A lógica do Sistema Imune

Claudio Marinho, 2015

cowpox ou vaccínia = varíola de bovinos

Foi a partir do surgimento da Imunologia que , pela primeira vez a medicina foi capaz de mostrar intervir no curso de uma doença. Os primeiros indícios de interferência na saúde humana se fez através de um instrumento imunológico: A VACINA.

Eduard Jenner (1749-1823), foi o pioneiro no processo de criação da vacinação (1798).

Logo, a compreensão da imunização e da proteção, surgiu no final do século XVIII, bem mesmo antes de se conhecer os microorganismos, quando foi criada por Louis Pasteur a Teoria dos Germes no final do século XIX.

No final do século XIX, Louis Pasteur lançou a idéia de que as doenças epidêmicas eram causadas por microorganismos (chamados de corpos quando vistos ao microscópio) e que haveria possibilidades que fossem evitados. Este ilustre pesquisador interessou-se pelas técnicas de isolamento de microorganismos e pelos estudos das doenças com suas respectivas bactérias. Estudou as infecções responsáveis pelas bactérias, onde defendeu a idéia de que as doenças devem ser tratadas previamente pela Medicina, antes de se instalarem nos indivíduos.

Wood engraving of Louis Pasteur watching Joseph Meister receive the rabies vaccine, 1885. [*From* Harper's Weekly *29:836;*[*National Library of Medicine*]

Emil Adolf von Behring

Shibasaburo Kitasato

Em 1888, Von Behring e Kitassato encontraram no soro de animais imunizados contra a difteria e o tétano, substâncias neutralizantes específicas, as quais foram denominadas anticorpos (anti-corpos). Eles demonstraram que a proteção contra estas duas doenças podem ser transferidas passivelmente de um animal doente (imune) para outro animal normal, quando transferimos soro deste contendo estas moléculas chamadas de anticorpos. Assim, estava criada a soroterapia, a qual iniciou um processo de cura na Medicina em crianças com difteria em todo o mundo.

Paul Erlich também destacou-se na história da ciência Imunologia, desde o início do século. Foi um pesquisador nato, fez carreira como químico, quando iniciou seus trabalhos científicos com a implantação da indústria química alemã.

Responsável pela síntese dos primeiros corantes biológicos, criou métodos de coloração das células sanguíneas, onde conseguiu distinguir neutrófilos, eosinófilos e basófilos, depois descobrindo o mastócito no tecido. Erlich interessou-se pela especificidade dos fenômenos imunológicos, sendo capaz de diferenciar os mecanismos de imunização ativa e passiva, demonstrando para a comunidade científica, que existia uma transmissão de anticorpos de mãe para seus filhos, através do processo de amamentação.

O SISTEMA IMUNE ASSEGURA
<u>IDENTIDADE MOLECULAR</u> E <u>HOMEOSTASE</u>
NOS "MANDIBULADOS"

IMMUNIDADE INATA *vs* ADAPTATIVA
ou
IMUNIDADE INESPECIFICA *vs* ESPECIFICA

<u>DIVERSIDADE</u>: MOLECULAS DE REGIAO VARIAVEL
(ANTICORPOS E "T CELL-RECEPTORS")

Imunidade inata *vs.* imunidade adquirida

	Inata	adquirida
Tempo de resposta	imediata	alguns dias
Diversidade dos receptores	limitada	muito grande
Especificidade	não	sim
Memória	não	sim

EXTRAORDINARIA DIVERSIDADE DE VRMs

$>10^{12}$ vs $<10^{5}$

VRM: Variable-Region Molecules

- Anticorpos & B Cell Receptors (BCR)
- T Cell Receptors (TCR)
  - alpha-beta TCR
  - gamma-delta TCR

O SISTEMA IMUNE DOS VERTEBRADOS

"VÊ"

- O "OUTSIDE" DAS MOLÉCULAS FORA DAS CÉLULAS
- O "INSIDE" DAS MOLÉCULAS DENTRO DAS CÉLULAS

Propriedades do sistema imune

- Ter poder de cognição e de discriminação; para tanto deve ser capaz de “aprender” a reconhecer;

- Ser clonalmente organizado;

- Ser capaz de gerar moléculas antecipatórias;

- Ser capaz de efetuar respostas específicas e como corolário, ter memória;

- Ser auto-controlável

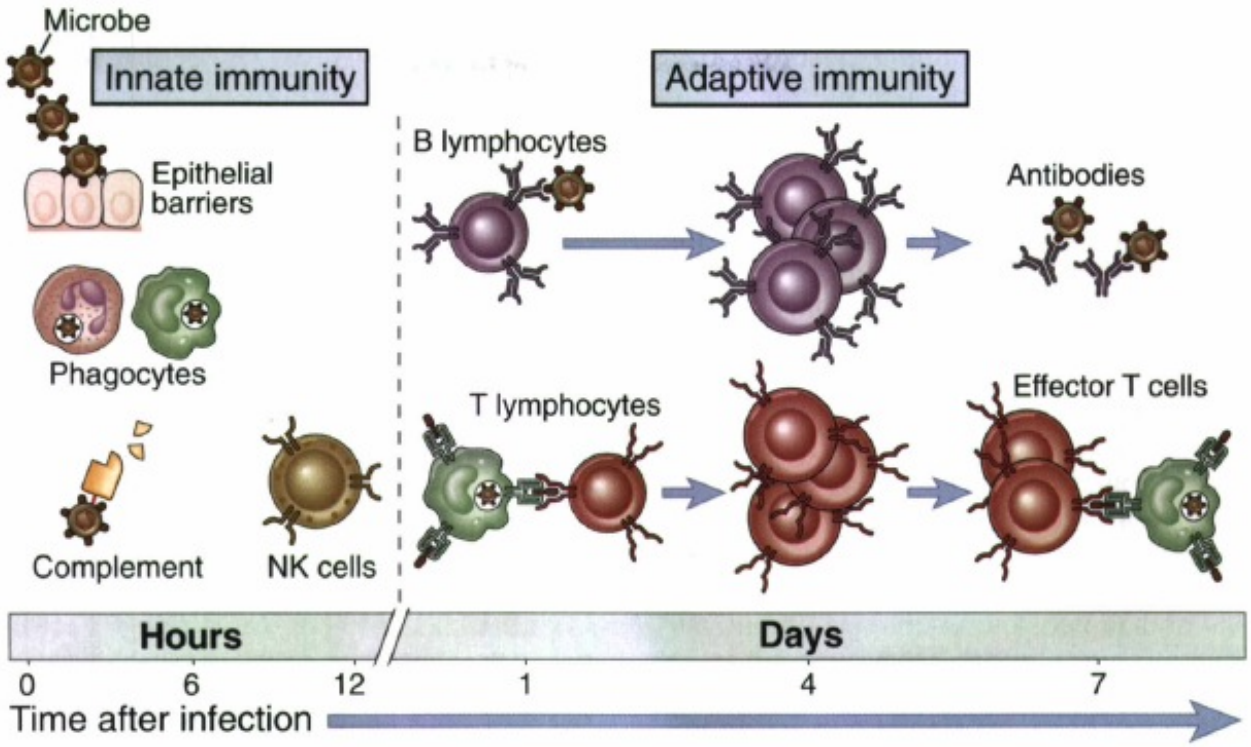


FIGURE 1–1 Innate and adaptive immunity. The mechanisms of innate immunity provide the initial defense against infections. Adaptive immune responses develop later and consist of activation of lymphocytes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections.

Abbas, 2007

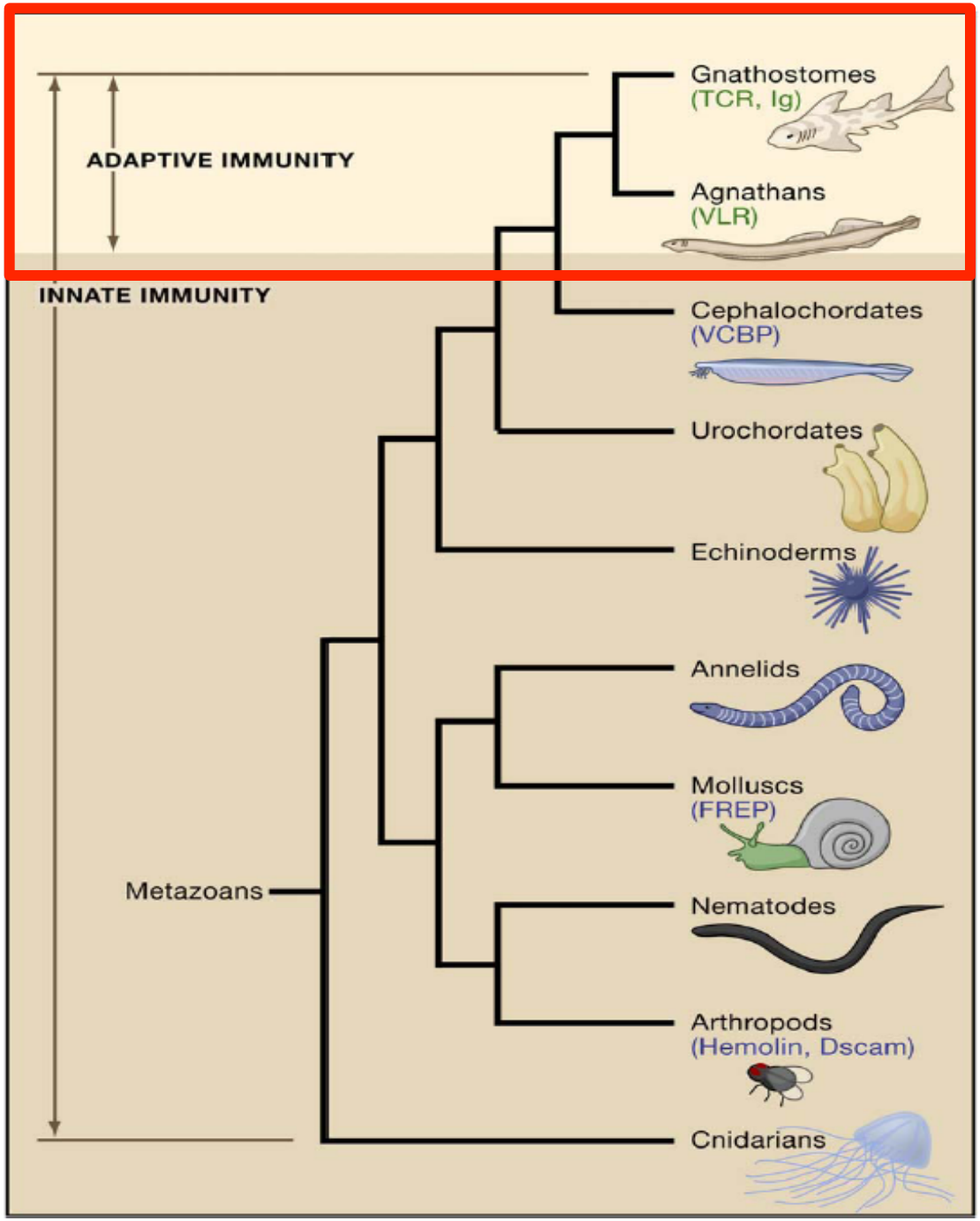


Figure 1. Phylogenetic Tree Indicating Theoretical Evolutionary Relationships of Metazoans and the Emergence of Adaptive Immunity in Conjunction with Innate Immunity

Families of immune molecules, other than Toll-like receptors, discussed in this review are indicated in blue: V type Ig domains and a chitin binding domain containing proteins (VCBP), fibrinogen-related proteins (FREPs), hemolin, and Down's syndrome cell adhesion molecule (Dscam). The recombinatorial-based immune receptors are indicated in green: T cell receptors (TCR), immunoglobulins (Ig), and variable lymphocyte receptors (VLR).

Cell *124*, 815–822, February 24, 2006

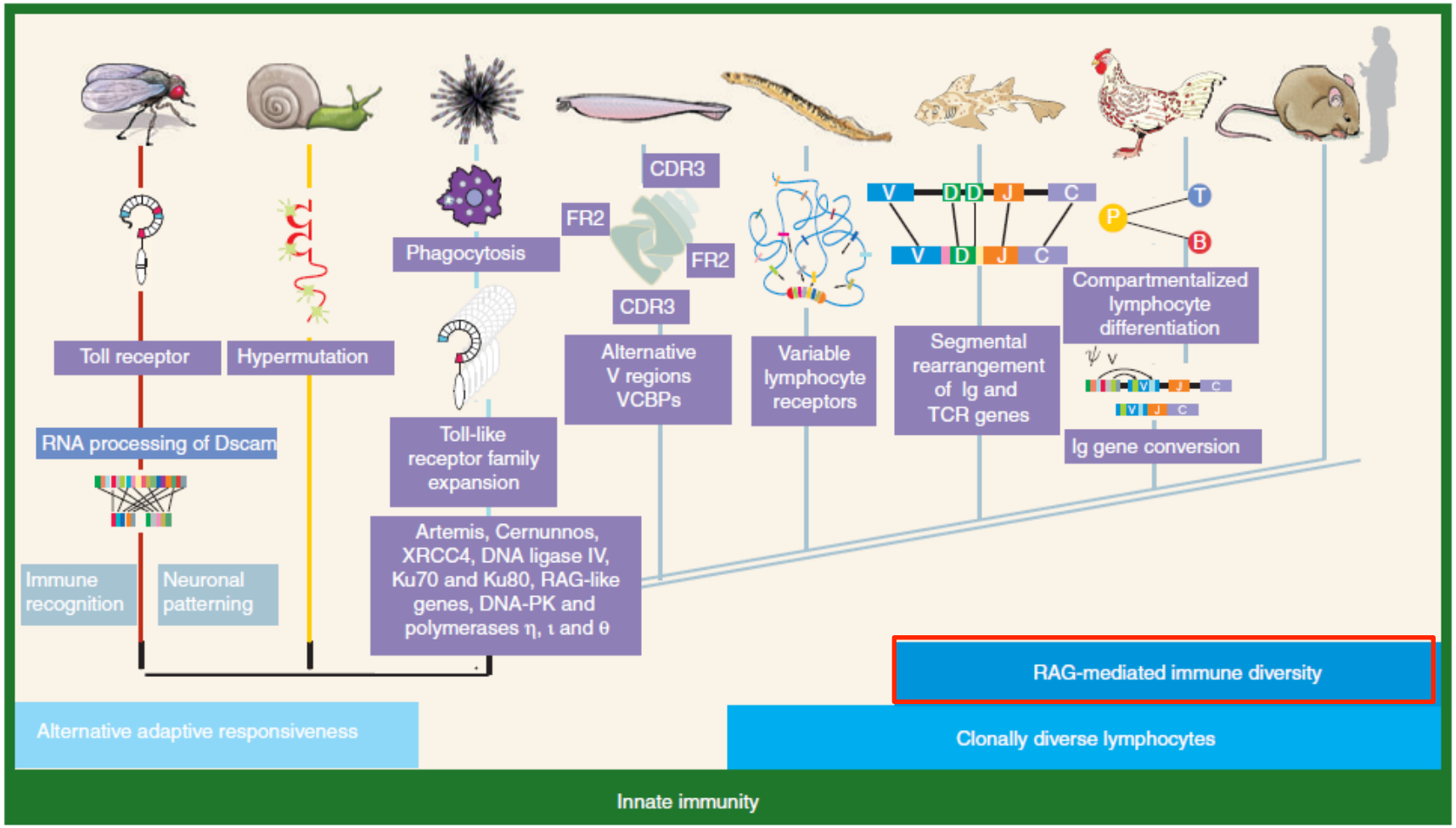
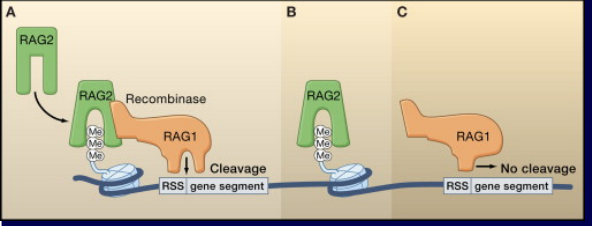
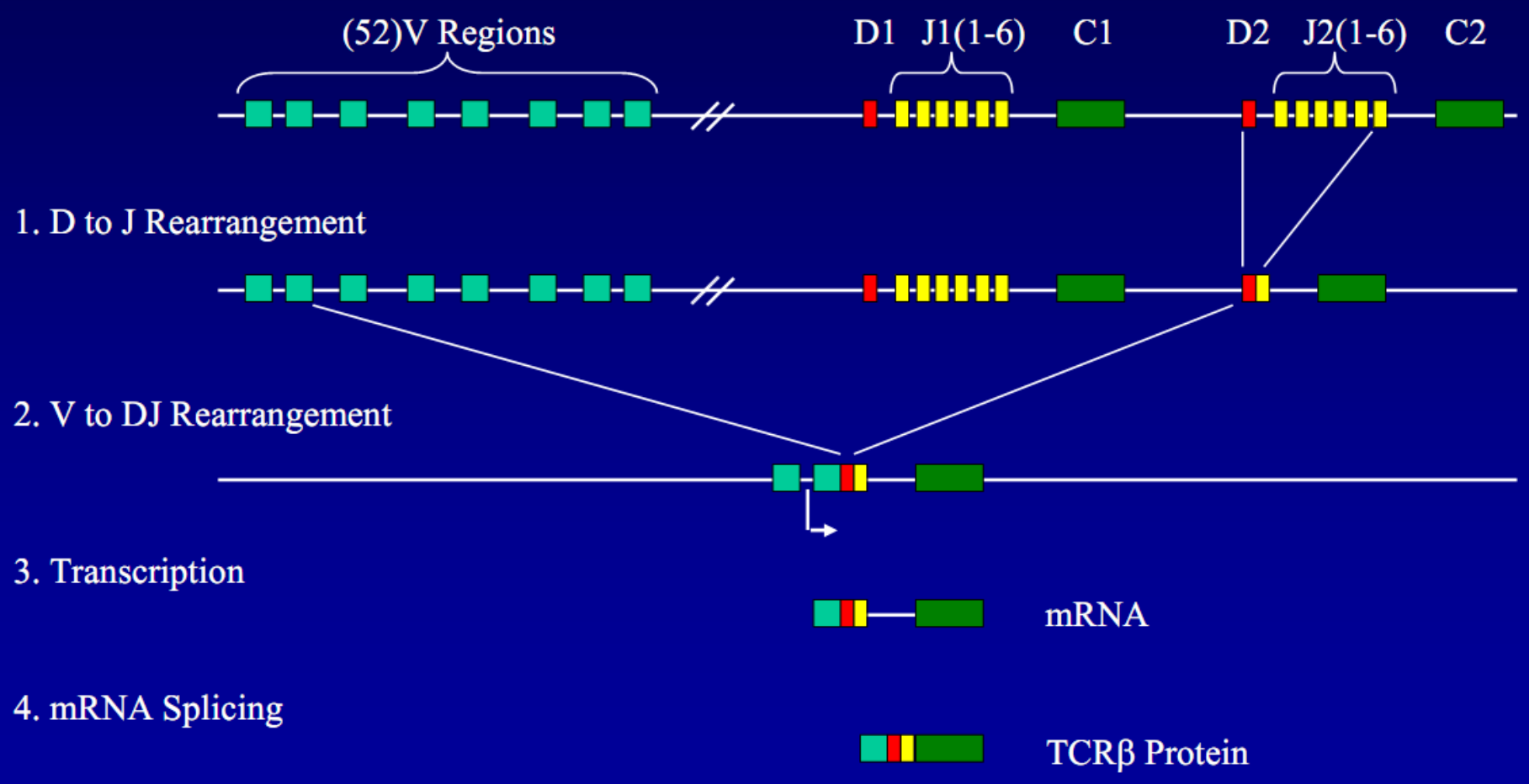


