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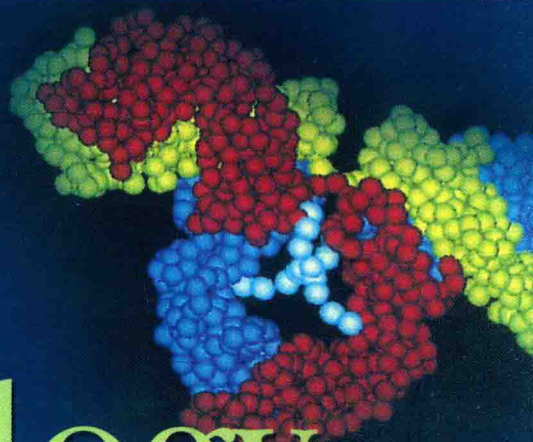

Roitt's Essential Immunology

Roitt 免疫学基础 影印版

Tenth Edition

• Ivan M. Roitt

• Peter J. Delves

高等教育出版社
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Ivan M. Roitt
University College London

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Ivan M. Roitt, Peter J. Delves

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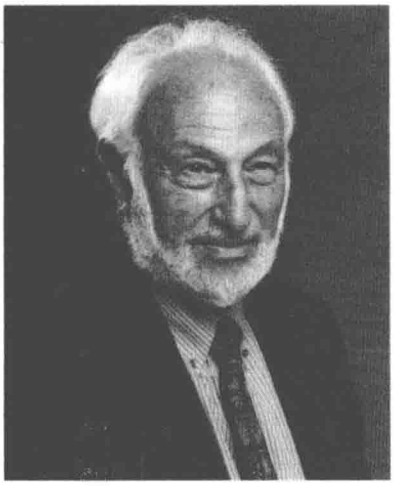
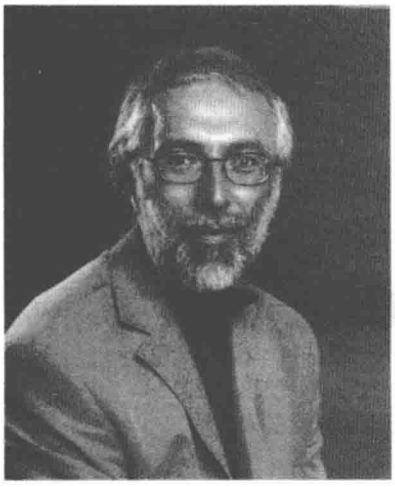


Ivan M. Roitt

Professor Roitt was born in 1927 and educated at King Edward's School, Birmingham and Balliol College, Oxford. In 1956, together with Deborah Doniach and Peter Campbell, he made the classic discovery of thyroglobulin autoantibodies in Hashimoto's thyroiditis which helped to open the whole concept of a relationship between autoimmunity and human disease. The work was extended to an intensive study of autoimmune phenomena in pernicious anaemia and primary biliary cirrhosis. In 1983 he was elected a Fellow of The Royal Society, and has been elected to Honorary Membership of the Royal College of Physicians and appointed Honorary Fellow of The Royal Society of Medicine.



Peter J. Delves

Dr Delves obtained his PhD from the University of London in 1986 and is currently a Reader in Immunology at University College London. His research focuses on molecular aspects of antigen recognition. He has authored and edited a number of immunology books, and teaches the subject at a broad range of levels.

出 版 前 言

随着克隆羊的问世和人类基因组计划的完成，生命科学成为21世纪名副其实的领头学科，生物高新技术产业逐步成为高科技产业的核心。生物科技和生物产业的发展对世界科技、经济、政治和社会发展等方面产生着深刻的影响，这也是我国赶超世界发达国家生产力水平最有前途和希望的领域。生命科学与技术全方位的发展呼唤高等教育培养更多高水平的复合型科技人才。

为此，教育部在《关于加强高等学校本科教学工作　提高教学质量的若干意见》[教高(2001)4号文件]中提出，高等学校要大力提倡编写、引进和使用先进教材，其中信息科学、生命科学等发展迅速、国际通用性强、可比性强的学科和专业可以直接引进先进的、能反映学科发展前沿的原版教材。教育部高等教育司还于2001年11月向全国主要大学和出版社下发了“关于开展‘国外生命科学类优秀教学用书’推荐工作的通知”，有力推动了生命科学类教材的引进工作。

