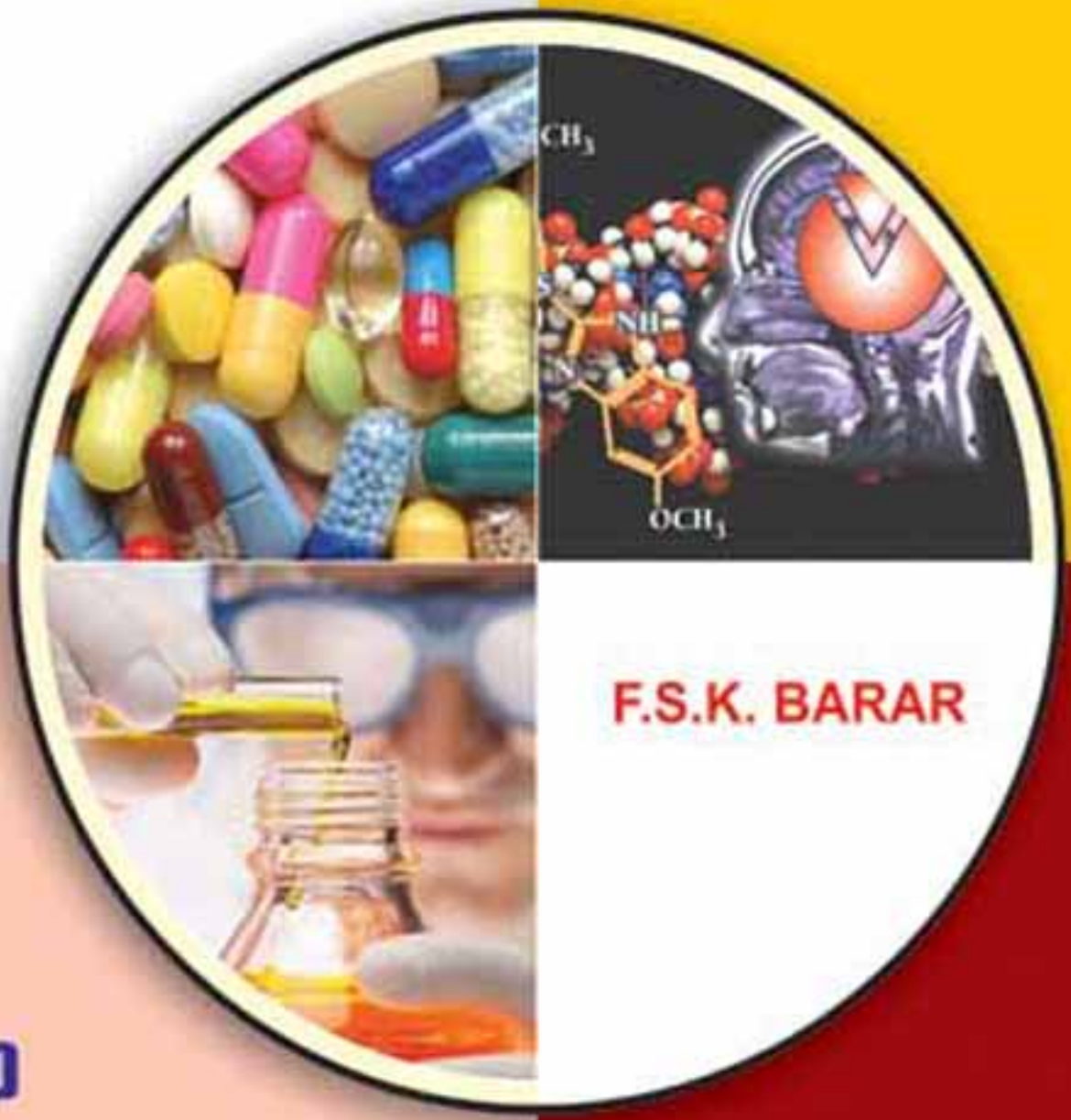
TEXTBOOK OF PHARMACOLOGY

(For Pharmacy Students)



F.S.K. BARAR

S. CHAND

TEXTBOOK OF PHARMACOLOGY

(For Pharmacy Students)

A man would do nothing,
if he waited until he could do it so well
that no one would find fault
with what he has done

—Cardinal Newman

TEXTBOOK OF PHARMACOLOGY

(For Pharmacy Students)

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Dedicated to

My wife, and my children

and

my students

PREFACE

"Science cannot grow by routine work alone, it cannot even live, because, like a tree if it is not growing it is dying. If routine gets the upper hand science becomes fossilized into formulae and rules. once these become rigid they become fallacious, reflecting the errors and limitations of those who originated them in their once living form".

