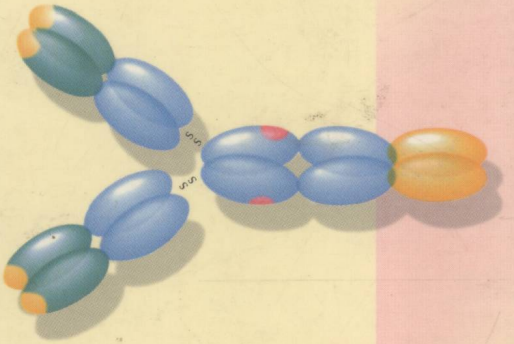
THIEME FLEXIBOOK

Gerd-Rüdiger Burmester
Antonio Pezzutto
With contributions by
Timo Ulrichs·Alexandra Aicher

Color Atlas of Immunology

免疫学彩色图谱



Thieme
CHINA SCIENCE AND TECHNOLOGY PRESS
中国科学技术出版社

basic sciences

Color Atlas of Immunology

Gerd-Rüdiger Burmester, M.D.

Professor of Medicine
Charité University Hospital
Humboldt University of Berlin
Berlin, Germany

Antonio Pezzutto, M.D.

Professor of Hematology and Oncology
Charité University Hospital
Humboldt University of Berlin
Berlin, Germany

With contributions by
Timo Ulrichs and Alexandra Aicher

131 color plates by Jürgen Wirth
13 tables

Thieme
Stuttgart · New York

图书在版编目（CIP）数据

免疫学彩色图谱/(德)布尔梅斯特尔(Burmester, G. R.),(德)佩楚托(Pezzuto, A.)著. —北京：中国科学技术出版社，2006.1

ISBN 7-5046-4221-5

Ⅰ. 免... Ⅱ.①布... ②G... ③佩... ④A... Ⅲ. 免疫学—图谱 Ⅳ. Q939.91-64

中国版本图书馆 CIP 数据核字（2005）第 135575 号

策划编辑 肖 叶 单 亭

责任编辑 周静远

责任印制 安利平

法律顾问 宋润君

中国科学技术出版社出版

北京市海淀区中关村南大街 16 号 邮政编码：100081

http://www.kjpbooks.com.cn

电话：010-62103210 传真：010-62183872

科学普及出版社发行部发行

北京汇文商业艺术制作有限公司 • 制版

上海盛杰印刷厂印刷

开本：850×1165 毫米 1/32 印张：10.5 字数：252 千字

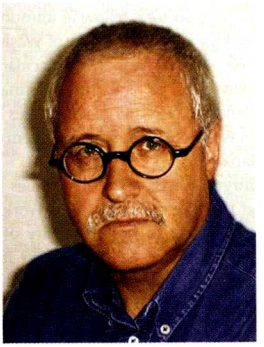
2006 年 1 月第 1 版 2006 年 1 月第 1 次印刷

印数：1—2000 册 定价：53.00 元

About the Authors

Gerd-Rüdiger Burmester

Antonio Pezzutto



Jürgen Wirth

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.

Spring 2003

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.

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

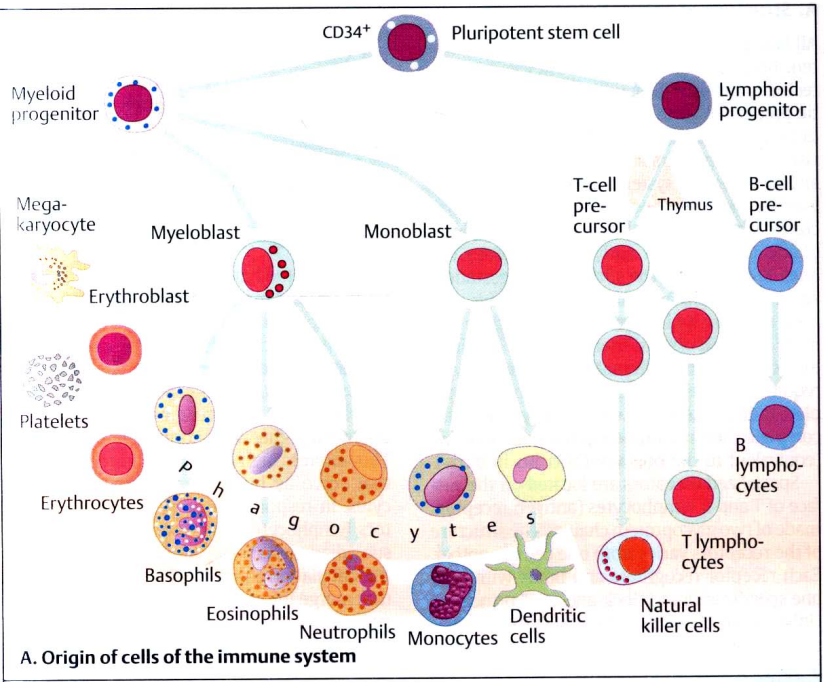
The primary function of the immune system is the protection of the organism against infection. *Innate immunity* is a more ancient line of defense, which is highly conserved between the different species. It consists mainly of phagocytic cells, blood proteins, and natural killer cells. All of its strategies 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.