高等教育出版社对国外生命科学教材进行了充分的调研，并委托教育部高等学校生物科学与工程教学指导委员会的专家教授开展了“引进国外优秀生命科学教材及其教学辅助材料专项研究”，并就国内外同类教材进行了比较，提出了具体的引进教材书目。经过版权谈判，目前我社已经购买了Pearson Education，McGraw－Hill，John Wiley & Sons，Blackwell Science，Thomson Learning，Cambridge University Press，Lippincott Williams & Wilkins等出版的13种教材的影印权，学科领域涉及生物化学、细胞生物学、遗传学、微生物学、生态学、免疫学、神经科学、发育生物学、解剖学与生理学、分子生物学、普通生物学等。这些教材具有以下特点：(1) 所选教材基本是近2年出版的，及时反映了学科发展的最新进展，在国际上使用广泛，具有权威性和时代感；(2) 内容简明，篇幅适中，结构合理，兼具一定的深度和广度，适用范围广；(3) 插图精美、丰富，既有很强的艺术性，又不失严谨的科学性，图文并茂，与正文相辅相成；(4) 语言简练、流畅，十分适合非英语国家的学生阅读。其中9种已入选教育部高等教育司推荐“国外优秀生命科学教学用书”。

考虑到中国国情，为了让学生买得起，同时又能让学生看到原版书彩色精美的插图，我们在引进学生用原版教材时，一方面采用黑白影印，最大限度地降低定价，另一方面随书附赠含有原书彩色插图的光盘，以充分体现原教材的风格、特色，为读者提供方便。

引进国外优秀生命科学教学用书是我社一项长期的重点工作，因此，我们衷心希望广大专家教授和同学提出宝贵的意见和建议，如有更好的教材值得引进，请与高等教育出版社生命科学分社联系，联系电话：010－68344002，E－mail地址：lifesciences－hep@x263.net。

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2002年11月

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A number of scientists very generously provided illustrations for inclusion in this edition, and we have acknowledged our gratitude to them in the relevant figure legends.

Preface

It is now 30 years since the 1st Edition of *Essential Immunology* appeared, and it seemed that the time was now appropriate for the task of producing the 10th Edition to be shared. The new co-author, Peter Delves, has been a close colleague of Professor Roitt for many years and is a highly experienced teacher.

A wide range of subjects have been extensively revised, restructured or updated, and advanced material is included in the figure legends to avoid disruption of the basic text. These subjects include:

- dendritic cells
- intraepithelial lymphocytes
- NK-T and γδ T-cells
- NK receptors
- receptor editing relating to receptor diversity
- non-classical MHC and the presentation of non-peptidic antigens
- the role of chaperone proteins in antigen processing
- T-cell recognition of peptide–MHC reflecting the latest crystallographic studies
- arrays for analysis of gene expression
- tetramer evaluation of antigen-specific T-cells
- experimental genetic manipulation using conditional 'knockouts' employing the Lox/Cre system and 'knockins' to replace endogenous genes
- B- and T-cell signaling pathways and the role of adaptor proteins
- cytokine physiology
- chemokines and their receptors
- memory cells
- intimate links of innate and adaptive immunity
- the role of complement in modulating the adaptive immune response
- regulatory T-cells
- activation-induced cell death
- neuroendocrine influences on the immune system
- critical role of *Pax 5* in B-cell differentiation
- molecular basis of thymic development
- signaling through pattern recognition systems
- prions
- viral hijacking of host processes as evasion mechanisms
- DNA vaccines
- mucosal adjuvants
- 'shot gun' approach to identification of vaccine candidates
- primary immunodeficiency including IL-7 receptor mutation, and deficiency of *VDJ* recombination in severe combined immunodeficiency
- CCR5 co-receptor for HIV infection of cells
- the importance of highly active anti-retroviral drug therapy and of healthy CD8 response dependent on robust CD4 Th1 effectors in control of HIV infection
- pivotal role of IgE antibodies in pathogenesis of asthma and atopic dermatitis, and remarkable therapeutic benefit of monoclonal anti-IgE
- the excessive hygiene hypothesis related to the development of allergy
- the role of Fcγ receptors in the pathogenesis of type II and III hypersensitivities
- suppression of graft rejection by synergy between fungal metabolites and other drugs and by induction of antigen-specific tolerance with high-dose bone marrow transplantation combined with co-stimulatory blockade by anti-CD40L and CTLA-4-Ig
- engineering grafts from recipient cells
- the role of hsp70 and 90 in natural and induced tumor immunity
- peptide priming of dendritic cells to provoke anti-cancer cytotoxic responses
- the avoidance of graft vs. host disease in allogeneic bone marrow transplantation for leukemias
- inhibition of B-cell lymphomas and tumor angiogenesis by radiolabeled monoclonals
- thymic expression of some organ-specific antigens
- role of autoimmunity to hsp65 in atherosclerosis
- autologous stem cell transplantation after cytotoxic ablative therapy for some cases of SLE, scleroderma and juvenile rheumatoid arthritis.

All in all, quite a mouthful!

