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With contributions by
Timo Ulrichs·Alexandra Aicher

Color Atlas of Immunology

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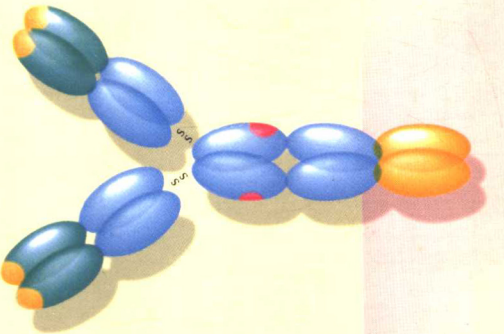

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Color Atlas of Immunology

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Gerd-Rüdiger Burmester was born in Hanover, Germany in 1953. He studied medicine at the University of Hanover Medical School from 1972 to 1978 and did his doctoral research under the aegis of Professor Joachim R. Kalden in Hanover. His active interest in clinical immunology and rheumatology began during medical school and intensified after his studies as a Postdoctoral Fellow in the laboratories of Professors Henry Kunkel and Robert Winchester at the Rockefeller University in New York on a scholarship from the Deutsche Forschungsgemeinschaft. Dr. Burmester subsequently took up a teaching position at the University of Erlangen Medical School. He completed his additional research requirements for a *Habilitation* (German qualification for professorship) in 1989 and was appointed Associate Professor in 1990. He later accepted a chair at the Department of Rheumatology and Clinical Immunology, Charité Hospital, Humboldt University in Berlin. Professor Burmester is engaged in clinical and experimental rheumatology and clinical immunology. Other interests include medical didactics on both the undergraduate and postgraduate levels. Professor Burmester has a wife and two children.

This pocket atlas was made with substantial help from **Timo Ulrichs**, MD at the Department of Microbiology, Free University of Berlin, and lecturer at the Department of Rheumatology, Charité Hospital. Dr. Ulrichs studied in Marburg and did his doctoral research in immunology. He is currently engaged in studies of immunological infectology in tuberculosis and vaccine development.

Antonio Pezzutto was born in Mirano near Venice in 1953. He studied medicine at the University of Padua from 1972 to 1978 and did his doctoral research in tumor immunology and was subsequently licensed as a specialist for clinical hematology and laboratory hematology. In 1983 he transferred to the University of Heidelberg's Medical Clinic and Policlinic, where he was influenced for 10 years by the exceptional professional competence and personality of Professor Werner Hunstein. Dr. Pezzutto did his *Habilitation* in hematology and clinical immunology. He has served as a professor at the Department of Hematology, Oncology, and Tumor Immunology, Charité Hospital, Humboldt University in Berlin since 1994. He heads the Work Group "Molecular Immunotherapy" at the Max-Delbrück-Center for Molecular Medicine in the Berlin district of Buch. His work mainly focuses on tumor immunology. Professor Pezzutto's wife is a scientist from Great Britain; they have two children.

Alexandra Aicher was essential in compiling the illustrations and texts. She obtained her M.D. at the University of Ulm in 1995 and received post-doctoral training at the Max-Delbrück-Center/ Robert-Rössle-Clinic, Berlin until 1997. After 2 years as post-doctoral fellow in immunology and microbiology at the University of Washington in Seattle, USA, she now works in molecular cardiology at the University of Frankfurt, Germany, focusing on dendritic cells and macrophages in atherosclerosis as well as on hematopoietic stem cells in neovascularization.

Jürgen Wirth began his studies in graphic design at the Offenbach School of Working Arts. He later transferred to the University of Graphic Arts in Berlin, where he majored in free graphics and illustration. He later completed his undergraduate degree at the Offenbach College of Design. Jürgen Wirth developed innovative exhibition concepts as a member of the exhibition design team during the renovation of the Senckenberg Museum in Frankfurt/Main. By that time, he was also working as a freelance graphic designer for several publishing companies, designing the illustrations for a number of school textbooks, nonfiction books, and scientific publications. Jürgen Wirth has received several awards for outstanding book graphics and design. In 1978, he was appointed professor at the School of Design in Schwäbisch Gmünd. Professor Wirth has taught foundation studies, design, and visualization at the Faculty of Design at the University of Applied Sciences in Darmstadt since 1986.

Preface

Immunology is a dynamic discipline with rapid research developments unparalleled by those of any other field except, perhaps, the neurosciences. This research has provided valuable new data for medicine and biology. Immunology, including its fundamental principles and clinical applications, is a very exciting field in which to specialize.