— A.D. Ritchie, 1950

Paleopharmacological studies bear evidence to the use of medicinal plants in the treatment of disease even in the pre-historic era. In ancient **Egypt** pharmacological knowledge was recorded in various papyri like the **Ebers Papyrus** of 1550 BC, and the **Edwin Smith Papyrus** of the 16th century BC. **Aesculapius** whose descent was traced by the ancient Greeks directly from Apollo was considered to be the Greek God of Medicine. **Hippocrates** (born about 460 BC), renowned as the "*Father of Medicine*" , was the embodiment of the highest ideals in medical ethics. His famous "*Hippocratic Oath*" continues to be an everlasting memorial to his greatness. He eschewed 'superstition' and brought in scientific methods into the domain of healing. The name of **Chang Ching Chung** known as the "Hippocrates of China" occupies a prominent place in the history of Chinese medicine. His famous "Treatise of Fevers" dates back to about 170 AD. The greatest name in Roman medicine was **Claudius Galen** (130-c.200). Galen was educated in the Alexandrian School where Anatomy was taught at advanced levels. He worked on the nervous system and settled in Rome in the year 161, and wrote over 200 treatises. In the Middle East **Rhazes** (865-915AD) promoted the use of chemicals in the treatment of disease.

Ancient Indian Medicine was also very advanced comparable to the Greeks. The earliest compilation of medicinal substances was the **Sushruta Samhita**, an Indian Ayurvedic treatise attributed to the great philosopher **Sushruta Muni**, dating back to the 6th century BC. Two ancient preserved texts date back to the 3rd or 4th century AD: the **Charaka Samhita**, attributed to Charaka Muni, the renowned physician of ancient Indian medicine; and the Sharngadara Samhita attributed to Sharngadara Muni. These compilations form the foundation of the *Indian Ayurvedic System of medicine*.

Historically, pharmacy as an independent science is relatively young. Its origin dates back to early 19th century. As a discipline pharmacy has always been connected to the practice of medicine. Advances in the Middle East in botany and chemistry led to the development of pharmacy.

Rhazes (850-932 AD), promoted the medicinal uses of chemicals, and **Abulcasis** (936-1013 AD) started preparing medicines by *sublimation* and *distillation*. Later, **Al-Biruni** (973-1050 AD) wrote a valuable book on pharmacology titled *Kitab al-Saydalah* (*The Book of Drugs*) detailing properties of drugs, outlining the role of pharmacy, and duties of a pharmacist. **Avicenna** (980-1037 AD), Persian physician and philosopher, was known for his *Canon of Medicine* (describing about 700 preparations, with their mode of action, properties and uses). It was a standard medical textbook used in Europe until the 17th century. In Europe pharmacy developed as a science from the 13th century onwards in the reign of Emperor Fredric II.

In the 1990s *clinical pharmacy* as an important branch of pharmacy came up, which involves pharmacists and pharmacoeconomists responsible for optimizing the use of medication to promote health and prevent disease in hospitals, nursing homes and clinics. They work in unison with physicians, and health professionals. Now disease that struck down thousands of suffering humans can now be treated by drugs.

The text has 17 main chapters, followed by 3 appendices, and an index for rapid consultation and revision. Relevant basic information related to the use of drugs has been provided in each chapter. The subject material covers the current syllabus prescribed for pharmacy students. In addition, the "*Newer Drug's Digest*" provides information on drugs in the process of research and development. Any suggestions from readers are solicited.

Last but not the least, I offer profound thanks to editorial and management team at S. Chand & Company Ltd., New Delhi for their efficient and prompt cooperation towards the printing and publication of this work.