Abbreviations

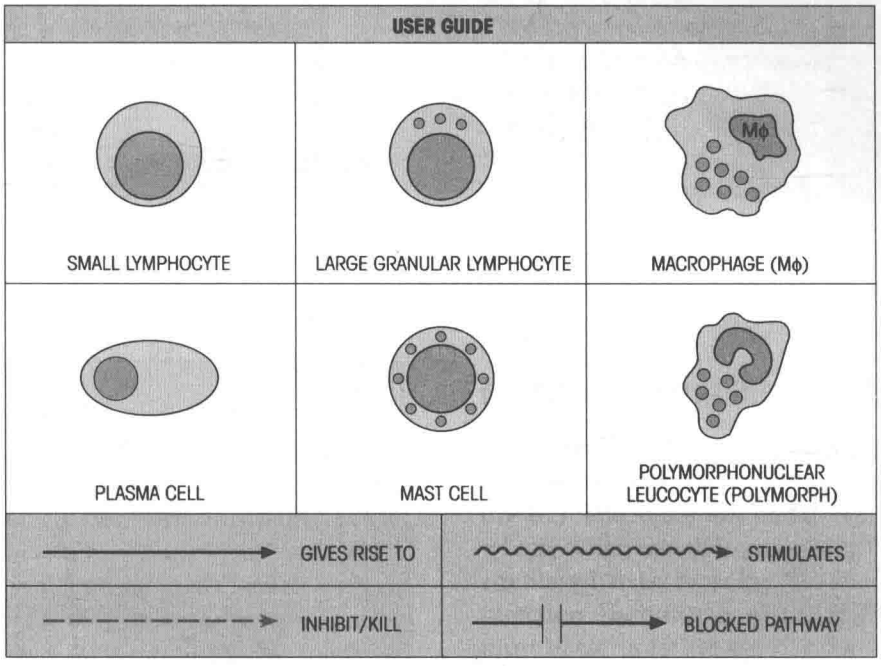
Ab	antibody
ACh-R	acetylcholine receptor
ACTH	adrenocorticotropic hormone
ADA	adenosine deaminase
ADCC	antibody-dependent cellular cytotoxicity
Ag	antigen
AIDS	acquired immunodeficiency syndrome
ANCA	antineutrophil cytoplasmic antibodies
APC	antigen-presenting cell
ARRE-1	antigen receptor response element-1
ARRE-2	antigen receptor response element-2
AZT	zidovudine (3′-azido-3′-deoxythymidine)
B-cell	lymphocyte which matures in bone marrow
BCG	bacille Calmette–Guérin attenuated form of tuberculosis
BCR	B-cell receptor
BM	bone marrow
BSA	bovine serum albumin
BUDR	bromodeoxyuridine
C	complement
Cα(β/γ/δ)	constant part of TCR α(β/γ/δ) chain
CALLA	common acute lymphoblastic leukemia antigen
cAMP	cyclic adenosine monophosphate
CCP	complement control protein repeat
CD	cluster of differentiation
CDR	complementarity determining regions of Ig or TCR variable portion
CEA	carcinoembryonic antigen
CFA	complete Freund's adjuvant
cGMP	cyclic guanosine monophosphate
$C_{H(L)}$	constant part of Ig heavy (light) chain
CMI	cell-mediated immunity
CML	cell-mediated lympholysis
CMV	cytomegalovirus
Cn	complement component 'n'
Cn̄	activated complement component 'n'
iCn	inactivated complement component 'n'
Cna	small peptide derived by proteolytic activation of Cn
CpG	guanosine–cytosine
CR(n)	complement receptor 'n'
CRP	C-reactive protein
CsA	cyclosporin A
CSF	cerebrospinal fluid
D gene	diversity minigene joining V and J segments to form variable region
DAF	decay accelerating factor
DAG	diacylglycerol
DC	dendritic cells
DNP	dinitrophenyl
DTP	diphtheria, tetanus, pertussis triple vaccine
EAE	experimental allergic encephalomyelitis
EBV	Epstein–Barr virus
ELISA	enzyme-linked immunosorbent assay
EM	electron microscope
Eϕ	eosinophil
ER	endoplasmic reticulum
ES	embryonic stem (cell)
F(B)	factor (B, etc.)
Fab	monovalent Ig antigen-binding fragment after papain digestion
$F(ab')_2$	divalent antigen-binding fragment after pepsin digestion
FACS	fluorescence-activated cell sorter
Fc	Ig crystallisable-fragment originally; now non-Fab part of Ig
FcγR	receptor for IgG Fc fragment
FDC	follicular dendritic cells
(sc)Fv	(single chain) V_H–V_L antigen binding fragment
G	granulocyte
g.b.m.	glomerular basement membrane
GM-CSF	granulocyte–macrophage colony-stimulating factor
gp*n*	*n*kDa glycoprotein
g.v.h.	graft versus host
H-2	the mouse major histocompatibility complex
H-2D/K/L	main loci for classical class I (class II)
(A/E)	murine MHC molecules
HAMA	human antimouse antibodies
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HEV	high walled endothelium of post capillary venule
Hi	high
HIV-1(2)	human immunodeficiency virus-1 (2)
HLA	the human major histocompatibility complex
HLA-A/B/C	main loci for classical class I (class II)
(DP/DQ/DR)	human MHC molecules
HRF	homologous restriction factor
HSA	heat-stable antigen
hsp	heat-shock protein
5HT	5-hydroxytryptamine
HTLV	human T-cell leukemia virus
H-Y	male transplantation antigen

