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RANG AND DALE'S
Pharmacology

H. P. RANG • M. M. DALE • J. M. RITTER • R. J. FLOWER • G. HENDERSON

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RANG AND DALE'S
Pharmacology

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**Cover image shows white blood cells
emigrating from blood vessels.**

The inner surface of blood vessels are lined with endothelial cells which express a protein called PECAM-1 at the junction between cells, and less strongly on the cell body. This protein was labelled red with a fluorescently tagged antibody, and genetic modification was used to make the white blood cells (leukocytes) express green fluorescent protein. These can be seen sticking to the endothelial cells, and beginning to transmigrate through the blood vessel wall in response to an inflammatory stimulus.

The image was captured by confocal microscopy with laser excitation of the green and red fluorescent labels. A series of flat images through the vessel were taken, and these slices were reconstructed to make a 3D object.

Image generated by S. Nourshagh, A. Woodfin and M. Benoit-Voisin (William Harvey Research Institute, London).

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Rang and Dale's Pharmacology 7th Edition Preface

In this edition, as in its predecessors, we set out not just to describe what drugs do but to emphasise the mechanisms by which they act. This entails analysis not only at the cellular and molecular level, where knowledge and techniques are advancing rapidly, but also at the level of physiological mechanisms and pathological disturbances. Pharmacology has its roots in therapeutics, where the aim is to ameliorate the effects of disease, so we have attempted to make the link between effects at the molecular and cellular level and the range of beneficial and adverse effects that humans experience when drugs are used for therapeutic or other reasons. Therapeutic agents have a high rate of obsolescence, and new ones appear each year. An appreciation of the mechanisms of action of the class of drugs to which a new agent belongs provides a good starting point for understanding and using a new compound intelligently.

Pharmacology is a lively scientific discipline in its own right, with an importance beyond that of providing a basis for the use of drugs in therapy, and we aim to provide a good background, not only for future doctors but also for scientists and practitioners of other disciplines. We have therefore, where appropriate, described how drugs are used as probes for elucidating cellular and physiological functions, even when the compounds have no clinical use.

Names of drugs and related chemicals are established through usage and sometimes there is more than one name in common use. For prescribing purposes, it is important to use standard names, and we follow as far as possible the World Health Organization's list of recommended international non-proprietary names (rINN). Sometimes these conflict with the familiar names of drugs (e.g. amphetamine becomes amfetamine in the rINN list, and the endogenous mediator prostaglandin I₂ – the standard name in the scientific literature – becomes 'epoprostenol' – a name unfamiliar to most scientists – in the rINN list. In general, we use rINN names as far as possible in the context of therapeutic use, but often use the common name in describing mediators and familiar drugs. Sometimes English and American usage varies (as with adrenaline/epinephrine and noradrenaline/norepinephrine). Adrenaline and noradrenaline are the official names in EU member states and relate clearly to terms such as 'noradrenergic', 'adrenoceptor' and 'adrenal gland' and we prefer them for these reasons.

Drug action can be understood only in the context of what else is happening in the body. So at the beginning of most chapters, we briefly discuss the physiological and biochemical processes relevant to the action of the drugs described in that chapter. We have routinely included the chemical structures of drugs, but have only done so where this information helps in understanding their pharmacological and pharmacokinetic characteristics.

The overall organization of the book has been retained, with sections covering: (1) the general principles of drug action; (2) the chemical mediators and cellular mechanisms with which drugs interact in producing their therapeutic effects; (3) the action of drugs on specific organ systems;

(4) the action of drugs on the nervous system; (5) the action of drugs used to treat infectious diseases and cancer; (6) a range of special topics such as individual variation in drug effects, adverse effects, non-medical uses of drugs, etc. This organization reflects our belief that drug action needs to be understood, not as a mere description of the effects of individual drugs and their uses, but as a chemical intervention that perturbs the complex network of chemical and cellular signaling that underlies the function of any living organism. In addition to updating all of the chapters, we have, within this general plan, reorganized the text in various ways, to keep abreast of modern developments:

- A new chapter (Ch. 6) on host defense mechanisms has been included in the section on cellular mechanisms.
- Pharmacogenetics, an increasingly important topic for prescribers, is treated in a separate chapter (Ch. 11).
- A new chapter on the pharmacology of purines (Ch. 16) has been included.
- A new chapter (Ch. 17) on local hormones and other mediators involved in inflammatory and immune responses has been included in the section on chemical mediators, with information on immunosuppressant and anti-inflammatory drugs (Ch. 26) presented separately.
- Several chapters in Section 3 (Drugs affecting major organ systems) and Section 4 (Nervous system) have been substantially revised and reorganized to include recent developments.