A tribute to Researchers Anonymous

"If you take a prescription to a drugstore today, the chances are overwhelming that the pharmacist will have to use at least one wonder drug to fill it. Yet 90 percent of the prescriptions written by doctors today could not have been filled in 1935, because one or more of the prescribed drugs was then unknown".

— Donald G. Cooley, 1954

F.S.K. Barar

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CONTENTS

ABBREVIATIONS

ACh	Acetylcholine
AChE	Acetylcholinesterase
ACTH	Adrenocorticotrophic hormone, Corticotrophin
ADH	Antidiuretic hormone
ADP	Adenosine diphosphate
AIDS	Acquired Immunodeficiency Syndrome
ANS	Autonomic nervous system
ATP	Adenosine triphosphate
AV	Atrioventricular
BP	Blood pressure
c-AMP	Cyclic adenosine 3′, 5′ monophosphate
ChE	Cholinesterase
CNS	Central nervous system
CoA	Coenzyme A
COMT	Catechol-O-methyltransferase
CSF	Cerebrospinill fluid
CtZ	Chemoreceptor trigger zone
CVP	Central venous pressure
DNA	Deoxyribonucleic acid
DOPA	Dihydroxyphenylalanine
ECF	Extracellular fluid
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EEG	Electroencephillogram
FFA	Free fatty acid
FSH	Follicle stimulating hormone
g	Gram
GABA	Gamma-aminobutyric acid
GFR	Glomerular filtration rate
GH	Growth hormone
c-GMP	Cyclic guanosine 3′, 5′ monophosphate
G-6-PD	Glucose-6-phosphate dehydrogenase
GTP	Guanosine triphosphate
HCG	Human chorionic gonadotrophin
HMG	Human menopausal gonadotrophin
5-HT	5-Hydroxytryptamine
HVA	Homovanillic acid
Hz	Hertz (1 Hertz is 1 cycle per second)
Ig	Immunoglobulin
IM	Intramuscular
IV	Intravenous
l	Litre
LH	Luteinizing hormone
log	Logarithm
LSD	Lysergic acid diethylamide
M	Molar
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
mcg	Microgram
mg	Milligram
MIC	Minimal inhibitory concentration
min	Minute
mol	Mole (gram molecular weight)
mRNA	messenger ribonucleic acid
Na	Noradrenaline
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced)
ng	Nanogram
PABA	Para-aminobenzoic acid
PG	Prostaglandlin
pH	Negative log of hydrogen ion concentration
pKa	Negative log of dissociation constant
P450	Cytochrome with maximum absorption at wavelength 450 nm.
RNA	Ribonucleic acid
SA	Sinoatrial
SC	Subcutaneous
SRS-A	Slow reacting substance of anaphylaxis
$t_{1/2}$	Half life
THC	Tetrahydrocannabinol
tRNA	Transfer RNA
TSH	Thyroid stimulating hormone, Thyrotrophin
v/v	Volume per unit volume
WHO	Wold Health Organisation
w/v	Weight per unit volume
w/w	Weight per unit Weight

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GENERAL PARMACOLOGY

1.1 SCOPE OF PHARMACOLOGY

Definitions

Pharmacology, Pharmacognosy, Pharmacy, Pharmacokinetics, Pharmacodynamics, Pharmacotherapeutics, Therapeutics, Toxicology, Pharmacogenetics, Clinical Pharmacology

Historical Development
Drug Information Sources
The Pharmacopoeias, etc.

Pharmacology is the study of drugs. Drugs are chemicals that produce therapeutically useful effects. They modify functions of living organisms, and are generally given to **prevent**, **diagnose**, or **cure** disease processes. Pharmacology has a wide scope, and derives from various other disciplines like physiology, microbiology, pathology, biochemistry and various clinical specialities.

DEFINITIONS

Pharmacology is defined as the science of drugs. The term is derived from the Greek words ***pharmakon***, meaning a drug, and *logos*, meaning a study. Pharmacology has the following major subdivisions:

Pharmacognosy (Greek *gnosis*, knowledge) is the study of the sources of drugs derived from plants and animals, and of the physical and chemical properties of such substances.