ICAM-1	intercellular adhesion molecule-1
Id (αId)	idiotype (anti-idiotype)
IDC	interdigitating dendritic cells
IDDM	insulin-dependent diabetes mellitus
IFNα	α-interferon (also IFNβ, IFNγ)
Ig	immunoglobulin
IgG	immunoglobulin G (also IgM, IgA, IgD, IgE)
sIg	surface immunoglobulin
IgM-α/Ig-β	membrane peptide chains associated with sIgM B-cell receptor
IgSF	immunoglobulin superfamily
IL-1	interleukin-1 (also IL-2, IL-3, etc.)
iNOS	inducible nitric oxide synthase
IP_3	inositol triphosphate
ISCOM	immunostimulating complex
ITAM	immunoreceptor tyrosine-based activation motif
ITIM	immunoreceptor tyrosine-based inhibitory motif
ITP	idiopathic thrombocytopenic purpura
JAK	Janus kinases
J chain	peptide chain in IgA dimer and IgM
J gene	joining gene linking V or D segment to constant region
*K*a(d)	association (dissociation) affinity constant (usually Ag–Ab reactions)
kDa	units of molecular mass in kilo Daltons
KLH	keyhole limpet hemocyanin
LAK	lymphocyte activated killer cell
LATS	long-acting thyroid stimulator
LBP	LPS binding protein
LCM	lymphocytic choriomeningitis virus
$Le^{a/b/x}$	$Lewis^{a/b/x}$ blood group antigens
LFA-1	lymphocyte functional antigen-1
LGL	large granular lymphocyte
LHRH	luteinizing hormone releasing hormone
LIF	leukemia inhibiting factor
Lo	low
LT(B)	leukotriene (B etc.)
LPS	lipopolysaccharide (endotoxin)
Mϕ	macrophage
mAb	monoclonal antibody
MAC	membrane attack complex
MAdCAM	mucosal addressin cell adhesion molecule
MALT	mucosal-associated lymphoid tissue
MAP kinase	mitogen-activated protein kinase
MBP	basic protein of eosinophils (also myelin basic protein)
MC	mast cell
MCP	membrane cofactor protein (C′ regulation)
MCP-1	monocyte chemotactic protein-1
M-CSF	macrophage colony-stimulating factor
MDP	muramyl dipeptide
MHC	major histocompatibility complex
MIF	macrophage migration inhibitory factor
MLA	monophosphoryl lipid A
MLR	mixed lymphocyte reaction
MMTV	mouse mammary tumor virus
MS	multiple sclerosis
MSH	melanocyte stimulating hormone
MuLV	murine leukemia virus
NADP	nicotinamide adenine dinucleotide phosphate
NAP	neutrophil activating peptide
NBT	nitro blue tetrazolium
NCF	neutrophil chemotactic factor
NFAT	nuclear factor of activated T-cells
NFκB	nuclear transcription factor
NK	natural killer cell
NO·	nitric oxide
NOD	Nonobese diabetic mouse
NZB	New Zealand Black mouse
NZB×W	New Zealand Black mouse×NZ White F1 hybrid
$\cdot O_2^-$	superoxide anion
OD	optical density
ORF	open reading frame
OS	obese strain chicken
Ova	ovalbumin
PAF(-R)	platelet activating factor (-receptor)
PCA	passive cutaneous anaphylaxis
PCR	polymerase chain reaction
PG(E)	prostaglandin (E etc.)
PHA	phytohemagglutinin
phox	phagocyte oxidase
PIP_2	phosphatidylinositol diphosphate
PKC	protein kinase C
PLC	phospholipase C
PMN	polymorphonuclear neutrophil
PMT	photomultiplier tube
PNH	paroxysmal nocturnal hemoglobinuria
PPD	purified protein derivative from *Mycobacterium tuberculosis*
PTK	protein tyrosine kinase
PWM	pokeweed mitogen
RA	rheumatoid arthritis
RANTES	*r*egulated upon *a*ctivation *n*ormal *T*-cell *e*xpressed and secreted chemokine
RAST	radioallergosorbent test
RF	rheumatoid factor
Rh(D)	rhesus blood group (D)
ROI	reactive oxygen intermediates
SAP	serum amyloid P
SC	Ig secretory component
SCF	stem cell factor
scFv	single chain variable region antibody fragment ($V_H + V_L$ joined by a flexible linker)
SCG	sodium cromoglycate
SCID	severe combined immunodeficiency
SDS-PAGE	sodium dodecylsulfate–polyacrylamide gel electrophoresis
SEA(B etc.)	*Staphylococcus aureus* enterotoxin A (B etc.)
SIV	Simian immunodeficiency virus
SLE	systemic lupus erythematosus
SRID	single radial immunodiffusion
STAT	signal transducer and activator of transcription
TAP	transporter for antigen processing
T-ALL	T-acute lymphoblastic leukemia
TB	tubercle bacillus
Tc	cytotoxic T-cell
T-cell	thymus-derived lymphocyte
TCR1(2)	T-cell receptor with γ/δ chains (with α/β chains)

