

GS

THE IMMUNE SYSTEM
PETER PARHAM
FOURTH EDITION

Immunology Core Issues 免疫學的核心議題

PART I. GENERAL TOPICS

- 1. Properties of Immunity and Biodefense Mechanism**
- 2. Factors, Cells and Organs of Immune System**
- 3. Immune Response and Regulation Network**
- 4. Hematopoietic Tree and Lymphocytes Anatomy**

PART II. CELLULAR AND MOLECULAR TOPICS

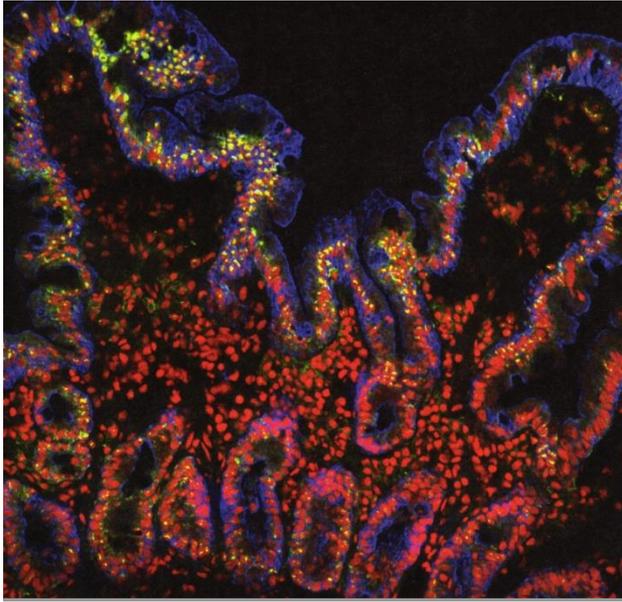
- 5. MHC, Recognizing Molecules and Transplantation**
- 6. T Cell Receptor, Maturation and Selection**
- 7. B Cell Maturation and Clonal Selection**
- 8. Genetics in Antibody Production**
- 9. Immunogenicity involved to Antigen Discrimination**
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PART III. MECHANISM FOR HUMORAL

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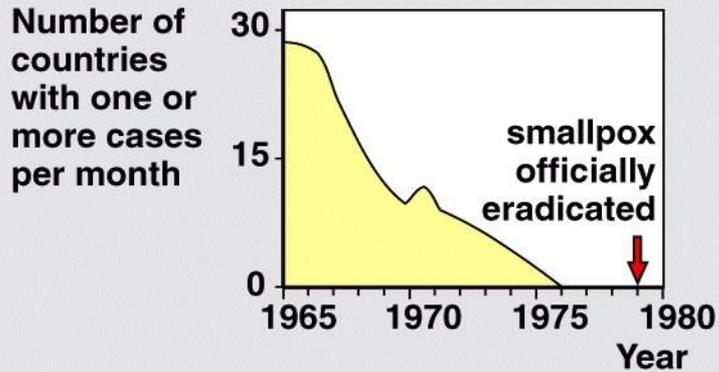
- 15. Infection and Vaccination**
- 16. Tolerance, Allergy and Hypersensitivity**
- 17. Immunity to Tumor**
- 18. Autoimmunity**
- 19. Congenital and Acquired Immunodeficiency**



Chapter **1**

Elements of the Immune System and their Roles in Defense

The small intestine is the major site in the human body that interacts with microorganisms



天花病毒

Figure 1.1 The eradication of smallpox by vaccination. Upper panel: smallpox vaccination was started in 1796. In 1979, after 3 years in which no case of smallpox was recorded, the World Health Organization announced that the virus had been eradicated. Since then the proportion of the human population that has been vaccinated against smallpox, or has acquired immunity from an infection, has steadily decreased. The result is that the human population has become increasingly vulnerable should the virus emerge again, either naturally or as a deliberate act of human malevolence. Lower panel: photograph of a child with smallpox and his immune mother. The distinctive rash of smallpox appears about 2 weeks after exposure to the virus. Photograph courtesy of the World Health Organization.



Dr. Edward Jenner 1796



接種年齡

接種疫苗種類

出生24小時內	B型肝炎免疫球蛋白	一劑
出生24小時後	卡介苗	一劑
出生滿3~5天	B型肝炎遺傳工程疫苗	第一劑
出生滿1個月	B型肝炎遺傳工程疫苗	第二劑
出生滿2個月	白喉百日咳破傷風混合疫苗 DPT	第一劑
	小兒麻痺口服疫苗	第一劑
出生滿4個月	白喉百日咳破傷風混合疫苗	第二劑
	小兒麻痺口服疫苗	第二劑
	B型肝炎遺傳工程疫苗	第三劑
出生滿6個月	白喉百日咳破傷風混合疫苗	第三劑
	小兒麻痺口服疫苗	第三劑
出生滿9個月	麻疹疫苗	一劑
	麻疹腮腺炎德國麻疹混合疫苗	一劑
滿1年3個月	日本腦炎疫苗	第一劑
	日本腦炎疫苗 (每年3月至5月接種)	隔二週 第二劑
滿1年6個月	白喉百日咳破傷風混合疫苗	追加
	小兒麻痺口服疫苗	追加
滿2年3個月	日本腦炎疫苗	第三劑
	破傷風減量白喉混合疫苗	追加
國小 1 年級	小兒麻痺口服疫苗	追加
	日本腦炎疫苗	追加

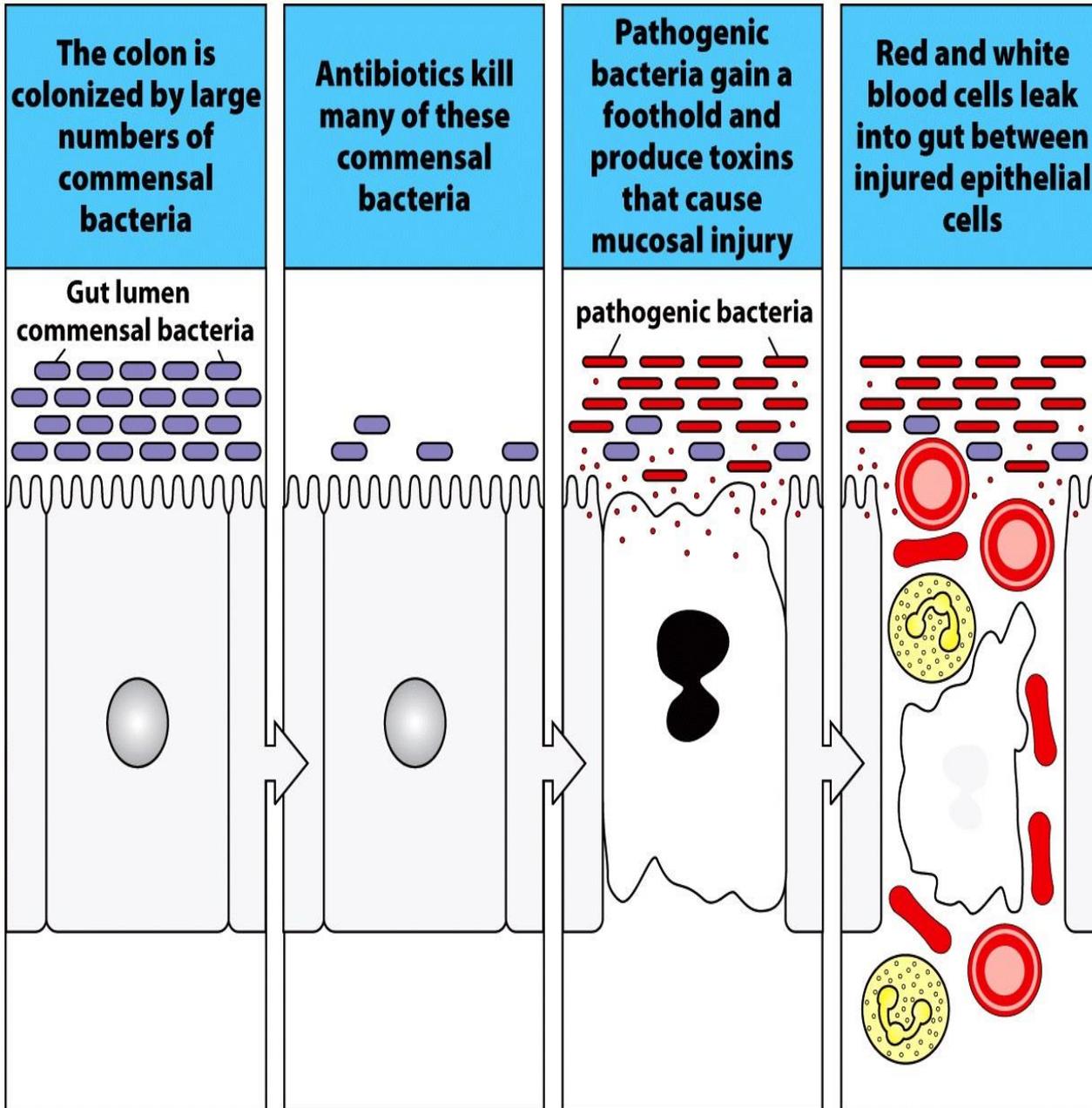


Figure 1.2 Antibiotic treatments disrupt the natural ecology of the colon. When antibiotics are taken orally to counter a bacterial infection, beneficial populations of commensal bacteria in the colon are also decimated. This provides an opportunity for pathogenic strains of bacteria to populate the colon and cause further disease. *Clostridium difficile* is an example of such a bacterium; it produces a toxin that can cause severe diarrhea in patients treated with antibiotics. In hospitals, acquired *C. difficile* infections are an increasing cause of death for elderly patients.

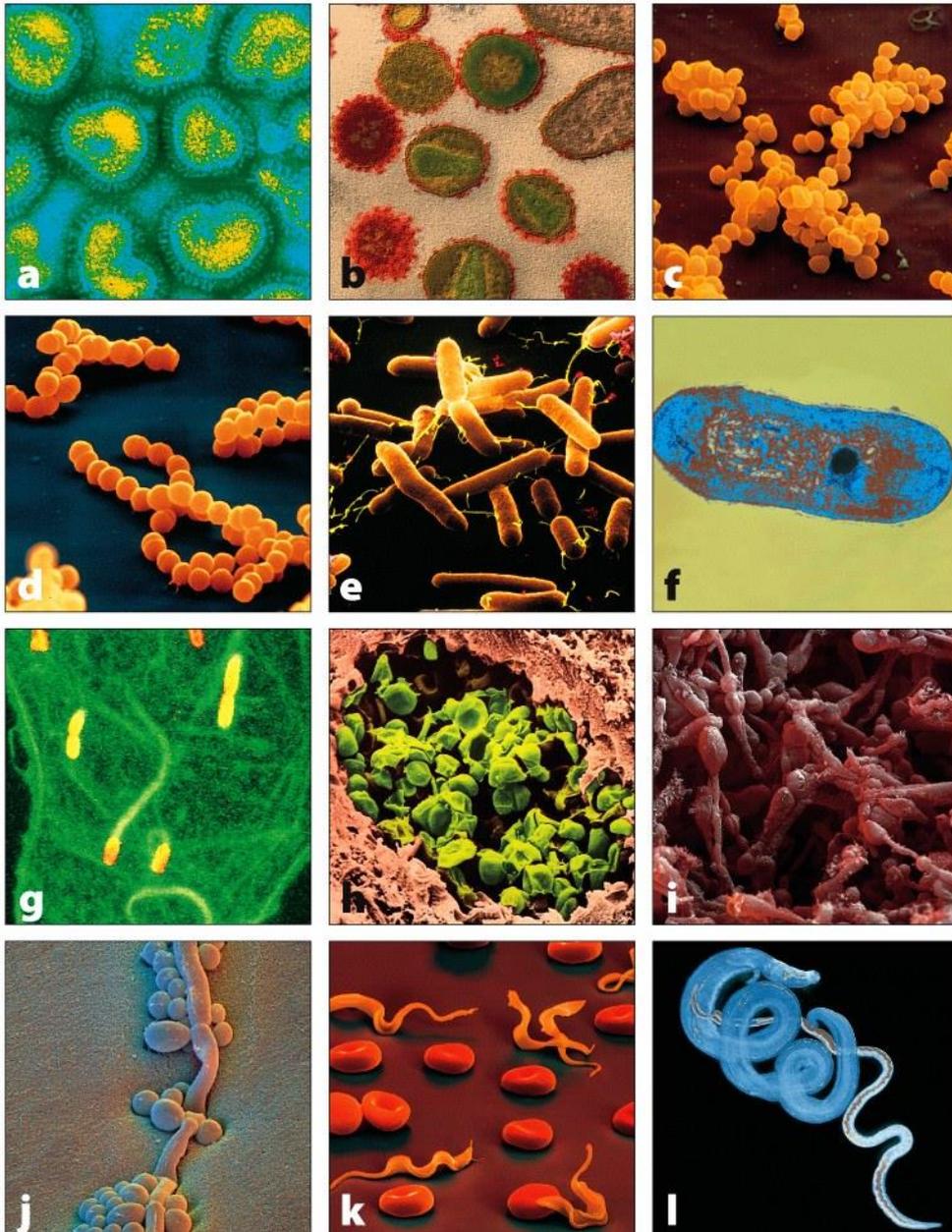
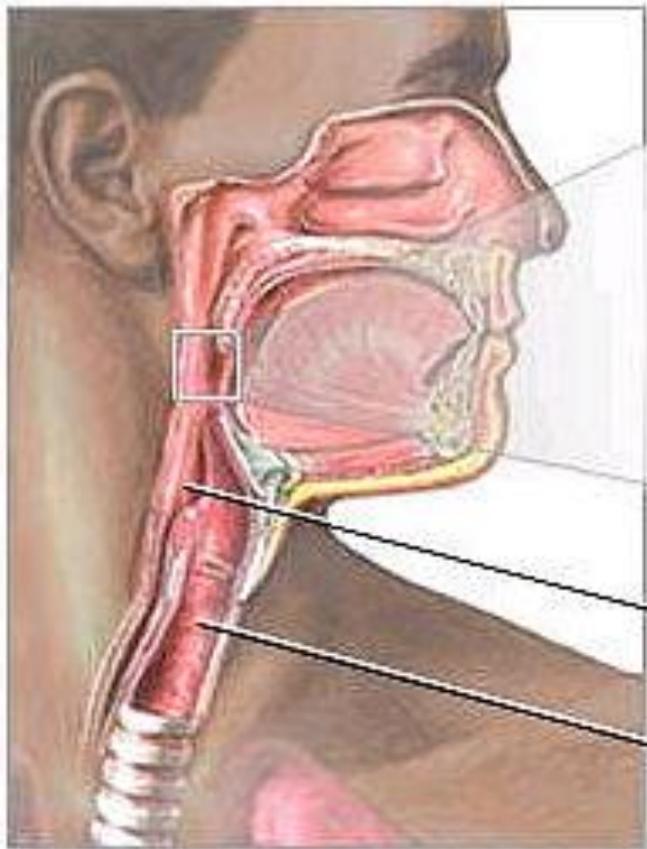


Figure 1.3 The diversity of microorganisms that are human pathogens.