Figure 1 Present ideas of immune diversity in alternative model systems. Left to right: fly (drosophila), snail (biomphalaria) sea urchin (strongylocentrotus), amphioxus (branchiostoma), lamprey (petromyzon), shark (heterodontus), chicken (gallus) and mouse-human (mus-homo). Molecules such as RAG-1 and RAG-2 have been identified in sea urchin[15], but only a gene like *RAG1* has been characterized thus far in amphioxus. Amphioxus VCBPs (variable (V) region–containing chitin-binding proteins) have a 'head-to-tail' organization, which defines a unique potential binding surface, and have a considerable genetic polymorphism. Hypermutation has been noted in genes encoding snail fibrinogen-related proteins (FREPs). Three independent phyletic lineages are presented in red and yellow (protostomes) and in blue (deuterostomes); phylogenetic relationships are not drawn to evolutionary time scale. This diagram emphasizes some of the findings that have influenced the understanding of immune function and/or suggest alternative mechanisms of immune recognition. They are not intended to be inclusive for any given system or to include all systems in which notable findings relevant to the subject of this commentary have been made. Findings not in the text are in refs. 4,7,16. Dscam, Down's syndrome cell adhesion molecule; CDR3, complementarity-determining region 3; FR2, framework region 2; XRCC4, DNA-repair protein; Ku70 and Ku80, DNA-binding proteins; DNA-PK, DNA-dependent protein kinase; TCR, T cell antigen receptor; Ig, immunoglobulin; Ψ, pseudo.



TCR Rearrangements

TCR β locus - Germline



A lógica estrutural do sistema imune

Células, moléculas, tecidos e circulações (linfática e sanguínea) organizados de forma a facilitar a apresentação de antígenos a células capazes de reconhece-los e efetuar a resposta imune.

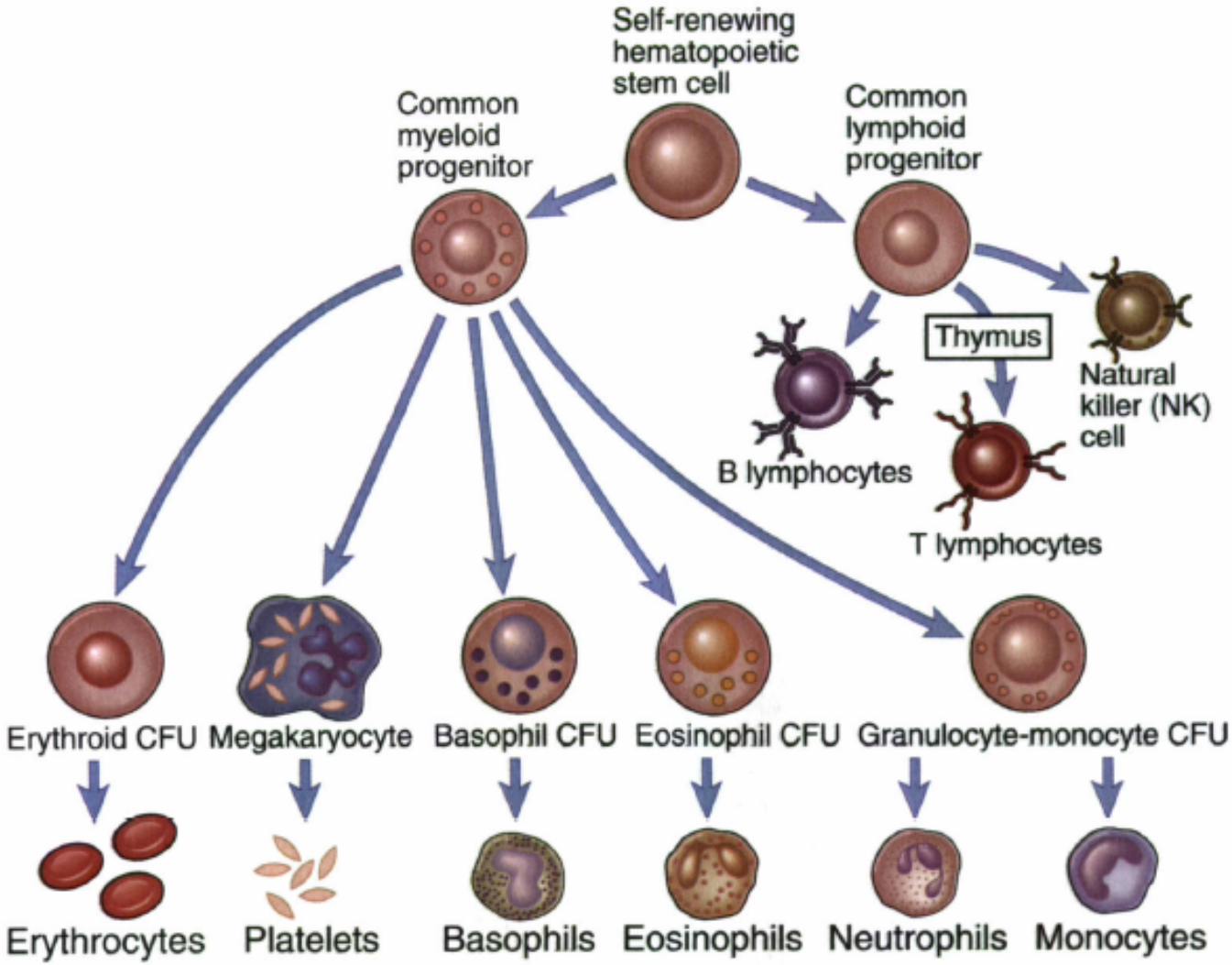
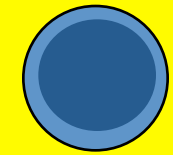


FIGURE 3–6 Hematopoiesis. The development of the different lineages of blood cells is depicted in this "hematopoietic tree." The roles of cytokines in hematopoiesis are illustrated in Chapter 12, Figure 12–15. CFU, colony-forming unit.

Abbas,2007

Cells of the Immune System



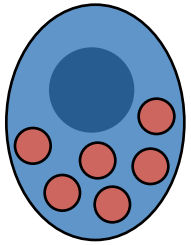
Lymphocyte *Adaptive immunity*

Macrophage *Phagocytosis*
Monocyte *Ag presentation*

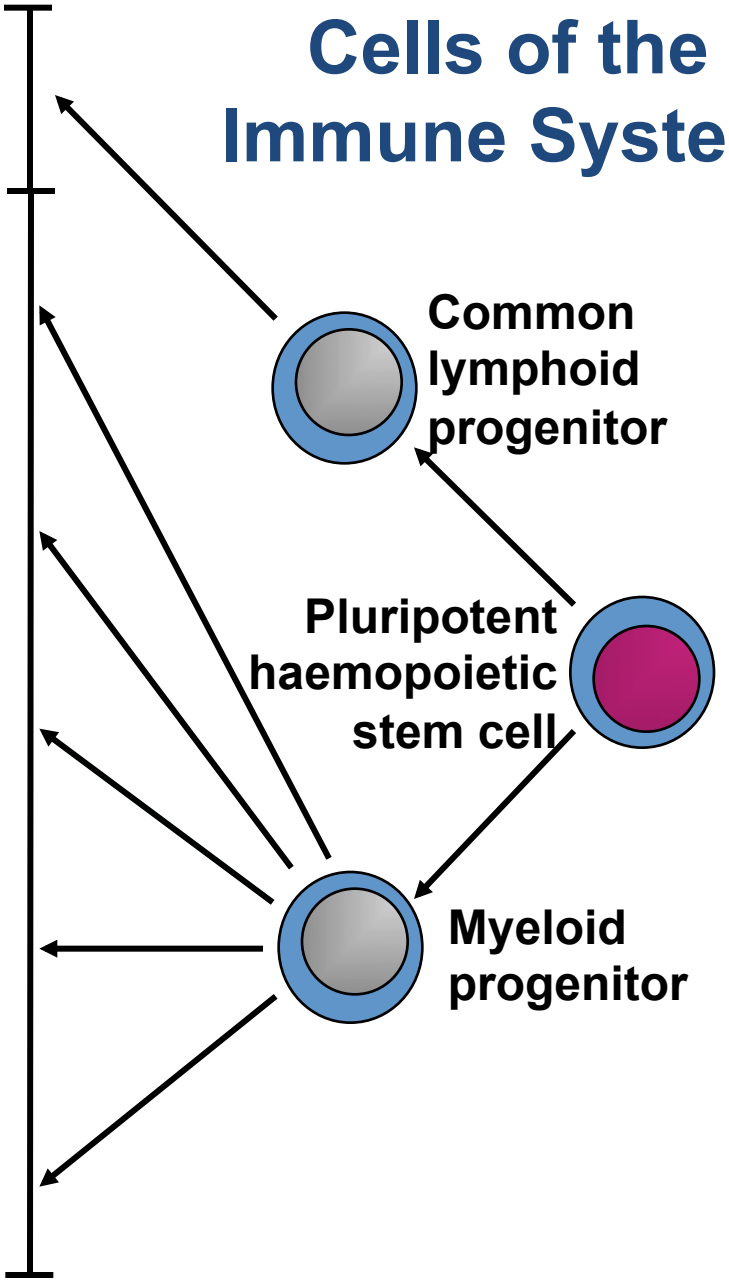
Neutrophil *Phagocytic*
PMN *Anti-bacterial*

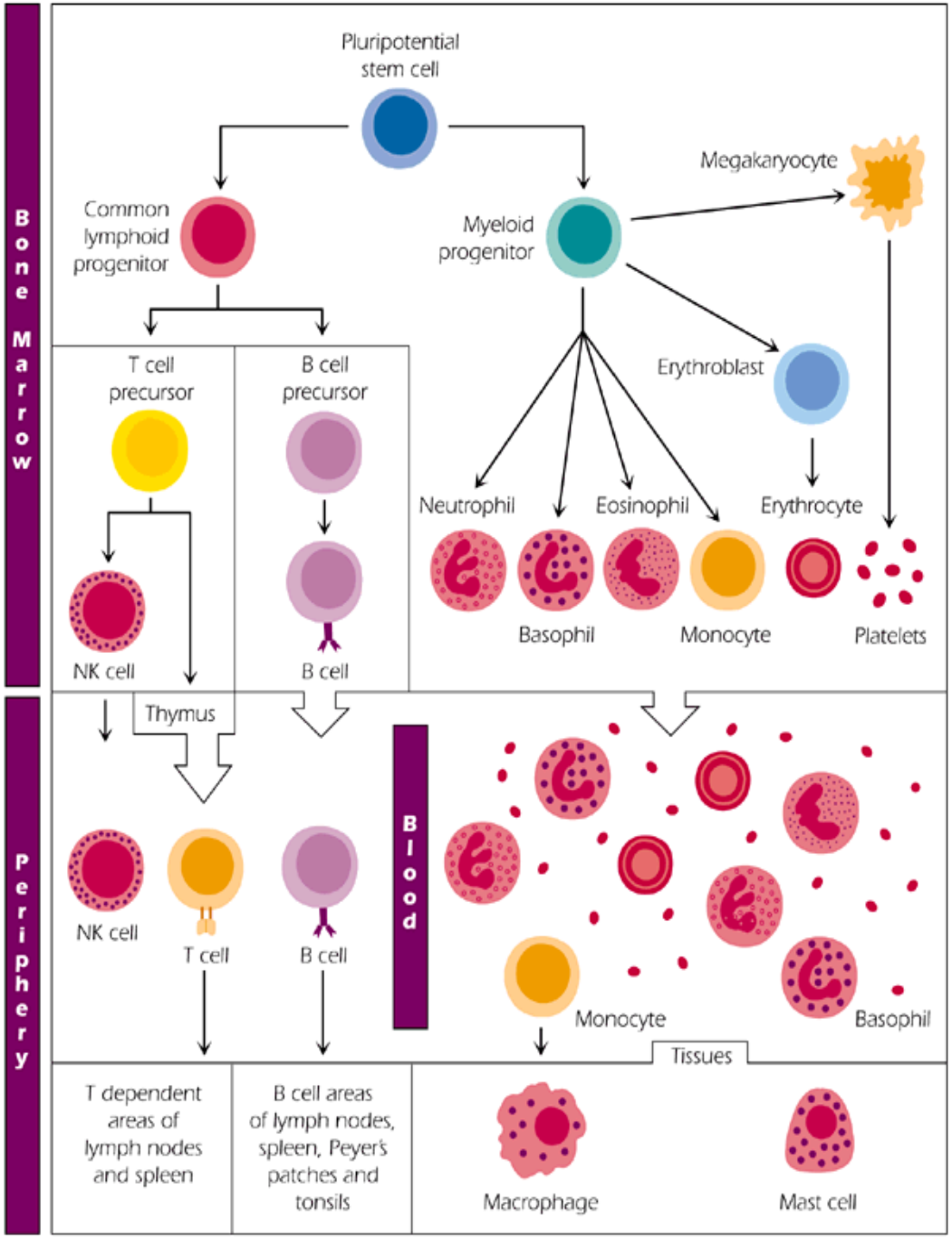
Eosinophil *Anti-parasite*
Immunity - Allergy

Basophil *?Protection of mucosal surfaces? - Allergy*



Mast cell *Protection of mucosal surfaces - Allergy*





Hematopoiese

Lymphoid organs

Organised tissue in which lymphocytes interact with lymphoid, non lymphoid cells and trapped antigen