Nowadays, we still live to a ripe old age despite hostile attacks by myriads of pathogenic organisms. Immunological mechanisms have become highly sensitive and specific in the process. This color atlas graphically depicts these mechanisms. Its main goal is to explain the diverse interactions between the fundamental principles and the laboratory and clinical applications of immunology so as to create a vivid mental picture. The book's main target group includes medical students, biology students, and students in other branches of the biosciences. However, it also targets physicians and biologists who are active in their respective fields.

By definition, an atlas must focus on the graphic presentation of subject matter, the explanation of which is limited to brief text segments. Especially in immunology, a graphic presentation of the subject matter must depict certain processes and their progression through time and different phases as well as the interactions between a number of different substances and elements. In order to present an unmistakable picture of these "protagonists," the graphic designers must create archetypal models and skillfully use colors to ensure a clear understanding of the subject matter. We have mainly concentrated on harmonization of the color plates for different topics. The goal was to ensure that the visual elements were not overloaded with internal structures and to have the individual pieces combine to form a mosaic whole. This was sometimes achieved at the expense of aesthetics, and there is inevitably a certain loss of anatomical detail.

Due to space limitations and the emphasis on human medicine, the book mainly focuses on human immunology; space does not permit us to present all areas of the immense field of immunology in their entirety. A number of excellent textbooks of immunology are already on the market. Some of our colleagues may prefer a more comprehensive presentation of the subject matter. We must also remember the enormous developments in immunological research, the constant discovery of new information and processes that are still unclear today, but will soon be well understood. A constant exchange of paradigms is taking place, especially on the subject of tolerance and autoimmunity. The current edition cannot provide full coverage of this new information. We naturally hope that there will be many future editions that will allow us to revise the contents of the book to keep abreast of the latest advances. We would greatly appreciate any suggestions, additions, and corrections proposed by the readers of this color atlas.

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Gerd-Rüdiger Burmester, Berlin
Antonio Pezzutto, Berlin
Jürgen Wirth, Darmstadt

Introduction

This book targets students of medicine and biosciences as well as physicians and bioscientists. As was mentioned in the preface, the book mainly focuses on human immunology. This information will be conveyed in 131 color plates accompanied by explanatory texts on the facing pages.

The atlas is broken down into three main segments. The fundamental principles of human immunology are presented in the opening segment, the essential laboratory tests used in immunology are described in the second section, and the clinical aspects of immunological diseases are presented in the final section. The appendix contains a glossary of important immunological terms and tables including CD nomenclature for immunologically relevant molecules, criteria for classification of rheumatic diseases, an overview of the most important cytokines and growth factors, and important reference values for immunology. Besides providing an introduction to all relevant aspects of modern immunology, this color atlas also serves as an important source of reference for important questions in clinical medicine and laboratory practice.

The **fundamental principles** section begins with the organs of the immune system, followed by a description of the relevant cells of the immune system and the mechanisms by which T and B lymphocytes acquire high levels of specificity. Surface molecules are described in detail in deference to the enormous emphasis placed on them in most immunological publications. A description of accessory cells and natural killer cells follows. Next, the human lymphocyte antigen system is analyzed, followed by the principles of antigen processing and hypersensitivity reactions. Autoimmunity and tolerance are described in the last part of the section.

The **laboratory applications** section describes the most important test systems in immunology. "Conventional" methods such as precipitation, agglutination, and complement-binding reactions are presented along with newer methods such as immunoblotting, molecular biology tests, and a number of test systems for the detection of expressed genes.

The **clinical immunology** section describes immunodeficiencies and the essential immunological features of a number of immune diseases. The main focus is on rheumatology and hematology.

Uniform symbols are used to represent the various cell systems as well as their receptors and products. The symbols are explained on the inside front and inside back covers.

Acknowledgments

The authors thank Professor Falk Hiepe, Dr. Susanne Priem, Dr. Bruno Stuhlmüller, and Dr. Bernhard Thiele, Department of Medicine, Rheumatology and Clinical Immunology, Charité Hospital, for their help in preparing the laboratory section. Our special thanks go to Professor Hans-Eberhard Völker and Professor Herrmann Krastel, Department of Ophthalmology, University of Heidelberg, for their helpful suggestions and for supplying slides on immunological diseases of the eye, and to Professor Wolfgang Schneider, Head of the Pathological Institute, Krankenhaus Berlin Buch, for his constructive comments and a number of photographs on immunological diseases of the kidney.

