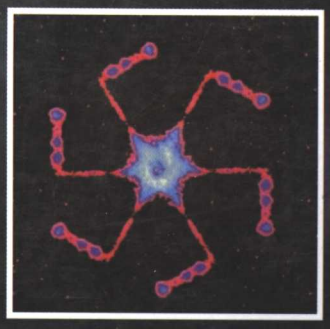
国外生命科学优秀教材

Human Molecular Biology

人类分子生物学

影印版



Richard J. Epstein

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（影印版）

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Richard J. Epstein

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内 容 简 介

本书通过整合分子遗传与生物化学及现代临床信息，有机地将生物学与人类疾病症状、遗传信息与发育表型、蛋白质功能与药物作用等方面知识联系在一起。本书结构合理，特色鲜明，反映了该学科的最新进展。

本书适应面较广，适合作为高等院校生命科学专业、医学专业基础课教材，同时也可供科技工作者参考。

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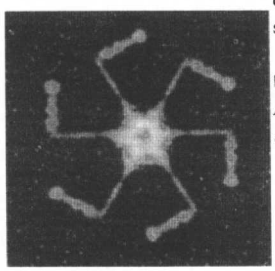
Human Molecular Biology

An Introduction to the Molecular Basis of Health and Disease

Human Molecular Biology is an introduction to health and disease for the new generation of life scientists and medical students. By integrating cutting-edge molecular genetics and biochemistry with the latest clinical information, the book weaves a pattern that unifies biology with syndromes, genetic pathways with disease phenotypes, and protein function with drug action. From the origins of life to the present day, a narrative is traced through the workings of genomes, cells and organ systems, culminating in the linking of laboratory technologies to future research. Lavishly illustrated throughout with two-color diagrams and full color clinical pictures, this text brings the complexities and breadth of human molecular biology clearly to life. By merging the fields of molecular biology and medicine, this groundbreaking account launches the reader into a new dimension where health and disease are seen to be complementary components of the same biomolecular spectrum.



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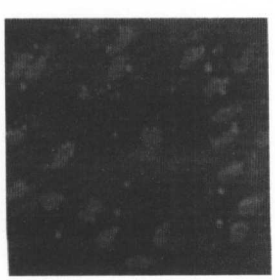

Preface

Good health is a matter of having the right molecules in the right place at the right time. This may seem self-evident, but the idea that health is determined *mainly* by molecules has only gained acceptance in recent years.

Consider this in historical perspective. A century ago health was regarded as a function of body parts – if you had a regular bowel and a strong heart you were OK. This anatomic model of health was superseded in due course by models based on organ function, the so-called system-based (physiologic) approach. But physiologic systems are interdependent: you can't have an effective gastrointestinal system without a nervous system, or a competent immune system without a hemopoietic system, or a responsive cardiovascular system without an endocrine system. This limitation has so far prevented even the most integrated biomedical curricula from communicating a wholly holistic view of human biology.

A popular response to such difficulties has been the proposal that students of the twenty-first century should no longer be force-fed so much information. Facts have become unfashionable, an irrelevance to the higher goal of imbuing trainees with creative insights and self-learning potential. What is needed, many believe, is a way of transmitting broad scientific principles without the burden of detail.

Sadly, this goal is no more feasible than that of teaching music without instruments. Details – facts – are essential for illustrating both general principles and instructive exceptions. A glut of detail may impair learning, but it is not the details per se that are at fault. Rather, it is the lack of a recurring *pattern* to those details which frustrates student and teacher alike.

The realization is now dawning that what is needed is not to teach less, but to teach more skillfully; not to memorize more facts but to assimilate more patterns. To do so it is essential to identify themes of structure and function within life, themes that have been collectively dubbed molecular biology by the uninitiated – for many of whom, one suspects, the word "molecular" may mean "incomprehensible". The good news is that this problem is now solved: there is no longer any such thing as molecular biology.

All biology is now about molecules. Molecular biology is little more than a buzzword from a bygone era in which technical change outpaced public understanding. The transition to a new biological world order is almost complete: technologies have matured, seed concepts are crystallizing, and a critical mass of knowledge is nearing accrual. The biological basis of health and disease has become inescapably molecular.