Sites of generation, maturation & initiation of adaptive immune responses

CENTRAL LYMPHOID ORGANS

Thymus

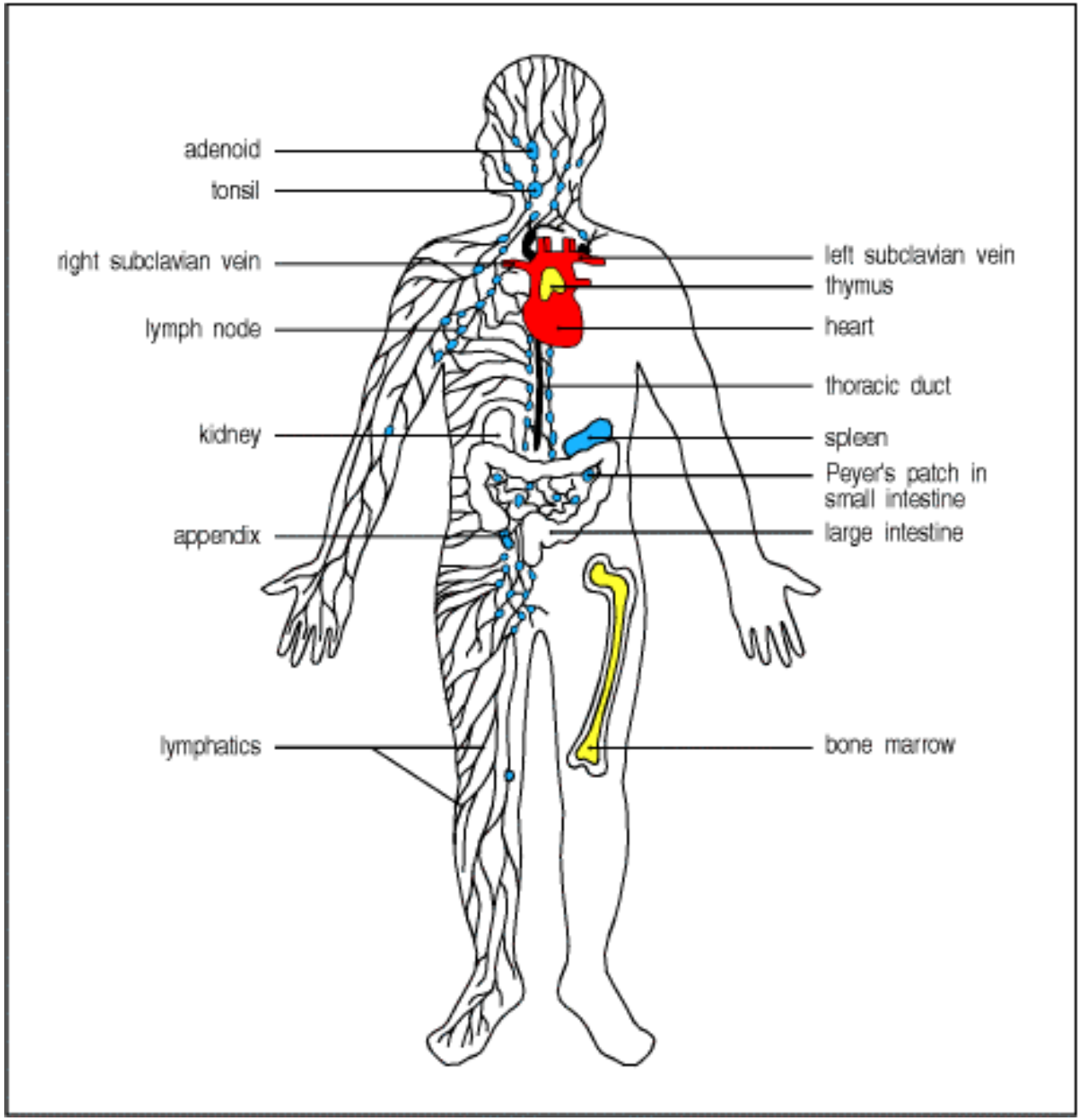
Bone marrow

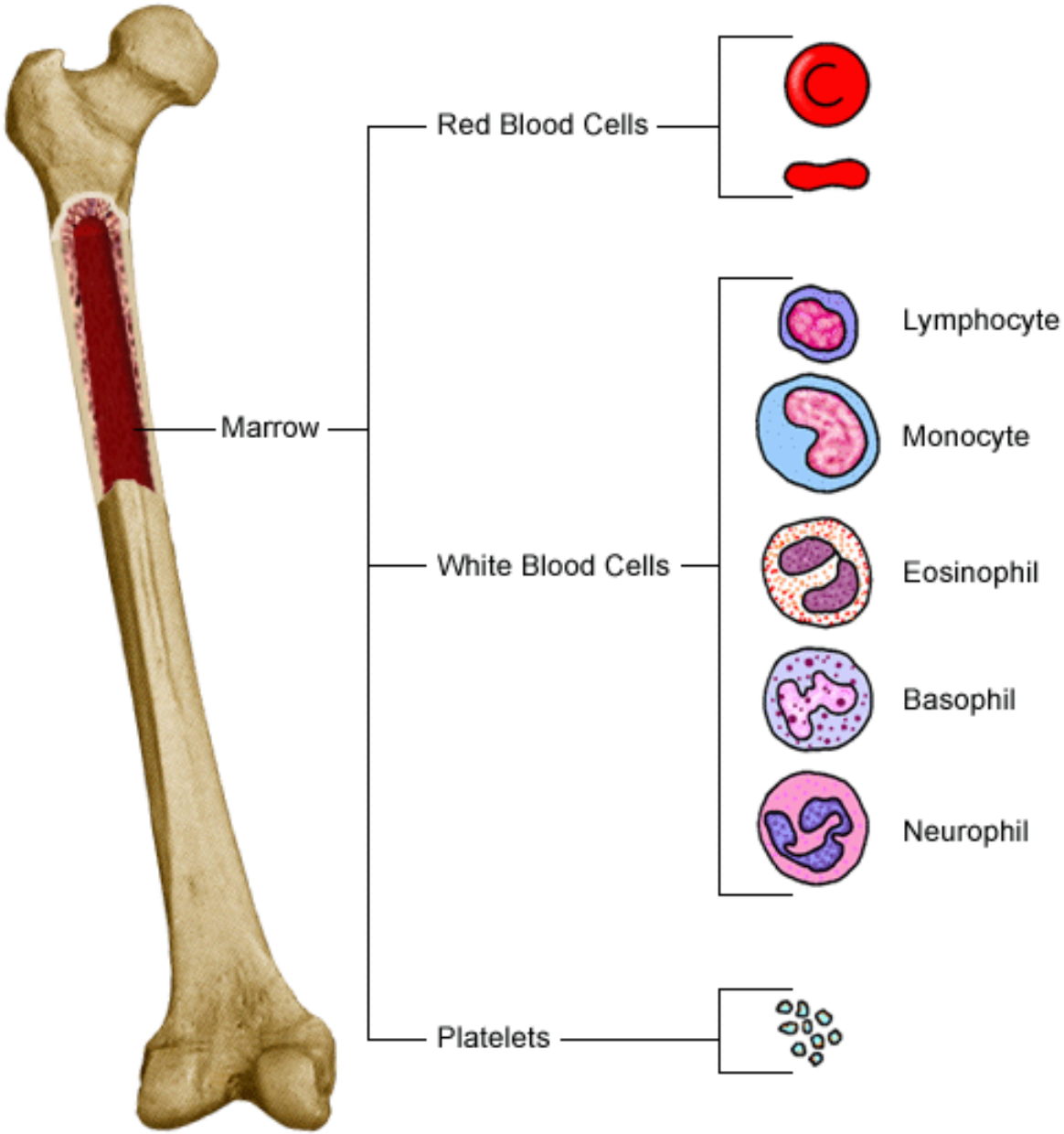
PERIPHERAL (SECONDARY) LYMPHOID ORGANS

Lymph nodes

Spleen white pulp

Mucosal-associated lymphoid tissue


adenoid
tonsil
right subclavian vein
lymph node
kidney
appendix
lymphatics
left subclavian vein
thymus
heart
thoracic duct
spleen
Peyer's patch in small intestine
large intestine
bone marrow


Marrow
Red Blood Cells
White Blood Cells
Platelets
Lymphocyte
Monocyte
Eosinophil
Basophil
Neurophil

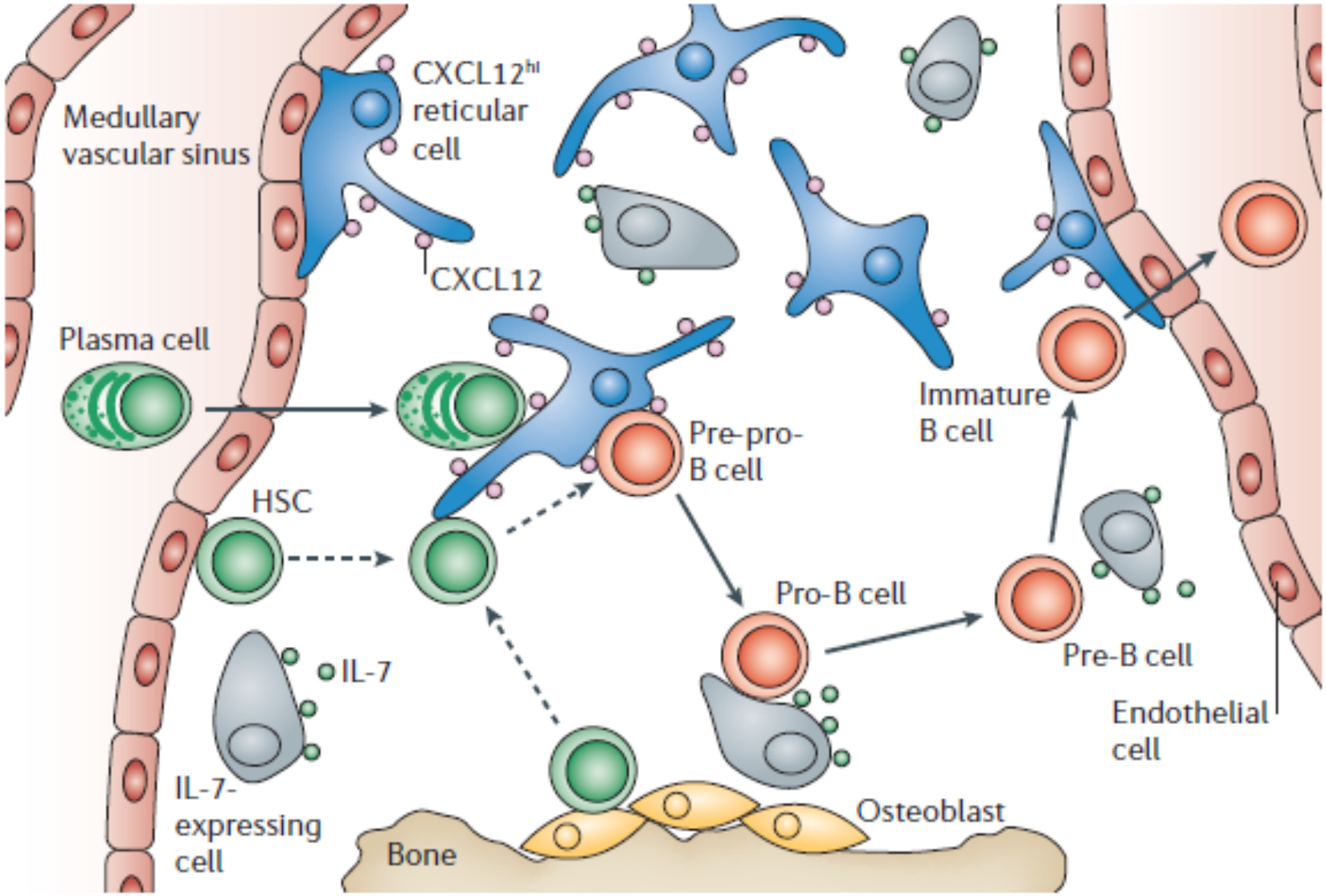
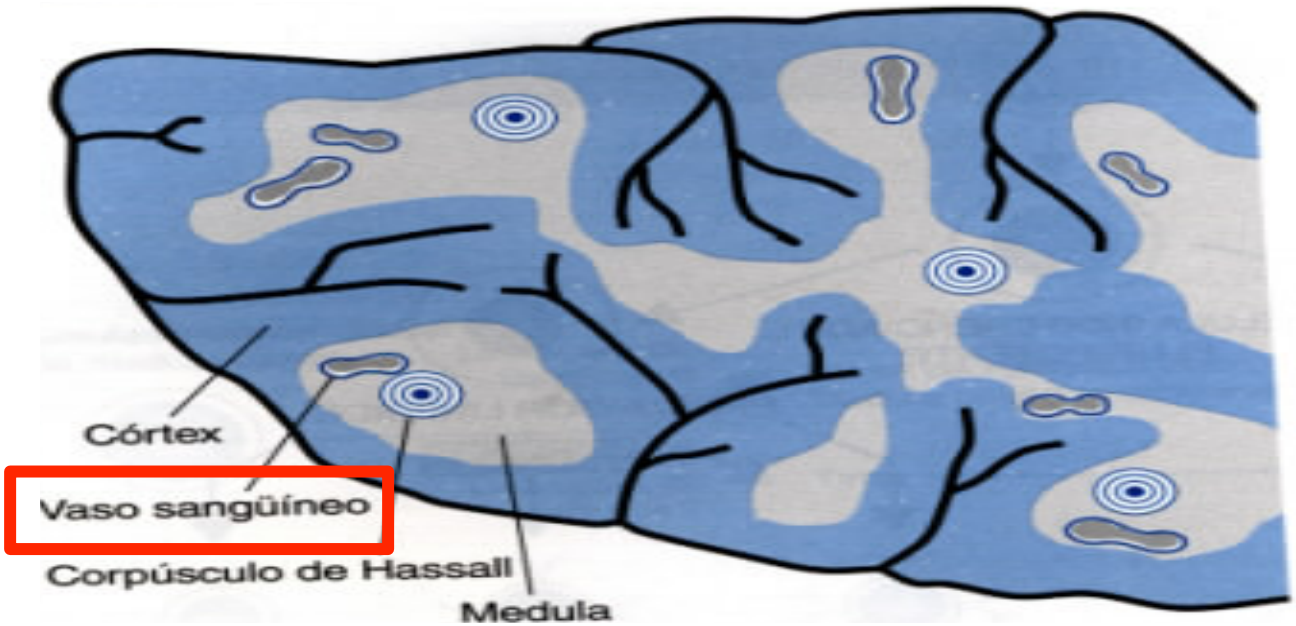
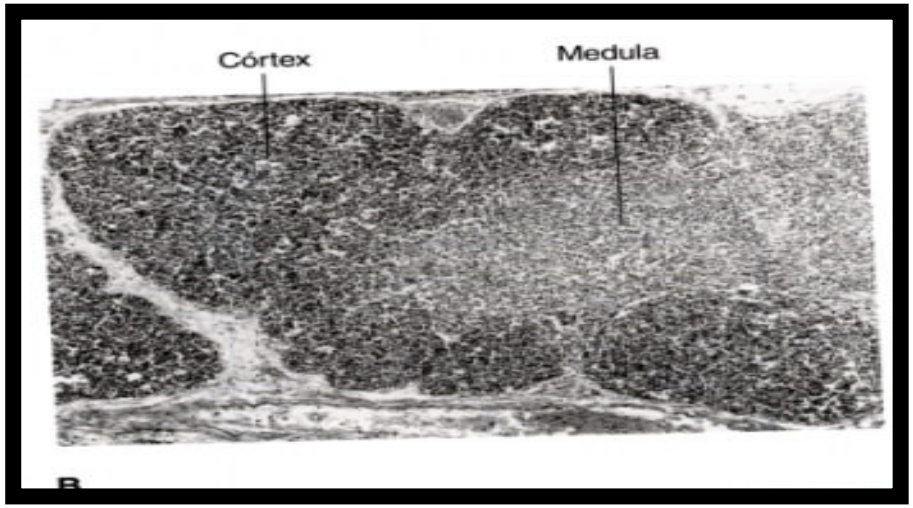


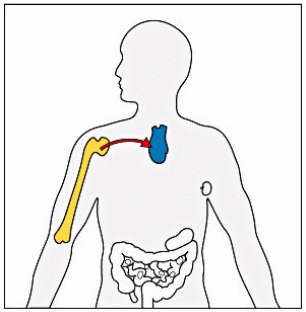
Figure 3 | **Candidates for cellular niches for B-cell development and a model of the movement of B cells and their precursors in the bone marrow.** In this model, the

