate☛☛
- Dipivefrine: Epinephrine☛☛
- Prednisone: Prednisolone☛☛
- Levodopa: Dopamine☛☛

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Other Prodrugs: ☛☛ (High Yield for AIIMS/AIPGME/DNB 2016)

• bacampacillin☛	
• Cefotaxime	
• cyclophosphamide☛	
• Fluorouracil, mercaptopurine☛	
• Losartan	
• Methyl dopa☛	
• Spironolactone	
• sulindac☛	PGI 2011
• terfenadine☛	
• Ticlopidine, Clopidregel	AIIMS 2007
• zidovudine☛	
• Bitolterol	PGI 2011

' Ticlopidine' is a ' prodrug' used as an antiplatelet agent. **JIPMER 2014**

ORPHAN DRUGS*

When a drug is not developed into a usable medicine because the costs will not be recovered by the developer then it is called an **orphan drug** and the disease as **orphan disease** and sufferer as **health orphan**☛☛

(AIIMS/AIPGME/DNB 2016)

Remember

- **Therapeutic window phenomenon**: best possible therapeutic effect is exerted by a drug only in narrow range of drug concentrations. Exhibited by: **tricyclic antidepressants, clonidine, and glipizide.** ☛
- **Hit and run drugs**: drugs **whose effects last much longer** than the drug itself. **Reserpine, guanethidine, MAO Inhibitors, omperazole.** ☛
- **Drugs with zero order kinetics**: **phenytoin, aspirin, ethanol, Theophylline, propafenone, warfarin, tolbutamide**☛
- **Drugs with First-order kinetics**, the time required to achieve steady-state levels can be predicted from the half-life, because accumulation is a first-order process with a half-life identical to that for elimination. Thus, accumulation reaches 90% of steady-state levels at the end of three to four half-lives. ☛

Drugs Undergoing Enterohepatic Circulation:

- **erythromycin**
- **ampicillin**
- **rifampicin**
- **tetracycline**
- **OCPS**
- **Phenolphthalein.**☛

- **Placebo: inert substance given in the form of medicine with no pharmacological effect but psycological Effect.** ☛
- **Nacebo: is reverse of placebo: refers to negative psycodynamic effect evoked by loss of faith in Medication or physician prescribing medication.**☛

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In Zero Order Reaction: ☛☛ (High Yield for AIIMS/AIPGME/DNB 2016)

- A 'constant **amount** '**of drug is eliminated per unit time.** ☛
- Rate of elimination is **independent** of plasma concentration. ☛
- Drugs with zero order elimination have no fixed half life. **($t_{½}$ is variable)** ☛
- **Phenytoin, Ethanol and Salicylates** show zero order kinetics. ☛ **AI 1996**

In First Order Reaction: ☛☛ (High Yield for AIIMS/AIPGME/DNB 2016)

- **A** 'Constant **fraction**' **of drug is eliminated per unit time.** ☛
- Rate of elimination is **directly dependent** on plasma concentration. ☛ **COMED 2008**
- Drugs with first order elimination have fixed half life. **($t_{½ \text{ is constant}}$)** ☛
- **Most drugs** show first order kinetics. ☛

Zero order: Elimination rate constant ☛

$t_{½}$ variable ☛

First order: Elimination rate variable ☛

$t_{½}$ Constant ☛

'Some drugs follow first order kinetics but at higher doses follow zero order kinetics. This is actually known as '**Pseudo zero order**'**. Phenytoin, Tolbutamide, Warfarin and Theophylline** follows both zero as well as first order kinetics.'

Important Points:

- **In 1st $t_{1/2}$** ☛ **50% drug eliminated**
- **In 2nd $t_{1/2}$** ☛ **75% drug eliminated**
- **In 3rd $t_{1/2}$** ☛ **87.5% drug eliminated**
- **In 4th $t_{1/2}$** ☛ **93.7%drug eliminated** **COMED 2003**
- **In 5th $t_{1/2}$** ☛ **97%drug eliminated**

- **Loading dose is governed by volume of distribution.**
  - **Loading dose helps in achieving target levels quickly** **JIPMER 2014**
  - **There is rapid activation of receptors** **JIPMER 2014**
  - **Depends on volume of distribution** **JIPMER 2014**
- **Maintenance dose is governed by clearance of drug and half life (t ½).**

- **Acidic drugs ionize more at alkaline pH** ☛
- **Basic drugs ionize more at acidic pH** ☛
- **Unionized drugs are lipid soluble and diffusible.** ☛
- **Ionized drugs are lipid insoluble and nondiffusible.** ☛
- Ionized drugs are excreted mainly by kidney. **AI 2006**
- **Acidic drugs are absorbed in stomach. (are unionized in acidic medium and hence defusable)** ☛
- Basic drugs are absorbed from intestine. ☛ (Proximal) **AI 1991**

- **Ionized drugs poorly pass across placenta.** ☛
- **Ionized drugs poorly pass across blood brain barrier** ☛
- Ionized drugs poorly pass across renal tubules (easily excreted) ☛

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Microsomal Enzyme Inducers: ☛☛ (AIIMS/AIPGME/DNB 2016)