TdT	terminal deoxynucleotidyl transferase
TG-A-L	polylysine with polyalanyl side-chains randomly tipped with tyrosine and glutamic acid
TGFβ	transforming growth factor-β
Th(1/2)	T-helper cell (subset 1 or 2)
Thp	T-helper precursor
TLI	total lymphoid irradiation
TM	transmembrane
TNF	tumor necrosis factor
TNP	trinitrophenol
Ts	suppressor T-cell
TSAb	thyroid stimulating antibodies
TSH(R)	thyroid stimulating hormone (receptor)
tum–	strongly immunogenic mutant tumors
Vα(β/γ/δ)	variable part of TCR α(β/γ/δ) chain
V gene	variable region gene for immunoglobulin or T-cell receptor
V_H	variable part of Ig heavy chain
VIP	vasoactive intestinal peptide
V_L	variable part of light chain
$V_{\kappa/\lambda}$	variable part of κ(λ) light chain
VCAM	vascular cell adhesion molecule
VLA	very late antigens
VNTR	variable number of tandem repeats
VP1	virus-specific peptide 1
XL	X-linked

User Guide

Throughout the illustrations standard forms have been used for commonly-occurring cells and pathways. A key to these is given in the figure below.



Contents

CHAPTER 1

Innate immunity

INTRODUCTION

We live in a potentially hostile world filled with a bewildering array of infectious agents (figure 1.1) of diverse shape, size, composition and subversive character which would very happily use us as rich sanctuaries for propagating their 'selfish genes' had we not also developed a series of defense mechanisms at least their equal in effectiveness and ingenuity (except in the case of many parasitic infections where the situation is best described as an uneasy and often unsatisfactory truce). It is these defense mechanisms which can establish a state of immunity against infection (Latin *immunitas*, freedom from) and whose operation provides the basis for the delightful subject called 'Immunology'.

Aside from ill-understood constitutional factors which make one species innately susceptible and another resistant to certain infections, a number of relatively nonspecific antimicrobial systems (e.g. phagocytosis) have been recognized which are **innate** in the sense that they are not intrinsically affected by prior contact with the infectious agent. We shall discuss these systems and examine how, in the state of **specific acquired immunity**, their effectiveness can be greatly increased.

EXTERNAL BARRIERS AGAINST INFECTION

The simplest way to avoid infection is to prevent the microorganisms from gaining access to the body (figure 1.2). The major line of defense is of course the skin which, when intact, is impermeable to most infectious agents; when there is skin loss, as for example in burns, infection becomes a major problem. Additionally, most bacteria fail to survive for long on the skin because of the direct inhibitory effects of lactic acid and fatty acids in sweat and sebaceous secretions and the low pH which they generate. An exception is *Staphylococcus aureus* which often infects the relatively vulnerable hair follicles and glands.

Mucus, secreted by the membranes lining the inner surfaces of the body, acts as a protective barrier to block the adherence of bacteria to epithelial cells. Microbial and other foreign particles trapped within the adhesive mucus are removed by mechanical stratagems such as ciliary movement, coughing and sneezing. Among other mechanical factors which help protect the epithelial surfaces, one should also include the washing action of tears, saliva and urine. Many of the secreted body fluids contain bactericidal components, such as acid in gastric juice, spermine and zinc in semen, lactoperoxidase in milk and lysozyme in tears, nasal secretions and saliva.