TIMO


Córtex
Vaso sangüíneo
Corpúsculo de Hassall
Medula


Córtex
Medula

Localização e organização do timo



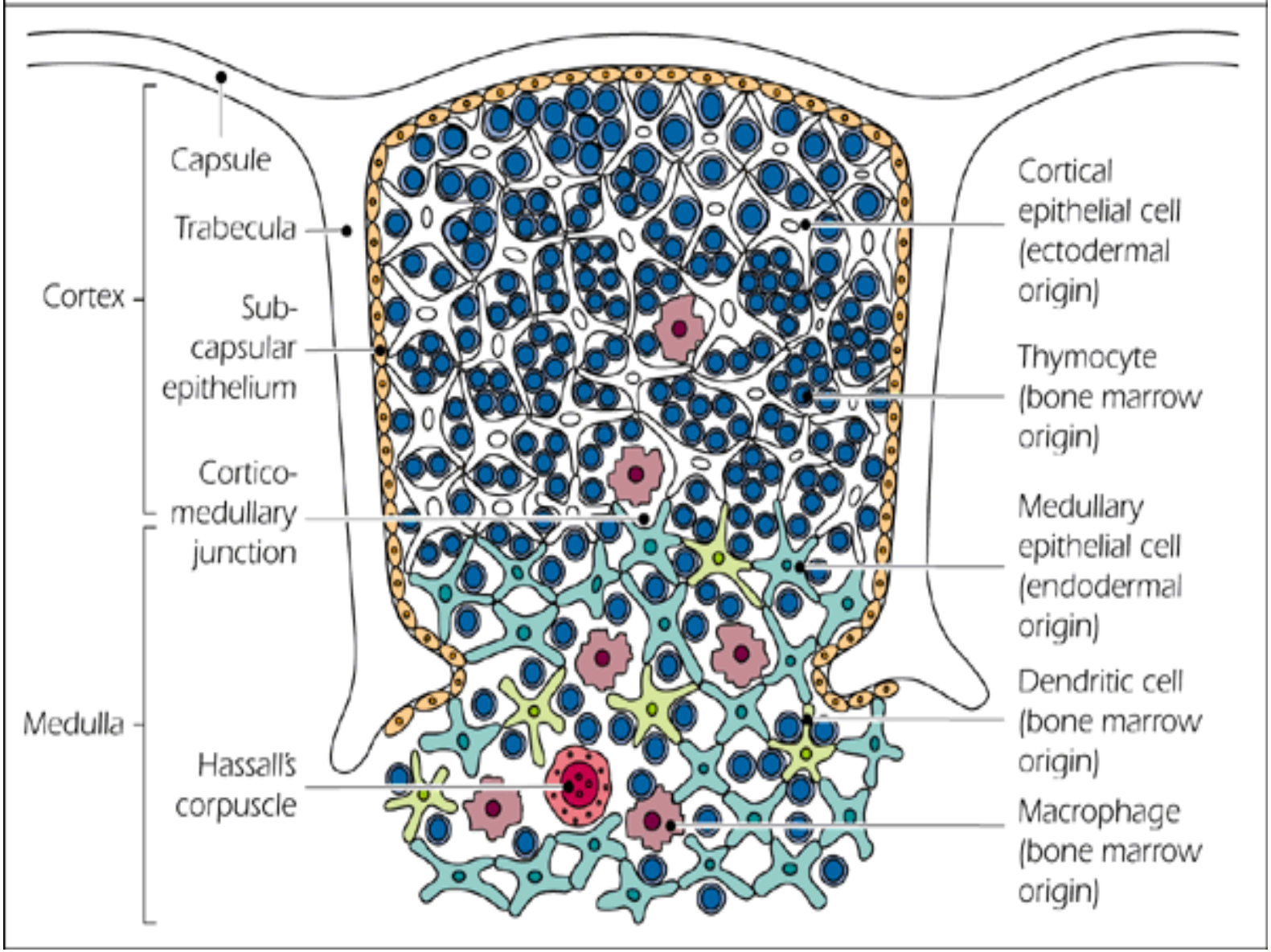
Cápsula

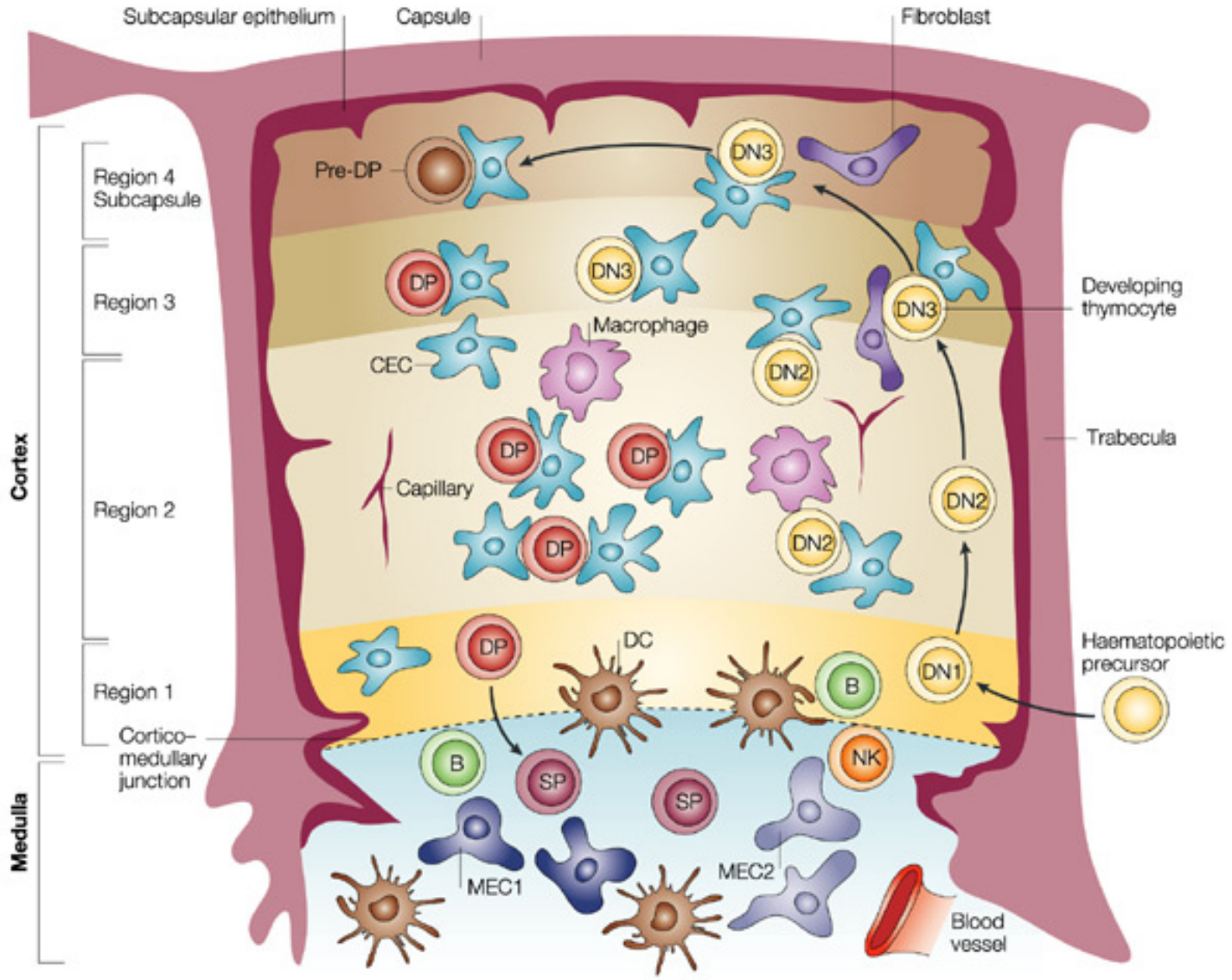
Córtex

Medula

Corpúsculo de Hassall

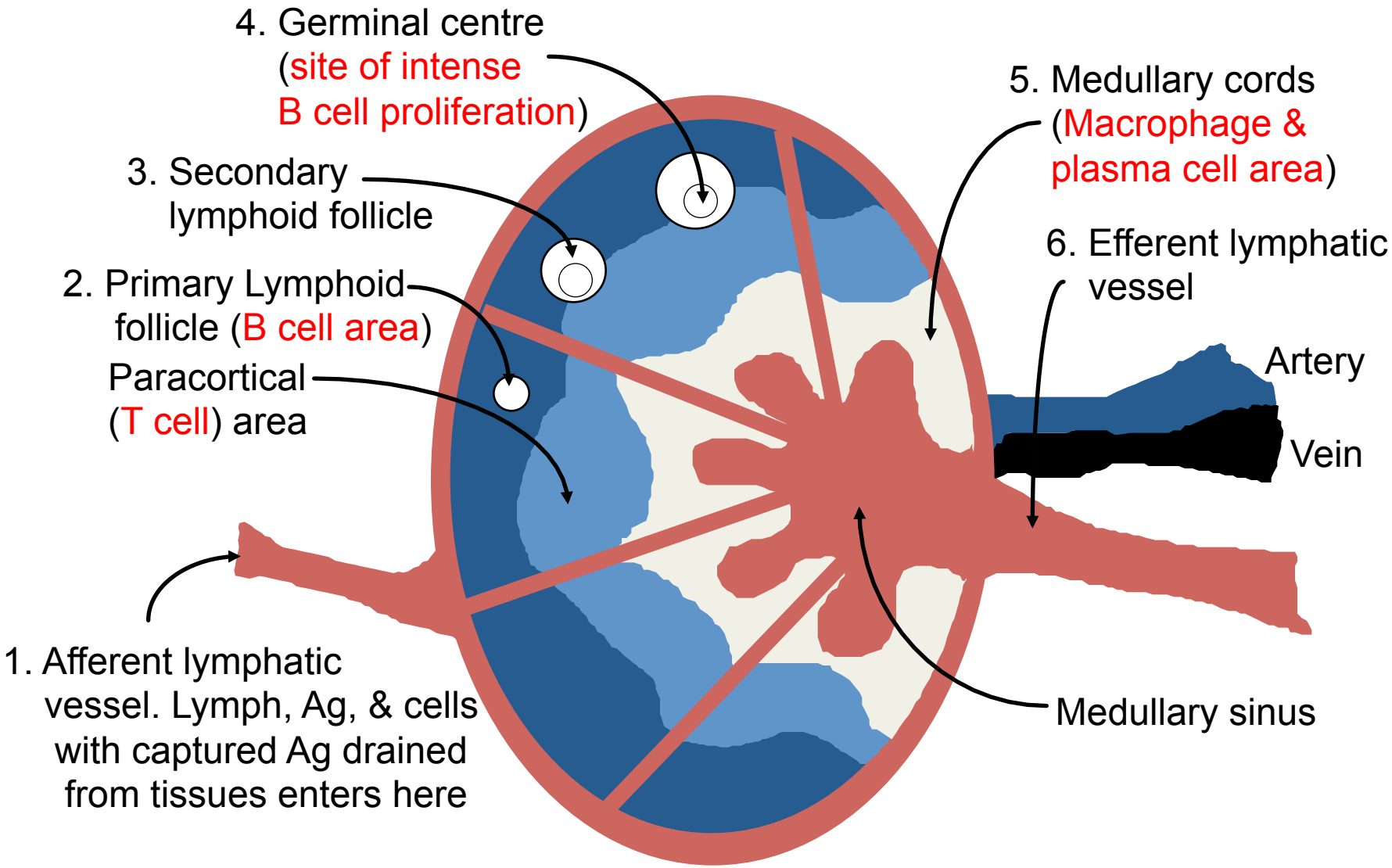
Schematic diagram of a normal thymus

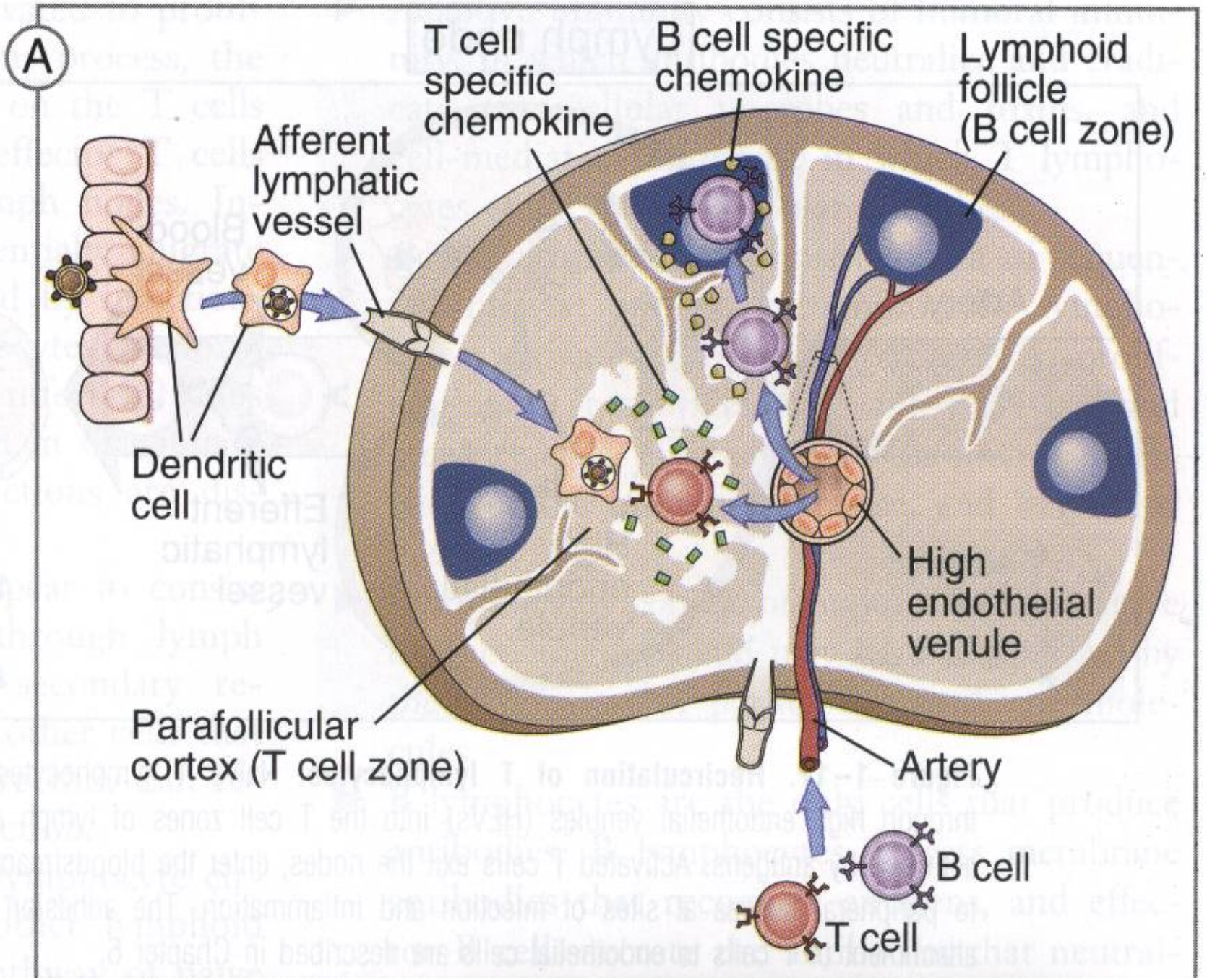




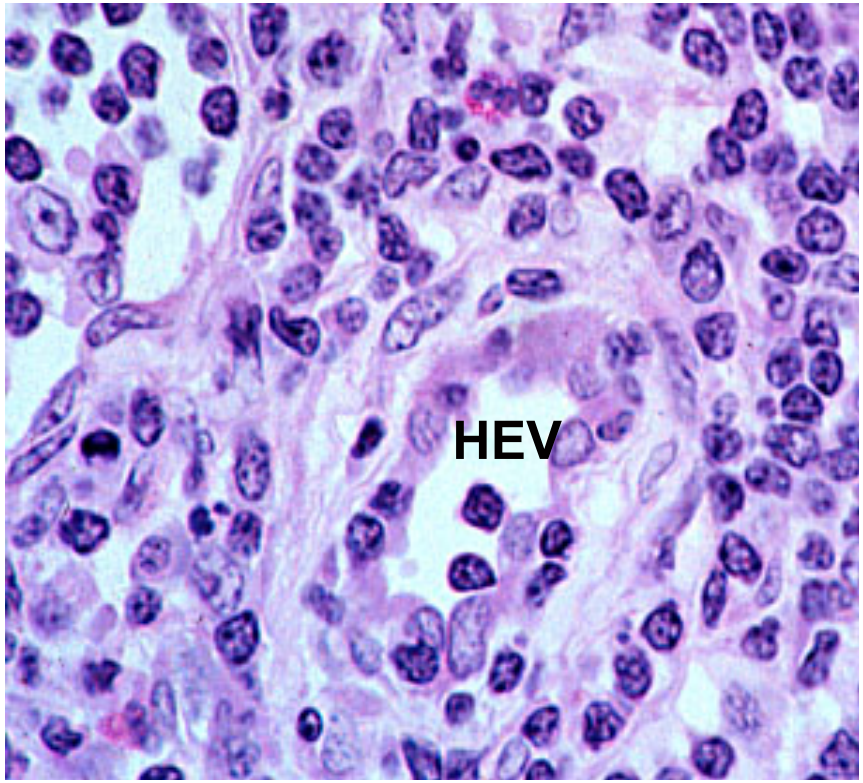
Nature Reviews | Immunology

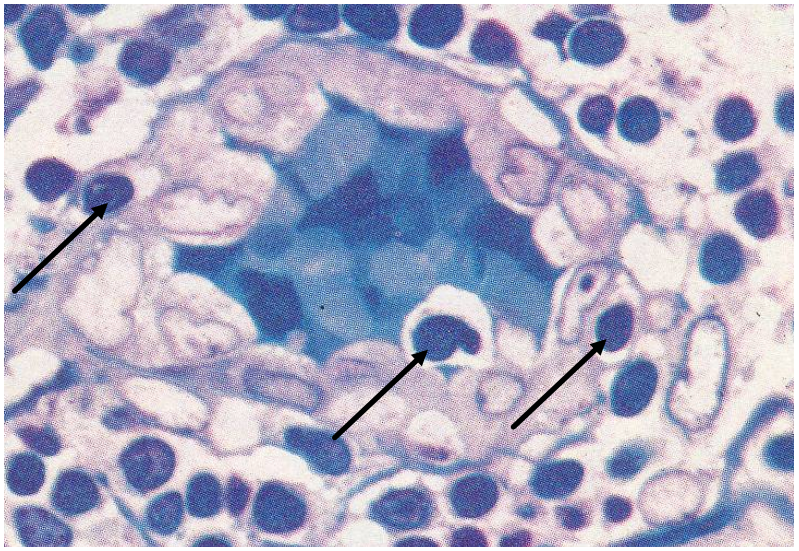
Lymph node


4. Germinal centre (site of intense B cell proliferation)
3. Secondary lymphoid follicle
2. Primary Lymphoid follicle (B cell area)
Paracortical (T cell) area
1. Afferent lymphatic vessel. Lymph, Ag, & cells with captured Ag drained from tissues enters here
5. Medullary cords (Macrophage & plasma cell area)
6. Efferent lymphatic vessel
Artery
Vein
Medullary sinus


A
T cell specific chemokine
B cell specific chemokine
Lymphoid follicle (B cell zone)
Afferent lymphatic vessel
Dendritic cell
High endothelial venule
Parafollicular cortex (T cell zone)
Artery
B cell
T cell