Despite the fact that pharmacology, like other branches of biomedical science, advances steadily, with the acquisition of new information, the development of new concepts and the introduction of new drugs for clinical use, we have avoided making the 7th edition any longer than its predecessor. We have cut out some material, including drugs that have become obsolete, and theories that have had their day, and have made extensive use of small print text to cover more specialized and speculative information that is not essential to understanding the key message, but will, we hope, be helpful to students seeking to go into greater depth.

In selecting new material for inclusion, we have taken into account not only new agents but also recent extensions of basic knowledge that presage further drug development. And where possible, we have given a brief outline of new treatments in the pipeline.

The References and Further Reading sections at the end of each chapter have been updated throughout, and include reliable websites. Short descriptions have been added to most references, summarising the main aspects covered. While the lists are by no means exhaustive, we hope that they will be helpful as a way in to the literature for students wanting to go into greater depth.

We are grateful to the readers who have taken the trouble to write to us with constructive comments and suggestions about the 6th edition. We have done our best to incorporate these. Comments on the new edition will be welcome.

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Abbreviations and Acronyms

α-Me-5-HT	α -methyl 5-hydroxytryptamine	ANF	atrial natriuretic factor
α-MSH	α -melanocyte-stimulating hormone	ANP	atrial natriuretic peptide
12-S-HETE	12-S-hydroxyeicosatetraenoic acid	AP	adapter protein
2-AG	2-arachidonoyl glycerol	Apaf-1	apoptotic protease-activating factor-1
2-Me-5-HT	2-methyl-5-hydroxytryptamine	APC	antigen-presenting cell
4S	Scandinavian Simvastatin Survival Study	APP	amyloid precursor protein
5-CT	5-carboxamidotryptamine	APTT	activated partial thromboplastin time
5-HIAA	5-hydroxyindoleacetic acid	AR	aldehyde reductase; androgen receptor
5-HT	5-hydroxytryptamine [serotonin]	Arg	arginine
8-OH-DPAT	8-hydroxy-2-(di- <i>n</i> -propylamino) tetraline	ARND	alcohol-related neurodevelopmental disorder
AA	arachidonic acid	ASCI	ATP-sensitive Ca ²⁺ -insensitive
AC	adenylyl cyclase	ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ACAT	acyl coenzyme A: cholesterol acyltransferase	ASIC	acid-sensing ion channel
AcCoA	acetyl coenzyme A	AT	angiotensin
ACE	angiotensin-converting enzyme	AT₁	angiotensin II receptor subtype 1
ACh	acetylcholine	AT₂	angiotensin II receptor subtype 2
AChE	acetylcholinesterase	ATIII	antithrombin III
ACTH	adrenocorticotrophic hormone	ATP	adenosine triphosphate
AD	Alzheimer's disease	AUC	area under the curve
ADH	antidiuretic hormone	AV	atrioventricular
ADHD	attention-deficit hyperactivity disorder	AZT	zidovudine
ADMA	asymmetric dimethylarginine	BARK	β -adrenoreceptor kinase
ADME	absorption, distribution, metabolism and elimination [studies]	BDNF	brain-derived neurotrophic factor
ado-B12	5'-deoxyadenosylcobalamin	B_{max}	binding capacity
ADP	adenosine diphosphate	BMI	body mass index
AF1	activation function 1	BMPR-2	bone morphogenetic protein receptor type 2
AF2	activation function 2	BNP	B-type natriuretic peptide
AGEPC	acetyl-glycerol-ether-phosphorylcholine	BSE	bovine spongiform encephalopathy
AGRP	agouti-related protein	BuChE	butyrylcholinesterase
Ah	aromatic hydrocarbon	CaC	calcium channel
AIDS	acquired immunodeficiency syndrome	CAD	coronary artery disease
AIF	apoptotic initiating factor	cADPR	cyclic ADP-ribose
ALA	δ -amino laevulinic acid	CaM	calmodulin
ALDH	aldehyde dehydrogenase	cAMP	cyclic 3',5'-adenosine monophosphate
AMP	adenosine monophosphate	CAR	constitutive androstane receptor
AMPA	α -amino-5-hydroxy-3-methyl-4-isoxazole propionic acid	CARE	Cholesterol and Recurrent Events [trial]
		CAT	choline acetyltransferase