Type	Disease	Pathogen	General classification*	Route of infection
Viruses	Severe acute respiratory syndrome	SARS virus	Coronaviruses	Oral/respiratory/ocular mucosa
	West Nile encephalitis	West Nile virus	Flaviviruses	Bite of an infected mosquito
	Yellow fever	Yellow fever virus	Flaviviruses	Bite of infected mosquito (<i>Aedes aegypti</i>)
	Hepatitis B	Hepatitis B virus	Hepadnaviruses	Sexual transmission; infected blood
	Chickenpox	Varicella-zoster 水痘	Herpes viruses	Oral/respiratory
	Mononucleosis	Epstein-Barr virus	Herpes viruses	Oral/respiratory
	Influenza	Influenza virus	Orthomyxoviruses	Oral/respiratory
	Measles	Measles virus 麻疹	Paramyxoviruses	Oral/respiratory
	Mumps	Mumps virus	Paramyxoviruses	Oral/respiratory
	Poliomyelitis	Polio virus	Picornaviruses	Oral
	Jaundice	Hepatitis A virus	Picornaviruses	Oral
	Smallpox	Variola 天花	Pox viruses	Oral/respiratory
	AIDS	Human immunodeficiency virus	Retroviruses	Sexual transmission, infected blood
	Rabies	Rabies virus	Rhabdoviruses	Bite of an infected animal
	Common cold	Rhinoviruses	Rhinoviruses	Nasal
Diarrhea	Rotavirus	Rotaviruses	Oral	
Rubella	Rubella	Togaviruses	Oral/respiratory	

Figure 1.4

Candida (yeast) infecting esophagus



Esophagus

Trachea

念珠菌病

Candidiasis





結核分枝桿菌

Mycobacterium tuberculosis



Leprosy 麻風

Mycobacterium leprae

Type	Disease	Pathogen	General classification*	Route of infection
Bacteria	Trachoma 沙眼	<i>Chlamydia trachomatis</i>	Chlamydias	Oral/respiratory/ocular mucosa
	Bacillary dysentery	<i>Shigella flexneri</i> 細菌性痢疾	Gram-negative bacilli	Oral
	Food poisoning	<i>Salmonella enteritidis, S. typhimurium</i>	Gram-negative bacilli	Oral
	Plague 鼠疫	<i>Yersinia pestis</i>	Gram-negative bacilli	Infected flea bite, respiratory
	Tularemia	<i>Pasteurella tularensis</i>	Gram-negative bacilli	Handling infected animals
	Typhoid fever 傷寒	<i>Salmonella typhi</i>	Gram-negative bacilli	Oral
	Gonorrhoea 淋病	<i>Neisseria gonorrhoeae</i>	Gram-negative cocci	Sexually transmitted
	Meningococcal meningitis	<i>Neisseria meningitidis</i>	Gram-negative cocci	Oral/respiratory
	Meningitis, pneumonia	<i>Haemophilus influenzae</i>	Gram-negative coccobacilli	Oral/respiratory
	Legionnaire's disease	<i>Legionella pneumophila</i>	Gram-negative coccobacilli	Inhalation of contaminated aerosol
	Whooping cough	<i>Bordetella pertussis</i>	Gram-negative coccobacilli	Oral/respiratory
	Cholera	<i>Vibrio cholerae</i>	Gram-negative vibrios	Oral
	Anthrax	<i>Bacillus anthracis</i>	Gram-positive bacilli	Oral/respiratory by contact with spores
	Diphtheria	<i>Corynebacterium diphtheriae</i>	Gram-positive bacilli	Oral/respiratory
	Tetanus	<i>Clostridium tetani</i>	Gram-positive bacilli (anaerobic)	Infected wound
	Boils, wound infections	<i>Staphylococcus aureus</i>	Gram-positive cocci	Wounds; oral/respiratory
	Pneumonia, scarlet fever	<i>Streptococcus pneumoniae</i>	Gram-positive cocci	Oral/respiratory
	Tonsillitis 扁桃腺炎	<i>Streptococcus pyogenes</i>	Gram-positive cocci	Oral/respiratory
	Leprosy	<i>Mycobacterium leprae</i>	Mycobacteria	Infected respiratory droplets
	Tuberculosis	<i>Mycobacterium tuberculosis</i>	Mycobacteria	Oral/respiratory
Respiratory disease	<i>Mycoplasma pneumoniae</i>	Mycoplasmas	Oral/respiratory	
Typhus 恙蟲斑疹傷寒	<i>Rickettsia prowazekii</i>	Rickettsias	Bite of infected tick	
Lyme disease 蟲萊姆	<i>Borrelia burgdorferi</i>	Spirochetes	Bite of infected deer tick	
Syphilis 梅毒	<i>Treponema pallidum</i>	Spirochetes	Sexual transmission	

Figure 1.4



dermatophytes

fungal dermatitis



TINEA CAPITIS

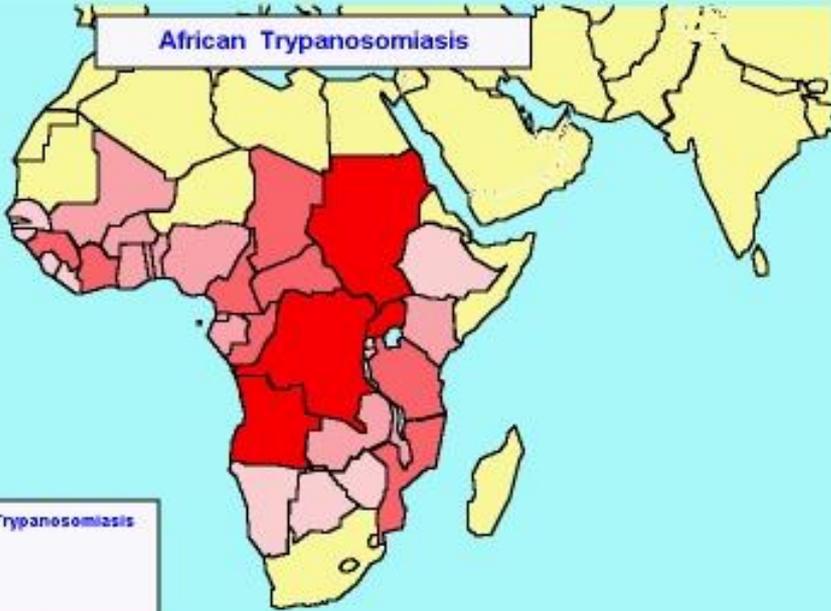
Tinea Pedis (Athlete's Foot)

Type	Disease	Pathogen	General classification*	Route of infection
Fungi	Aspergillosis	<i>Aspergillus</i> species	Ascomycetes	Opportunistic pathogen, inhalation of spores
	Athlete's foot	<i>Tinea pedis</i>	Ascomycetes	Physical contact
	Candidiasis, thrush	<i>Candida albicans</i>	Ascomycetes (yeasts)	Opportunistic pathogen, resident flora
	Pneumonia	<i>Pneumocystis carinii</i>	Ascomycetes	Opportunistic pathogen, resident lung flora
Protozoan parasites	Leishmaniasis	<i>Leishmania major</i>	Protozoa	Bite of an infected sand fly
	Malaria 瘧疾	<i>Plasmodium falciparum</i>	Protozoa	Bite of an infected mosquito
	Toxoplasmosis	<i>Toxoplasma gondii</i>	Protozoa	Oral, from infected material
	Trypanosomiasis	<i>Trypanosoma brucei</i>	Protozoa	Bite of an infected tsetse fly
Helminth parasites (worms)	Common roundworm	<i>Ascaris lumbricoides</i>	Nematodes (roundworms)	Oral, from infected material
	Schistosomiasis 血吸蟲病	<i>Schistosoma mansoni</i>	Trematodes	Through skin by bathing in infected water

Figure 1.4 (opposite page and above) Diverse microorganisms cause human disease. Pathogenic organisms are of four main types—viruses, bacteria, fungi, and parasites, which are mostly protozoans or worms. Some important pathogens in each category are listed along with the diseases they cause. *The classifications given are intended as a guide only

and are not taxonomically consistent; families are given for the viruses; general groupings often used in medical bacteriology for the bacteria; and higher taxonomic divisions for the fungi and parasites. The terms Gram-negative and Gram-positive refer to the staining properties of the bacteria; Gram-positive bacteria stain purple with the Gram stain, Gram-negative bacteria do not.

African Trypanosomiasis



Human African Trypanosomiasis

- Epidemic
- High Endemic
- Endemic
- At risk

ETD/WHO, Oct. 1997



采采蝇
tsetse fly

Trypanosomiasis



Warble Fly

牛皮蠅





**DISABLED BY
DARE Rugby player, 19,
left paralysed.**

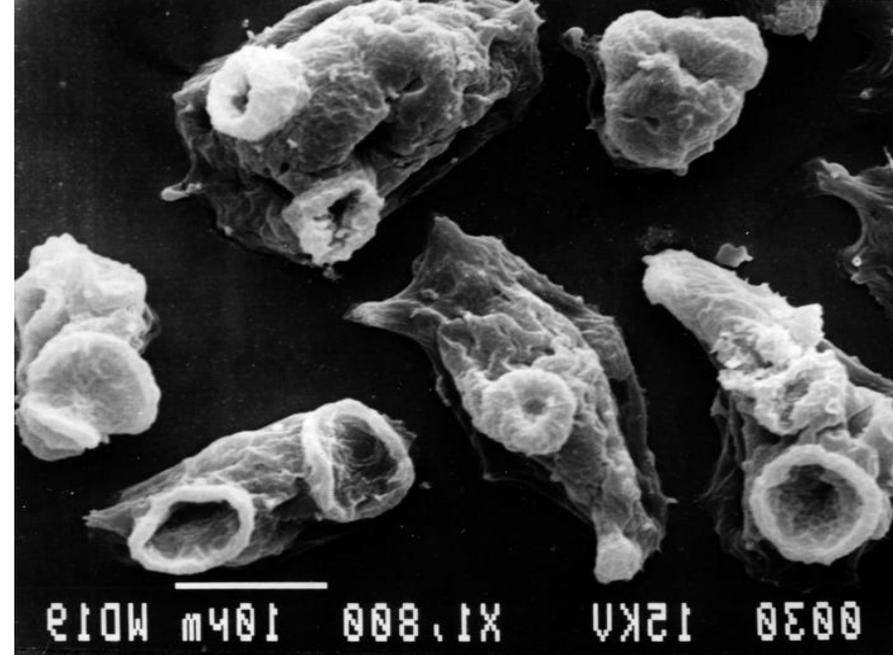
Sydney, Australia

**eosinophilic meningo-
encephalitis 蛞蝓**

After swallowing the slug,
found to be infected with rat
lungworm. 廣東住血線蟲

Sam, with mother Katie, now
needs 24/7 care and the family
are in debt.





Naegleria fowleri
福氏內格里蟲
brain-eating amoeba

台灣在2013年發生首起
因福氏阿米巴而喪命的案
例，患者是75歲的健康
男性，因泡溫泉入鼻腔

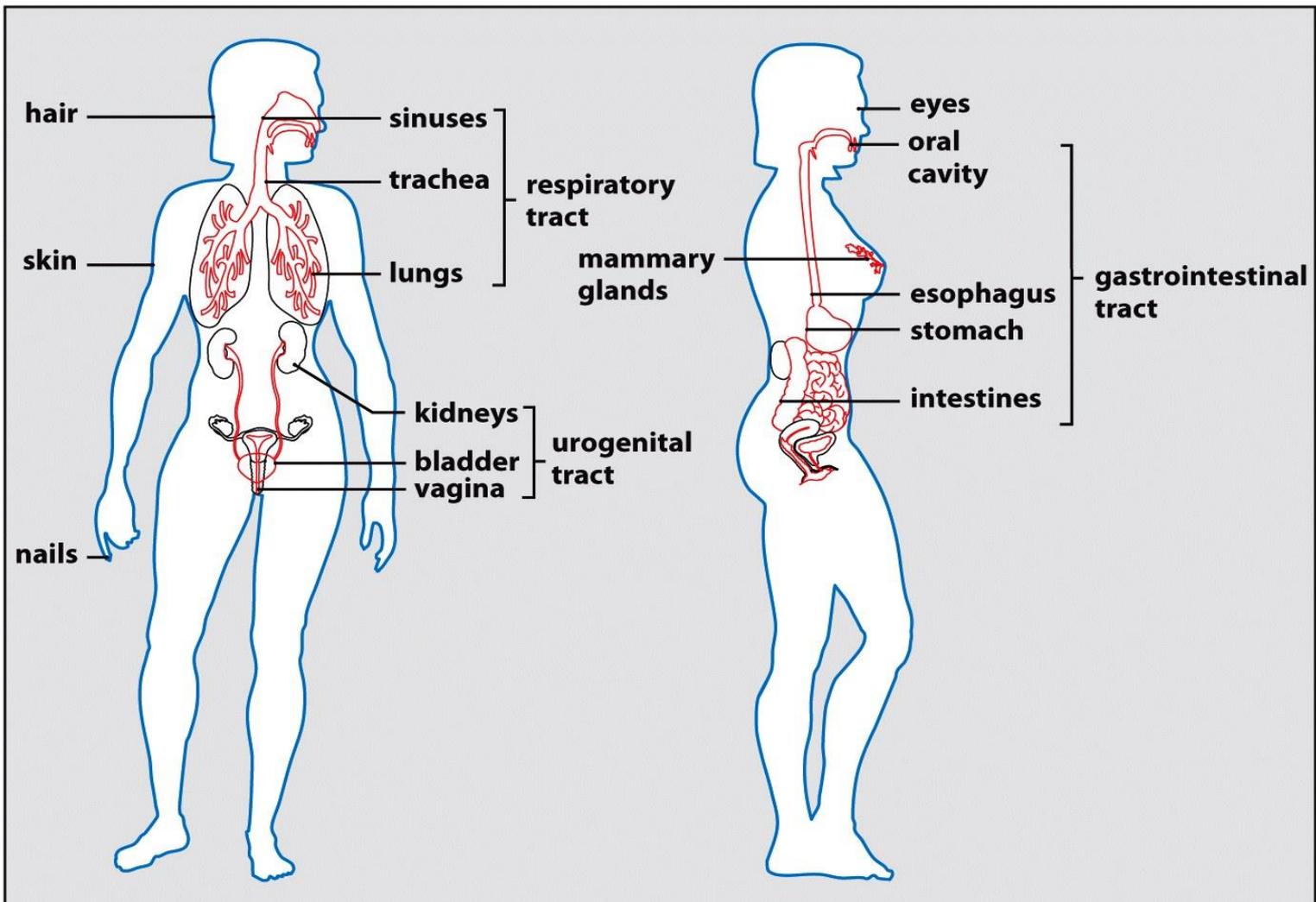
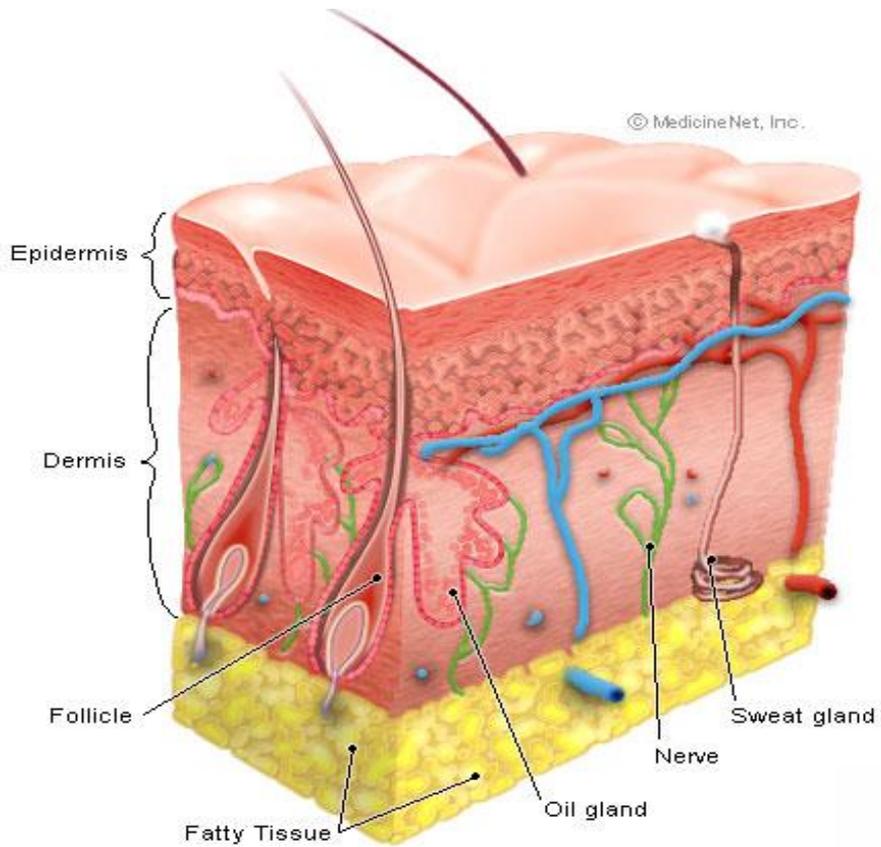
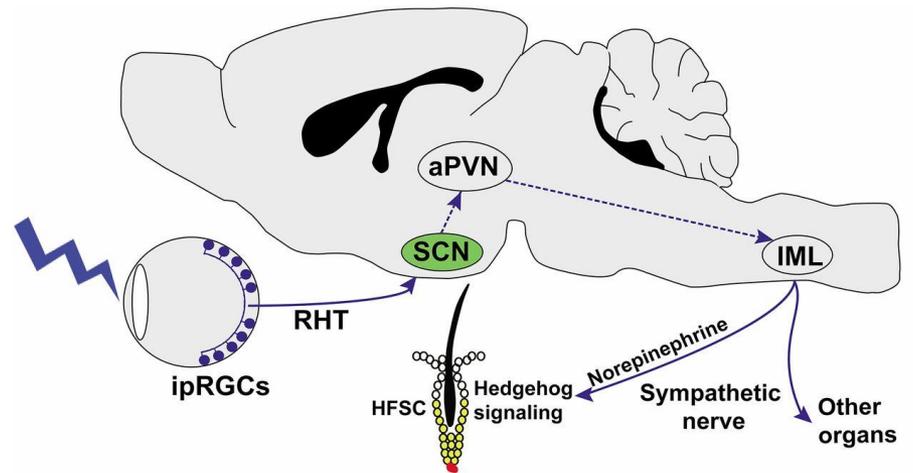
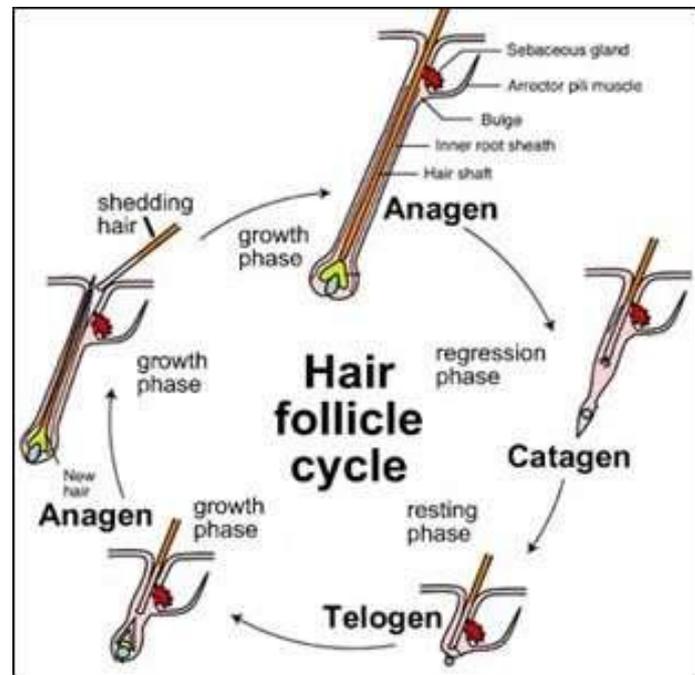