Pharmacy is the study of the preparation, compounding and dispensing of medicines. It is the science and art of preparing a drug or drug combination, in a suitable dosage form, fit for administration to the patient. The **pharmacist** is concerned primarily with preparing, compounding and dispensing medicines upon the written order of a licensed medical practitioner.

Pharmacokinetics (Greek *kinesis*, movement) is the study of the fate of drugs in body, right from the time they (drugs) enter the body until they, or their by-products, are eliminated from the body, *i.e.*, the movement of drugs in the body. In short, this includes absorption, distribution, metabolism and excretion of drugs.

Pharmacodynamics (Greek *dynamis*, force) is the experimental study of actions of drugs on the living organism, including their mode or mechanism of action.

Pharmacotherapeutics (Greek *therapeia*, medical treatment) is the treatment of disease by means of drugs. It utilizes information on drugs obtained by pharmacodynamic studies.

Therapeutics (Greek *therapeutike*, medical practice) is the practical branch of medicine dealing with the science and art of the treatment of disease.

Chemotherapy according to the definition proposed by Paul Ehrlich, deals with the use of drugs capable of inhibiting or destroying invading microbes, parasites, or cancer cells; while having minimal effect on healthy living tissues.

Toxicology (Greek *toxikon*, poison) is the science of poisons—their source, chemical composition, action, tests for detection and antidotes. **Clinical toxicology** deals with the detection, diagnosis and treatment of poisoning. **Toxicodynamics** describes the harmful effects that the poison produces on the body. **Toxicokinetics** encompasses the absorption, distribution, biotransformation and elimination of the poison.

Pharmacogenetics is a relatively new field, and deals with the study of genetically determined variations in drugs response.

Clinical pharmacology is the division which deals with the pharmacologic effects of drugs in man. It provides information about the usefulness, potency and toxicity of new drugs in humans.

Historical Development

Earliest prescriptions are recorded in a Sumerian tablet of 2100 B.C. describing ointments and medicines containing asafoetida, thyme (source of Thymol), sodium chloride and potassium nitrate. The **Ebers Papyrus** written in 1550 B.C. contains prescriptions of castor oil, opium, colchicum and other drugs. Perhaps, Chinese Medicine was about the earliest, dated at about 2500 B.C. Ephedra or *Ma huang* was used even in those early days. **Ayurveda** or *Indian Medicine* is about equally ancient, and it has given some useful remedies to modern medicine.

Some giants in the history of medicine were *Hippocrates*, *Aristotle*, *Theophrastus*, *Pliny*, *Dioscorides* and *Galen*. **Hippocrates** (460-370 B.C.) is referred to as the "father of medicine", and many of his writings dealt with anatomy and physiology. The "Hippocratic Oath" of modern day medicine reflects the high esteem with which this Greek physician is regarded. Hippocrates was the first to recognize disease as an abnormal reaction of the body rather than as a visitation from the Gods. **Aristotle** (384-322 B.C.), a student of Plato, is considered to be the most influential Greek Philosopher. He attempted to separate superstition from fact. **Theophrastus** (370-287 B.C.), a student of Aristotle, utilized his teacher's scientific reasoning, and applied it to the plant kingdom. **Dioscorides**, a Greek physician of the first century B.C. described several plants of medicinal value. Later, **Pliny** (23-70 A.D.) compiled 37 volumes of natural history, which served as reference data for many years. The Hippocratic concept of disease was then lost and did not reappear until the Renaissance (15th Century A.D. marking the transition from the Middle Ages to the modern world). During this dark period the concept of **Galen** (131-201 A.D.) and his dogmatic system of polypharmacy prevailed. Galen, a Greek pharmacist physician, who lived in Rome, described many formulae containing plant and animal drugs. He compiled this knowledge in 20 books. Galen's name is retained in the term "galenical" pharmacy, which includes preparation of crude vegetable drugs.

Paracelsus (1493-1541 A.D.), an outstanding leader of the Renaissance, reintroduced free thought and critical enquiry. He attacked the Galenic system of polypharmacy, and introduced the use of simple chemicals for treating disease. He introduced mercurials in the treatment of syphilis. During his time the first official pharmacopoeia was printed.