Valuable photographs and slides were also provided by Dr. Andreas Breitbart, Department of Hematology, University of Ulm, Dr. Uwe Pleyer, Department of Ophthalmology, Charité Hospital, Professor Heidrun Moll, Center for Infection Research, University of Würzburg, Professor Peter Möller, Director of the Institute of Pathology, University of Ulm, Professor Michael Hüfner, Medical Department and Policlinic, University of Göttingen, Professor Herwart Otto, Director of the Institute of Pathology, University of Heidelberg, Dr. Hans R. Gelderblom, Robert Koch Institute, Berlin, Professor Hans-Michael Meinck, Department of Neurology, University of Heidelberg, and Dr. Thomas Wolfensberger, Hôpital Jules Gonin, Lausanne.

List of Abbreviations

AA	amino acid
Ab	antibody
ACE	angiotensin-converting enzyme
ACh	acetylcholine
ADCC	antibody-dependent cell-mediated cytotoxicity
Ag	antigen
AIDS	acquired immunodeficiency syndrome
AIHA	autoimmune hemolytic anemia
AILD	angioimmunoblastic lymphadenopathy with dysproteinemia
ALCL	anaplastic large-cell lymphoma
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
AML	acute myeloid leukemia
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
AP	alkaline phosphatase
APC	antigen-presenting cell
ARC	AIDS-related complex
AST	aspartate aminotransferase
BAL	bronchoalveolar lavage
BALT	bronchus-associated lymphoid tissue
BCG	bacillus Calmette–Guérin
BCR	B-cell receptor
C*n*	complement factor *n*
CALLA	common acute lymphoblastic leukemia-associated antigen
CBR	complement-binding reaction
CD	cluster of differentiation
CDR	complementarity-determining region
CFU	colony-forming unit
CLL	chronic lymphatic leukemia
CMV	cytomegalovirus
COX	cyclooxygenase
CR	complement receptor
CRP	C-reactive protein
CSF	colony-stimulating factor
CTL	cytotoxic T lymphocyte
CVID	common variable immune deficiency
cyt	intracytoplasmic
Da	dalton
DAF	decay-accelerating factor
DC	dendritic cell
del	chromosomal deletion
DPT	diphtheria, pertussis, tetanus
DT	diphtheria, tetanus (vaccination)
DTH	delayed-type hypersensitivity
EAE	experimental autoimmune encephalitis
EAU	experimental autoimmune uveoretinitis
EBV	Epstein–Barr virus
EC	endothelial cell
ECP	eosinophil cationic protein
EGF	epithelial growth factor
ELISA	enzyme-linked immunosorbent assay
EMA	epithelial membrane antigen
ENA	extractable nuclear antigen
ER	endoplasmic reticulum
ESR	erythrocyte sedimentation rate
FACS	fluorescence-activating cell sorter
Fc(γ–ε)R	Fc receptors for γ, α, δ, μ, and ε immunoglobulins
FDC	follicular dendritic cell
FGH	fibroblast growth factor
FISH	fluorescence in situ hybridization
FITC	fluorescein isothiocyanate
GAD	glutamate decarboxylase
GALT	gut-associated lymphoid tissue
GBM	glomerular basal membrane
GCDC	germinal center dendritic cell
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GN	glomerulonephritis
GPI	glycosylated phosphatidylinositol
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia (effect)
HAMA	human antimurine antibody
HCV	hepatitis C virus
HD	Hodgkin's disease
HEV	high endothelial venules
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
hsp	heat-shock protein
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus
IC	immune complex
ICAM	intercellular adhesion molecule
ICE	interleukin-1β-converting enzyme
IDC	interdigitating cell
IDDM	insulin-dependent diabetes mellitus
IFN	interferon
Ig	immunoglobulin