Figure 1.5 The physical barriers that separate the body from its external environment. In these images of a woman, the strong barriers to infection provided by the skin, hair, and nails are colored blue and the more vulnerable mucosal membranes are colored red.



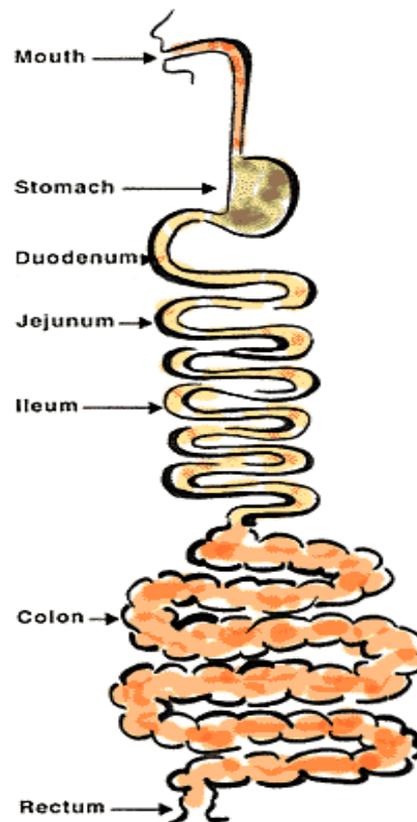
Normal Skin

alopecia





microbiome



helicobacter pylori

LACTOSE DIGESTION

IMMUNOMODULATION

REGULATION OF
PROCARCINOGENIC
ENZYMATIC
ACTIVITY

TRANSIT REGULATION

IMMUNOMODULATION

糞腸球菌

(*Enterococcus faecalis*)

屎腸球菌

(*Enterococcus faecium*)

Phylum	BMI category			
	<18.5	18.5-24.9	25-29.9	≥30
Actinobacteria	5 (3-6)	6 (4-9)	6 (3.5-8)	6 (4-11)
Firmicutes	35 (22-37)	32 (29-43)	48 (33-56)	52 (36-56)
Bacteroidetes	47 (35-54)	42 (34-46)	38 (29-47)	33 (25-38)
F/B	0.7 (0.6-0.7)	0.8 (0.7-1.0)	1.3 (0.7-2.0)	1.6 (1.1-2.2)

	Skin	Gastrointestinal tract	Respiratory tract	Urogenital tract	Eyes
Mechanical	Epithelial cells joined by tight junctions				
	Flow of fluid, perspiration, sloughing off of skin	Flow of fluid, mucus, food, and saliva	Flow of fluid and mucus, e.g., by cilia Air flow	Flow of fluid, urine, mucus, sperm	Flow of fluid, tears
Chemical	Sebum (fatty acids, lactic acid, lysozyme)	Acidity, enzymes (proteases)	Lysozyme in nasal secretions	Acidity in vaginal secretions Spermine and zinc in semen	Lysozyme in tears
	Antimicrobial peptides (defensins)				
Microbiological	Normal flora of the skin	Normal flora of the gastrointestinal tract	Normal flora of the respiratory tract	Normal flora of the urogenital tract	Normal flora of the eyes

Figure 1.6 Various barriers prevent bacteria from crossing epithelia and colonizing tissues. Surface epithelia provide mechanical, chemical, and microbiological barriers to infection.

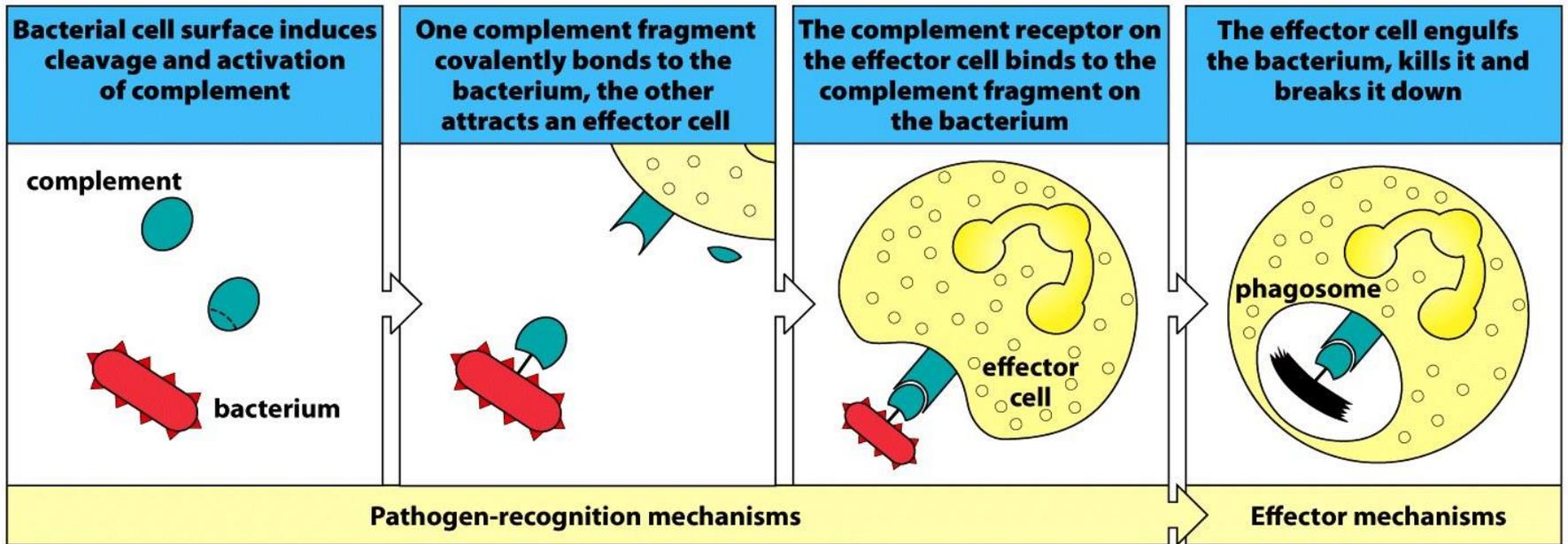


Figure 1.7 Immune defense involves recognition of pathogens followed by their destruction.

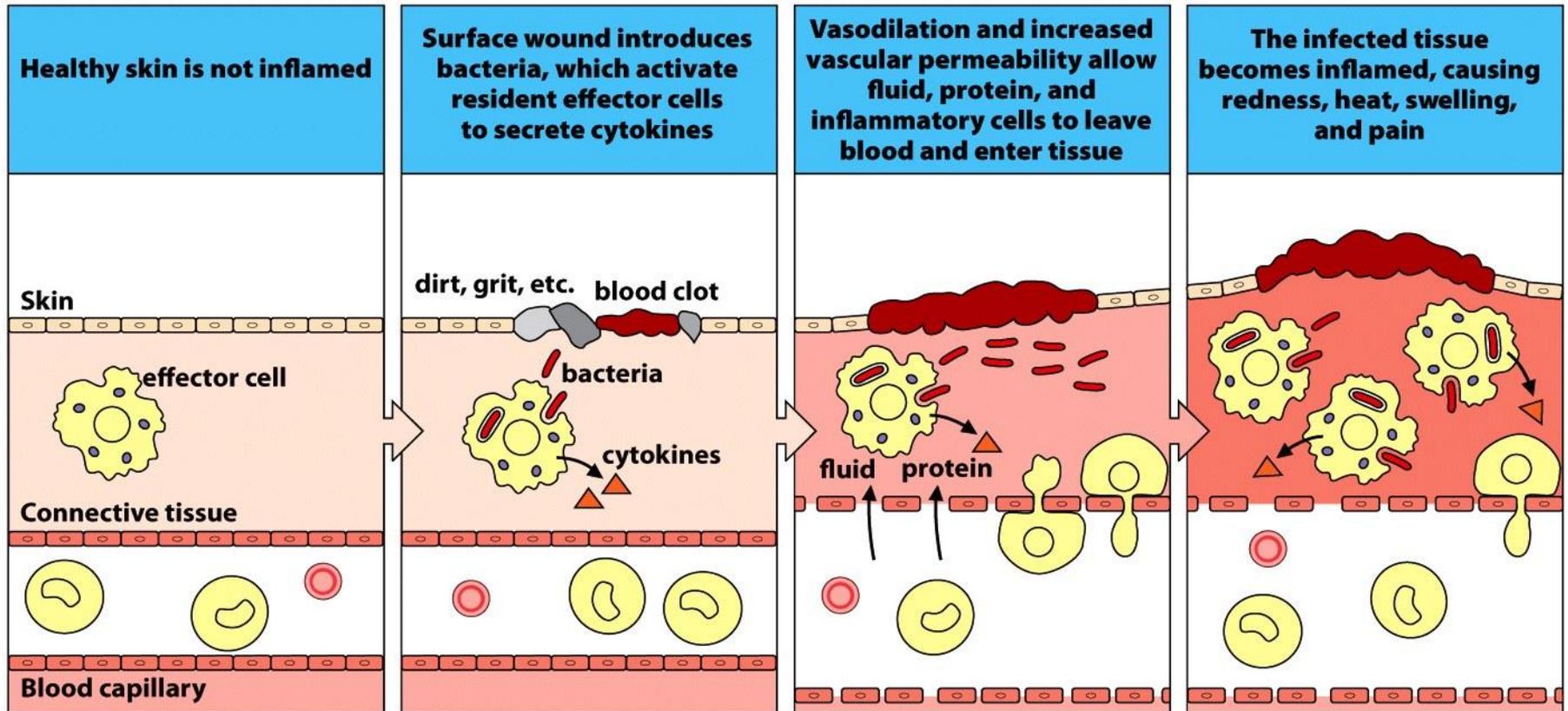


Figure 1.8 Innate immune mechanisms establish a state of inflammation at sites of infection.

Illustrated here are the events following an abrasion of the skin. Bacteria invade the underlying connective tissue and stimulate the innate immune response.

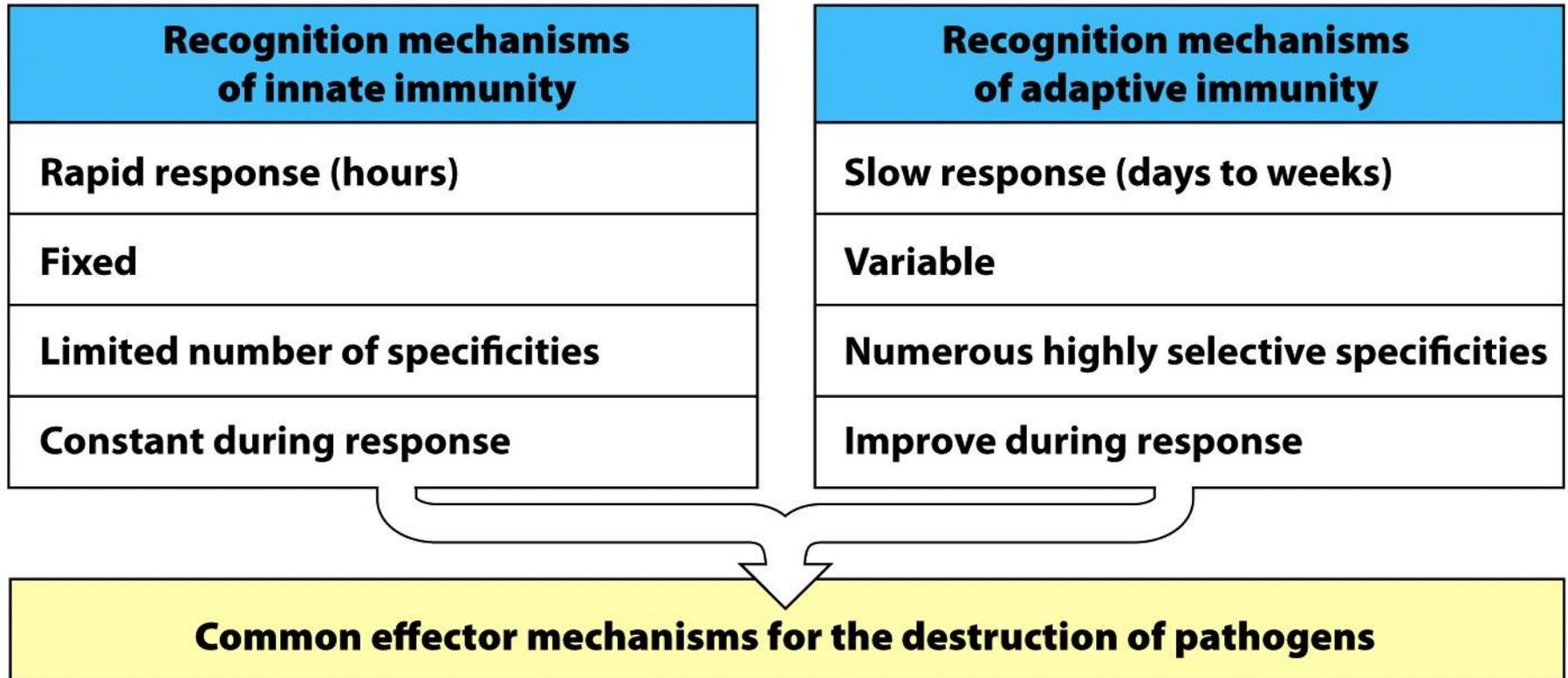


Figure 1.9 The principal characteristics of innate and adaptive immunity.