A totally different mechanism is that of microbial

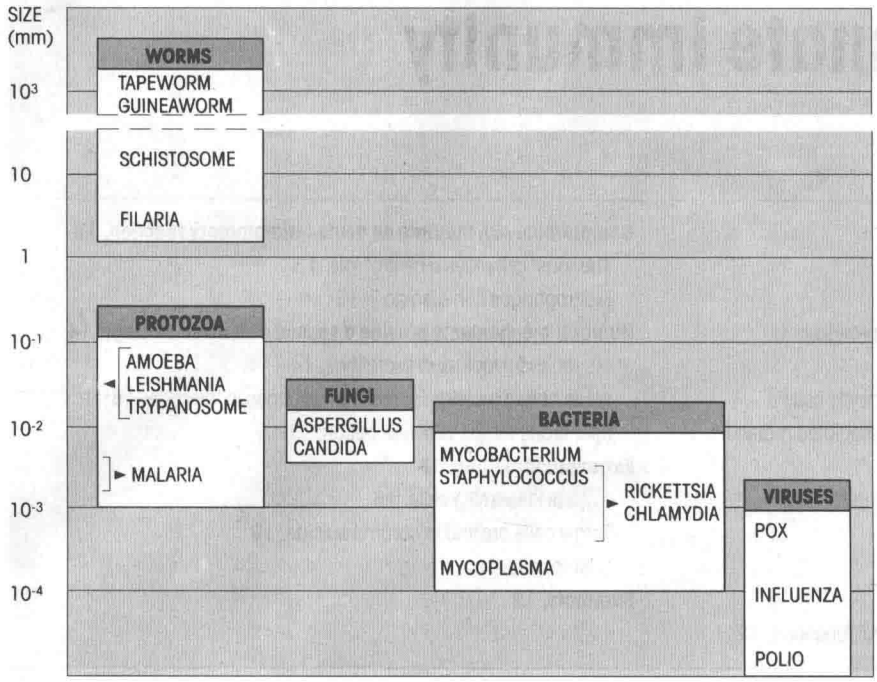


Figure 1.1. The formidable range of infectious agents which confronts the immune system. Although not normally classified as such because of their lack of a cell wall, the mycoplasmas are included under bacteria for convenience. Fungi adopt many forms and approximate values for some of the smallest forms are given.]►, range of sizes observed for the organism(s) indicated by the arrow; ◄[, the organisms listed have the size denoted by the arrow.

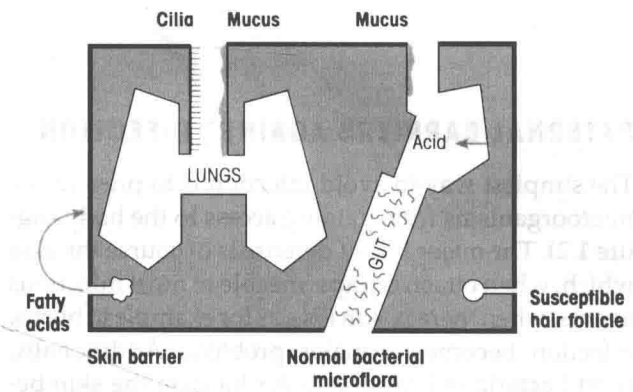


Figure 1.2. The first lines of defense against infection: protection at the external body surfaces.

antagonism associated with the normal bacterial flora of the body. This suppresses the growth of many potentially pathogenic bacteria and fungi at superficial sites by competition for essential nutrients or by production of inhibitory substances. To give one example, pathogen invasion is limited by lactic acid produced by particular species of commensal bacteria which metabolize glycogen secreted by the vaginal epithelium. When protective commensals are disturbed by antibiotics, susceptibility to opportunistic infections by *Candida* and *Clostridium difficile* is increased. Gut commensals may also produce colicins, a class of bactericidins which bind to the negatively charged surface of susceptible bacteria and insert a hydrophobic helical hairpin into the membrane; the molecule then undergoes a 'Jekyll and Hyde' transformation to become completely hydrophobic and forms a voltage-dependent channel in the membrane which kills by destroying the cell's energy potential. Even at this level, survival is a tough game.

If microorganisms do penetrate the body, two main defensive operations come into play, the destructive effect of soluble chemical factors such as bactericidal enzymes and the mechanism of **phagocytosis**—literally 'eating' by the cell (Milestone 1.1).

PHAGOCYTIC CELLS KILL MICROORGANISMS

Neutrophils and macrophages are dedicated 'professional' phagocytes

The engulfment and digestion of microorganisms are assigned to two major cell types recognized by Metchnikoff at the turn of the last century as microphages and macrophages.

The polymorphonuclear neutrophil

This cell, the smaller of the two, shares a common hematopoietic stem cell precursor with the other formed elements of the blood and is the dominant white cell in the bloodstream. It is a nondividing short-lived cell with a multilobed nucleus and an array of granules which are virtually unstained by histologic dyes such as hematoxylin and eosin, unlike those

Milestone 1.1—Phagocytosis

The perceptive Russian zoologist, Elie Metchnikoff (1845–1916), recognized that certain specialized cells mediate defense against microbial infections, so fathering the whole concept of cellular immunity. He was intrigued by the motile cells of transparent starfish larvae and made the critical observation that, a few hours after the introduction of a rose thorn into these larvae, they became surrounded by these motile cells. A year later, in 1883, he observed that fungal spores can be attacked by the blood cells of *Daphnia*, a tiny metazoan which, also being transparent, can be studied directly under the microscope. He went on to extend his investigations to mammalian leukocytes, showing their ability to engulf microorganisms, a process which he termed **phagocytosis**.

Because he found this process to be even more effective in animals recovering from infection, he came to a somewhat polarized view that phagocytosis provided the main, if not the only, defense against infection. He went on to define the existence of two types of circulating phagocytes: the polymorphonuclear leukocyte, which he termed a 'microphage', and the larger 'macrophage'.