IL	*interleukin*
ILT	Ig-like transcript
inv	chromosomal inversion
IRAK	IL-1 receptor-associated kinase
IRBP	interphotoreceptor retinoid-binding protein
ITAM	immunoreceptor tyrosine-based activation motif
ITIM	immunoreceptor tyrosine-based inhibiting motif
ITP	*idiopathic thrombocytopenic purpura*
IVIG	intravenous immunoglobulin therapy
JCA	juvenile chronic arthritis
JRA	juvenile rheumatoid arthritis
kDa	kilodalton
KIR	killer cell Ig-like receptor
L	ligand
LAM	lipoarabinomannane
LBL	lymphoblastic lymphoma
LC	Langerhans cell
LCF	*lymphocyte chemotactic factor*
LFA	lymphocyte function-associated antigen
LGL	large granular lymphocyte
LIR	leukocyte Ig-like receptor
LKM	liver-kidney microsomal antibody
LPS	lipopolysaccharide
LTR	long terminal repeats
MAb	monoclonal antibody
MAG	myelin-associated glycoprotein
MALT	mucosa-associated lymphoid tissue
MASP	*mannan-binding lectin-associated* serine protease
MBP	major basic protein
MCP	monocyte chemoattractant protein
M-CSF	monocyte colony-stimulating factor
MCTD	mixed connective tissue disease
MGUS	monoclonal gammopathy of unknown significance
MHC	major histocompatibility complex
MIF	migration inhibition factor
MIRL	membrane inhibitor of reactive lysis
MOG	myelin oligodendrocyte glycoprotein
MPGN	membranoproliferative glomerulonephritis
MPO	myeloperoxidase
MPS	mononuclear phagocytic system
NF	nuclear factor
NFAT	nuclear factor-activated T cell
NGF	nerve growth factor
NHL	non-Hodgkin's lymphoma
NK	natural killer (cell)
NPM-ALK	*nucleophospamine anaplastic* lymphoma kinase
NSAID	nonsteroidal anti-inflammatory drugs
PAF	platelet-activating factor
PALS	periarteriolar lymphocyte sheath
PAMP	pathogen-associated molecular pattern
PBC	primary biliary cirrhosis
PCR	polymerase chain reaction
PDGF	platelet-derived growth factor
PE	phycoerythrin
PEG	*polyethylene glycol*
PFC	plaque-forming cell
PIBF	progesterone-induced blocking factor
PLP	proteolipid protein
PMN	polymorphonuclear neutrophil granulocyte
PMR	polymyalgia rheumatica
poly-IgR	polymeric immunoglobulin receptor
POX	peroxidase
PRR	pattern recognition receptors
PSC	primary sclerosing cholangitis
RA	rheumatoid arthritis
REAL	revised European-American *lymphoma classification*
RF	rheumatoid factor
Rh	rhesus
RID	radial immunodiffusion
RPGN	rapidly progressive glomerulonephritis
RR	relative risk
RS	Reed–Sternberg
S	Svedberg unit
SAA	serum amyloid A
SAP	serum amyloid P
SCID	*severe combined immune deficiency*
SLE	systemic lupus erythematosus
t (*n*:*n*)	chromosomal translocation from chromosome *n* to *n*
TAP	transporter associated with presentation
TBII	TSH-binding inhibiting immunoglobulin
TCR	T-cell receptor
TdT	terminal desoxyribonucleotransferase
TG	thyroglobulin
TGF	*transforming growth factor*
TIL	tumor-infiltrating lymphocyte
TNF	tumor necrosis factor
TPO	thyroidal peroxidase
TSBI	thyroid stimulation-blocking immunoglobulin
TSH	thyroid-stimulating hormone
TSI	thyroid-stimulating immunoglobulin
VCAM	vascular cell adhesion molecule

Contents

Fundamental Principles

Laboratory Applications

Clinical Immunology

Appendix

The Immune System

It took more than 400 million years of evolution for our immune system to develop into the highly complex and adaptable defense mechanism that it is today. Its primary task is to protect us from foreign and harmful substances, microorganisms, toxins, and malignant cells. Only through the continuous development of the immune system was it possible to protect living organisms against constant attacks from both the external and internal environments. In the process, the immune system has learned to inactivate destructive responses to endogenous substances and to prevent irreparable damage to the surrounding tissue. Most immunological responses are of limited duration and are restricted by regulatory mechanisms to prevent overreactions.

An essential task of the immune system is to distinguish dangerous from harmless. Infiltration with microorganisms or bacterial toxins, for example, is a dangerous attack on an organism, whereas the inhalation of pollen or the infiltration of food antigens from the stomach into the blood system is harmless. The destruction of malignant cells or foreign cell material is desirable (e.g., in parasite infestation), but direct attacks against the host tissue are undesirable (e.g., in autoimmune disease). The processes by which the immune system avoids the development of destructive self-reactivity are collectively referred to as *tolerance*. The large majority of lymphocytes directed against self-antigens present throughout the primary lymphoid organs are destroyed in a process known as *central tolerance*. *Peripheral tolerance* is still another mechanism that occurs in less common endogenous structures or in those present only in certain regions of the body.