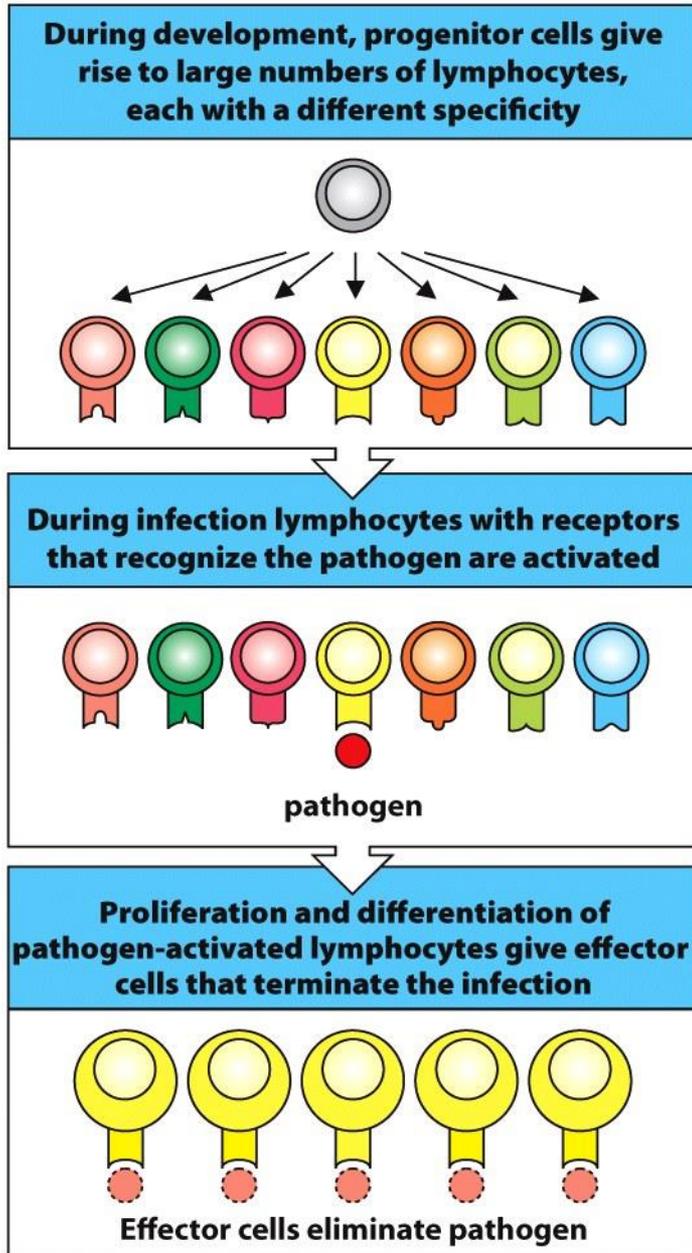


Figure 1.10 Selection of lymphocytes by a pathogen. Top panel: during its development from a progenitor cell (gray) a lymphocyte is programmed to make a single species of cell-surface receptor that recognizes a particular molecular structure. Each lymphocyte makes a receptor of different specificity, so that the population of circulating lymphocytes includes many millions of such receptors, all recognizing different structures, which enables all possible pathogens to be recognized. Lymphocytes with different receptor specificities are represented by different colors. Center panel: upon infection by a particular pathogen, only a small subset of lymphocytes (represented by the yellow cell) will have receptors that bind to the pathogen or its components. Bottom panel: these lymphocytes are stimulated to divide and differentiate, thereby producing an expanded population of effector cells from each pathogen-binding lymphocyte.

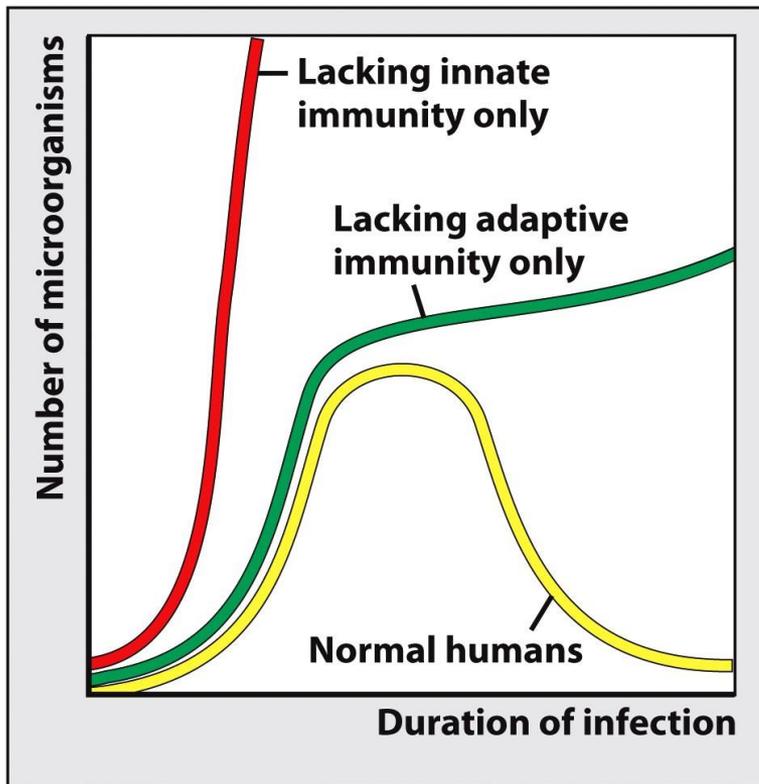


Figure 1.11 The benefits of having both innate and adaptive immunity. In normal individuals, a primary infection is cleared from the body by the combined effects of innate and adaptive immunity (yellow line). In a person who lacks innate immunity, uncontrolled infection occurs because the adaptive immune response cannot be deployed without the preceding innate response (red line). In a person who lacks adaptive immune responses, the infection is initially contained by innate immunity but cannot be cleared from the body (green line).

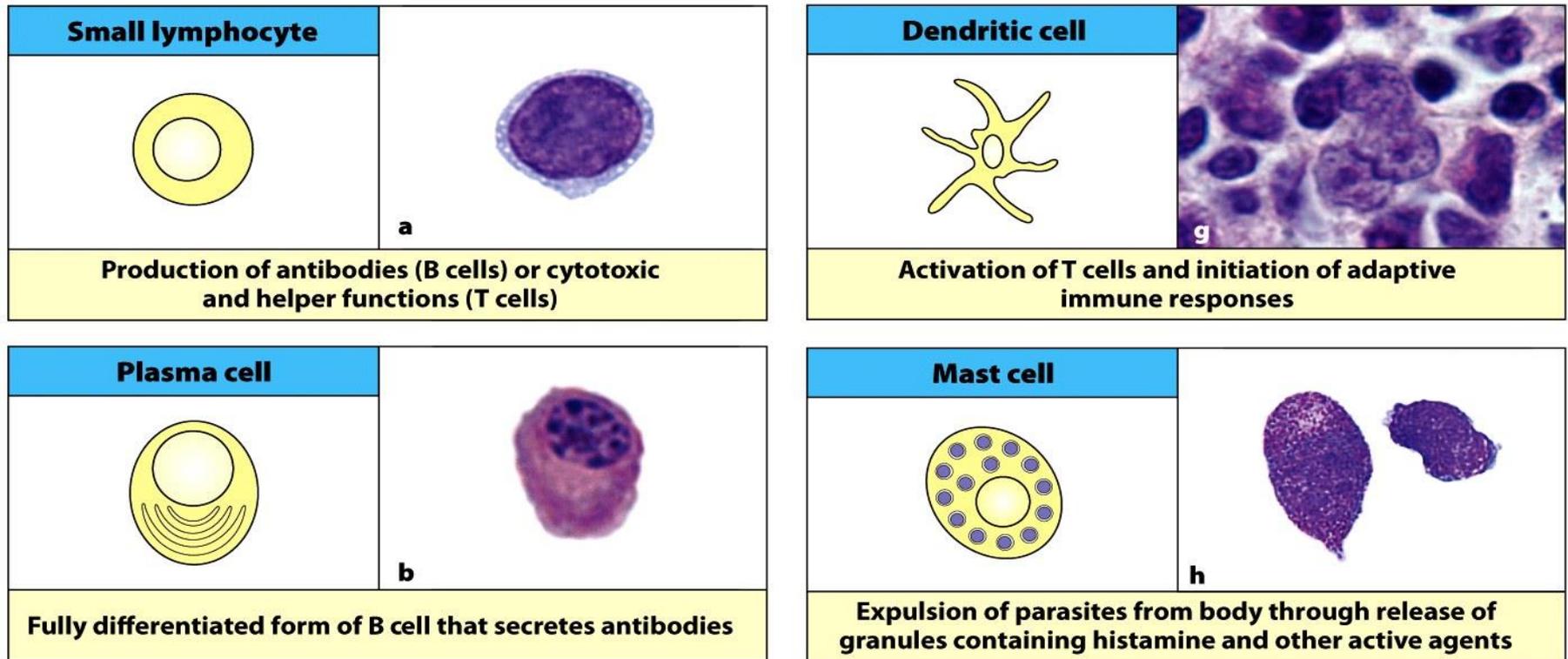


Figure 1.12 (opposite page) Types of hematopoietic cell. The different types of hematopoietic cell are depicted in schematic diagrams, which indicate their characteristic morphological features, and in accompanying light micrographs. Their main functions are indicated. We shall use these schematic representations for these cells throughout the book. Megakaryocytes (k) reside in bone marrow and release tiny non-nucleated, membrane-bound packets of cytoplasm, which circulate in the blood and are known as platelets. Red blood cells (erythrocytes) (l) are smaller than the white blood cells and have no nucleus. Original magnification $\times 15,000$. Photographs courtesy of Yasodha Natkunam.

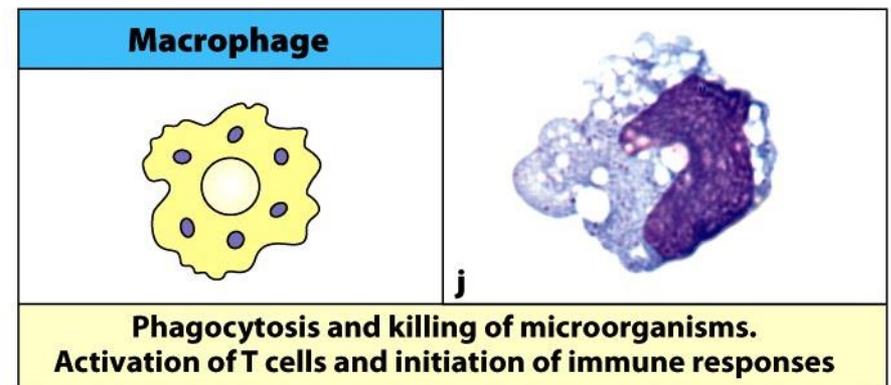
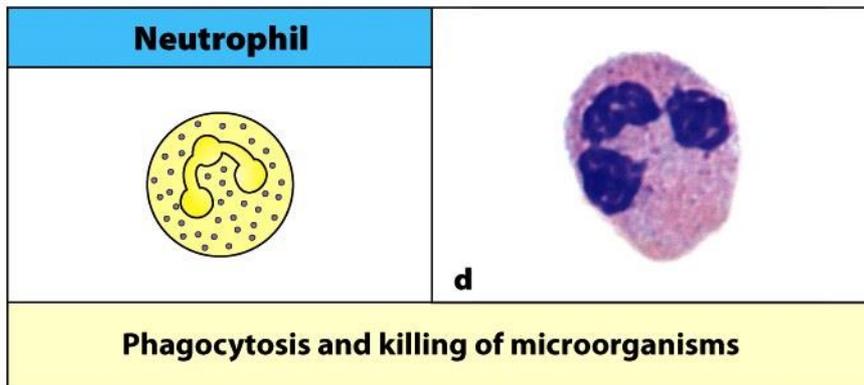
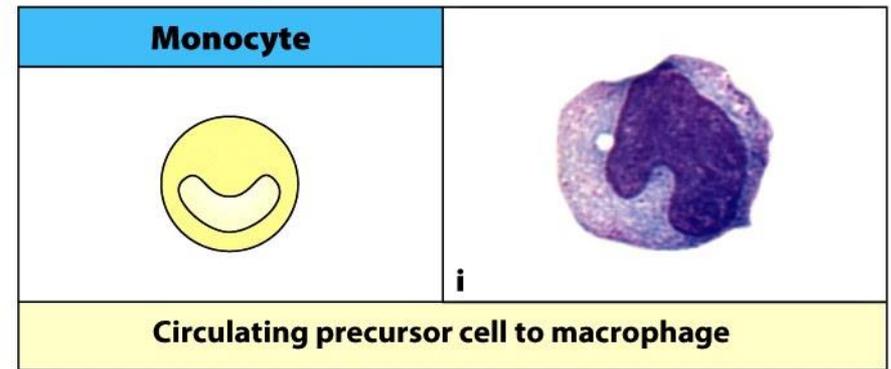
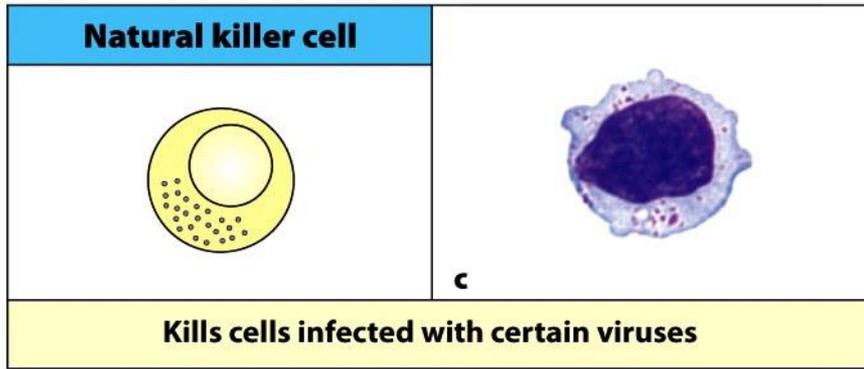