High endothelial venules

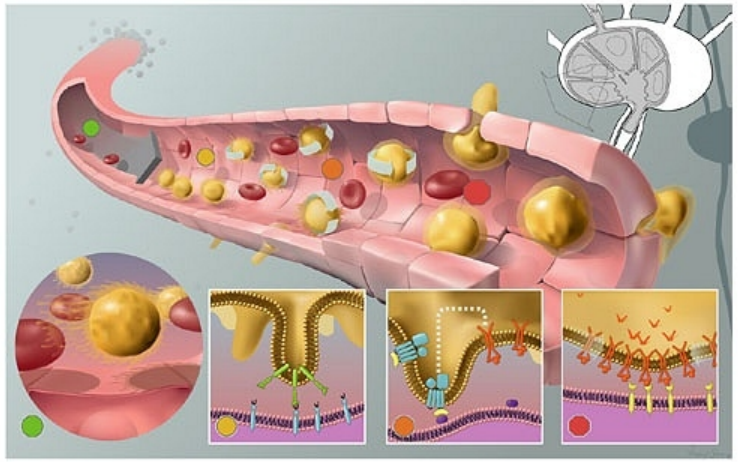


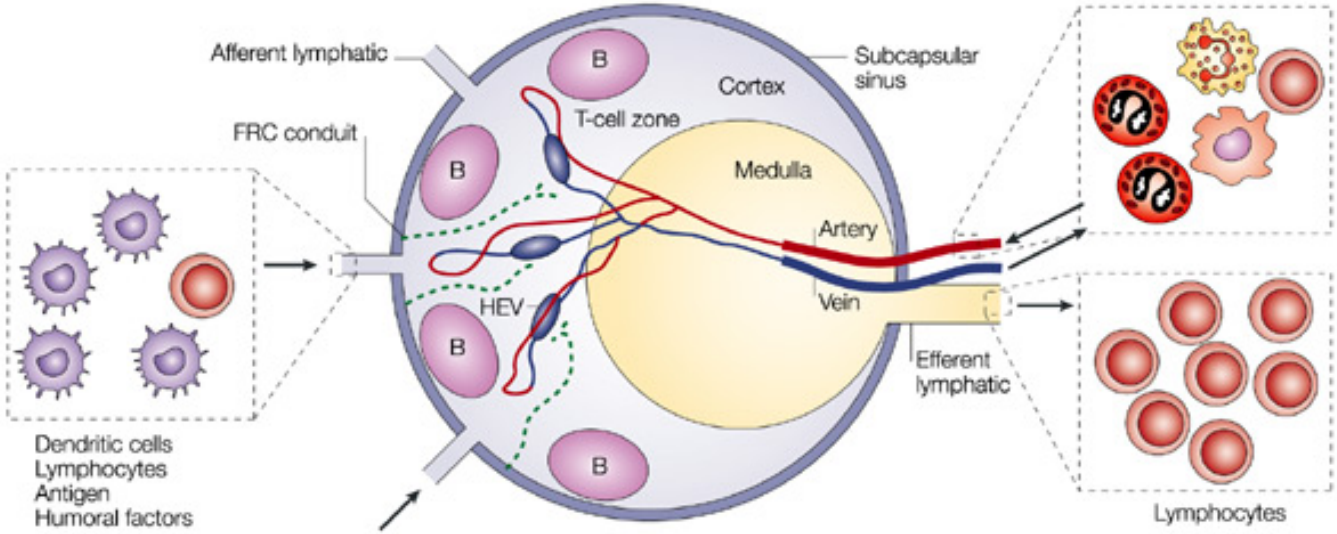


Blood enters lymph node via the artery
Post capillary venules in the paracortex have cuboidal endothelial cells

HIGH ENDOTHELIAL VENULES - specialised properties to allow lymphocytes and nothing else into the lymph node

High endothelial venules





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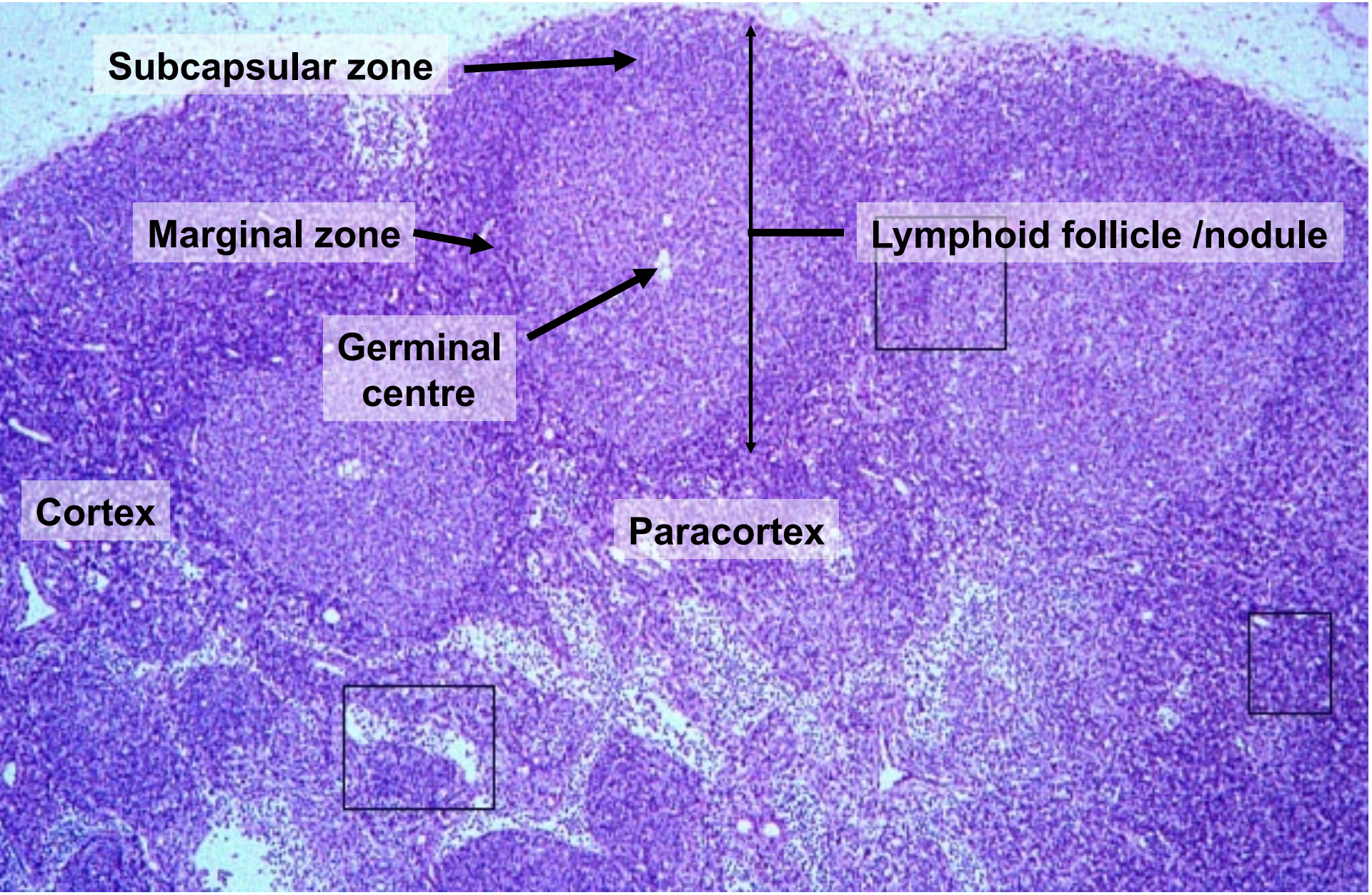
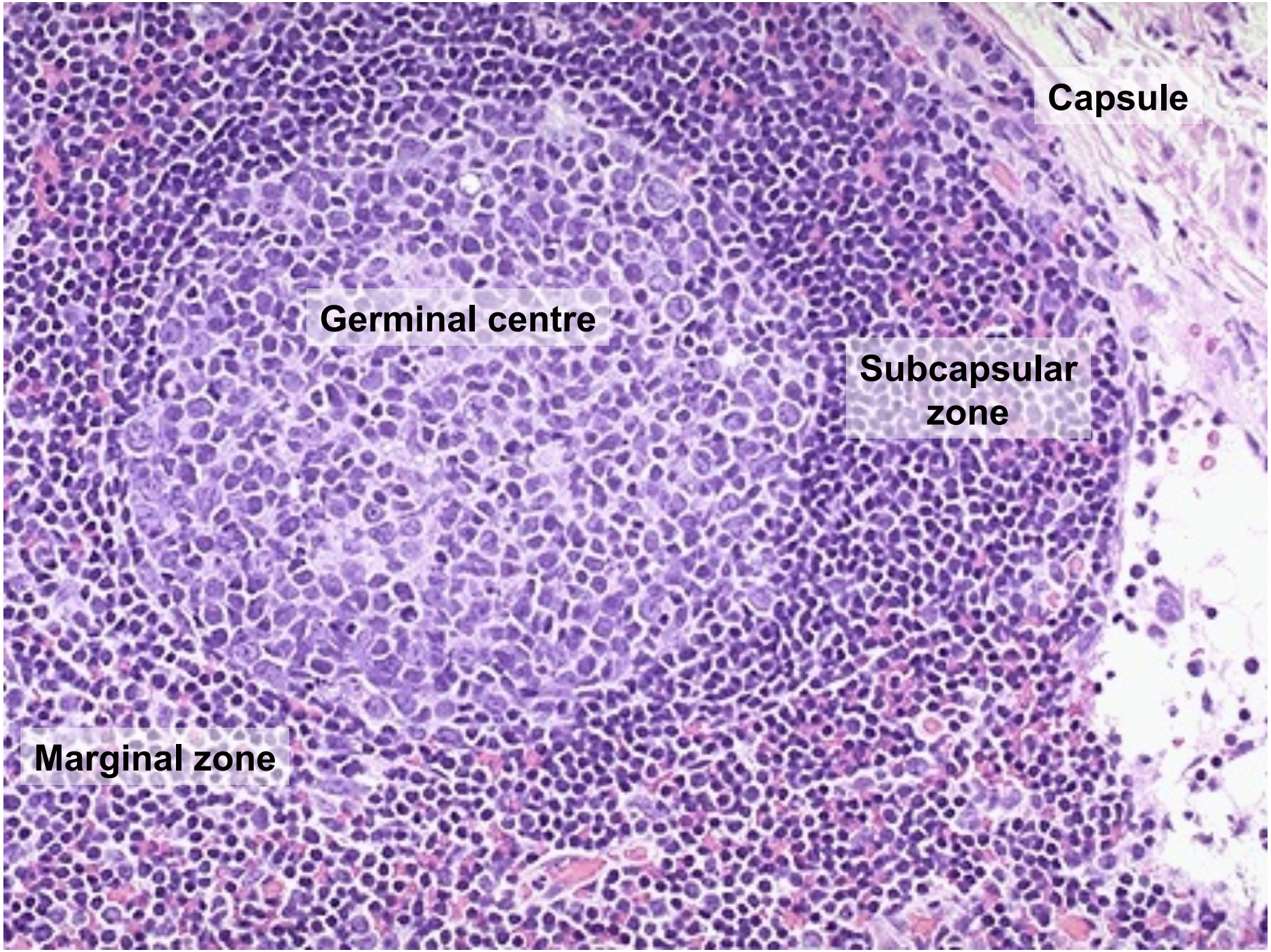
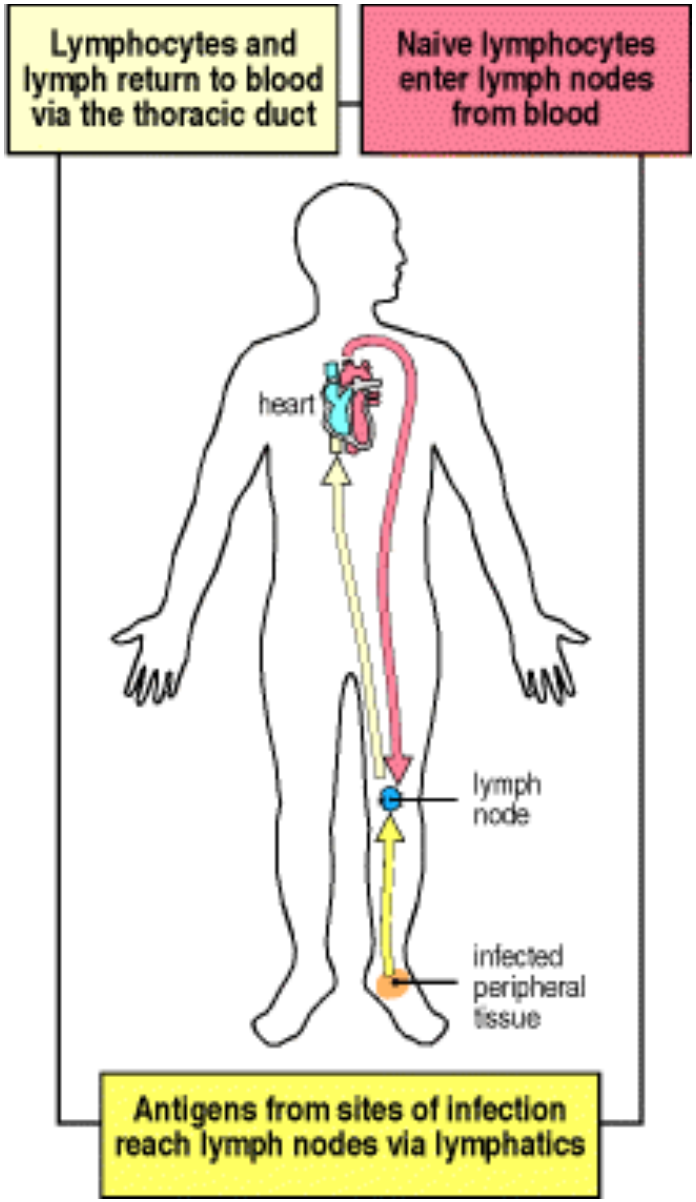
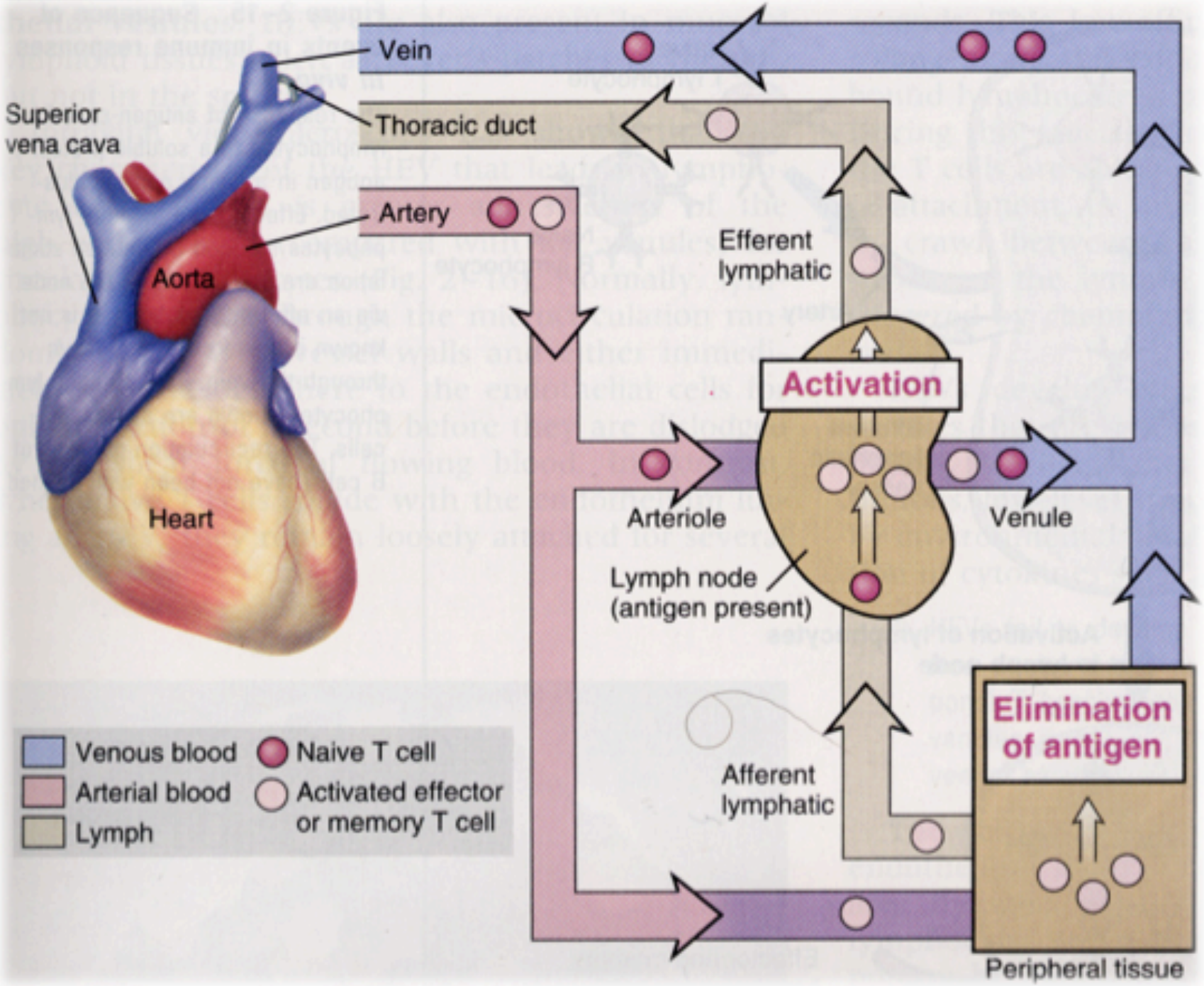