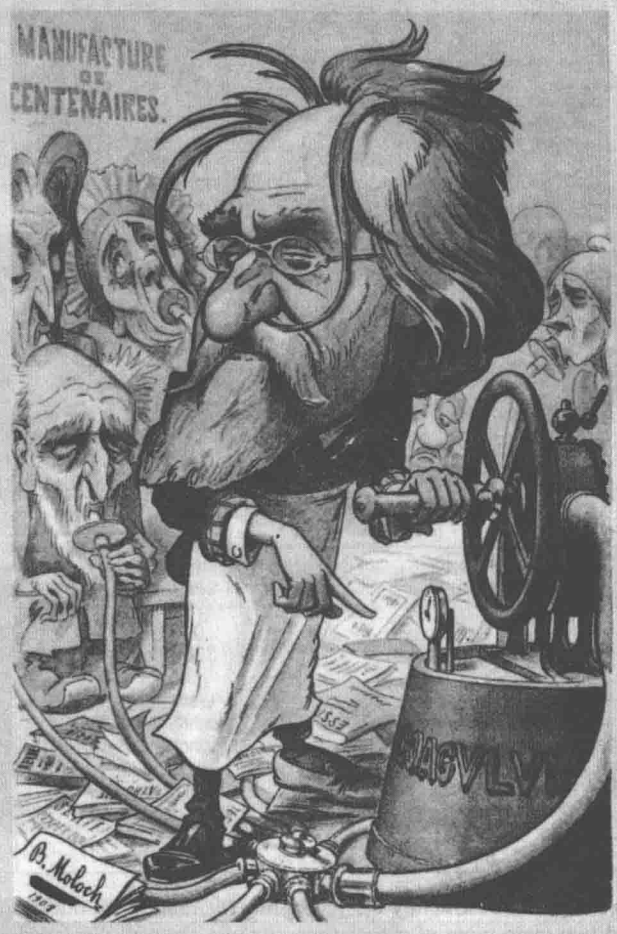


Figure M1.1.1. Caricature of Professor Metchnikoff from *Chanteclair*, 1908, No. 4, p. 7. (Reproduction kindly provided by The Wellcome Institute Library, London.)

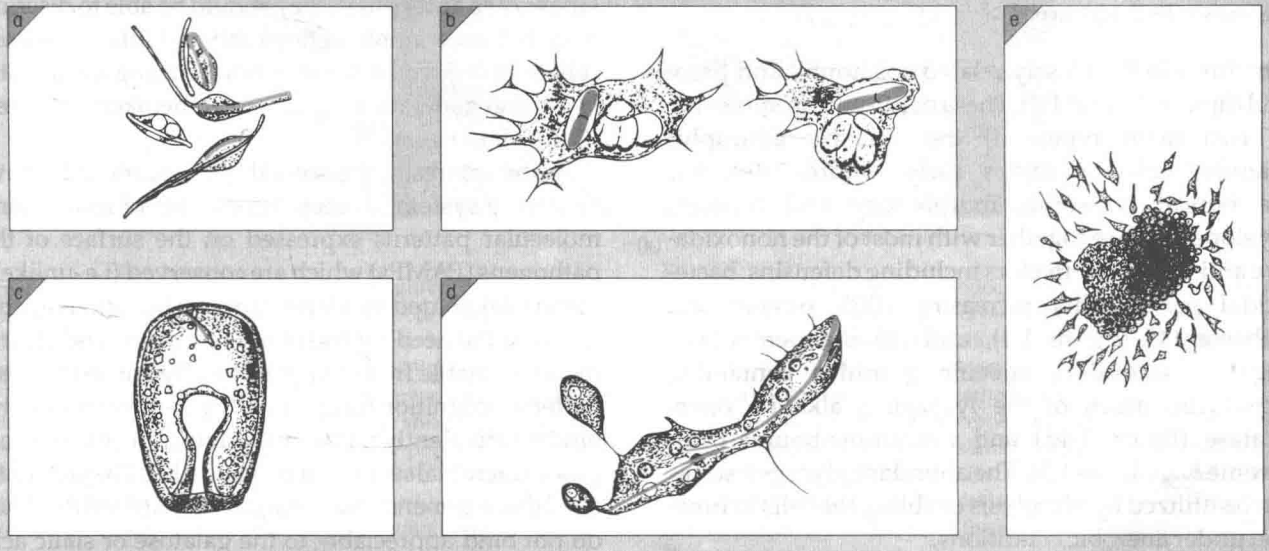
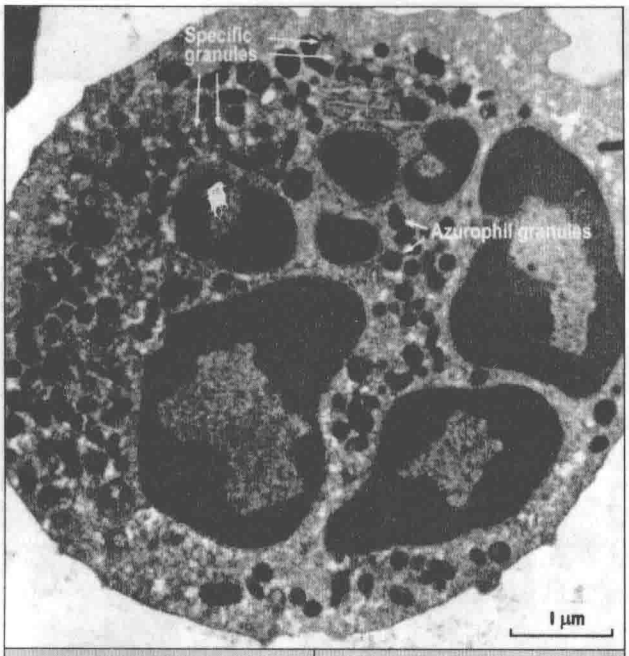