CBG corticosteroid-binding globulin	DOH oxidised [hydroxylated] drug
CCK cholecystokinin	DOPA dihydroxyphenylalanine
cdk cyclin-dependent kinase	DOPAC dihydroxyphenylacetic acid
cDNA circular deoxyribonucleic acid	DSI depolarisation-induced suppression of inhibition
CETP cholesteryl ester transfer protein	DTMP 2-deoxythymidylate
CFTR cystic fibrosis transport [transmembrane conductance] regulator	DUMP 2-deoxyuridylate
cGMP cyclic guanosine monophosphate	EAA excitatory amino acid
CGRP calcitonin gene-related peptide	EC₅₀/ED₅₀ concentration/dose effective in 50% of the population
ChE cholinesterase	ECG electrocardiogram
CHO Chinese hamster ovary [cell]	ECM extracellular matrix
CICR calcium-induced calcium release	ECP eosinophil cationic protein
CIP cdk inhibitory protein	ECT electroconvulsive therapy
CJD Creutzfeldt-Jakob disease	EDHF endothelium-derived hyperpolarising factor
CL total clearance of a drug	EDRF endothelium-derived relaxing factor
CNP C-natriuretic peptide	EEG electroencephalography
CNS central nervous system	EET epoxyeicosatetraenoic acid
CO carbon monoxide	EGF epidermal growth factor
CoA coenzyme A	EG-VEGF endocrine gland-derived vascular endothelial growth factor
COMT catechol- <i>O</i> -methyl transferase	E_{max} maximal response that a drug can produce
COPD chronic obstructive pulmonary disease	EMBP eosinophil major basic protein
COX cyclo-oxygenase	EMT endocannabinoid membrane transporter
CREB cAMP response element-binding protein	ENaC epithelial sodium channel
CRF corticotrophin-releasing factor	eNOS endothelial nitric oxide synthase [NOS-III]
CRH corticotrophin-releasing hormone	epp endplate potential
CRLR calcitonin receptor-like receptor	EPS extrapyramidal side effects
CSF cerebrospinal fluid; colony-stimulating factor	epsp excitatory postsynaptic potential
C_{ss} steady-state plasma concentration	ER endoplasmic reticulum; (o)estrogen receptor
CTL cytotoxic T lymphocyte	FA kinase focal adhesion kinase
CTZ chemoreceptor trigger zone	FAAH fatty acid amide hydrolase
CYP cytochrome P450 [system]	FAD flavin adenine dinucleotide
DAAO D-amino acid oxidase	FAS fetal alcohol syndrome
DAG diacylglycerol	FDUMP fluorodeoxyuridine monophosphate
DAGL diacylglycerol lipase	Fe²⁺ ferrous iron
DAT dopamine transporter	Fe³⁺ ferric iron
DBH dopamine-β-hydroxylase	FeO³⁺ ferric oxene
DDAH dimethylarginine dimethylamino hydrolase	FEV₁ forced expiratory volume in 1 second
DHFR dihydrofolate reductase	FGF fibroblast growth factor
DHMA 3,4-dihydroxymandelic acid	FH₂ dihydrofolate
DHPEG 3,4-dihydroxyphenylglycol	FH₄ tetrahydrofolate
DIT di-iodotyrosine	FKBP FK-binding protein
DMARD disease-modifying antirheumatic drug	FLAP five-lipoxygenase activating protein
DMPP dimethylphenylpiperazinium	FMN flavin mononucleotide
DNA deoxyribonucleic acid	