Subcapsular zone
Marginal zone
Germinal centre
Lymphoid follicle /nodule
Cortex
Paracortex

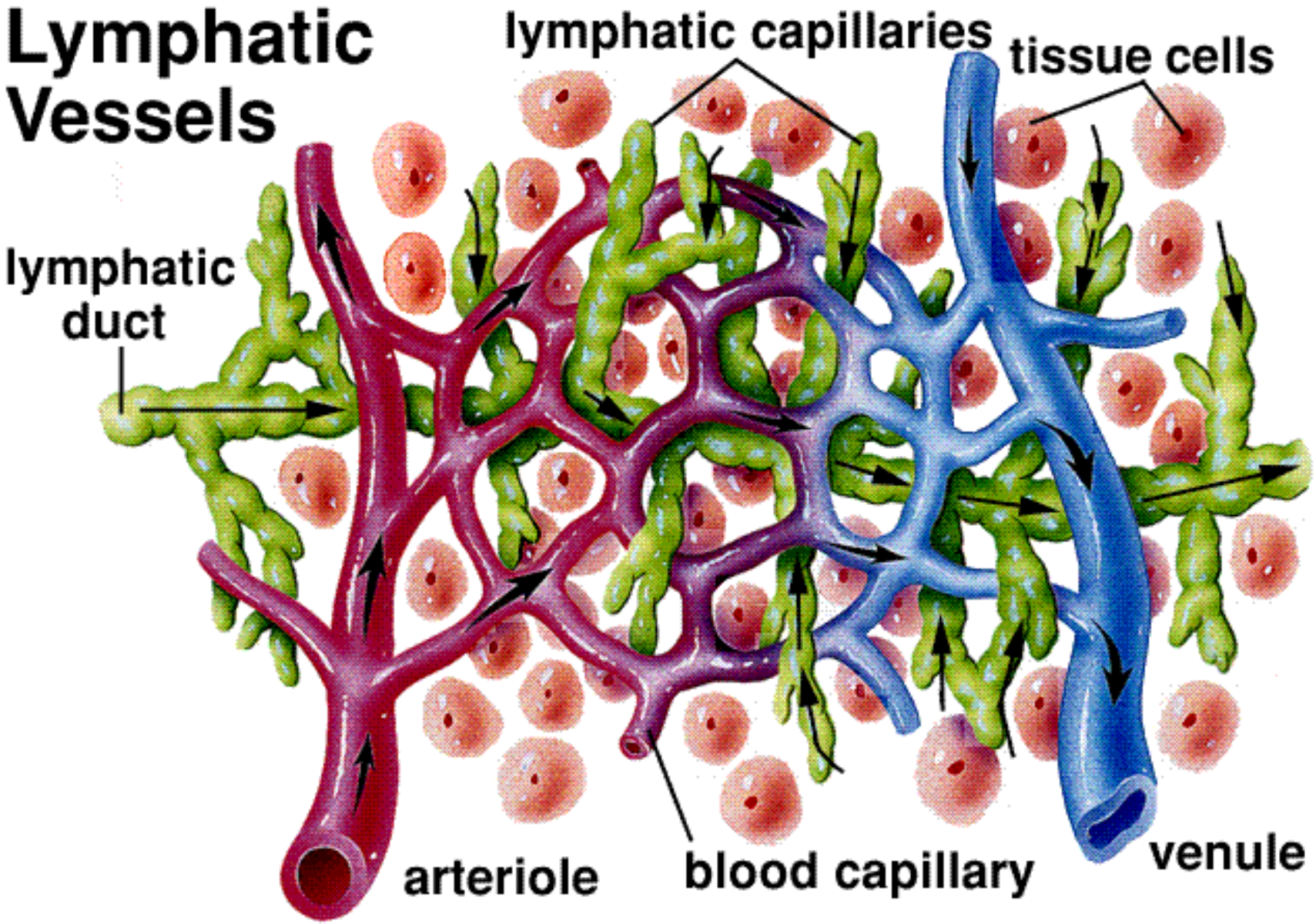

Capsule
Germinal centre
Subcapsular zone
Marginal zone

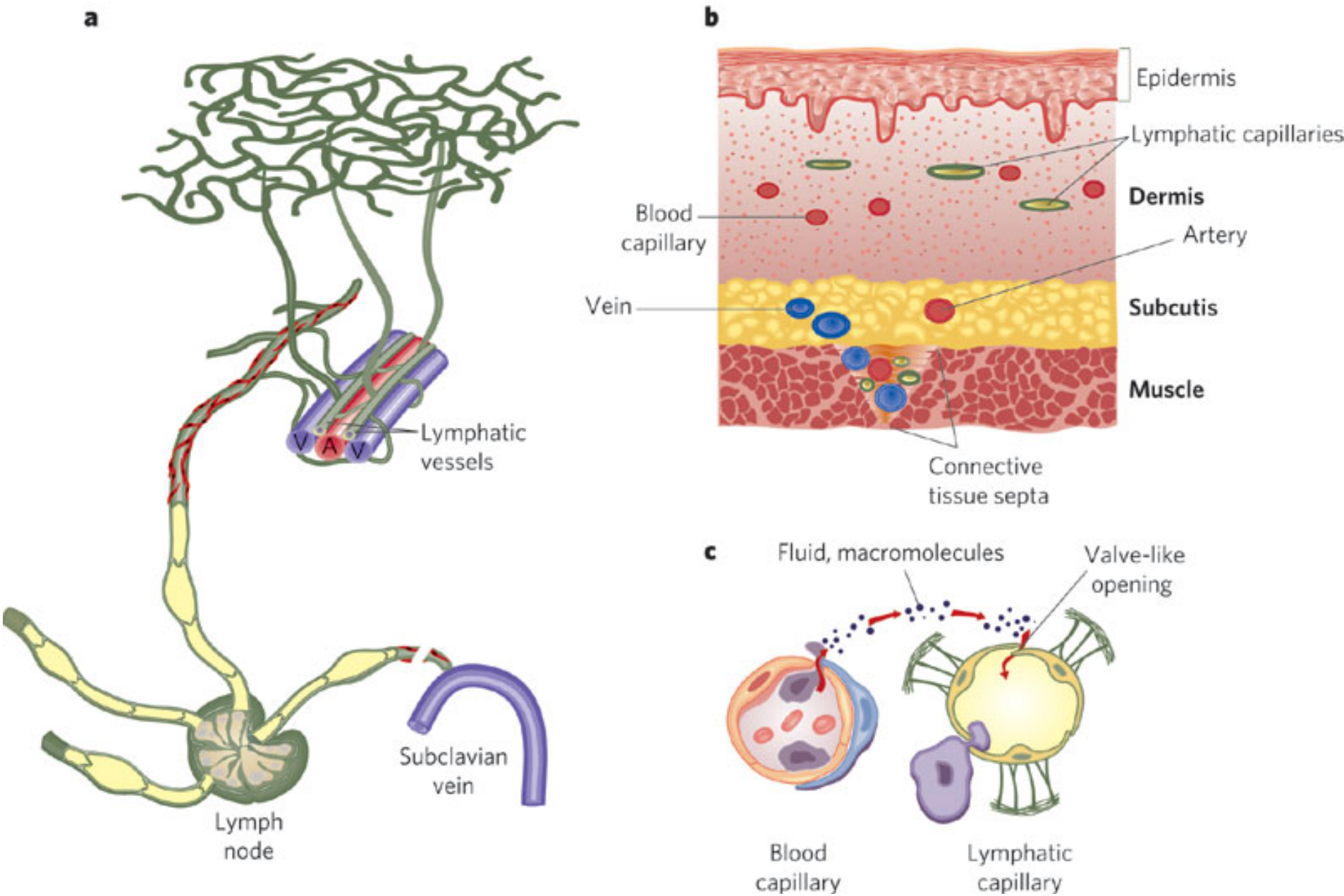

Lymphocytes and lymph return to blood via the thoracic duct
Naive lymphocytes enter lymph nodes from blood
heart
lymph node
infected peripheral tissue
Antigens from sites of infection reach lymph nodes via lymphatics

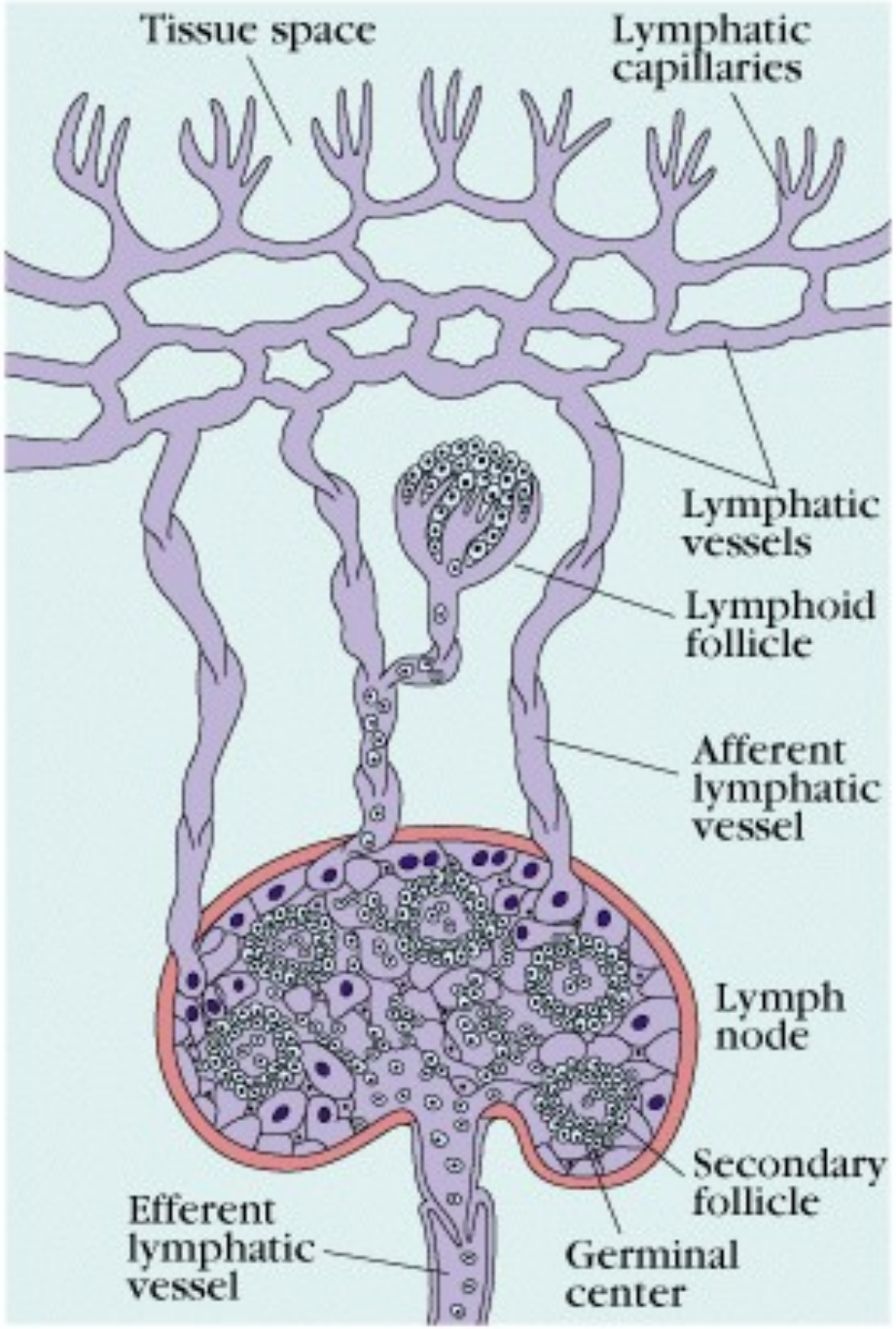

Vein
Thoracic duct
Superior vena cava
Artery
Aorta
Heart
Efferent lymphatic
Activation
Arteriole
Venule
Lymph node (antigen present)
Elimination of antigen
Afferent lymphatic
Peripheral tissue
Venous blood
Arterial blood
Lymph
Naive T cell
Activated effector or memory T cell

Sylvia S. Mader, Inquiry Into Life, 8th ed. Copyright © 1997 Wm. C. Brown Publishers

Lymphatic Vessels




a
V
A
V
Lymphatic vessels
Subclavian vein
Lymph node
b
Epidermis
Lymphatic capillaries
Dermis
Blood capillary
Artery
Vein
Subcutis
Muscle
Connective tissue septa
c
Fluid, macromolecules
Valve-like opening
Blood capillary
Lymphatic capillary


Tissue space
Lymphatic capillaries
Lymphatic vessels
Lymphoid follicle
Afferent lymphatic vessel
Lymph node
Secondary follicle
Germinal center
Efferent lymphatic vessel