Figure M1.1.2. Reproductions of some of the illustrations in Metchnikoff's book, *Comparative Pathology of Inflammation* (1893). (a) Four leukocytes from the frog, enclosing anthrax bacilli; some are alive and unstained, others which have been killed have taken up the vesuvine dye and have been colored; (b) drawing of an anthrax bacillus, stained by vesuvine, in a leukocyte of the frog; the two figures represent two phases of movement of the same frog leukocyte which contains stained anthrax bacilli within its phagocytic vacuole; (c and d) a foreign body (colored) in a starfish larva surrounded by phagocytes which have fused to form a multinucleate plasmodium shown at higher power in (d); (e) this gives a feel for the dynamic attraction of the mobile mesenchymal phagocytes to a foreign intruder within a starfish larva.



AZUROPHIL GRANULES	SPECIFIC GRANULES
0.5 μm 1500/cell	0.2 μm 3000/cell
Lysozyme Myeloperoxidase Elastase Cathepsin G H^+ hydrolases	Lysozyme Cytochrome b_{558} OH^- phosphatase
Defensins BPI	Lactoferrin Vit B_{12} binding protein

Figure 1.3. Ultrastructure of neutrophil. The multilobed nucleus and two main types of cytoplasmic granules are well displayed. (Courtesy of Dr D. McLaren.)

structures in the closely related eosinophil and basophil (figures 1.3 and 1.4). These neutrophil granules are of two main types: (i) the **primary azurophil granule** which develops early (figure 1.4e), has the typical lysosomal morphology and contains myeloperoxidase together with most of the nonoxidative antimicrobial effectors including defensins, bactericidal permeability increasing (BPI) protein and cathepsin G (figure 1.3), and (ii) the peroxidase-negative **secondary specific granules** containing lactoferrin, much of the lysozyme, alkaline phosphatase (figure 1.4d) and membrane-bound cytochrome b_{558} (figure 1.3). The abundant glycogen stores can be utilized by glycolysis enabling the cells to function under anerobic conditions.

The macrophage

These cells derive from bone marrow promonocytes which, after differentiation to blood monocytes, finally settle in the tissues as mature macrophages where they constitute the **mononuclear phagocyte system** (figure 1.5). They are present throughout the connective tissue and around the basement membrane of small blood vessels and are particularly concentrated in the lung (figure 1.4h; alveolar macrophages), liver (Kupffer cells) and lining of spleen sinusoids and lymph node medullary sinuses where they are strategically placed to filter off foreign material. Other examples are mesangial cells in the kidney glomerulus, brain microglia and osteoclasts in bone. Unlike the polymorphs, they are long-lived cells with significant rough-surfaced endoplasmic reticulum and mitochondria (figure 1.8b) and, whereas the polymorphs provide the major defense against pyogenic (pus-forming) bacteria, as a rough generalization it may be said that macrophages are at their best in combating those bacteria (figure 1.4g), viruses and protozoa which are capable of living within the cells of the host.

Pattern recognition receptors (PRRs) on phagocytic cells recognize and are activated by pathogen-associated molecular patterns (PAMPs)

It hardly needs to be said but the body provides a very complicated internal environment and the phagocytes continuously encounter an extraordinary variety of different cells and soluble molecules. They must have mechanisms to enable them to distinguish these friendly self components from unfriendly and potentially dangerous microbial agents—as Charlie Janeway so aptly put it, they should be able to discriminate between 'noninfectious self and infectious nonself'. Not only must the infection be recognized, but it must also generate a signal which betokens 'danger' (Polly Matzinger).

In the interests of survival, phagocytic cells have evolved a system of receptors capable of recognizing molecular patterns expressed on the surface of the pathogens (PAMPs) which are conserved (i.e. unlikely to mutate), shared by a large group of infectious agents (sparing the need for too many receptors) and clearly distinguishable from self patterns. By and large these pattern recognition receptors (PRRs) are lectin-like and bind multivalently with considerable specificity to exposed microbial surface sugars with their characteristic rigid three-dimensional configurations (PAMPs). They do not bind appreciably to the galatose or sialic acid groups which are commonly the penultimate and ultimate sugars of mammalian surface polysaccharides. PAMPs linked to extracellular infections include Gram-negative lipopolysaccharide (LPS), Gram-positive lipoteichoic acid, yeast cell wall mannans (cf. figure 1.8) and mycobacterial glycolipids. Unmethy-