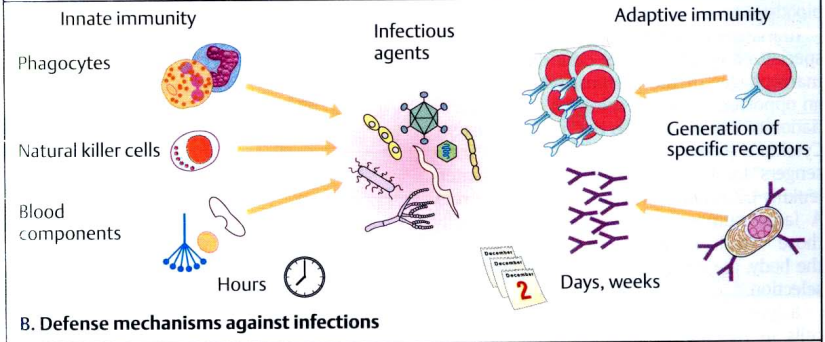
Adaptive immunity, the phylogenetically modern mechanism, is based on the presence of receptors that are highly specific for certain regions (epitopes) of the pathogens. These receptors are either cell-bound (T lymphocytes and some B lymphocytes) or secreted (antibodies produced by B lymphocytes). A 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

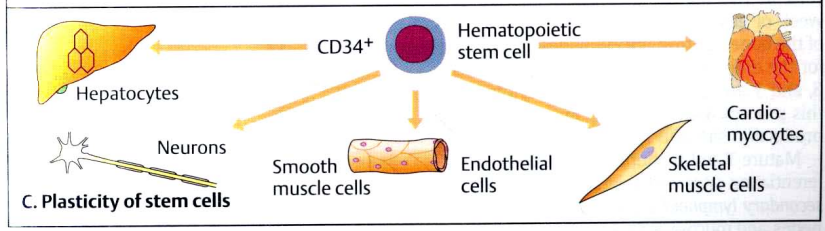
When present in specialized tissue, hematopoietic progenitor cells can differentiate into various different blood cells or tissue-specific cells, such as hepatocytes, neurons, muscle cells, or endothelial cells. The signals that regulate their differentiation into specialized cells are still largely 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.