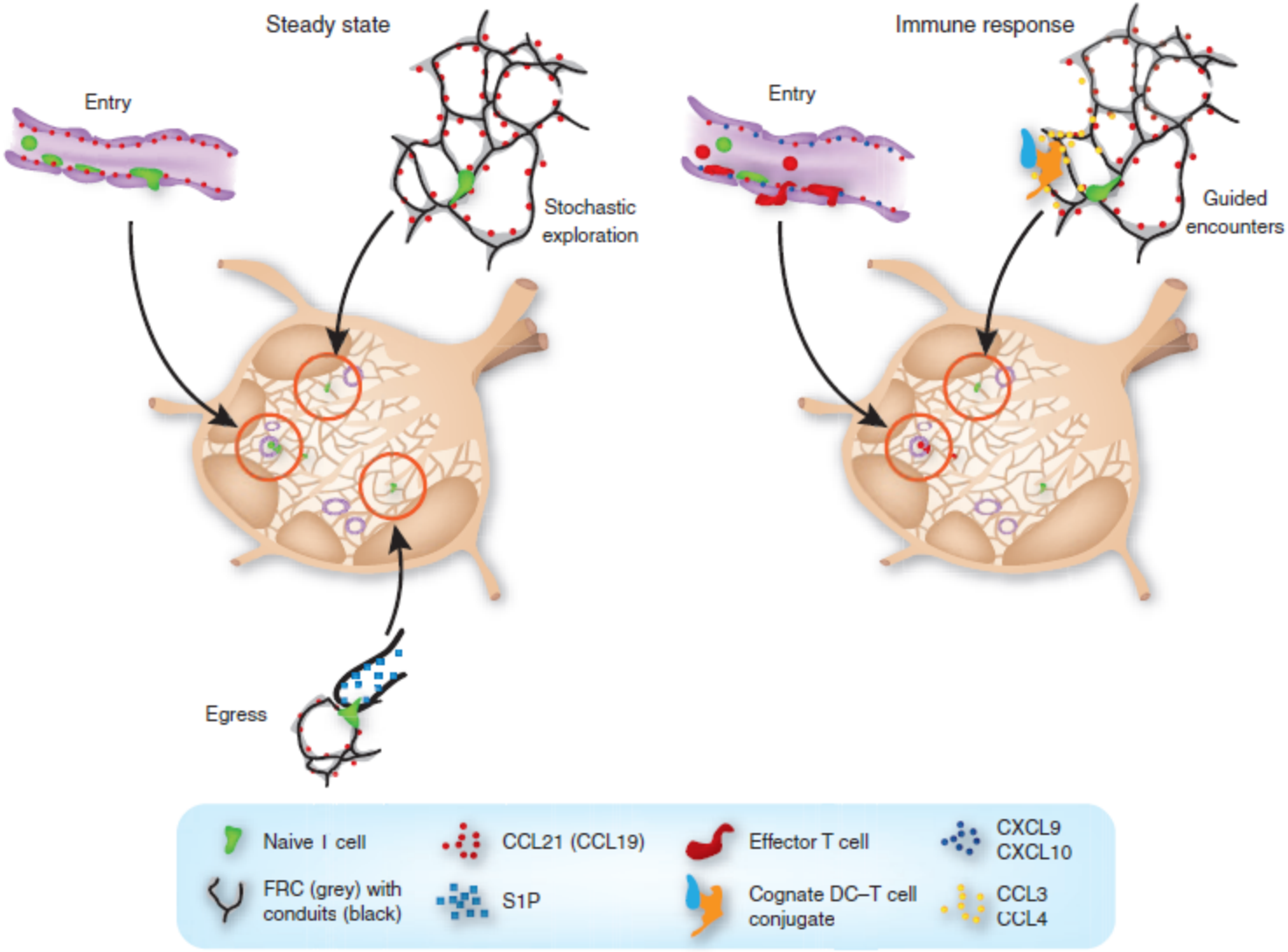
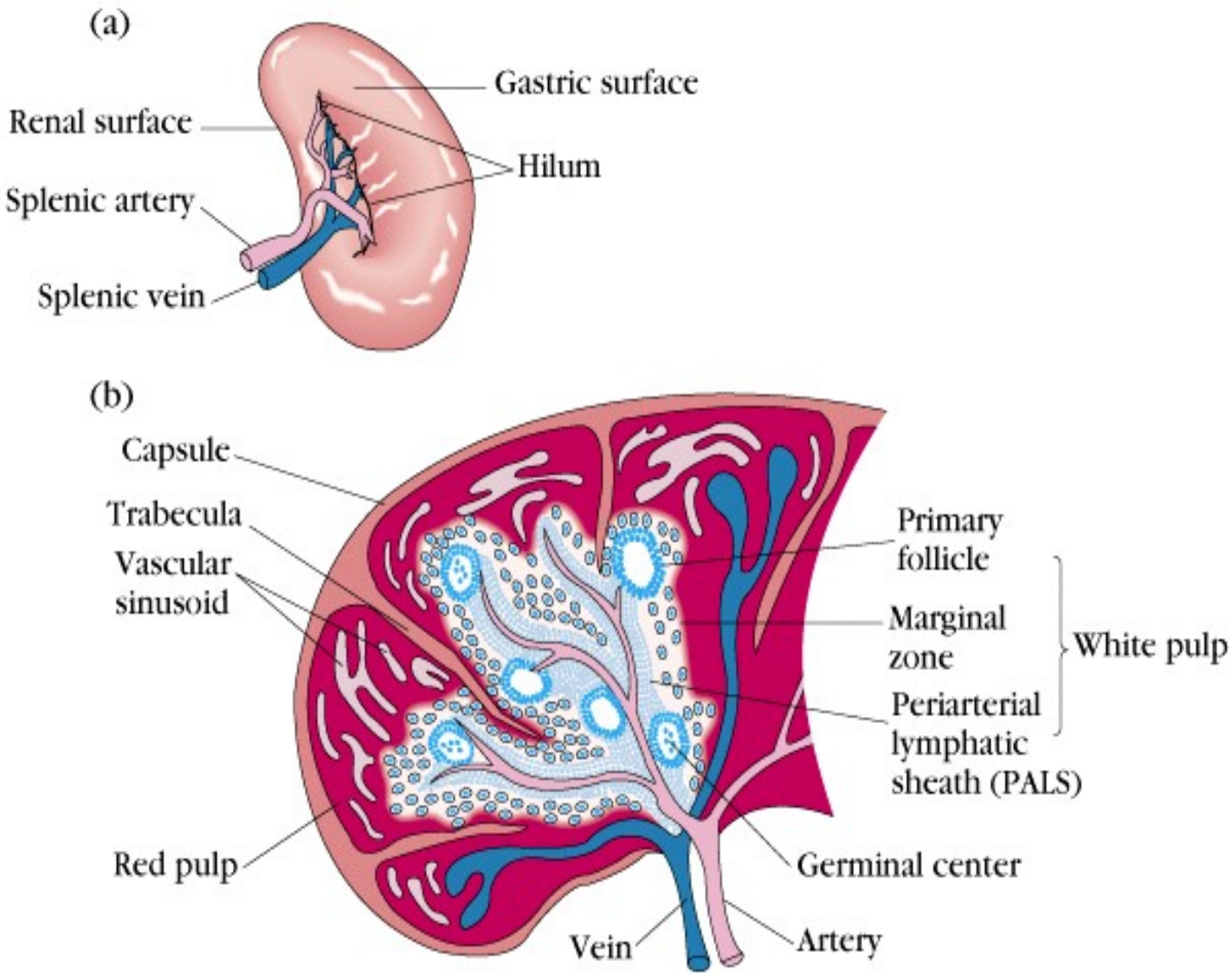
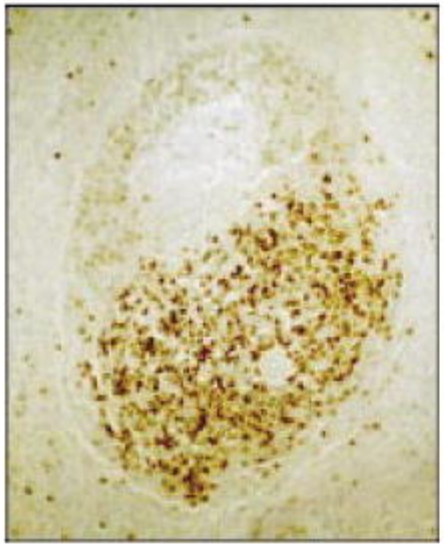
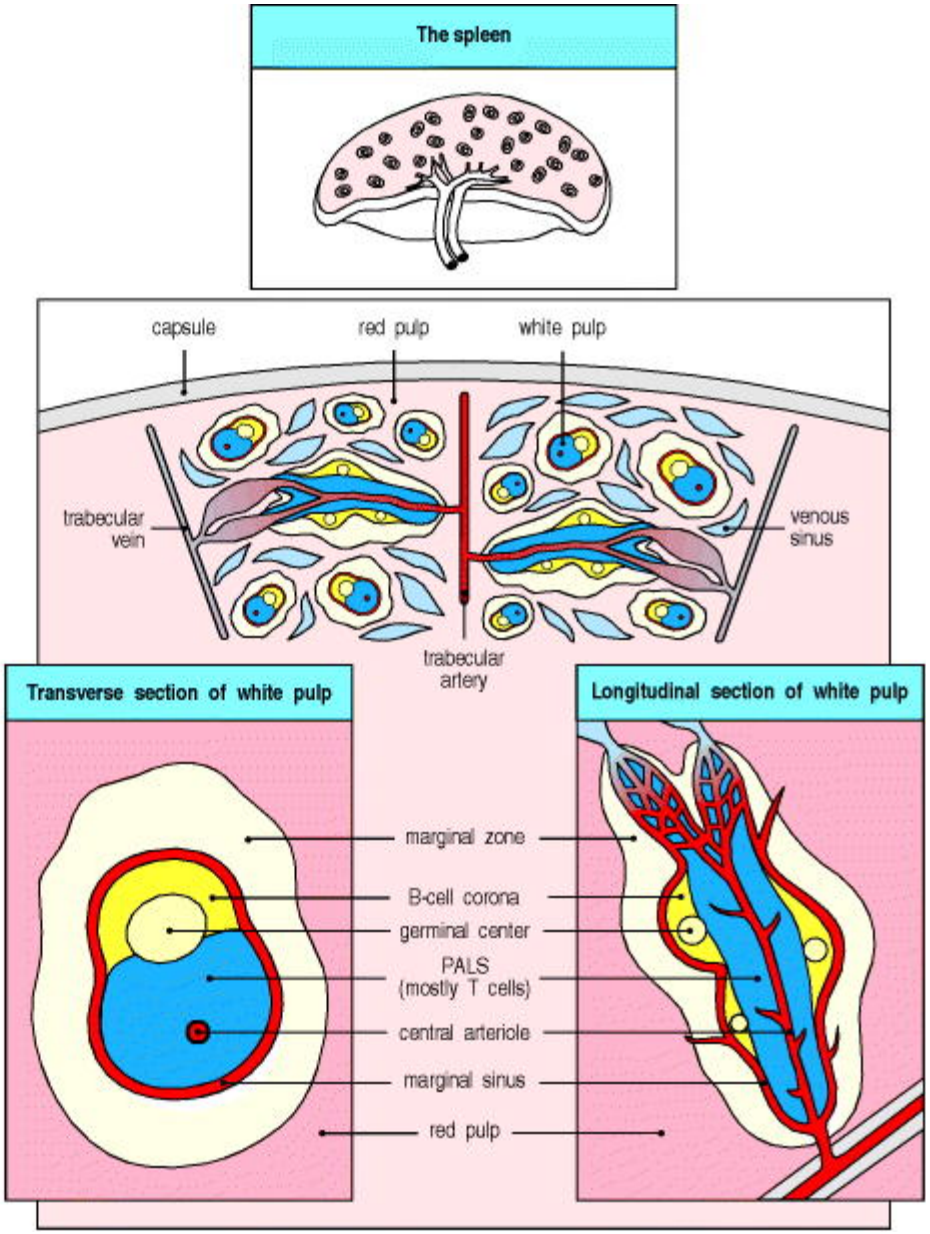


Figure 1 Chemokine control of T cell migration in the lymph node in the steady state and during the immune response. In the steady state (left), stromal cells are the chief source of the CCR7 ligand


(a)
Gastric surface
Renal surface
Hilum
Splenic artery
Splenic vein
(b)
Capsule
Trabecula
Vascular sinusoid
Primary follicle
Marginal zone
White pulp
Periarterial lymphatic sheath (PALS)
Red pulp
Germinal center
Vein
Artery

BAÇO




The spleen
capsule
red pulp
white pulp
trabecular vein
venous sinus
trabecular artery
Transverse section of white pulp
Longitudinal section of white pulp
marginal zone
B-cell corona
germinal center
PALS (mostly T cells)
central arteriole
marginal sinus
red pulp

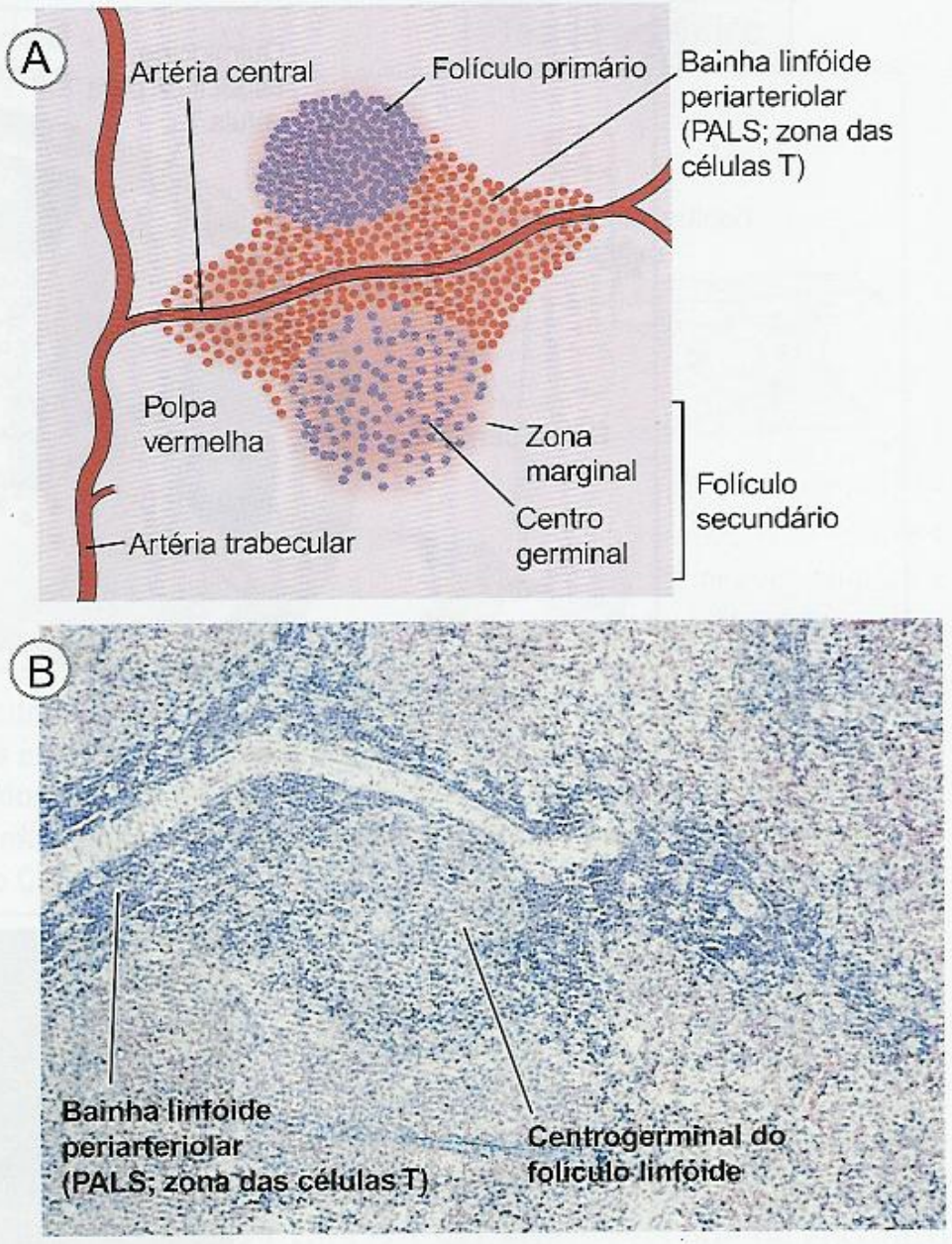
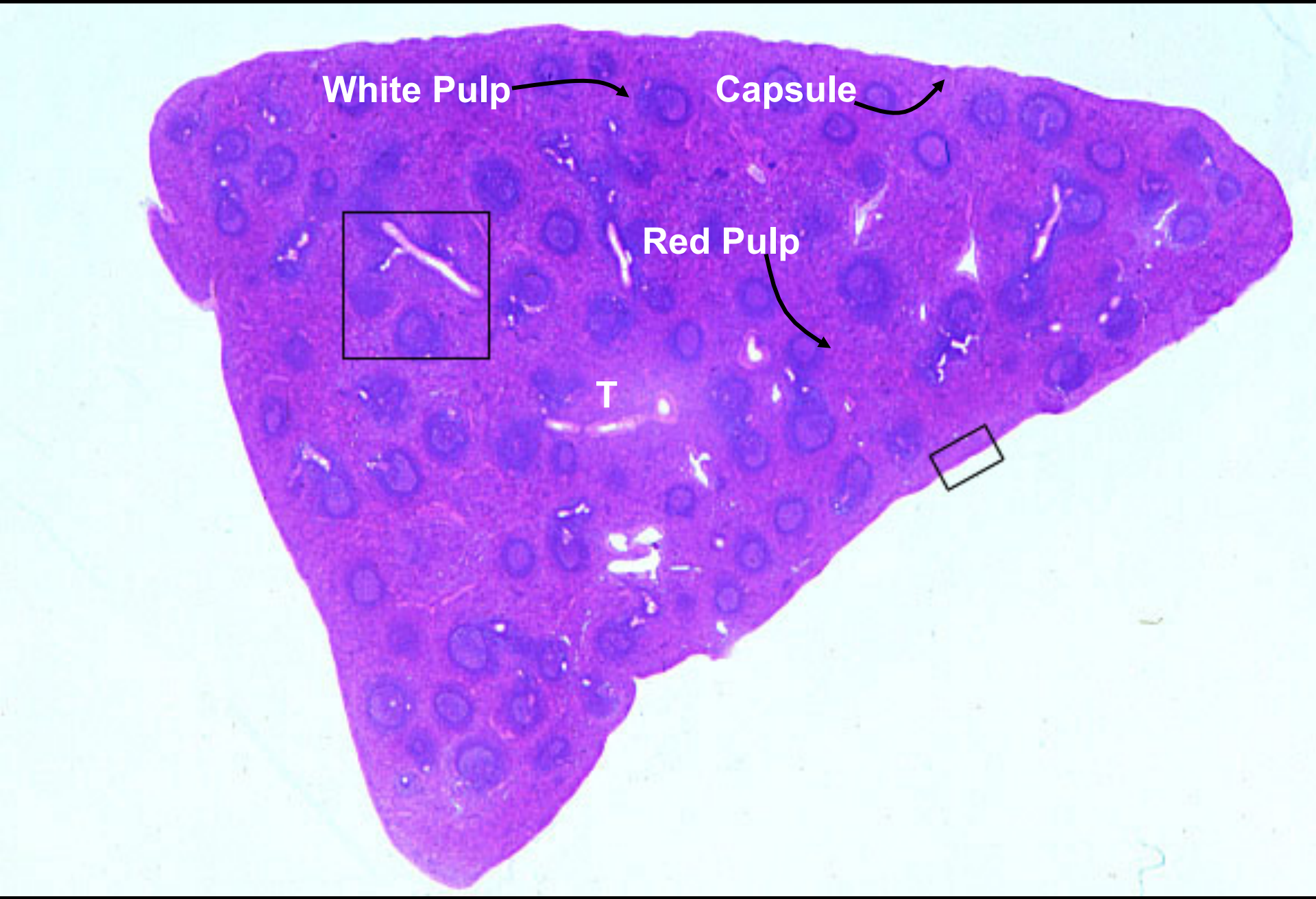
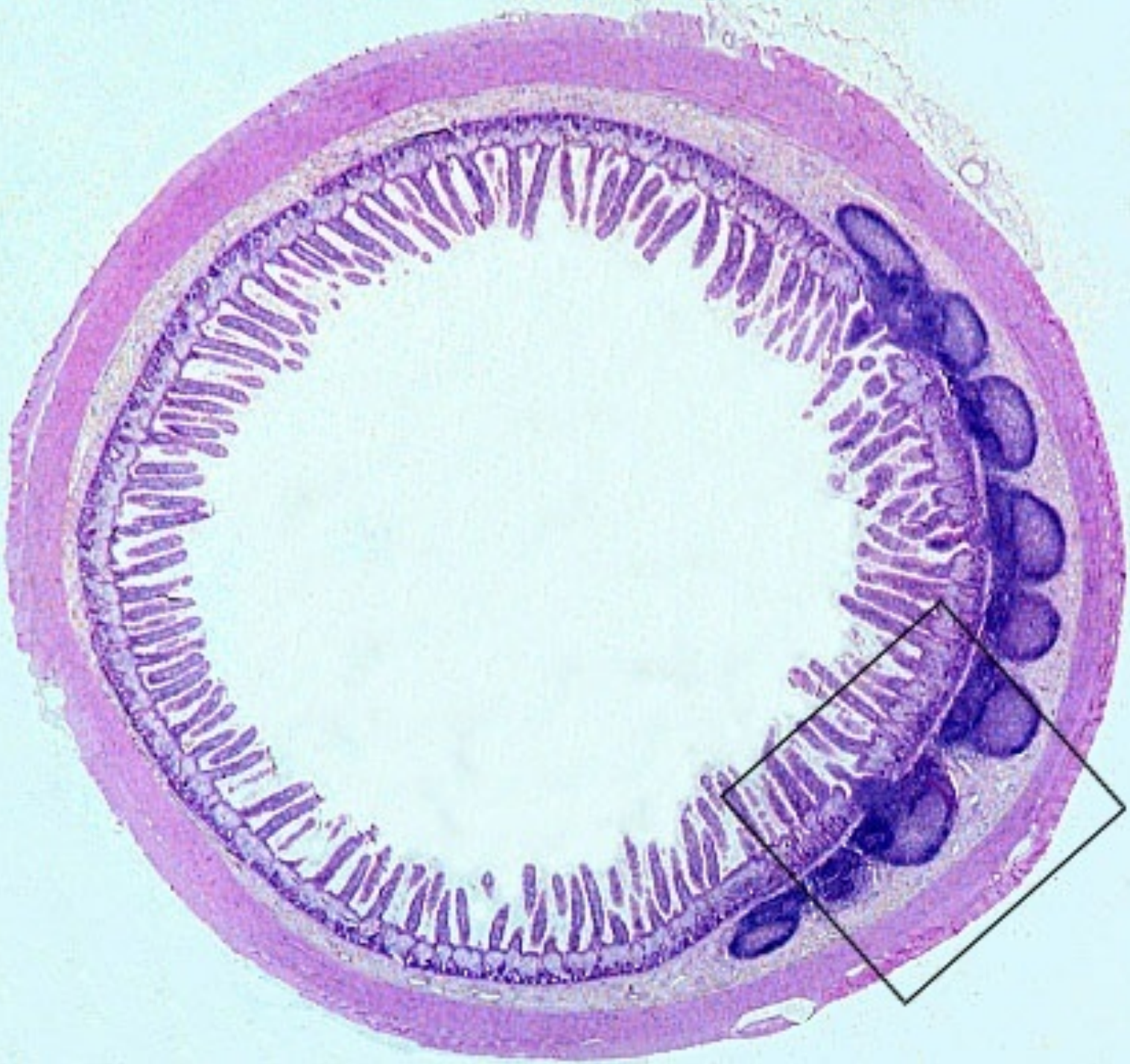
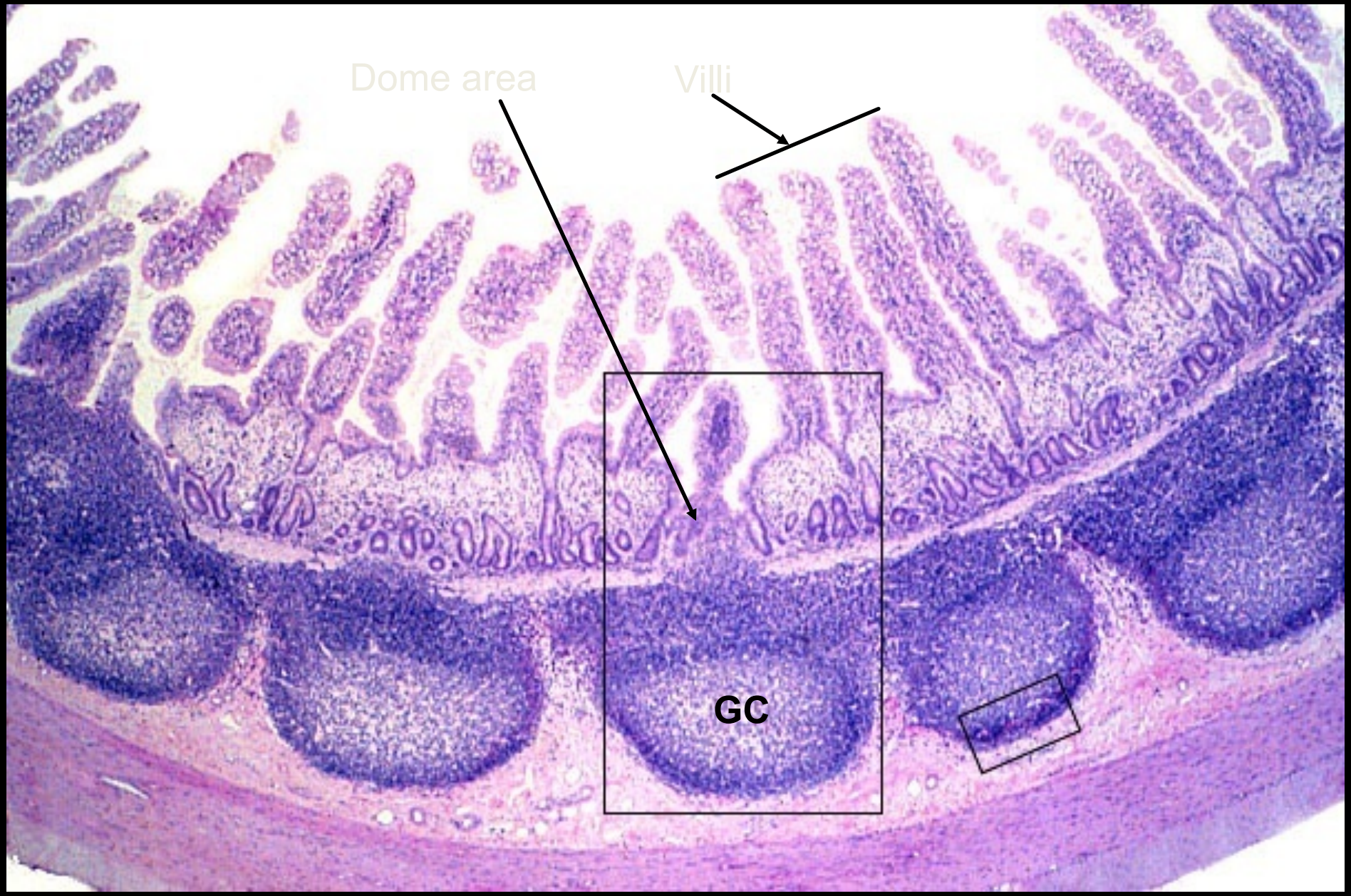
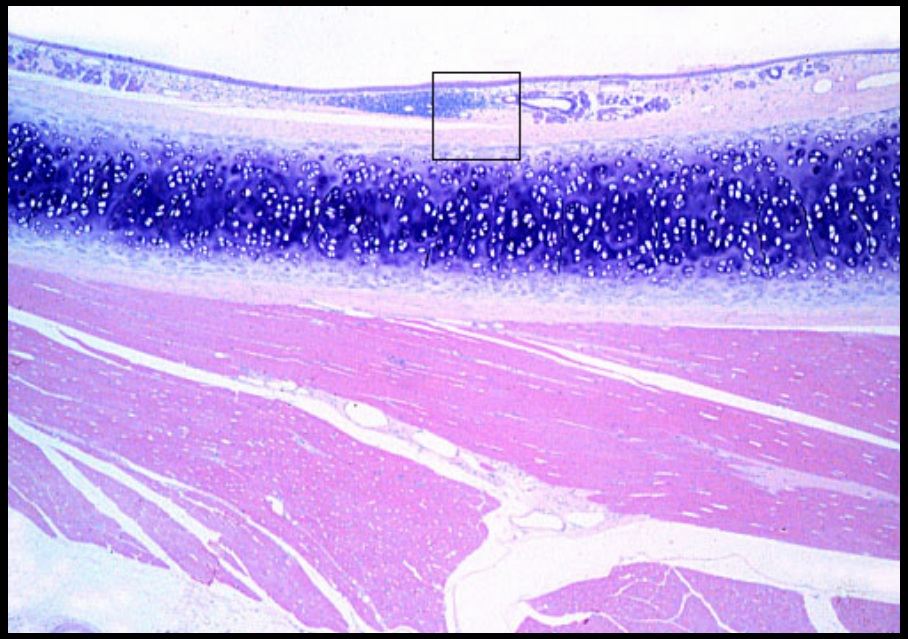