Nonspecific Immune System

The historically older congenital defense mechanisms are defined as nonspecific because they become active independently of the invading pathogen. They are also called *nonclonal defense mechanisms* because no individual cell clone is required for their specific development. Some examples include the acid layer of the skin, the intact epidermis, the complement system, antimicrobial enzyme systems, and nonspecific mediators such as interferons and interleukins. Examples on the cellular level include granulocytes, the monocyte–macrophage system, and natural killer (NK) cells. The latter represent an interface between the specific and nonspecific immune systems.

The inflammatory response permits an on-the-site concentration of defensive forces via the complex interplay of soluble and cellular components; this is an important nonspecific defense mechanism. The first step in this process is the release of mediators that dilate the blood vessels and make the capillary walls more permeable. The site of infection is then penetrated by granulocytes, which are replaced by macrophages in the later course of the reaction. The granulocytes carry out the "first line of defense" in which the majority of invading pathogens are destroyed. The remaining pathogenic organisms and waste products of this first-line defense are phagocytosed by macrophages.

Specific Immune System

The process of such an immune response paves the way for the specific immune response. In a specific cytokine environment, the body can decide whether to proceed to a more humoral line of defense or a more cellular line of defense. The migration of antigen-presenting cells (APC) to the lymphoid organs first triggers a systemic immune response, then a *memory response*. The specific immune system consisting of T and B lymphocytes is responsible for this. These cell systems can produce highly specific reactions to their respective antigens and undergo clonal expansion, thus achieving a highly effective response to and memory for those antigens.

A. Origin of Cells of the Immune System

All components of the blood, including the cells of the immune system, originate from pluripotent hematopoietic stem cells of the bone marrow. With the aid of soluble mediators (cytokines) and contact signals emitted by stromal cells, these highly undifferentiated progenitor cells can give rise to the different blood cells (A). These cells are among the few body cells capable of self-renewal. Hence, they can divide without differentiating, thereby producing an unlimited supply of blood cells. The bone marrow produces 1.75×10^{11} erythrocytes (red blood cells) and 7×10^{10} leukocytes (white blood cells) each day and has the capacity to increase this production up to severalfold if needed. In vitro, these so-called progenitor cells can form colonies of differentiated cells. Myeloid progenitor cells can differentiate into the following types of cells: *megakaryocytes*, very large multinucleated cells that break up into small particles which constitute the platelets (thrombocytes) of the blood; *erythroblasts*, which further multiply and differentiate into circulating erythrocytes (red blood cells); *myeloblasts*, which can differentiate into neutrophils, eosinophils, and basophils (they all have a segmented nucleus and are therefore called polymorphonuclear leukocytes in order to distinguish them from the other mononuclear cells); *monoblasts* (monocyte precursors); and *dendritic cells*. Granulocytes, monocytes, and dendritic cells have the ability to ingest particles, microorganisms and fluids and are therefore called *phagocytes* (from the Greek word "phago" = "eat").

In response to soluble mediators called *chemokines*, the leukocytes migrate from the blood into the tissue, where they repair damaged tissue and remove bacteria, parasites, and dead cells that induce inflammation. After migration into the tissue, the blood monocytes differentiate into macrophages.

The most important cells of the immune system are the lymphocytes, which originate from a common progenitor cell in the bone marrow. Two types of lymphocytes can be distinguished: T lymphocytes, which are responsible for the cellular immune reponse, and B lymphocytes, which produce antibodies (humoral immune response). Cells of a third type, the natural killer cells, are also part of the lymphatic system. These cells are related to T lymphocytes, but their origin is still a matter of debate since they also express some features of myeloid cells.