- Barbiturates ☛
- Carbamezapine, clofibrate ☛
- DDT ☛
- Ethanol ☛
- Griseofulvin ☛
- Phenytoin, phenobarbitone☛ **AIIMS 1991**
- Primidone, ☛

- Rifampicin, ritonavir ☛ **AIIMS 1991**
- Phenobarbitone ☛
- Smoking, **chronic** alcohol intake ☛

Microsomal Enzyme Inhibitors:*

- Quinolones ☛
- Erythromycin ☛
- Quinidine ☛
- Grape Fruit juice ☛
- Cimetidine ☛
- Allopurinol ☛
- Ketocanazole ☛
- Omprazole ☛
- Sulfonamides ☛
- MAO inhibitors ☛

Acetylation and Why it is an Important Reaction (AIIMS/AIPGME/DNB 2016)

- **Isoniazid, hydralazine, sulfonamides, procainamide,** and a number of other drugs are metabolized by **acetylation** of a hydrazino or amino group. **AIPGME 2012**
- This reaction is catalyzed by ***N*-acetyl transferase-2 (NAT-2),** an enzyme in the liver cytosol that transfers an acetyl group from acetyl coenzyme A to the drug.
- Individuals differ markedly in the rate at which drugs are acetylated, because of polymorphisms in the NAT-2 gene, resulting in a bimodal distribution of the population into **'rapid acetylators' and 'slow acetylators.'**

Features Related to Nephrotoxicity: ☛☛

- **Most** nephrotoxic cephalosporine: **cephaloridine** ☛
- **Most** nephrotoxic aminoglycoside: **gentamycin**. ☛
- **Least** nephrotoxic antitubercular: rifampicin ☛
- **Least** nephrotoxic aminoglycoside: tobramycin. ☛
- Tetracycline **safe** in renal failure: doxycycline. ☛

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DRUGS AFFECTING LIVER* (REPEATED IN 2008, 2009, 2010, 2011)

Causing 'Hepatitis' PGI 2003
- Halothane☛
- MAO inhibitors☛
- Anticonvulsants☛
- Methyl dopa☛
- Rimapicin, Isoniazid, Pyrizanamide☛

Causing 'Intrahepatic Cholestasis'
- Phenothiazines☛
- TCA☛
- NSAIDs☛
- Erythromycin, Carbenicillin, Sulfonamides☛

Hepatotoxins
- Tetracycline☛
- CCL_4☛
- Paracetamol☛
- Methotrexate☛
- Alfatoxin☛

Remember

Hepatotoxic Drugs and Type of Hepatotoxicity
- **Acetaminophen hepatotoxicity** (direct toxin)
- **Halothane hepatotoxicity** (idiosyncratic reaction)
- **Methyldopa hepatotoxicity** (toxic and idiosyncratic reaction)
- **Isoniazid hepatotoxicity** (toxic and idiosyncratic reaction)
- **Sodium valproate hepatotoxicity** (toxic and idiosyncratic reaction)
- **Phenytoin hepatotoxicity** (idiosyncratic reaction)
- **Chlorpromazine hepatotoxicity** (cholestatic idiosyncratic reaction)
- **Amiodarone hepatotoxicity** (toxic and idiosyncratic reaction)
- **Erythromycin hepatotoxicity** (cholestatic idiosyncratic reaction)
- **Oral contraceptive hepatotoxicity** (cholestatic reaction)
- **17,a-alkyl-substituted anabolic steroids** (cholestatic reaction)
- **Trimethoprim-sulfamethoxazole hepatotoxicity** (idiosyncratic reaction)
- **Hydroxymethylglutaryl-coenzyme (HMG-CoA) reductase inhibitors** ('statins') (idiosyncratic mixed hepatocellular and cholestatic reaction)
- **Total parenteral nutrition** (steatosis, cholestasis)

Cardiotoxic Drugs: ☛☛ (High Yield for AIIMS/AIPGME/DNB 2016)

- Doxarubicin, ☛
- Daunorubicin, ☛
- Vincristine ☛
- Halothane ☛
- Alcohol ☛

Drugs Causing Porphyria:

- Clindamycin
- Chloramphenicol
- Carbamazepine

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- Hydralazine
- Phenytoin
- Valproate
- Tamoxifen
- Nitrofurantoin
- Mefiprestone
- Fosphenytoin
- Indinavir
- Ketamine
- Ketocanozole
- Lidocaine

Drugs Causing Gingival Hyperplasia:

- phenytoin
- phenobarbitone
- lamotrigine
- vigabatrin
- ethoxsuccimide
- primidone
- topiromate
- nefidepine
- amlodepine
- verapamil
- cyclosporin
- pregnancy
- puberty
- CML

Drugs Causing Pulmonary Fibrosis: ☛☛ (High Yield for AIIMS/AIPGME/DNB 2016)

- Busulfan☛
- Bleomycin☛
- Methotrexate☛
- Nitrofurantoin☛
- Sulfasalazine☛
- Practolol☛
- Amiadarone☛

Drugs Causing Osteoporosis: (High Yield for AIIMS/AIPGME/DNB 2016)

- Glucocorticoids
- Anticonvulsants
- Cytotoxic drugs
- Cyclosporine
- Lithium
- Heparin
- GnRH analogues
- Aluminium
- Throxine in increased doses

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Volume 1: Preclinical Sciences

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