Human Molecular Biology is about molecules. This book is intended as a language primer for the life sciences – a translation aid for students seeking to decipher the Rosetta stone of *Homo sapiens*. In these pages an attempt has been made to portray molecular structure and function in the frame of human health and disease, such that:

- Biomedical science is taught *from the molecules up* rather than *from the diseases down* – that is, the molecular basis of health is used to predict and elucidate disease rather than vice versa, with disease serving mainly as a teaching aid to illustrate normal molecular function.
- Diseases are presented not as invariant clinicopathologic entities (spot diagnoses or syndromes) but rather as dynamic molecular processes which overlap in time, degree, and quality with normal biology.
- The emphasis on understanding disease has shifted away from the anatomy of bones and veins and towards the anatomy of genes and proteins.

Human Molecular Biology is not a comprehensive catalog of medicine or molecular biology, nor is it a textbook of biochemistry or physiology. It doesn't embrace prokaryotic genetics or genealogical charts, and includes no name-dropping anecdotes from biohistory. Rather, it presents a beginner's guide to the language of human biology – a molecule-by-molecule account of life and its problems. Note that the term "molecule" here includes proteins, sugars, and lipids as well as the more fashionable nucleic acids. For DNA is only half the story: it is the interconnected workings of genes, proteins, and intermediary molecules which define health and disease.

Most attempts to translate cutting-edge research into textbooks suffer from prematurity, oversimplification, outdatedness, errors, irrelevance . . . and *Human Molecular Biology* is unlikely to prove immune to all these faults. You shouldn't expect to become a handle-turning molecular biologist by reading this book, since to do that you need to work in a laboratory for several years; a hand-waving familiarity with the basics of biomedical science is a more realistic goal. The placement of molecular biology methodology at the end of this book emphasizes that an encyclopedic knowledge of laboratory techniques is no longer a prerequisite for understanding molecular biology.

How much training will the biomedical professional of the twenty-first century need to understand the language of life? It is as crazy to insist that everyone is equally familiar with Okazaki fragments and 14-3-3 proteins as it would be for all of us to learn stereotactic brain surgery. Yet it is not too much to expect that future biomedical graduates will, for example:

- Know what is meant by terms such as **transcription factor, tumor suppressor, leucine zipper, homeobox gene, RFLP,** and **G-protein.**
- Be able to explain the principles behind methodologies such as **PCR, nuclear magnetic resonance, gene knockout,** and **DNA microarray.**
- Comprehend the difference between **candidate gene** and **positional cloning** approaches to identifying disease genes.
- Have at least a vague familiarity with **homologous recombination, post-translational modification, polyadenylation, linkage disequilibrium, protein trafficking, evolutionary conservation,** and **molecular chaperones.**
- Understand in broad outline processes such as **immunoglobulin gene rearrangement, developmental hemoglobin switching, long-term potentiation** and **reverse cholesterol transport.**
- Have at least heard of terms such as **snurp, signal peptide, cyclin-dependent kinase, topoisomerase, Alu, p53, Ras,** and **Tat.**
- Be aware of technologies such as **recombinant protein production, subtractive hybridization, two-dimensional gel electrophoresis, retroviral gene transfer** and **antisense oligonucleotides.**

Demystification is the key to fluency in the molecular biosciences. The grammar of this language involves notions of hydrophobicity and hydrogen bonding and hybridization, of aromaticity and electrophilicity, of splicing and

insertion and ligation and recombination, of randomness and repetition, of reversibility and commitment. But the vocabulary required for this grammar need not be exhaustive.

Human Molecular Biology is organized to cater for readers of different levels. Newcomers should begin at the beginning, whereas others may consult specific areas of interest. Each chapter is punctuated by sandwich sections called *Clinical Keynotes, Molecular Minireviews, Pharmacologic Footnotes,* and *Superfamily Spotlights.* The details of laboratory practice are left until the final section.

This is a great time to be a student in the biomedical sciences. A page-turning molecular narrative is beginning to displace the hypnotic anatomic/physiologic lectures so familiar to students of earlier decades. Biomedical education is thus presented with a challenge on the one hand and an opportunity on the other: to formulate a coherent body of knowledge such as our forefathers would not have dreamed possible, while using this knowledge to reinvent biomedical education from the inside out. Today's students and teachers need to decide for themselves whether it is riskier to surf this tidal wave of knowledge or to paddle aside and watch it disappear over the horizon of the twenty-second century. *Human Molecular Biology* is an invitation to catch the wave.

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Read me first . . .