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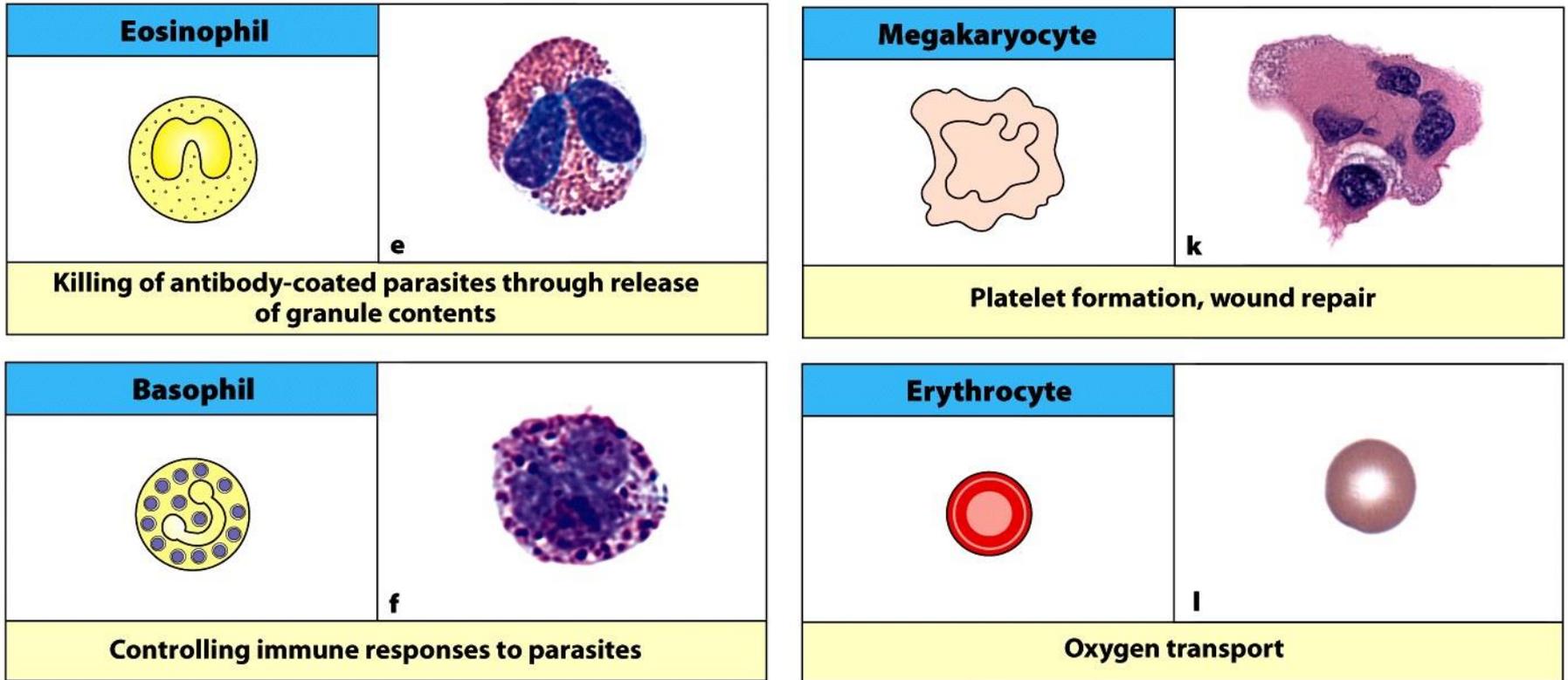


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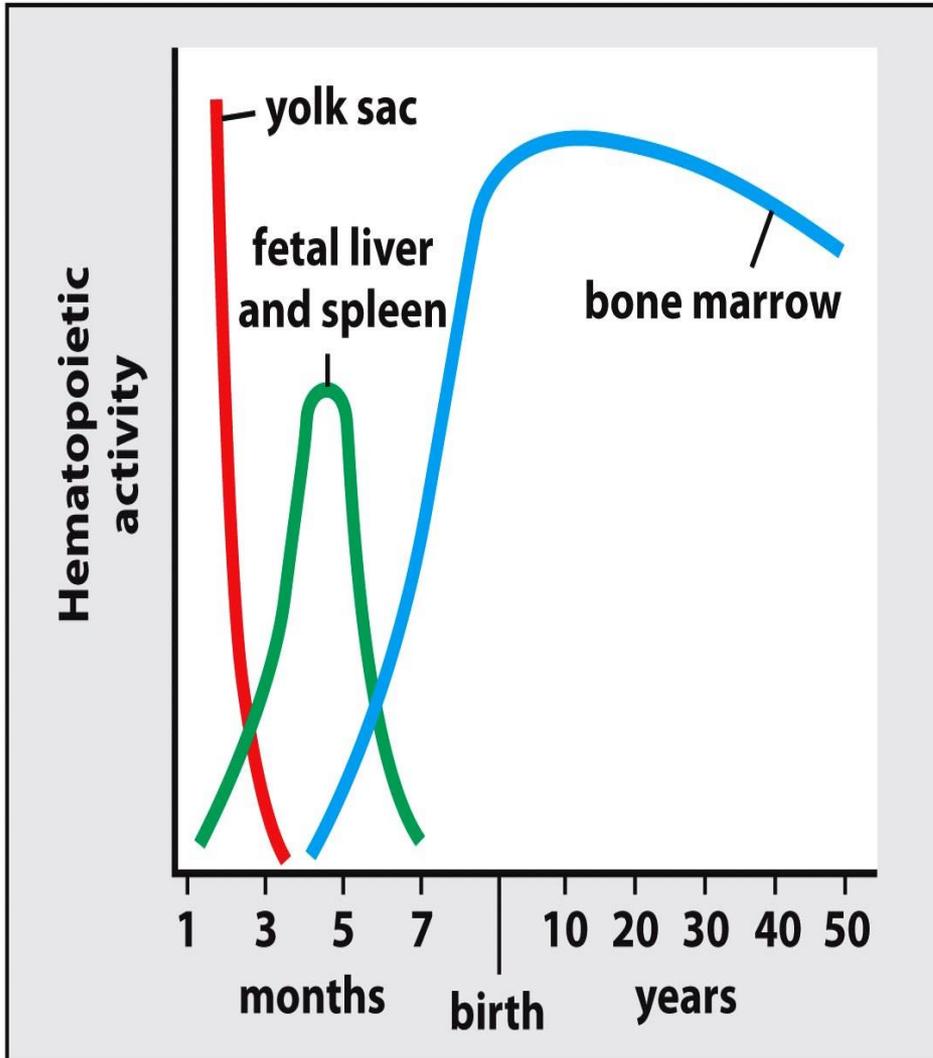


Figure 1.13 The site of hematopoiesis in humans changes during development. Blood cells are first made in the yolk sac of the embryo and subsequently in the embryonic liver. They start to be made in the bone marrow before birth, and by the time of birth this is the only tissue in which hematopoiesis occurs.

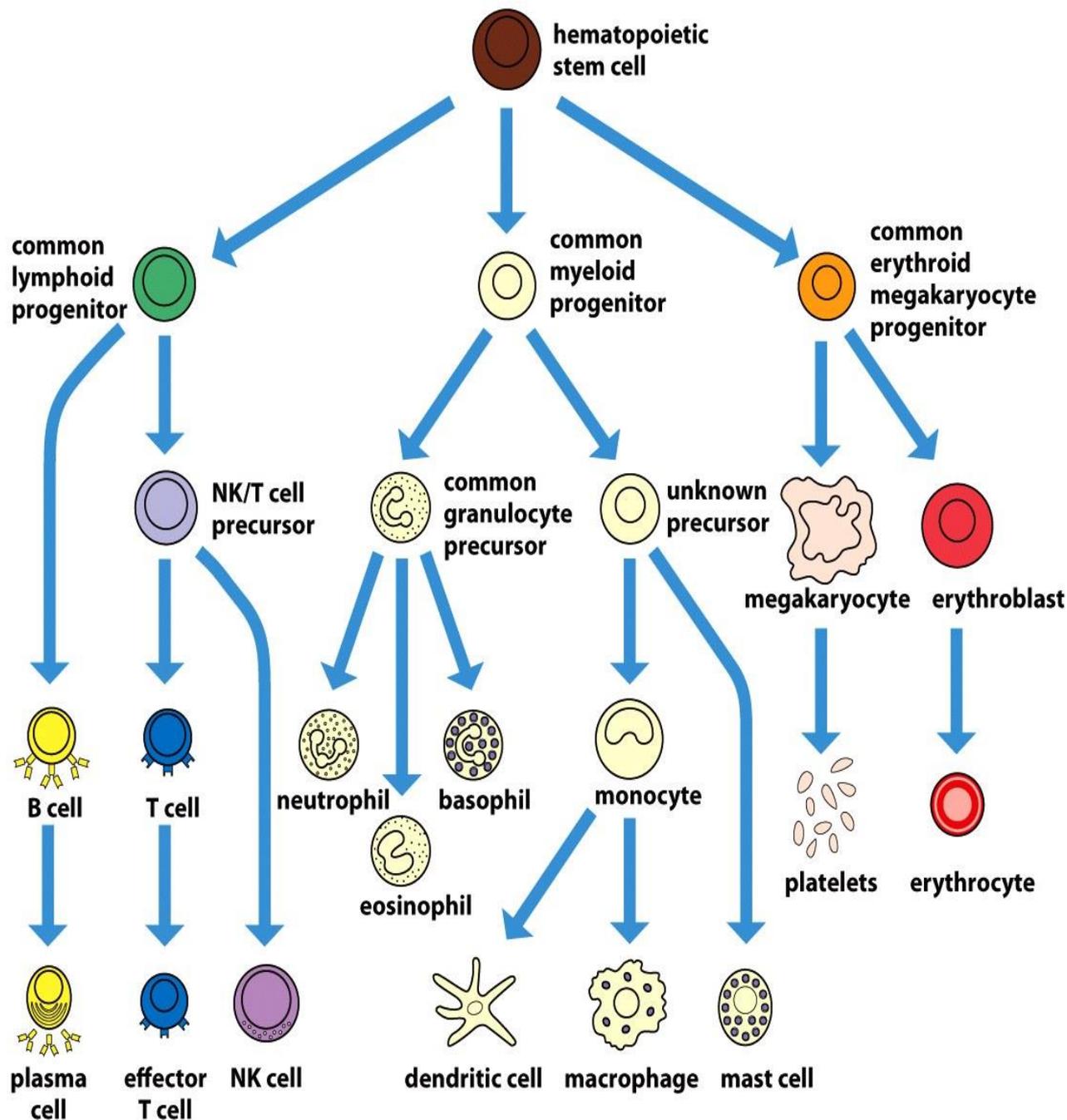
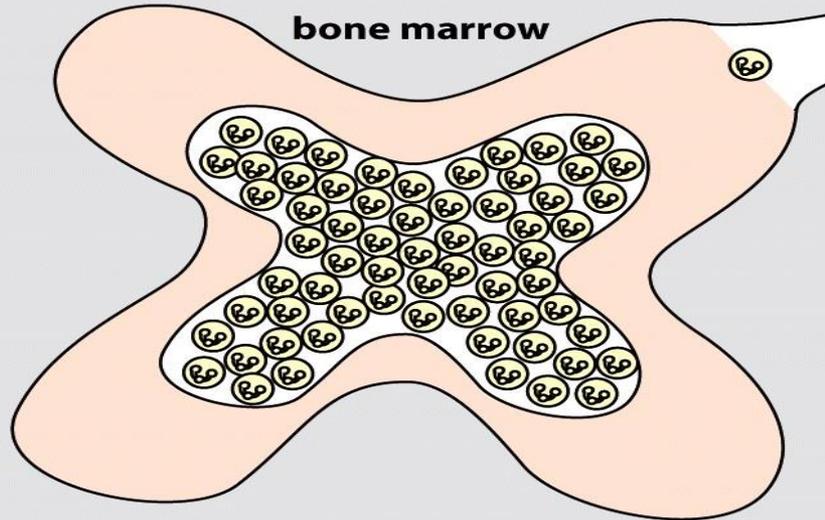


Figure 1.14 Blood cells and certain tissue cells derive from a common hematopoietic stem cell. The pluripotent stem cell (brown) divides and differentiates into more specialized progenitor cells that give rise to the lymphoid lineage, the myeloid lineage, and the erythroid lineage. The common lymphoid progenitor divides and differentiates to give B cells (yellow), T cells (blue), and NK cells (purple). On activation by infection, B cells divide and differentiate into plasma cells, whereas T cells differentiate into various types of effector T cell. The myeloid progenitor cell divides and differentiates to produce at least six cell types. These are: the three types of granulocyte—the neutrophil, the eosinophil, and the basophil; the mast cell, which takes up residence in connective and mucosal tissues; the circulating monocyte, which gives rise to the macrophages resident in tissues; and the dendritic cell. The word myeloid means ‘of the bone marrow.’

Cell type	Proportion of leukocytes (%)
Neutrophil	40–75
Eosinophil	1–6
Basophil	<1
Monocyte	2–10
Lymphocyte	20–50

Figure 1.15 The relative abundance of the leukocyte cell types in human peripheral blood. The values given for each cell type are the normal ranges found in venous blood taken from healthy donors.

Large reserves of neutrophils are stored in the bone marrow and are released when needed to fight infection



Neutrophils travel to and enter the infected tissue, where they engulf and kill bacteria. The neutrophils die in the tissue and are engulfed and degraded by macrophages

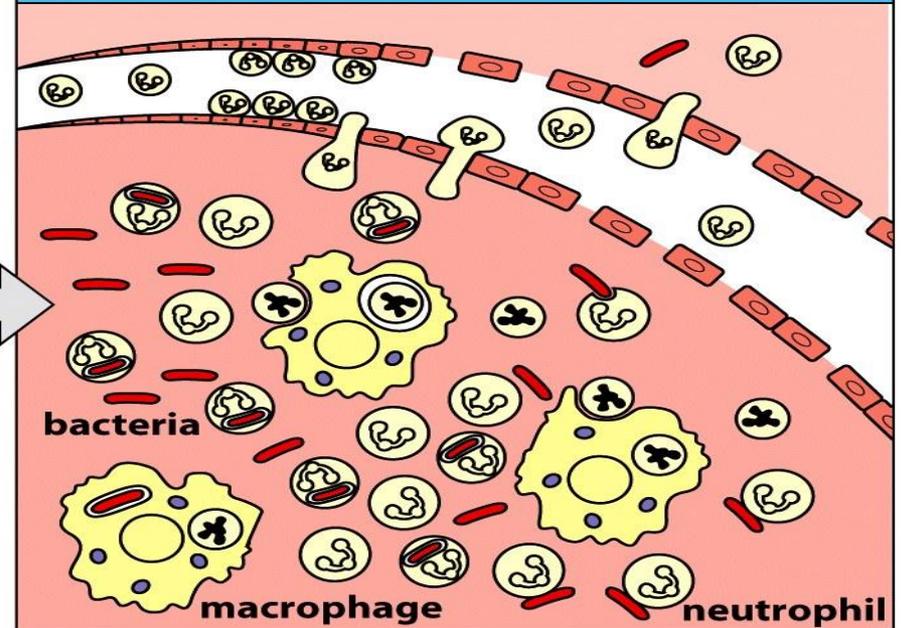
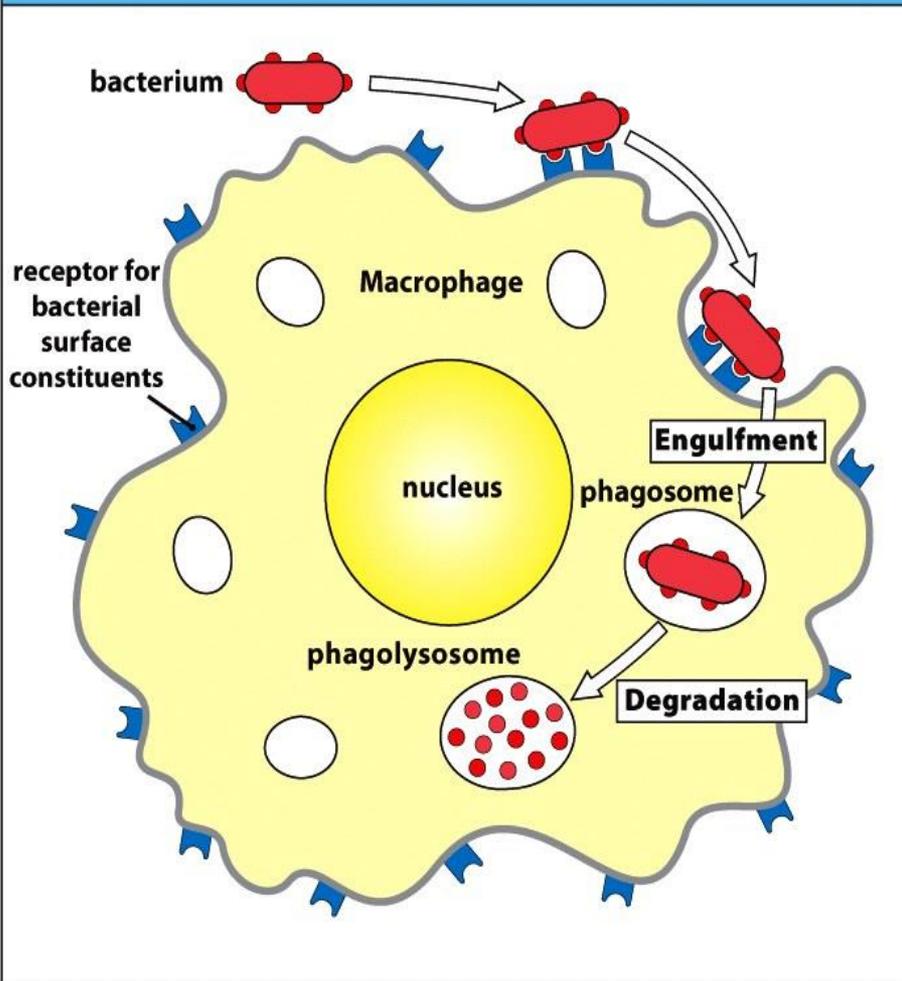


Figure 1.16 Neutrophils are stored in the bone marrow and move in large numbers to sites of infection, where they act and then die. After one round of ingestion and killing of bacteria, a neutrophil dies. The dead neutrophils are eventually mopped up by long-lived tissue macrophages, which break them down. The creamy material known as pus is composed of dead neutrophils.