formyl-FH₄ formyl tetrahydrofolate	hGH human growth hormone
FSH follicle-stimulating hormone	HIT heparin-induced thrombocytopenia
FXR farnesoid [bile acid] receptor	HIV human immunodeficiency virus
G6PD glucose 6-phosphate dehydrogenase	HLA histocompatibility antigen
GABA gamma-aminobutyric acid	HMG-CoA 3-hydroxy-3-methylglutaryl-coenzyme A
GAD glutamic acid decarboxylase	HnRNA heterologous nuclear RNA
GC guanylyl cyclase	HPA hypothalamic-pituitary-adrenal [axis]
G-CSF granulocyte colony-stimulating factor	HPETE hydroperoxyeicosatetraenoic acid
GDP guanosine diphosphate	HRT hormone replacement therapy
GFR glomerular filtration rate	HSP heat shock protein
GH growth hormone	HVA homovanillic acid
GHB γ -hydroxybutyrate	IAP inhibitor of apoptosis protein
GHRF growth hormone-releasing factor	IC₅₀ concentration causing 50% inhibition in the population
GHRH growth hormone-releasing hormone	ICAM intercellular adhesion molecule
GI gastrointestinal	ICE interleukin-1-converting enzyme
GIP gastric inhibitory polypeptide	ICSH interstitial cell-stimulating hormone
GIRK G-protein-sensitive inward-rectifying potassium [channel]	IDDM insulin-dependent diabetes mellitus [now known as type 1 diabetes]
GIT gastrointestinal tract	IFN interferon
Gla γ -carboxylated glutamic acid	Ig immunoglobulin
GLP glucagon-like peptide	IGF insulin-like growth factor
Glu glutamic acid	IL interleukin
GM-CSF granulocyte-macrophage colony-stimulating factor	Ink inhibitors of kinases
GnRH gonadotrophin-releasing hormone	iNOS inducible nitric oxide synthase
GP glycoprotein	INR international normalised ratio
GPCR G-protein-coupled receptor	IP inositol phosphate
GPL glycerophospholipid	IP₃ inositol trisphosphate
GR glucocorticoid receptor	IP₃R inositol trisphosphate receptor
GRE glucocorticoid response element	IP₄ inositol tetraphosphate
GRK GPCR kinase	ipsp inhibitory postsynaptic potential
GSH glutathione	IRS insulin receptor substrate
GSSG glutathione, oxidised	ISI international sensitivity index
GTP guanosine triphosphate	ISIS International Study of Infarct Survival
H₂O₂ hydrogen peroxide	ISO isoprenaline
HAART highly active antiretroviral therapy	IUPHAR International Union of Pharmacological Sciences
hCG human chorionic gonadotrophin	JRA juvenile rheumatoid arthritis
HCl hydrochloric acid	K_{ACh} potassium channel
HDAC histone deacetylase	K_{ATP} ATP-sensitive potassium [activator, channel]
HDL high-density lipoprotein	KIP kinase inhibitory protein
HDL-C high-density-lipoprotein cholesterol	LA local anaesthetic
HER2 human epidermal growth factor receptor 2	LC locus coeruleus
HERG human ether-a-go-go related gene	LCAT lecithin cholesterol acyltransferase
HETE hydroxyeicosatetraenoic acid	

LD₅₀ dose that is lethal in 50% of the population	NADH nicotinamide adenine dinucleotide, reduced
LDL low-density lipoprotein	NADPH nicotinamide adenine dinucleotide phosphate, reduced
LDL-C low-density-lipoprotein cholesterol	NANC non-noradrenergic non-cholinergic
LGC ligand-gated cation channel	NAPBQI <i>N</i> -acetyl- <i>p</i> -benzoquinone imine
LH luteinising hormone	NAPE <i>N</i> -acyl-phosphatidylethanolamine
LMWH low-molecular-weight heparin	NASA National Aeronautics and Space Administration
L-NAME <i>N</i> ^G -nitro-L-arginine methyl ester	NAT <i>N</i> -acyl-transferase
L-NMMA <i>N</i> ^G -monomethyl-L-arginine	NCX Na ⁺ -Ca ²⁺ exchange transporter
LQT long QT [channel, syndrome]	NET norepinephrine transporter
LSD lysergic acid diethylamide	NF nuclear factor
LT leukotriene	NFκB nuclear factor kappa B
LTP long-term potentiation	NGF nerve growth factor
LXR liver oxysterol receptor	nGRE negative glucocorticoid response element
lyso-PAF lysoglyceryl-phosphorylcholine	NIDDM non-insulin-dependent diabetes mellitus [now known as type 2 diabetes]
mAb monoclonal antibody	NIS Na ⁺ /I ⁻ symporter
MAC minimal alveolar concentration	NK natural killer [cell]
mAChR muscarinic acetylcholine receptor	NM normetanephrine
MAGL monoacyl glycerol lipase	NMDA <i>N</i> -methyl-D-aspartic acid
MAO monoamine oxidase	nNOS neuronal nitric oxide synthase [NOS-I]
MAOI monoamine oxidase inhibitor	NNT number needed to treat
MAP mitogen-activated protein	NOS nitric oxide synthase
MAPK mitogen-activated protein kinase	NPR natriuretic peptide receptor
MCP monocyte chemoattractant protein	NPY neuropeptide Y
M-CSF macrophage colony-stimulating factor	NRM nucleus raphe magnus
MDMA methylenedioxyamphetamine ['ecstasy']	NRPG nucleus reticularis paragigantocellularis
MeNA methylnoradrenaline	NSAID non-steroidal anti-inflammatory drug
methyl-FH₄ methyltetrahydrofolate	ODQ 1H-[1,2,4]-oxadiazole-[4,3- α]-quinoxalin-1-one
MGluR metabotropic glutamate receptor	OPG osteoprotegerin
MHC major histocompatibility complex	oxLDL oxidised low-density lipoprotein
MHPEG 3-methoxy-4-hydroxyphenylglycol	PA partial agonist; phosphatidic acid
MHPG 3-hydroxy-4-methoxyphenylglycol	PABA <i>p</i> -aminobenzoic acid
MIT monoiodotyrosine	P_ACO₂ partial pressure of carbon dioxide in arterial blood
MLCK myosin light-chain kinase	PAF platelet-activating factor
MPTP 1-methyl-4-phenyl-1,2,3,5-tetrahydropyridine	PAG periaqueductal grey
MR mineralocorticoid receptor	PAH <i>p</i> -aminohippuric acid
mRNA messenger ribonucleic acid	PAI plasminogen activator inhibitor
MRSA meticillin-resistant <i>Staphylococcus aureus</i>	PAMP pathogen-associated molecular pattern
MSH melanocyte-stimulating hormone	P_AO₂ partial pressure of oxygen in arterial blood
NA noradrenaline [norepinephrine]	PAR protease-activated receptor
NAADP nicotinic acid dinucleotide phosphate	PARP poly-[ADP-ribose]-polymerase
NaC voltage-gated sodium channel	PC phosphorylcholine
nAChR nicotinic acetylcholine receptor	PCPA <i>p</i> -chlorophenylalanine
NAD nicotinamide adenine dinucleotide	