Everything in molecular biology is connected to everything else. It is therefore tempting to support a text of this nature by including every conceivable citation, and by cross-referencing every mention of a molecule or malady. However, since the resulting rash of references would mesmerize most readers, a range of remedies has been instituted:

1. Journal citations have been omitted. This is not an attempt to deny credit to the biomedical storm troopers who first captured the information that has been rearranged herein. Rather, the task of using citations to credit even a proportion of these pioneers overwhelmed this writer's best efforts early on, and surrender became unconditional on realizing that tens of thousands of attributions would be needed.
2. The book is organized as a narrative. Any given section of the text thus assumes knowledge of the foregoing sections, obviating the need to include retrospective page references. The book can still be used as a reference (rather than programmed) text, but the appearance of unreferenced allusions should prompt the interested reader to consult the index for an earlier reference.
3. Page cross-references are not always included for text items emphasized by either **blue** or **bold type**. In such instances, the index provides references.
4. In the figures, disease pathways are marked as filled red triangles (▲), whereas medicinal treatments are indicated using filled red capsules (⬬).

When used for the first time, or on reintroducing a major concept in a new section of the text, molecular names and concepts are indicated in **bold**. A passing reference to a new molecule or concept will usually be accompanied by a forward page reference, but under these circumstances the name may be left visually unemphasized.

Finally, names of diseases and toxins are highlighted in **sans serif**, whereas names of drugs are shown in **sans serif blue**. Eponymous disease names are used without apostrophe (e.g., **Parkinson disease**). Gene names are rendered in *italics*. Human molecules are usually indicated by a capital first letter, whereas genes and proteins of lower organisms are shown in lower case.

Select glossary of confusing terms and abbreviations

ABH	blood group antigens
ABO	blood groups
ADH	alcohol dehydrogenase
ADH	antidiuretic hormone (vasopressin)
AID	activation-induced deaminase
AIDS	acquired immunodeficiency syndrome
a.k.a.	also known as
AKAP	A-kinase anchoring protein
ALA	5-aminolevulinate (δ-aminolevulinic acid)
Ala	alanine
ALAS	δ-aminolevulinate synthetase
ALDH	acetaldehyde dehydrogenase
anti-idiotype	antibody directed against an idiotope
anti-idiotypic antibody	antibody directed against an anti-idiotype
antisense	oligonucleotide sequence which binds complementary nucleic acid
AP	alkaline phosphatase
AP	amyloid P (fibril)
AP	apurinic/apyrimidinic (site)
AP1	activator protein-1 (Jun-Fos heterodimer)
APC	activated protein C
APC	adenomatous polyposis coli (gene)
apo (a)	plasminogen-like apoprotein of Lp(a)
apo A	apolipoprotein A (includes apoAI, apoAII)
araC	cytosine arabinoside
araC	gene-activating protein in *E. coli*
Bcl	oncogene family first associated with *B*-cell *l*ymphomas
Bcr	*B*reakpoint *c*luster *r*egion gene activated by Philadelphia chromosomal translocation interrupting the *Abl* gene in chronic myeloid leukemia
BNP	"brain natriuretic peptide"; most abundant in *heart*
bp	base pair (one nucleotide length)
CAM	cell adhesion molecule
CaM kinase	calcium/calmodulin-dependent protein kinase
cAMP-dependent kinase	protein kinase A
cap (lymphocyte)	plasma membrane modification
cap (mRNA)	modification (methylation) of 5′ end of transcript
CAP	catabolite activator protein
CaR	calcium (-sensing) receptor
CAR	constitutive androstane receptor
CAT (assay)	*c*hloramphenicol *a*cetyl *t*ransferase technique for measuring promoter strength by inserting this bacterial gene downstream of the promoter in question and measuring the amount of CAT mRNA transcribed
CAT (box)	(var., CAAT, CCAAT) DNA-binding upstream element