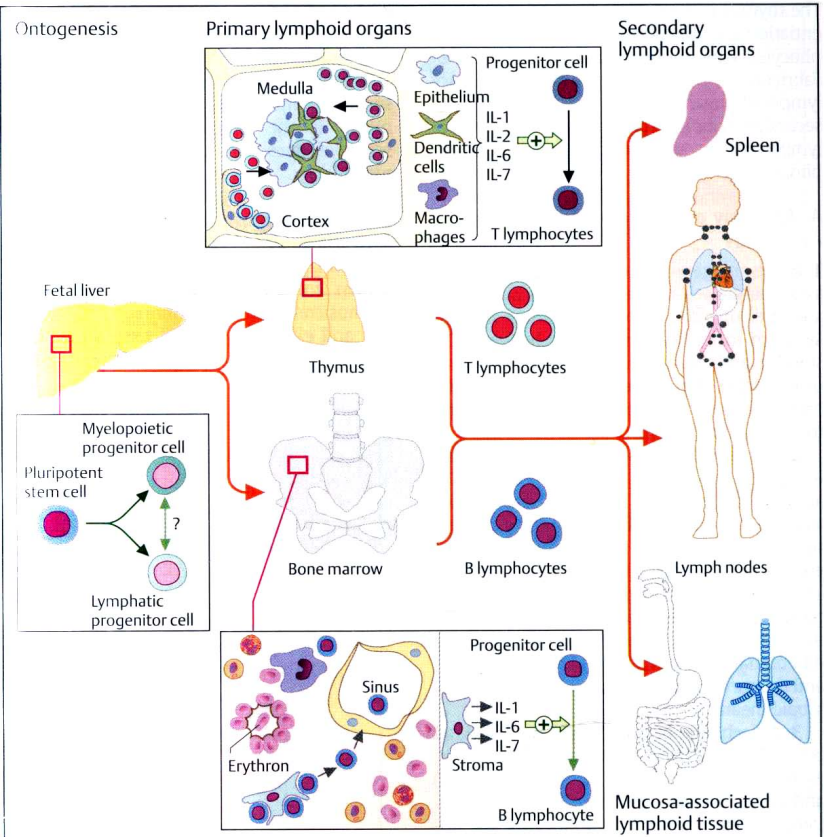
B lymphocytes start to develop from stem cells in the bone marrow around the 14th week of gestation. Contact with stromal cells of the bone marrow and cytokines is important for the differentiation of B cells. Interleukins 1, 6, and 7 are the most important cytokines in this process. The bone marrow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

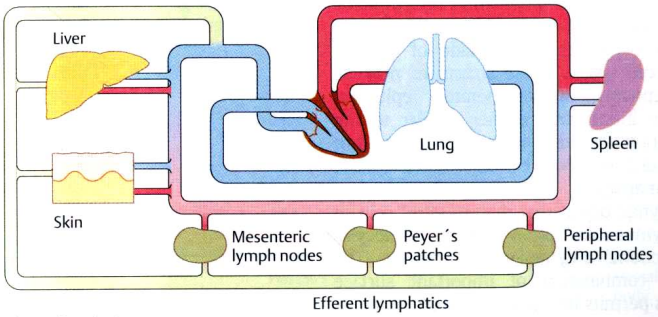
Mucosa-associated lymphoid tissue (MALT) is a collection of lymphatic cells in the submucosal tissue of the gastrointestinal (GI) tract, bronchial tract, urinary tract, and lacrimal glands. Organized lymphoid tissue (e.g., tonsils or Peyer's patches) and a large number of lymphatic cells loosely distributed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

The thymus is the central organ for the differentiation and functional maturation of T lymphocytes. Like the bone marrow and bursa of Fabricius (in birds), it is one of the primary lymphoid organs and is distinguished from secondary lymphoid organs, such as the spleen, lymph nodes, and mucosa-associated lymphoid tissue.

A. Anatomy and Development of the Thymus

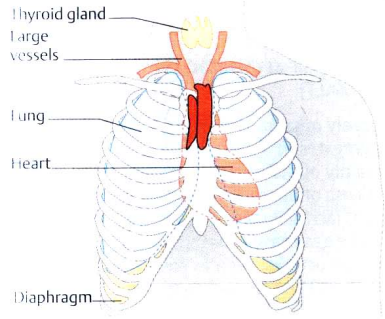
1 In the ontogenic sense, the thymus develops as an outgrowth of the third branchial pouch and later migrates through the anterior mediastinum to its final destination between the sternum and the major vessel trunks. It consists of two lobes that unite cranially to form the horns of the thymus, which sometimes extend to the thyroid gland.

2 The size of the thymus is age-dependent. It reaches a maximum weight of around 40 g around the 10th year of life and then undergoes a continuous process of involution. As a result, the parenchyma of the thymus consists almost entirely of fat and fibrous tissue in old age. Only a few clusters of parenchyma and lymphocytes remain intact (see also paragraphs **3** and **4**). In many cases, it is not possible to reliably differentiate between the involuted organ and the surrounding mediastinal fat by macroscopic means.