Experimental medicine and therapeutics had to wait long for the advances in physiology, which during the decade (1850-1860) became an experimental science. **Virchow**, the German physiologist in 1855 propounded the concept of "all cells from cells". Later, with advances in the knowledge of the physiology of circulation, central nervous system, the hormones and enzymes in the body, the study of pharmacology and therapeutics was stabilized. *In fact, pharmacology originated as a branch of physiology*. The application of scientific method to studies on drugs was generated in France by **Francois Megendie** (1783-1855), and was expanded by **Claude Bernard** (1813-1878), who came to be known as the "father of experimental medicine". The name of **Oswald Schmiedeberg** (1838-1921) is associated with the development of experimental pharmacology in Germany, and **John Jacob Abel** (1857-1938) played a similar role in the United States of America. in India **Sir Ram Nath Chopra** (1882-1973) was responsible for the development of pharmacology as a well defined discipline. He was the Founder Director of the Drug Research Laboratory which is now known as the Regional Research Laboratory of the Council of Scientific and Industrial Research (CSIR), located at Jammu-Tawi. Sir Chopra has been widely acclaimed as the Father of Indian Pharmacology, because of his investigations on Indian indigenous drugs. The growth of pharmacology was further stimulated by the development of synthetic organic chemistry, which has provided many new therapeutic agents.

The Pharmacopoeias

The term *pharmacopoeia* is derived from the Greek words *pharmakon*, meaning "drug", and *poiein*, meaning "make". The term was first used in 1580 for a book of drug standards in Bergame, Italy. The pharmacopoeias are a class of drug compendia, and its main body contains monographs on drugs and ancillary substances. A pharmacopoeia is periodically revised and kept up-to-date. The **National Formulary** is a smaller and much more handy book containing formulations of therapeutic value. Drugs and substances which are included in the current edition of a pharmacopoeia are designated as *official*.

In England the first **British Pharmacopoeia** (BP) was published in 1864. In the USA Dr. Lyman Spalding planned a national pharmacopeia, and in the year 1820 the first **United States Pharmacopeia** (USP) was published. The **European Pharmacopoeia** (Vol. I, 1969; Vol. II, 1971) was published by the Public Health Committee and the European Pharmacopoeia Commission.

The **International Pharmacopoeia** is published by the World Health Organization (WHO). It is published in many languages (English, French, Russian, Spanish). This pharmacopoeia is meant for use and adoption all over the world. Some of the drug compendia are detailed below:

India

1. *Pharmacopoeia of India* (The Indian Pharmacopoeia), Sixth Edition, Two Volumes. Government of India, Ministry of Health & Family Welfare, New Delhi, 2010.
2. *National Formulary of India* (NFI), 4th Edition, Formulated by the Indian Pharmacopoeia Commission (IPC), New Delhi, 2010.
3. *Monthly Index of Medical Specialities*, *MIMS, INDIA*, Editor, Gulhati, C.M. (published every month).
4. *Drugs Bulletin*, Editor, P. Pandhi, Department of

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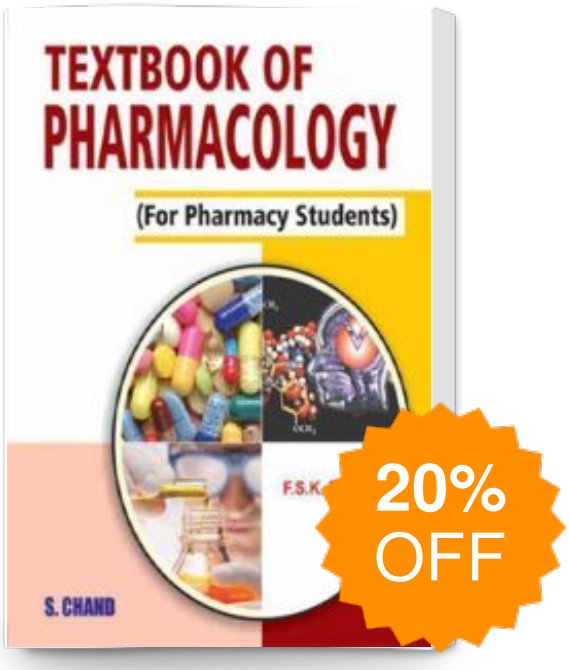

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