CAT (scan)	computerized axial tomography (CT) scan
CAT	cholesterol acyltransferase; lecithin-cholesterol acyltransferase (LCAT) or acyl-cholesterol acyltransferase (ACAT)
Cbp	Csk-binding protein
CBP	CREP-binding protein
CD (e.g., CD25)	cellular determinant (surface antigens first identified by monoclonal antibody binding)
cdc (e.g., cdc25)	*c*ell *d*ivision *c*ycle (genes/proteins; originally defined in yeast phenotypes)
cdc2	famous yeast homolog of (human) Cdk1
Cdk (e.g., Cdk1)	cyclin-dependent kinase
Cdk inhibitor	cell cycle control protein, e.g., p16, which inhibits a Cdk (e.g., see INK4)
CNP	C-type natriuretic peptide; most abundant in *brain*
Cos (cells)	monkey kidney cell line (lacks many human genes)
cos (sites)	12-bp *co*hesive-end *s*ites at the linear end of the phage λ genome
cosmids	large DNA cloning vectors derived by injecting λ *cos* sites into pBR322 plasmids (see *cos* above)
CRE	cAMP response element
CREB	cAMP response element binding protein
CREM	cAMP response element modulator
CRP	C-reactive protein (an acute phase reactant)
CSF	cerebrospinal fluid (for brain cells)
CSF	colony-stimulating factor (for hemopoietic cells)
CSF	cytostatic factor ($p39^{mos}$; for oocytes)
cyclin	family of cell-cycle regulating molecules
cyclin	outmoded name for PCNA (proliferating cell nuclear antigen)
DAG	diacylglycerol (protein kinase C activating ligand)
DAG	dystrophin-associated glycoprotein
DARPP-32	dopamine and cyclic AMP-regulated phosphoprotein, MWt 32
DNA fingerprinting	forensic technique for identifying DNA
DNA footprinting	research technique for determining DNA protein-binding site
E2F	mitogenic transcription factor repressed by pRb
EF (hand)	calcium-binding variety of helix-loop-helix domain
EF	elongation factor (for transcription)
eIF	elongation initiation factor (for translation)
ER	endoplasmic reticulum
ER	estrogen receptor
ErbA	co-transforming mouse steroid hormone receptor
ErbB	murine epidermal growth factor (EGF) receptor
ErbB2	the unliganded EGF receptor homolog, HER2/*neu*
ERE	estrogen-response element
ERKs	extracellularly-regulated kinases, a major subset of MAP kinases (*q.v.*)
factor X	coagulation factor (pronounced "factor ten")
fragile X	neurologic syndrome (pronounced "fragile ex")
G1	cell-cycle phase (pronounced "gee-one")
gadolinium	radiographic contrast agent used in MRI
galanin	endogenous pain inhibitor
gamma-globin	fetal hemoglobin constituent
gammaglobulin	electrophoretic subgroup of immunoglobulins
GAS	group A streptococcus
Gas	growth arrest-specific (gene)
GIP	gastric inhibitory polypeptide
GIP	glucose-dependent insulinotrophic polypeptide

Gla	γ-carboxyglutamic acid (pronounced "glar")
glucose-6-phosphatase (G6P)	gluconeogenetic enzyme
glucose-6-phosphate dehydrogenase (G6PD)	antioxidant enzyme in red blood cells
glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	glycolytic enzyme
GRP	gastrin-releasing peptide (bombesin)
HAT	hypoxanthine-aminopterin-thymine (medium)
HD	Hodgkin disease
HD	Huntington disease
HDM2 see MDM2	
HER2	human EGF receptor-like protein 2 (= ErbB2)
HGPRTase	hypoxanthine-guanine phosphoribosyltransferase (see HPRT)
HLH	helix-loop-helix
Hox	homeobox
HPRT	hypoxanthine-guanine phosphoribosyltransferase (= HGPRTase)
hTERT	human telomerase reverse transcriptase
IKK	IκB kinase
IκB	inhibitor of NFκB
IL-1α	interleukin-1 alpha
IL-1R	interleukin-1 receptor
IL-1Ra	interleukin-1 receptor antagonist
INK4	inhibitor of Cdk4
kb	kilobase (1000 bp)
kinase	enzyme which phosphorylates a substrate protein or lipid
kinase kinase	enzyme which phosphorylates a kinase
kinase kinase kinase	enzyme which phosphorylates a kinase kinase
linkage	genomic proximity between two markers
linkers	synthetic oligonucleotides used for ligation
MAP kinase kinase	molecule which phosphorylates MAP kinase (see MEK)
MAP kinase	mitogen-activated protein kinase
MAP	microtubule-associated protein
Mb	megabase (1000 kb)
MDM2	mouse double minute gene: endogenous p53 antagonist first discovered in extrachromosomal DNA of murine tumor cells; human homolog is termed HDM2 by analogy, though not extrachromosomal
MEK	MAP/ERK kinase (protein which kinases ERKs, or MAP kinases)
MEKK	MEK kinase (protein which kinases MEK)
melanin	skin pigment molecule
melatonin	hormone that controls circadian rhythm in response to light
met	*E. coli* repressor protein for methionine biosynthesis
Met	methionine
Met	receptor (c-Met) for hepatocyte growth factor/scatter factor
MHC	major histocompatibility complex
MHC	myosin heavy chain
missense	mutation which substitutes a different amino acid
MPF	historically, maturation-promoting factor (in yeast)
MPF	now denotes M-phase (mitosis)-promoting factor (i.e., *cdc2* kinase)
MRI	magnetic resonance imaging
MRS	methicillin-resistant staphylococci
MWt	molecular weight
NAP	neutrophil alkaline phosphatase
NAP-1	neutrophil activating peptide-1 (IL-8)
NAT	*N*-acetyltransferase