B. Defense Mechanisms against Infections

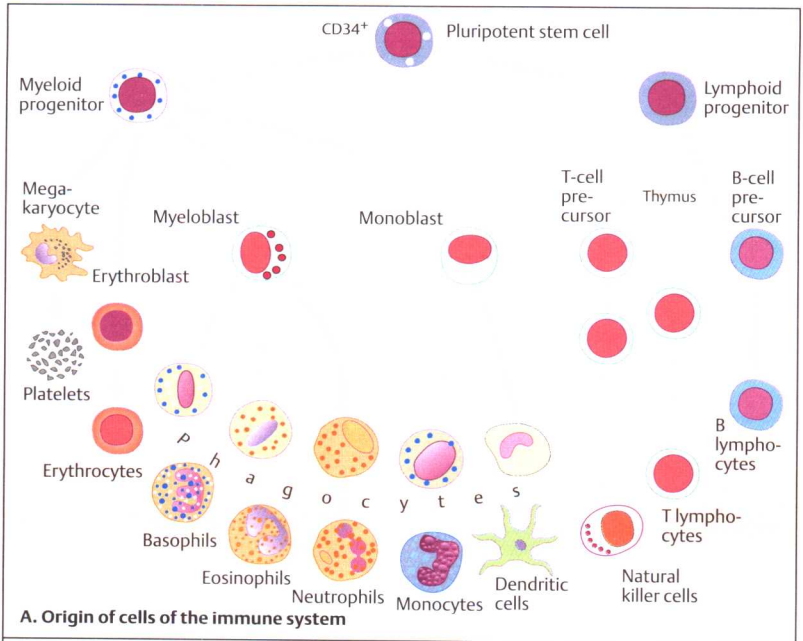
The primary function of the immune system is the protection of the organism against infection. *Innate immunity* is a more ancient line of defense, which is highly conserved between the different species. It consists mainly of phagocytic cells, blood proteins, and natural killer cells. All of its strategies are based on the recognition of typical molecular structures that are shared among different pathogens. The mechanisms of innate immunity are deployed shortly after the body has been invaded by a pathogen—usually within hours.

Phagocytosis is the main mechanisms of innate immunity. In this process, the microorganism is coated with blood components such as complement, which induces lysis of the invader or the release of cytotoxic lytic enzymes from killer cells.

Adaptive immunity, the phylogenetically modern mechanism, is based on the presence of receptors that are highly specific for certain regions (epitopes) of the pathogens. These receptors are either cell-bound (T lymphocytes and some B lymphocytes) or secreted (antibodies produced by B lymphocytes). A single T or B lymphocyte proliferates and produces large quantities of identical daughter cells (clonal expansion). This specific response process takes days to weeks.

C. Plasticity of Stem Cells

When present in specialized tissue, hematopoietic progenitor cells can differentiate into various different blood cells or tissue-specific cells, such as hepatocytes, neurons, muscle cells, or endothelial cells. The signals that regulate their differentiation into specialized cells are still largely unknown. Hematopoietic stem cells circulate in small numbers in the peripheral blood. They are morphologically indistinguishable from small lymphocytes.



A. Origin of cells of the immune system

B. Defense mechanisms against infections

C. Plasticity of stem cells

A. Structure of the Lymphatic System

All blood cells develop from common, pluripotent bone marrow stem cells. They can be detected in the fetal liver, which has hematopoietic properties, from the 8th week of gestation until shortly before birth. The stem cells give rise to the precursor cells of the lymphatic and myelopoietic systems. Erythrocytes, granulocytes, and thrombocytes have common precursor stages (progenitor cells), whereas lymphatic cells develop early into separate cell lines. Starting from the 13th week of gestation, some stem cells migrate to the thymus and bone marrow, which are referred to as the *primary lymphoid organs*. There, the cells continue to proliferate and differentiate. **T** lymphocytes require passage through the **t**hymus to complete their maturation, whereas **B** lymphocytes complete their maturation in the bone marrow (equivalent to the **b**ursa of Fabricius in birds).

Specialized receptors are located on the surface of T and B lymphocytes (antigen receptors made of two glycoprotein chains). The structure of the receptors varies from one cell to another. Each receptor recognizes and binds with only one specific antigen ("lock-and-key" principle). Unlike T lymphocytes, B lymphocytes can mature into plasma cells, produce large quantities of receptors in modified form, and enter the bloodstream as circulating antibodies.

Immature T lymphocytes make contact with specialized epithelial cells, dendritic cells, and macrophages in the thymus, which provides an opportunity for the selection and differentiation of T cells useful to the immune system. Cytokines (soluble regulatory factors or "messengers" for the immune system), such as interleukins 1, 2, 6, and 7, also play an important role. A large number of lymphocytes, especially those which recognize self-components of the body, are destroyed during this process of selection.