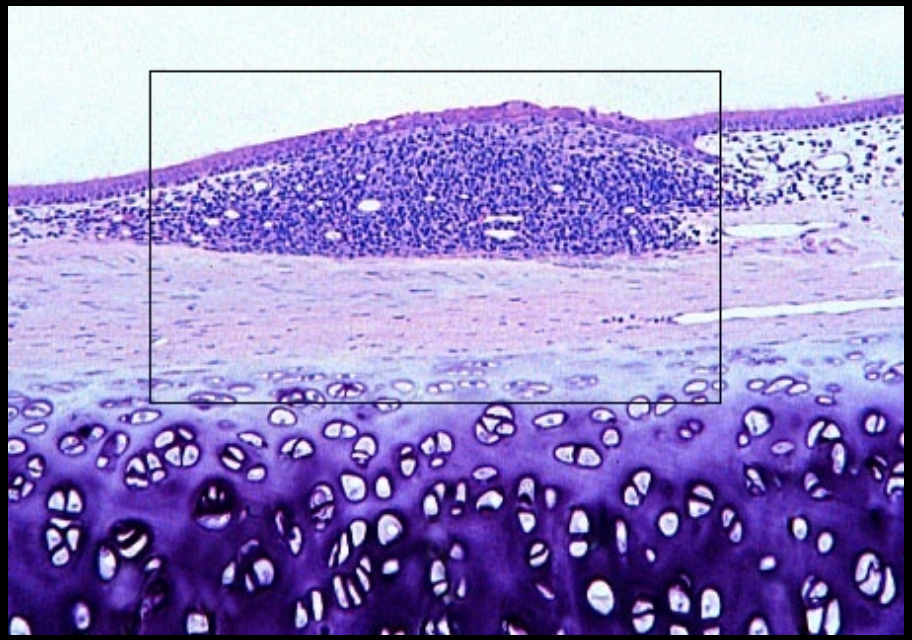
Figura 1-15. A morfologia do baço. A. Este diagrama esquemático mostra uma arteríola esplênica cercada pelas bainhas linfóides periarteriolares (PALS) e dois folículos linfóides anexados; o folículo abaixo da arteríola contém um centro germinativo proeminente. As PALS e os folículos linfóides juntos constituem a polpa branca. B. Essa microfotografia de um corte do baço mostra uma arteríola com as PALS e um folículo secundário. Esses estão cercados pela polpa vermelha que é rica em sinusóides vasculares.


White Pulp
Capsule
Red Pulp
T




Dome area
Villi
GC



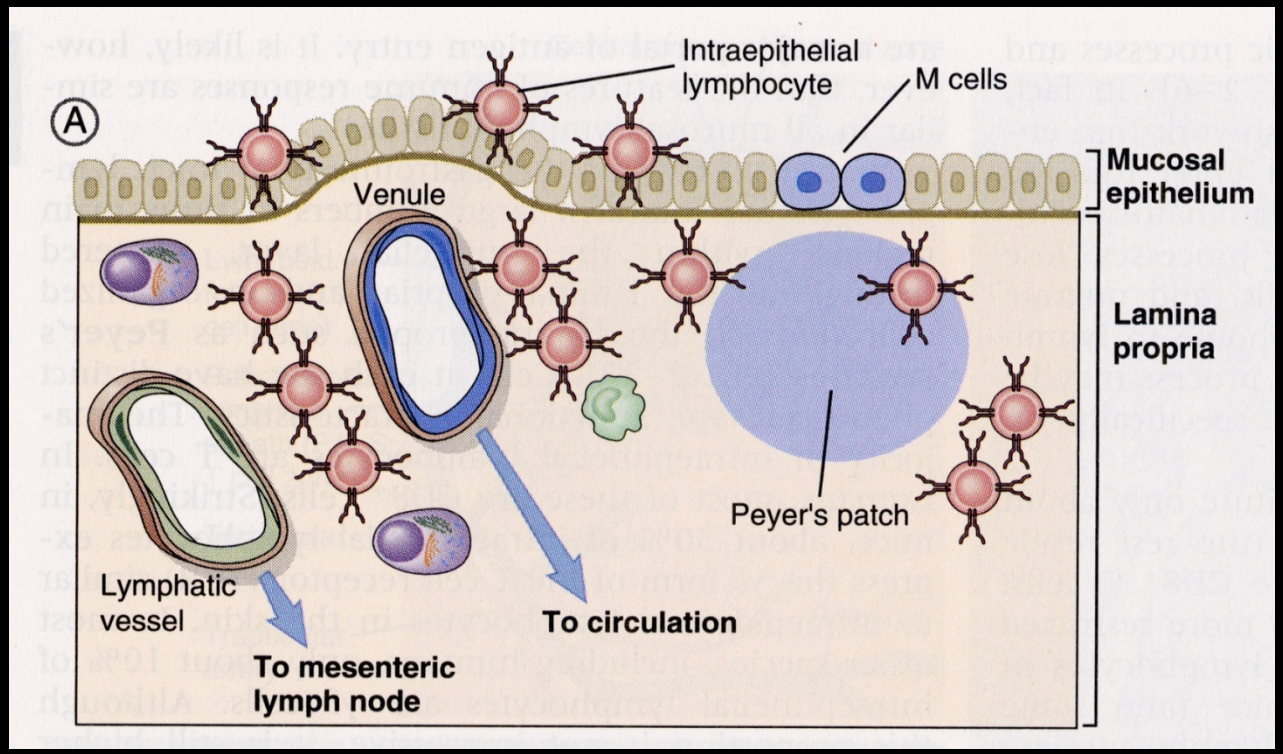


Lymphoid tissue in the airway

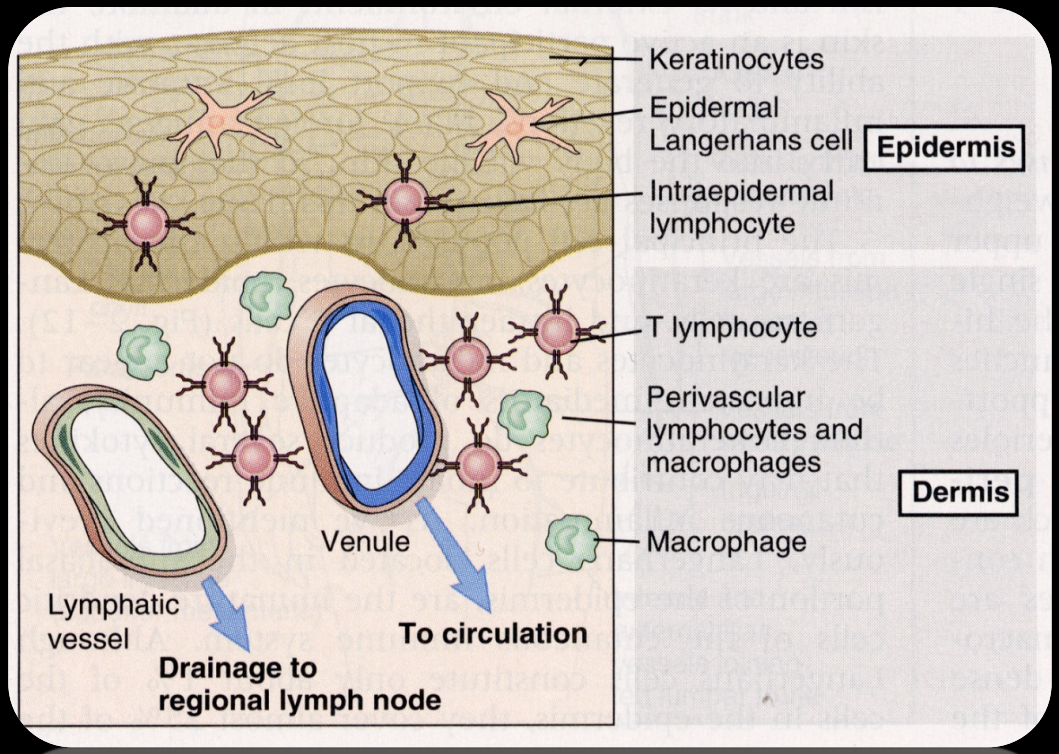
Órgãos Linfóides Periféricos

Sistema Imune de Mucosas

- Primeira barreira aos antígenos externos
- Maior área exposta do organismo
- Linfócitos Intraepiteliais: TCRαβ CD8$^+$ (homem) / TCRγδ (camundongo)
- Lâmina própria: CD4$^+$ ativados / Macrófagos / DCs / Eosinófilos / Mastócitos
- Folículos linfóides de mucosa: Células B (R. Central) / Células T CD4$^+$(R. interfolicular)
- Células M: transporte de antígenos
- Alta produção de IgA
- Imunização oral: Tolerância



Órgãos Linfóides Periféricos

Sistema Imune Cutâneo

- **Primeira barreira aos antígenos externos**
- **Queratinócitos: citocinas (IMUNIDADE INATA)**
- **Células de Langerhans: cobrem 25% da superfície (Migram para os LN nas inflamações)**
- **Linfócitos Intraepidérmicos: 2% do total da pele / Maioria $CD8^+$ / TCRγδ**
- **Linfócitos da derme: TCRαβ $CD4^+$ (ativados ou memória)**