neu	carcinogen-induced rodent oncogenic homolog of ErbB2
NF1	neurofibromatosis-associated tumor suppressor gene
NF1	nuclear factor 1; an adenovirus replication protein
NFAT	nuclear factor of activated T cells
NFκB	*n*uclear *f*actor which transactivates the immunoglobulin κ light chain enhancer in *B* cells
nitric oxide	endogenous vasodilator and neurotransmitter
nitrous oxide	laughing gas
nonsense	mutation which terminates transcription
NSAID	nonsteroidal anti-inflammatory drug
$p14^{ARF}$	human Cdk4 inhibitor with *a*lternate *r*eading *f*rame to $p16^{INK4}$
$p19^{ARF}$	murine homolog of $p14^{ARF}$
PARP	poly(ADPribosyl) polymerase
PCNA	proliferating cell nuclear antigen
PCP	phencyclidine (angel dust)
PCR	polymerase chain reaction
PCT	porphyria cutanea tarda
PD-ECGF	platelet-derived endothelial cell growth factor
PDGF	platelet-derived growth factor
phosphatidylserine	membrane lipid
phosphoserine	post-translationally modified amino acid
PI3K	phosphatidylinositol-3′-kinase (PI-3′-kinase)
PIP_2	phosphatidylinositol bisphosphate
PIP_3	phosphatidylinositol trisphosphate
PLA_2	phospholipase A_2
PI^{A2}	platelet A2 polymorphism of the GPIIIA integrin subunit
platelet-activating factor	arachidonate derivative produced by and for platelets
platelet factor IV	an antiangiogenic platelet-derived coagulation cofactor
platelet-derived growth factor	mesenchymal growth factor produced by platelets for stromal cells
P-loop	structural motif within nucleotide phosphatases (e.g., GTPases)
protein C	endogenous circulating anticoagulant
protein kinase C	signaling molecule family with multiple isoforms
P-site	adenyl cyclase domain that interacts with purine ring of adenosine
PTC	human homolog of *patched* gene
PTC	papillary thyroid cancer
P-type	(ATPase) in which active site is activated by (auto)phosphorylation
q.v.	which see
RACE	rapid amplification of cDNA ends
RANTES	*r*egulated on *a*ctivation *n*ormal *T* cell *e*xpressed and *s*ecreted (chemokine)
SAA	serum amyloid A
SAGE	serial analysis of gene expression
SAP	serum alkaline phosphatase
SAP	serum amyloid P (fibril)
SAP	SLAM-associated protein
SLAM	signaling lymphocyte-activation molecule (CDw150)
SLAP	Src-like adaptor protein
spp.	species (e.g., of microorganism)
SRE	serum response element
SRF	serum response factor
SRP	(ribosomal) signal recognition particle
syndrome X	obesity syndrome
tandem genes	contiguous runs of multi-copy genes, e.g., encoding histones

tandem repeats	highly repetitive DNA sequences (satellite DNA)
TAP	transporter associated with antigen processing
TAP	trypsinogen activator peptide
Tar	bacterial aspartate (chemotaxis) receptor
TAR	*t*rans-*a*ctivation *r*esponsive RNA sequence in HIV
Tat	HIV1-encoded trans-activating protein
TAT	tyrosine aminotransferase
TBG	thyroxine-binding globulin
TGB	thyroglobulin
TPA	tetradeconyl phorbol ester acetate
tPA	tissue plasminogen activator
V1R	vomeronasal organ (pheromone) receptor type 1
VR1	vanilloid (spicy taste or pain) receptor type 1
Vegl	*Xenopus* morphogen
vegetable	neither animal nor mineral
vegetal	inferior end of embryo, opposite animal pole
VEGF	vascular endothelial growth factor ("vascular permeability factor")
VP-16	etoposide (cytotoxic drug)
VP16	herpes simplex transcription factor

Contents in brief