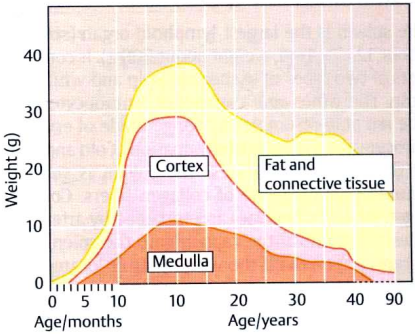
3, 4 Each lobe of the thymus is subdivided by fibrous septa (trabeculae) into smaller lobes, each of which consists of an outer layer (cortex) and an inner layer (medulla). The cortex contains a dense cluster of lymphocytes; the abundance of mitoses is indicative of extensive proliferation. The medulla, on the other hand, has a much smaller population of lymphatic cells. It also contains structures known as Hassall's bodies that are made of densely packed cell layers. These structures may be the remnants of degenerated epithelial cells. An intrathymic barrier similar to the blood–brain barrier divides the cortex from the circulating blood. No such barrier exists for the marrow.

The lymphocytes that mature into T cells in the thymus are often called *thymocytes* for functional and anatomical reasons. The specific combination of important surface markers permits immunophenotypic differentiation between thymocytes and mature T cells. Thymocytes are extremely cortisone-sensitive in the early stages of development (important for maturation studies), but as the process of differentiation continues, they become more and more cortisone-resistant. The cortisone-sensitive, immature thymocytes are located mainly in the cortex, and the cortisone-insensitive ones are mainly localized in the medulla.

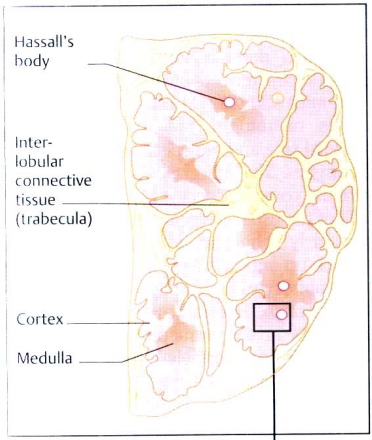
5 Apart from lymphocytes and Hassall's bodies, the thymus also contains epithelial cells with a large cytoplasm and dendritic cells and macrophages (the latter cell groups are not shown in the illustration). Moreover, the thymus contains a large number of blood vessels and efferent lymphoid tissues that drain into the mediastinal lymph nodes.



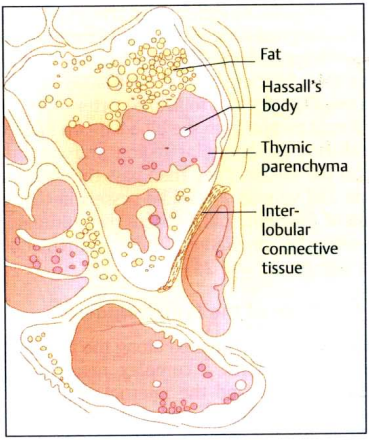
1. Position of the thymus



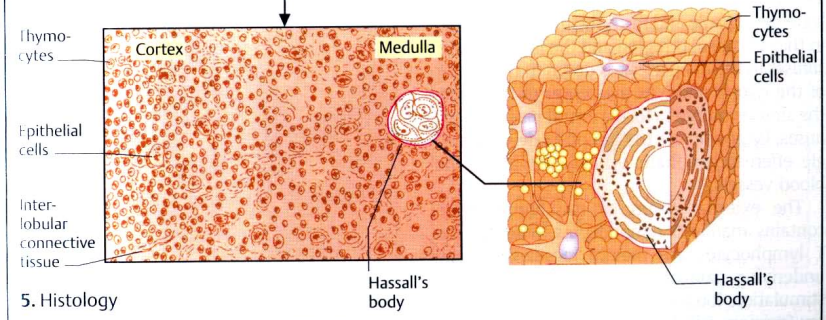
2. Growth curve



3. Thymus of a newborn



4. Thymus of an adult



5. Histology

A. Anatomy and development of the thymus