PD Parkinson's disease	R & D research and development
PDE phosphodiesterase	RA rheumatoid arthritis
PDGF platelet-dependent growth factor	RAMP receptor activity-modifying protein
PDS pendrin; paroxysmal depolarising shift	RANK receptor activator of nuclear factor kappa B
PE phosphatidylethanolamine	RANKL RANK ligand
PECAM platelet endothelium cell adhesion molecule	RANTES regulated on activation normal T-cell expressed and secreted (chemokine)
PEFR peak expiratory flow rate	RAR retinoic acid receptor
PEG polyethylene glycol	Rb retinoblastoma
PG prostaglandin	REM rapid eye movement [sleep]
PGE prostaglandin E	RGS regulator of G-protein signalling
PGI₂ prostacyclin [prostaglandin I ₂]	RIMA reversible inhibitor of the A-isoform of monoamine oxidase
PI phosphatidylinositol	RNA ribonucleic acid
PIN protein inhibitor of nNOS	RNAi ribonucleic acid interference
PIP₂ phosphatidylinositol bisphosphate	ROS reactive oxygen species
PKA protein kinase A	rRNA ribosomal ribonucleic acid
PKC protein kinase C	RTI reverse transcriptase inhibitor
PKK cGMP-dependent protein kinase	RTK receptor tyrosine kinase
PL phospholipid	RXR retinoid X receptor
PLA₂ phospholipase A ₂	RyR ryanodine receptor
PLC phospholipase C	SA sinoatrial
PLCβ phospholipase Cβ	SAH subarachnoid haemorrhage
PLD phospholipase D	SCF stem cell factor
Plk Polo-like kinase	SCID severe combined immunodeficiency
PLTP phospholipid transfer protein	SERCA sarcoplasmic/endoplasmic reticulum APTase
PMCA plasma membrane Ca ²⁺ -ATPase	SERM selective (o)estrogen receptor modulator
PMN polymodal nociceptor	SERT serotonin transporter
PNMT phenylethanolamine <i>N</i> -methyl transferase	SG substantia gelatinosa
PNS peripheral nervous system	SH sulfhydryl [e.g. -SH group]
PO₂ partial pressure of oxygen	siRNA small [short] interfering ribonucleic acid (see also sRNAi below)
POMC prepro-opiomelanocortin	SLE systemic lupus erythematosus
PPADS pyridoxal-phosphate-6-azophenyl-2',4'-disulfonate	SNAP S-nitrosoacetylpenicillamine
PPAR peroxisome proliferator-activated receptor	SNOG S-nitrosoglutathione
PR progesterone receptor; prolactin receptor	SNRI serotonin/noradrenaline reuptake inhibitor
PRF prolactin-releasing factor	SOC store-operated calcium channel
PRIF prolactin release-inhibiting factor	SOD superoxide dismutase
Pro-CCK procholecystokinin	SP substance P
pS picosiemens	SR sarcoplasmic reticulum
PT prothrombin time	sRNAi small ribonucleic acid interference (see also siRNA above)
PTH parathyroid hormone	SRS-A slow-reacting substance of anaphylaxis
PTZ pentylenetetrazol	SSRI selective serotonin reuptake inhibitor
PUFA polyunsaturated fatty acid	STX saxitoxin
PUVA psoralen plus ultraviolet A	
QALY quality-adjusted life year	