Binding of bacteria to phagocytic receptors on macrophages induces their engulfment and degradation



Binding of bacterial components to signaling receptors on macrophages induces the synthesis of inflammatory cytokines

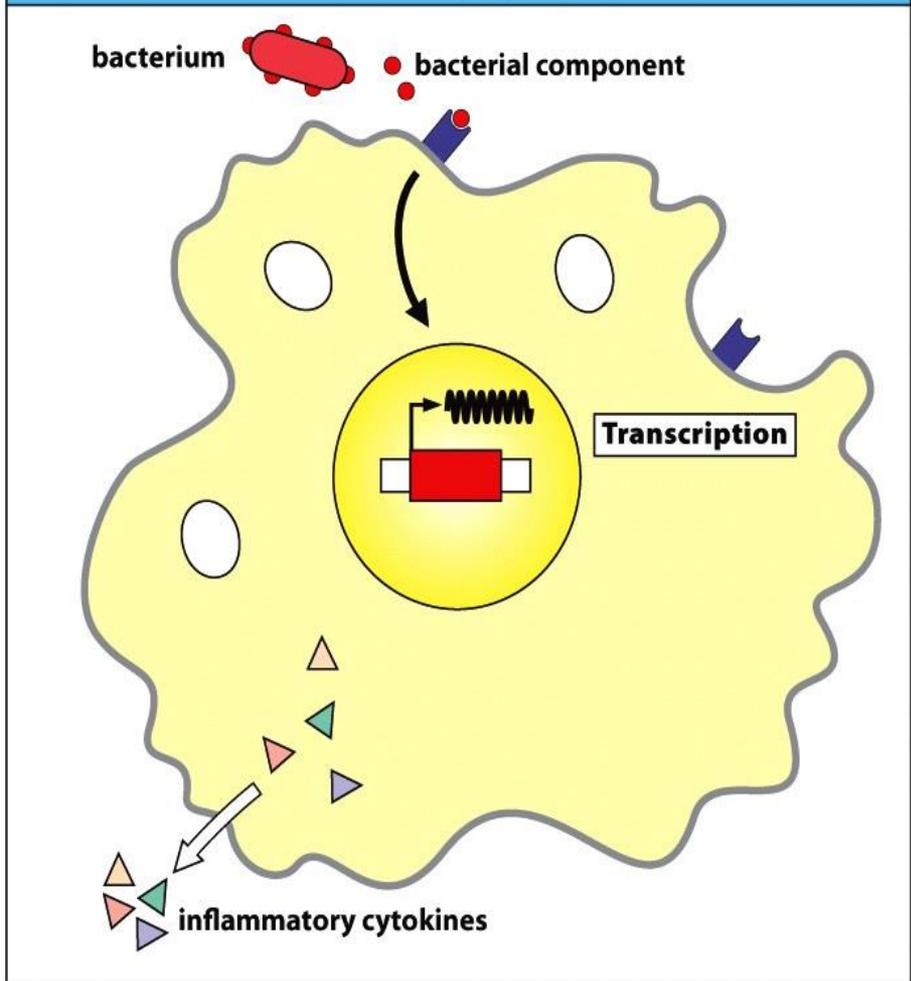


Figure 1.17 Macrophages respond to pathogens by using different receptors to stimulate phagocytosis and cytokine secretion.

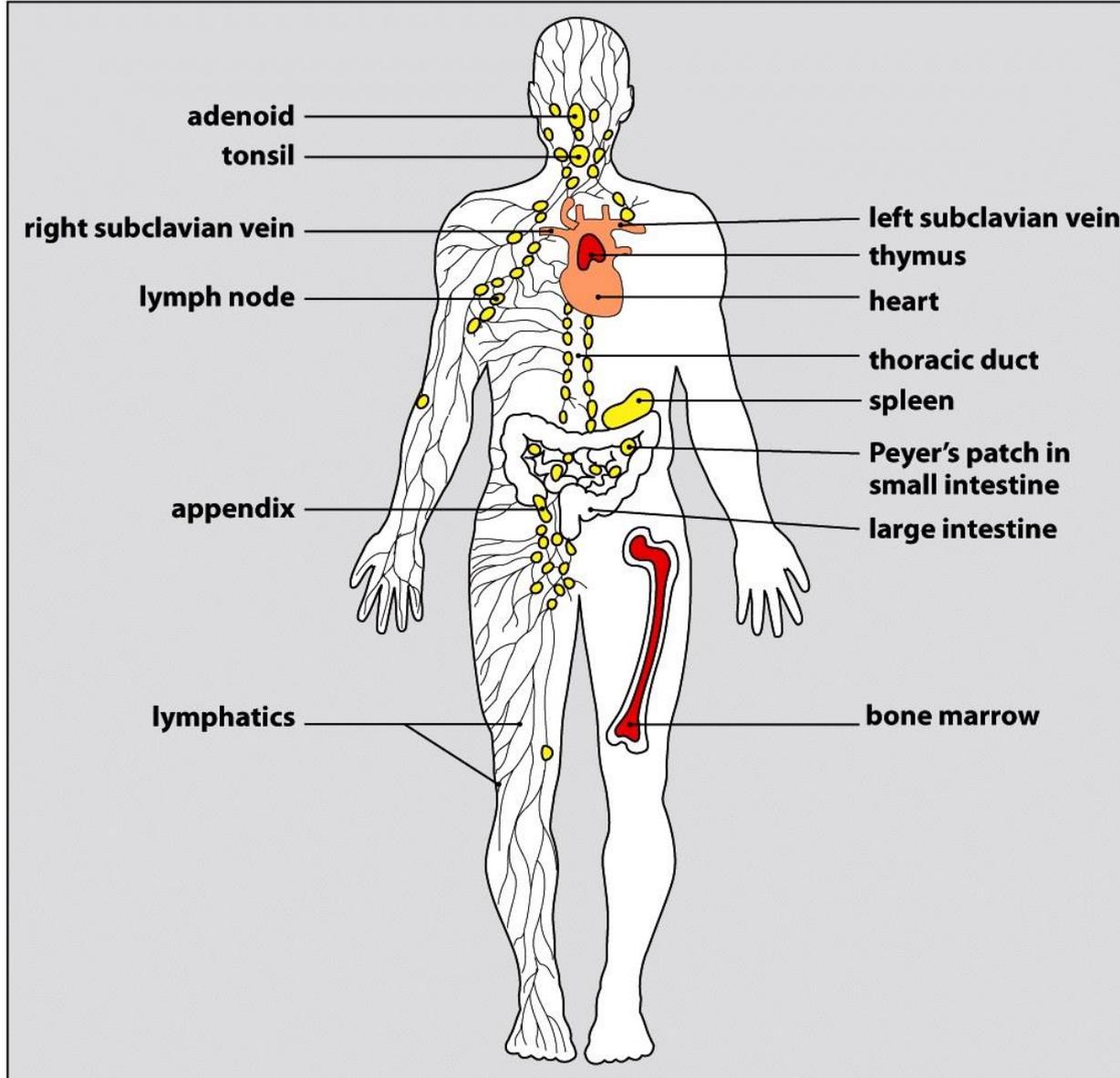


Figure 1.18 The sites of the principal lymphoid tissues within the human body. Lymphocytes arise from stem cells in the bone marrow. B cells complete their maturation in the bone marrow, whereas T cells leave at an immature stage and complete their development in the thymus. The bone marrow and the thymus are the primary lymphoid tissues and are shown in red. The secondary lymphoid tissues are shown in yellow and the thin black branching lines are the lymphatics. Plasma that has leaked from the blood is collected by the lymphatics as lymph and is returned to the blood via the thoracic duct, which empties into the left subclavian vein.

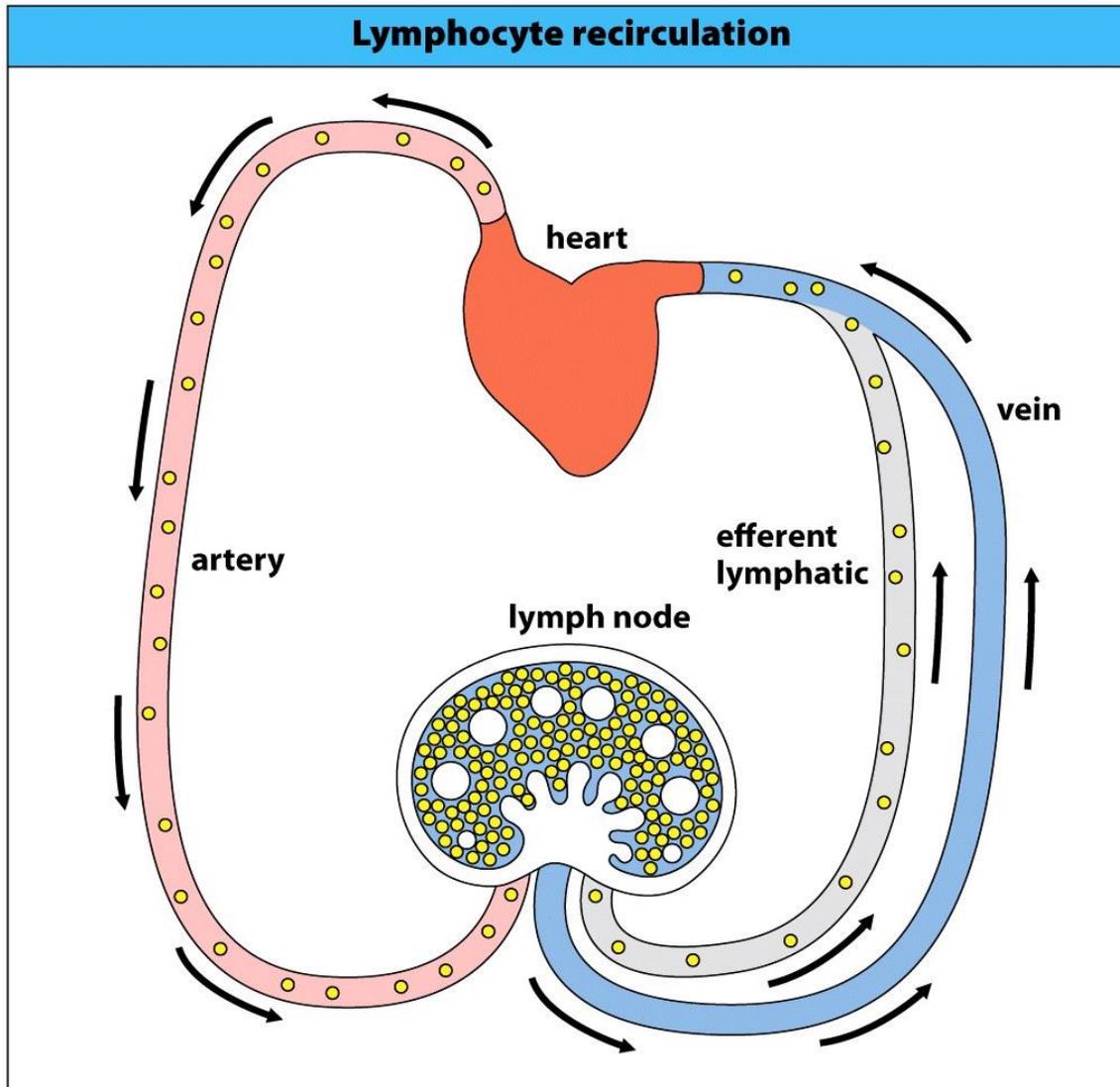


Figure 1.19 Lymphocyte recirculation. Small lymphocytes are unique among blood cells in traveling through the body in the lymph as well as the blood. That is why they were named lymphocytes. Lymphocytes leave the blood through the walls of fine capillaries in secondary lymphoid organs. A lymph node is illustrated here. After spending some time in the lymph node, lymphocytes leave in the efferent lymph and return to the blood at the left subclavian vein. If a lymphocyte in a lymph node encounters a pathogen to which its cell-surface receptor binds, it stops recirculating.