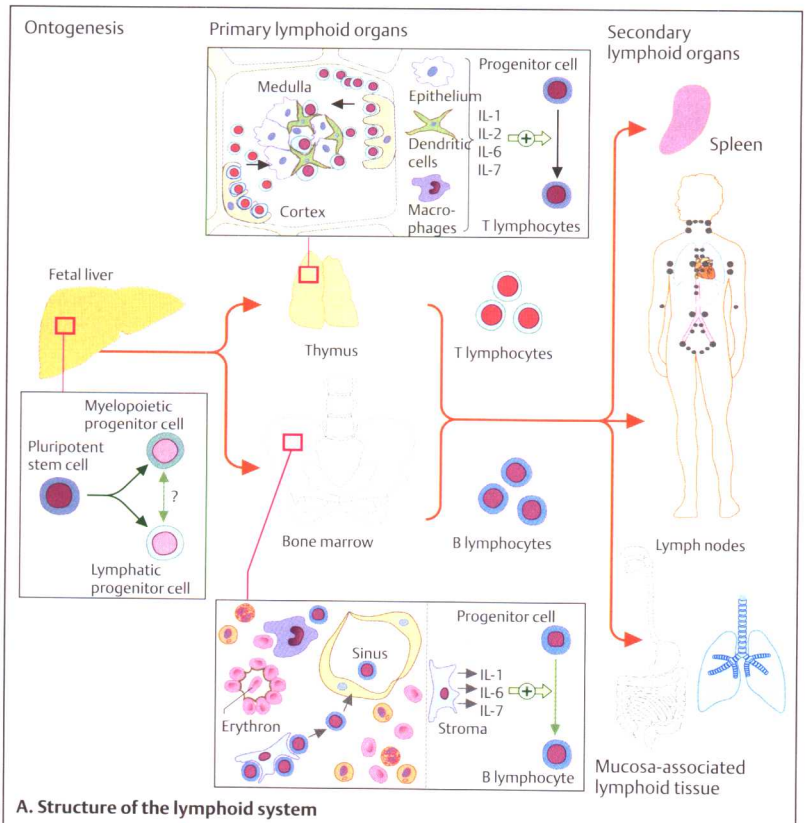
B lymphocytes start to develop from stem cells in the bone marrow around the 14th week of gestation. Contact with stromal cells of the bone marrow and cytokines is important for the differentiation of B cells. Interleukins 1, 6, and 7 are the most important cytokines in this process. The bone marrow is the lifetime production site of B lymphocytes.

Mature T and B lymphocytes leave their differentiation sites and migrate to peripheral or *secondary lymphoid organs* (e.g., spleen, lymph nodes, and mucosa-associated lymphoid tissue).

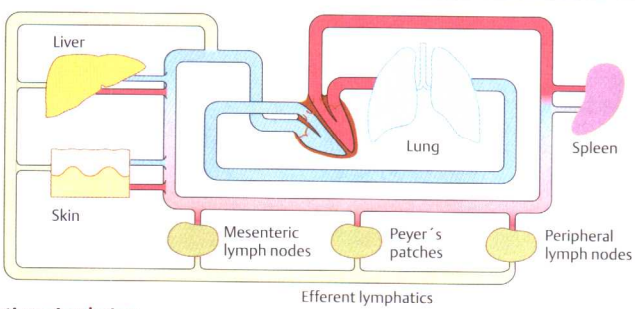
Mucosa-associated lymphoid tissue (MALT) is a collection of lymphatic cells in the submucosal tissue of the gastrointestinal (GI) tract, bronchial tract, urinary tract, and lacrimal glands. Organized lymphoid tissue (e.g., tonsils or Peyer's patches) and a large number of lymphatic cells loosely distributed throughout the pericapillary and periendothelial tissue can be found there.

B. Lymphatic Recirculation

The cells of the lymphatic system circulate continuously and reach all parts of the body with a few exceptions (e.g., vitreous body, brain, testicles). They reach the lymph nodes, skin, and intestine via a specialized endothelium of postcapillary venules, the so-called **h**igh **e**ndothelial **v**enules (**HEV**). The cells of this endothelium are much higher than normal endothelial cells. They express high levels of adhesion molecules that serve as homing receptors for lymphocytes. In response to certain chemotactic factors, lymphocytes migrate to the underlying tissue (diapedesis). The lymphatic cells reenter the circulation through efferent lymph vessels that merge into the thoracic duct. The lymphocytes enter the spleen via arterioles and sinusoids and exit the organ via the splenic vein.



A. Structure of the lymphoid system



B. Lymphatic recirculation