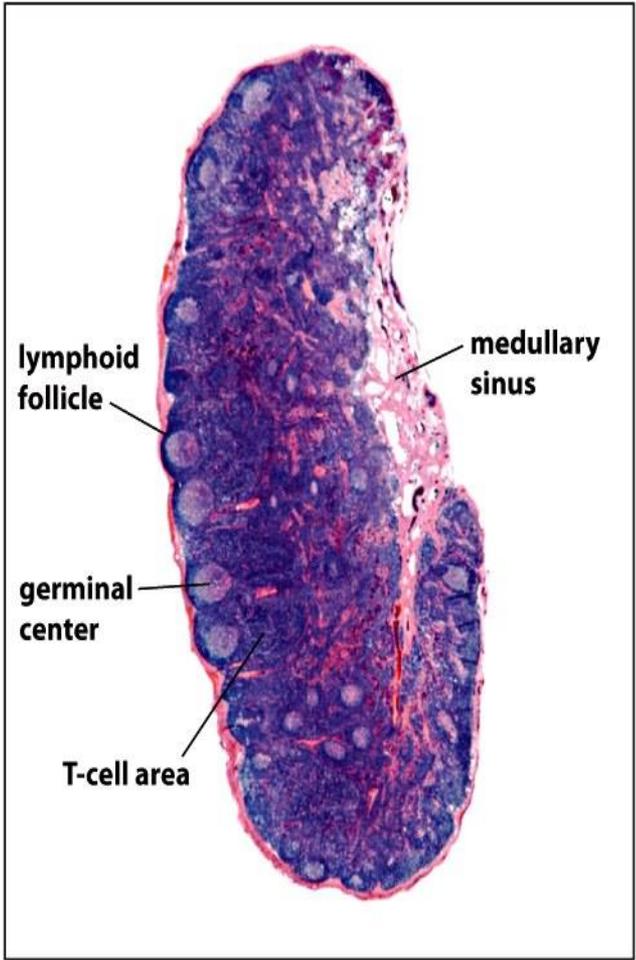
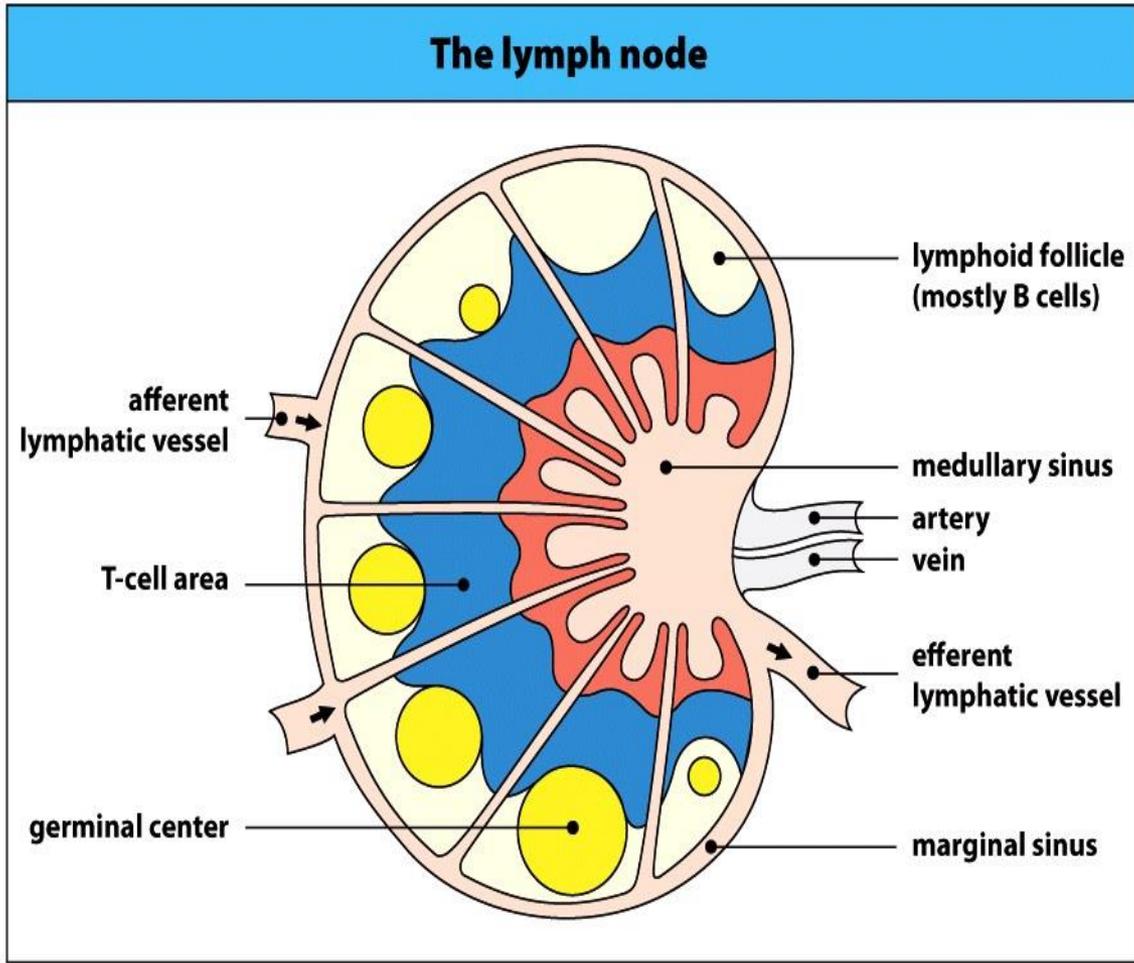


Figure 1.21 Architecture of the lymph node, the site where blood-borne lymphocytes respond to lymph-borne pathogens.

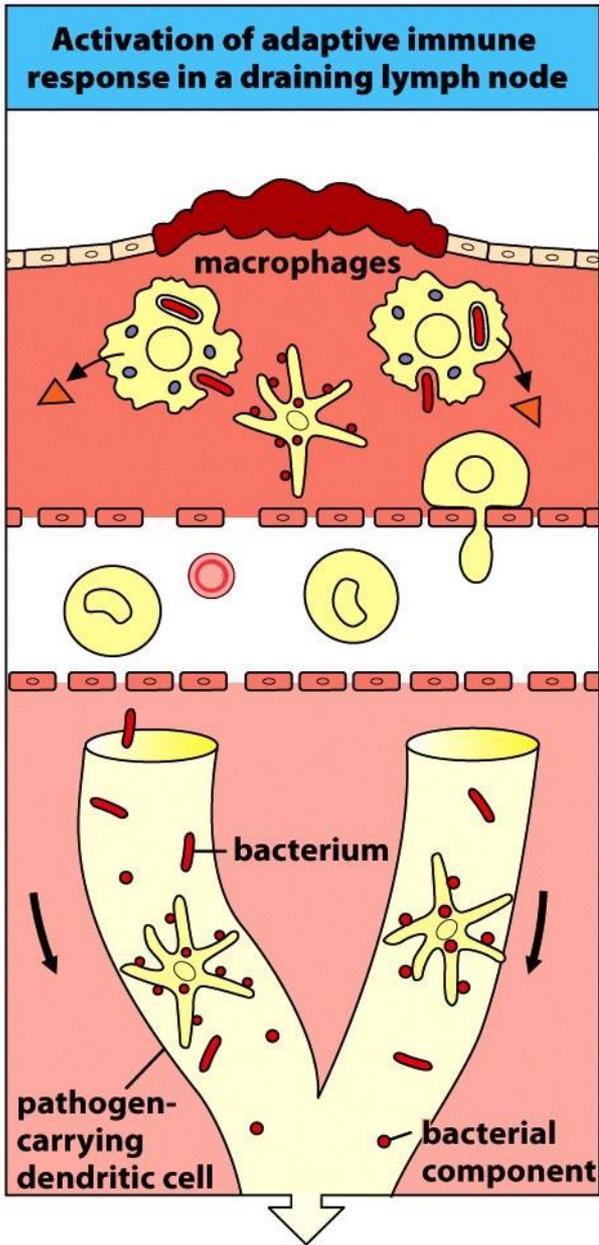
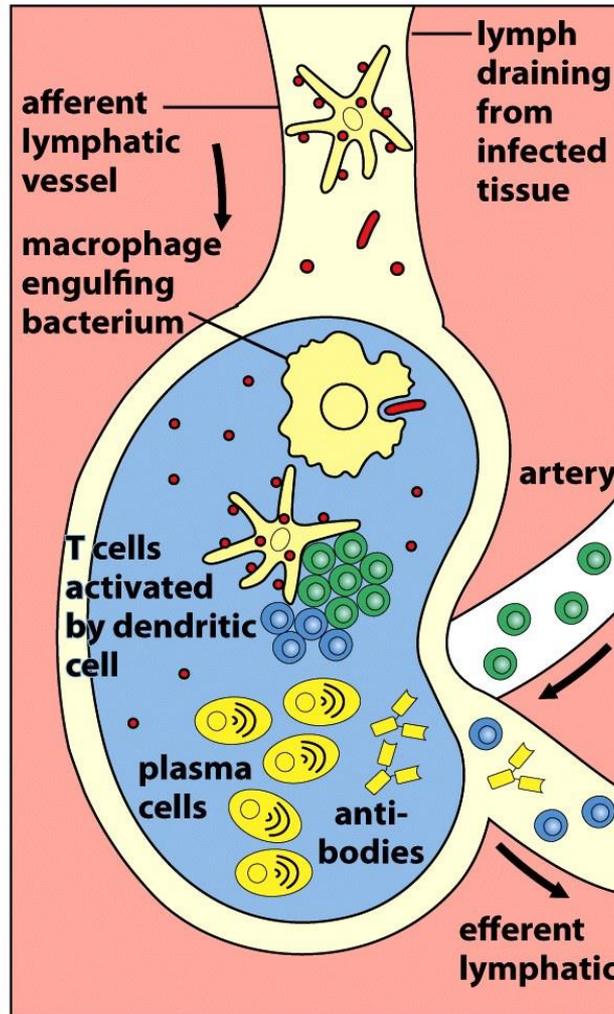


Figure 1.22 Activation of adaptive immunity in the draining lymph node.



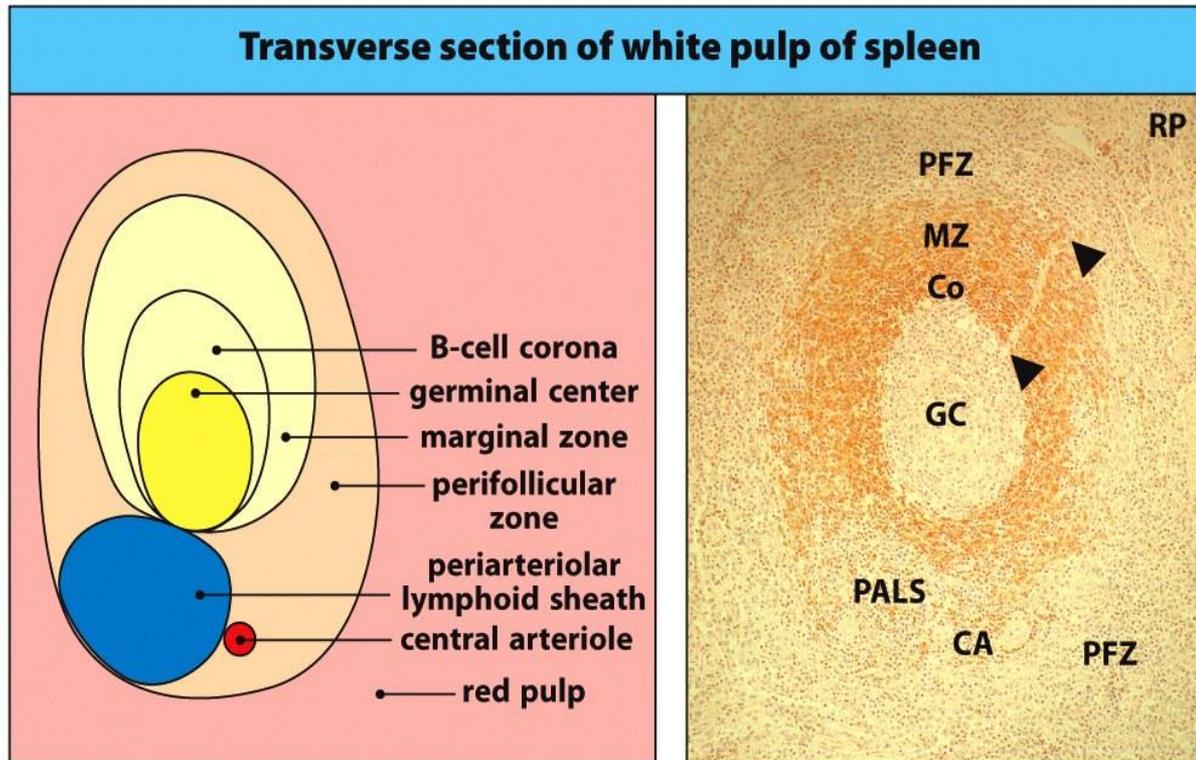
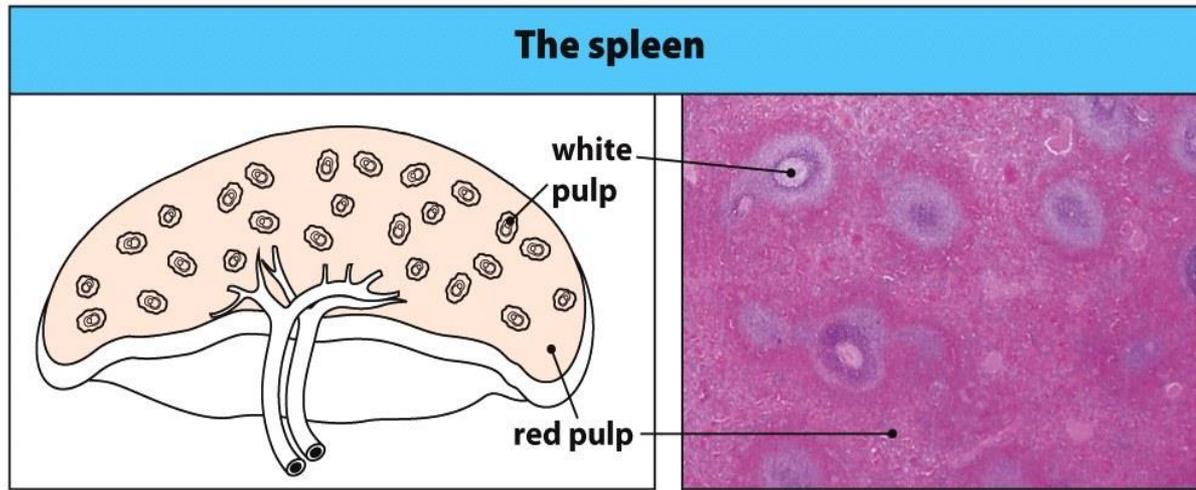


Figure 1.23 The spleen has aggregations of lymphocytes similar to those in lymph nodes. The human spleen is a large lymphoid organ in the upper left part of the abdomen, weighing about 150 grams. The upper diagram depicts a section of spleen in which nodules of white pulp are scattered within the more extensive red pulp. The red pulp is where old or damaged red cells are removed from the circulation; the white pulp is secondary lymphoid tissue, in which lymphocyte responses to blood-borne pathogens are made. The bottom diagram shows a nodule of white pulp in transverse section. It consists of a sheath of lymphocytes surrounding a central arteriole (CA). The sheath is called the periarteriolar lymphoid sheath (PALS). The lymphocytes closest to the arteriole are mostly T cells (blue region); B cells (yellow regions) are placed more peripherally. Lymphoid follicles each comprise a germinal center, a B-cell corona (Co) and a marginal zone (MZ), which contains differentiating B cells and macrophages. Both the follicle and the PALS are surrounded by a perifollicular zone (PFZ) abutting the red pulp and containing a variety of cell types, including erythrocytes, macrophages, T cells and B cells. Photographs courtesy of H.G. Burkitt and B. Young (top) and N.M. Milicevic (bottom).

Gut-associated lymphoid tissue

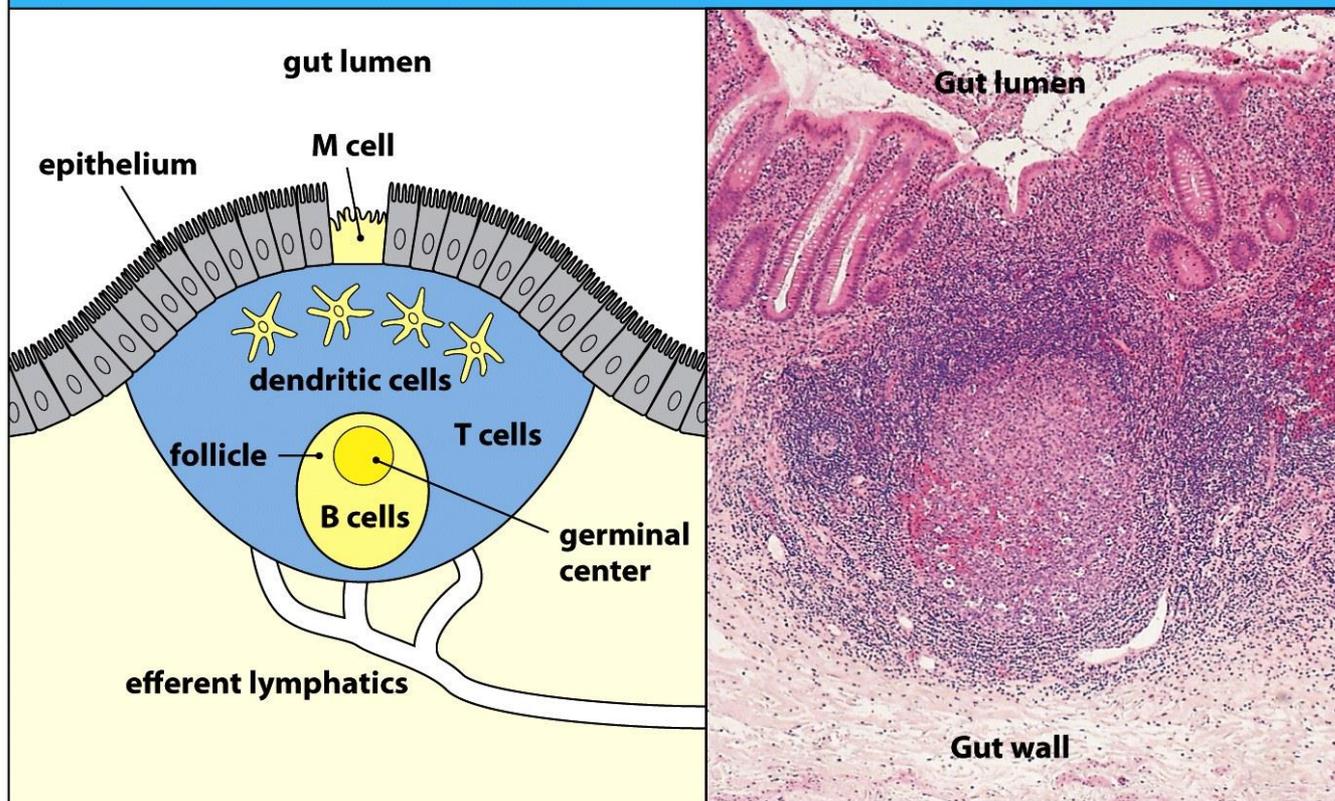


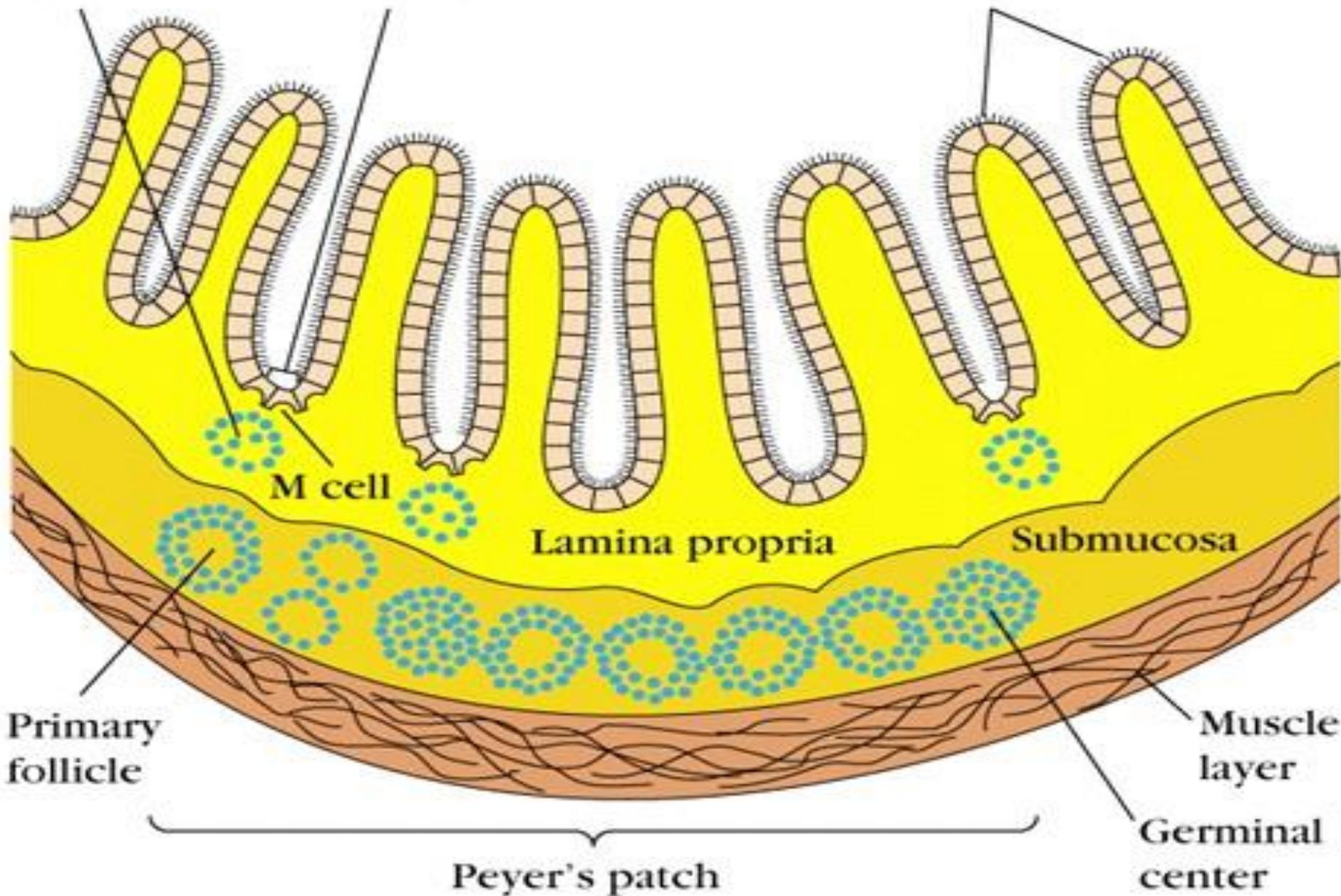
Figure 1.25 A typical region of gut-associated lymphoid tissue (GALT). A schematic diagram (left panel) and a light micrograph (right panel) of a typical region of organized GALT such as a Peyer's patch. M cells of the gut epithelial wall deliver pathogens from the luminal side of the gut mucosa to the lymphoid tissue within the gut wall. The lymphoid tissue is organized similarly to the lymph node and the white pulp of the spleen, with distinctive B- and T-cell zones, lymphoid follicles, and germinal centers. White blood cells, including lymphocytes, are delivered from the blood through the walls of small blood capillaries, as in the lymph node. Lymphocytes activated in the GALT leave in the efferent lymphatics and are delivered via the mesenteric lymph nodes (not shown) into the thoracic duct and back into the blood, from which they specifically reenter the gut as effector lymphocytes. Photograph courtesy of N. Rooney.

Intestinal lumen

Follicle

Inductive site

Villi



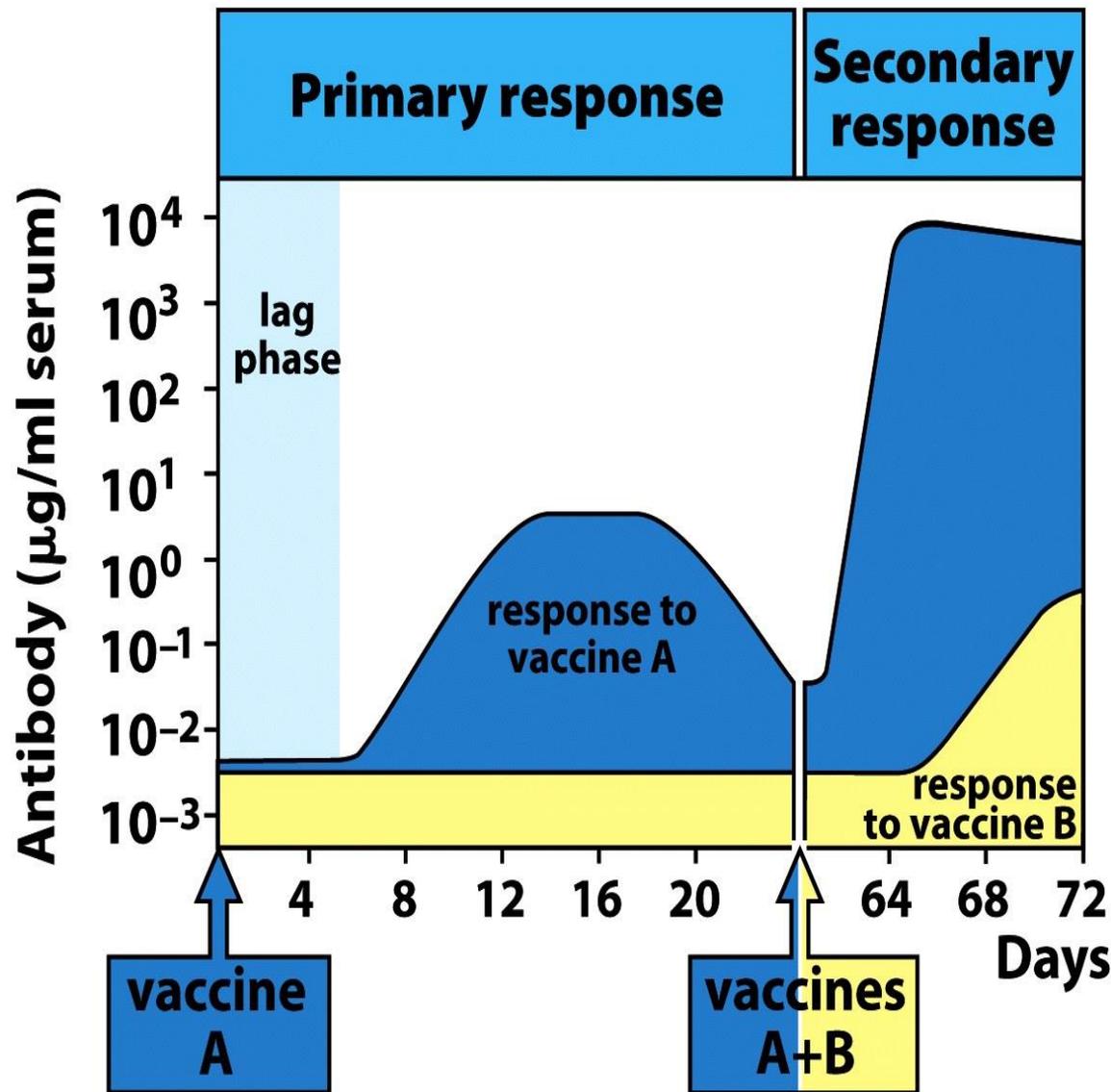


Figure 1.26 Comparison of primary and secondary immune responses. This diagram shows how the immune response develops during an experimental immunization of a laboratory animal. The response is measured in terms of the amount of pathogen-specific antibody present in the animal's blood serum, shown on the vertical axis, with time being shown on the horizontal axis. On the first day the animal is immunized with a vaccine against pathogen A. The levels of antibodies against pathogen A are shown in blue. The primary response reaches its maximum level 2 weeks after immunization. After the primary response has subsided, a second immunization with vaccine A on day 60 produces an immediate secondary response, which in 5 days is orders of magnitude greater than the primary response. In contrast, a vaccine against pathogen B, which was also given on day 60, produces a typical primary response to pathogen B as shown in yellow, demonstrating the specificity of the secondary response to vaccine A.

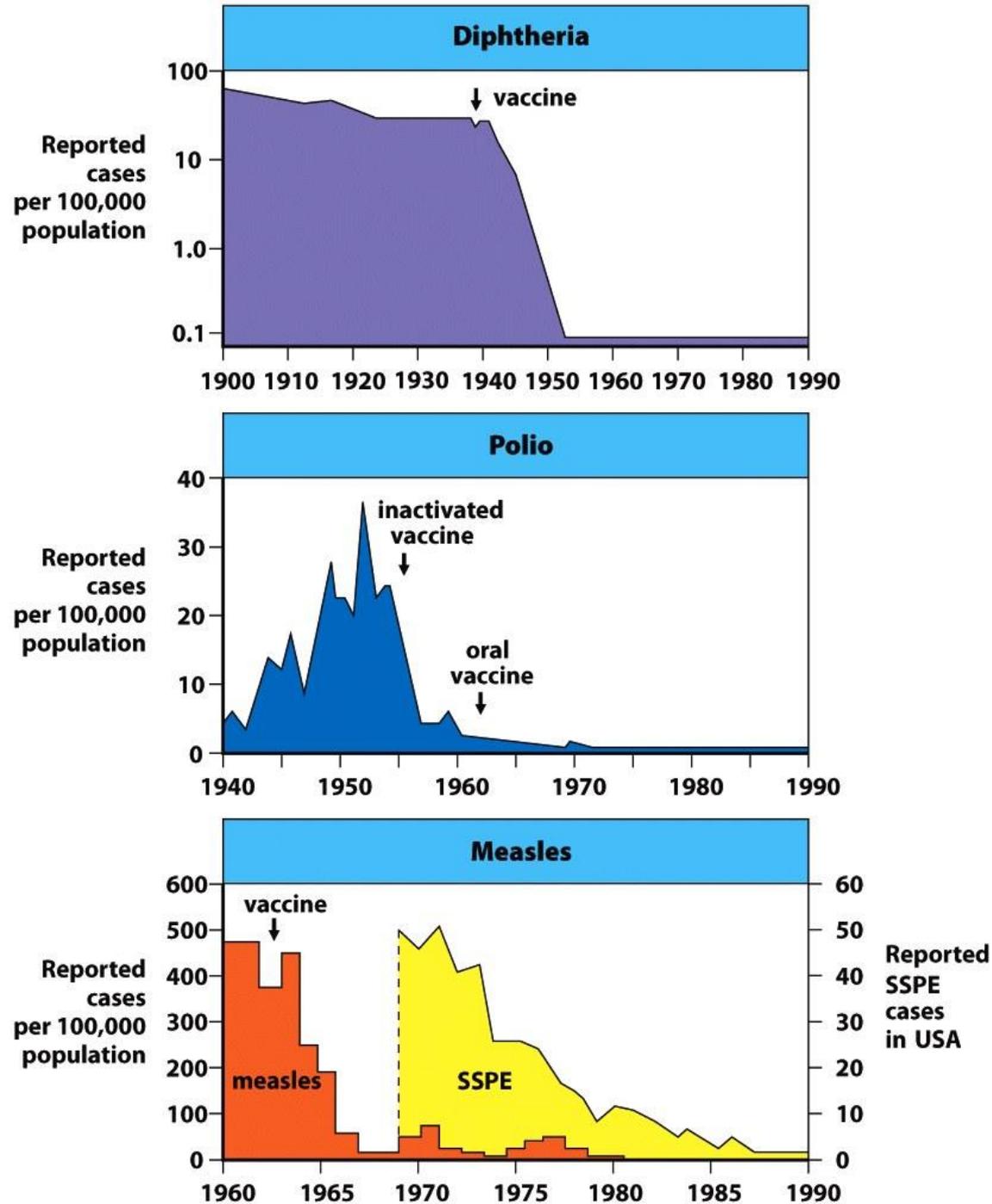


Figure 1.27 Successful vaccination campaigns. Diphtheria, poliomyelitis and measles have been virtually eliminated from the USA, as shown by these three graphs. The arrows indicate when the vaccination campaigns began. Subacute sclerosing panencephalitis (SSPE) is a brain disease that is a late consequence of measles infection for a minority of patients. Reduction of measles was paralleled by a reduction in SSPE 15 years later. Because these diseases have not been eradicated worldwide and the volume of international travel is so high, immunization must be maintained in much of the population to prevent recurrence of epidemic disease.