The thymus in the adult lies behind the sternum, above the heart.
Thymus

- Initially epithelial cells giving rise to thymus are contiguous
- Lymphocytes arriving from yolk sac and liver push the epithelial cells apart, week 10
- Cells remain connected via desmosomes between their processes forming a sponge-like meshwork of epithelial cells = reticular epithelial cells
- Induce lymphocytes to proliferate and distribute into medulla and cortex
- Blood vessels grow in, week 14-15
- Lymphocytes differentiate into T-cells, leave and populate other organs
The Thymus is the Site of T-cell Maturation

- Epithelial cells (thymic stroma)
  - forming a sponge-like meshwork of epithelial cells = reticular epithelial cells
- T-cells - Lymphopoiesis (proliferate and mature)
- Mature T-lymphocytes leave via venules in the medulla and travel through the blood to populate peripheral organs
- If the thymus fails to form, and T-cells do not develop
Thymus

Epithelial cell

Immature T-cells (Thymocytes)

Hassal’s corpuscle

Capillary
Fetal Thymus: **Lobes**

- **Cortex**: immature cells
- **Medulla**: mature cells
The cortex contains immature thymocytes which move into the medulla as they mature.
Adult thymus

- Rate of T-cell production peaks prior to puberty
- Greatly reduced but continuous through adulthood
- Thymus undergoes Involution
  - Fatty infiltration
  - Lymphocyte depletion
Figure 2-13

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Adult thymus undergoing involution

Cortex
Adipose
Medulla
DiGeorge syndrome

- deletion on chromosome 22
- defect of cranial neural crest cell migration into arches
- congenital thymic hypoplasia = anlage of the thymus does not form
- variety of other defects involving facial, thyroid, parathyroid and cardiovascular system

“Anlage” - an organ in its earliest stage of development; the foundation for subsequent development, primordium
Nude mice

- Lack T-lymphocytes
- Recessive nude gene, chromosome 11
- Failure of thymic anlage to form
  - no “home” for presumptive T-lymphocytes
- Hairlessness
- SCID mice are also immunodeficient but for a different reason (failure of TCR, BCR gene rearrangements and T&B cells do not mature)
Scientists have grown a fully functional organ from transplanted laboratory-created cells in a living animal for the first time.

- They grew a working thymus -- an important organ that supplies the body with immune cells.
- Left: thymus epithelial cells were developed from MEF cells by reprogramming.
- Right: transplanted to mouse kidney to form an organized and functional mini-thymus in a living animal - sustained T-cell develop

Nicholas Bredenkamp, Svetlana Ulyanchenko, Kathy Emma O’Neill, Nancy Ruth Manley, Harsh Jayesh Vaidya, Catherine Clare Blackburn. *An organized and functional thymus generated from FOXN1-reprogrammed fibroblasts. Nature Cell Biology, 2014; DOI: 10.1038/ncb3023*
Secondary lymphoid organs

• Specialized for trapping antigen facilitating presentation to lymphocytes
• Characterized by:
  – Localized areas for T-cells and B-cells
  – Follicles where B cells mature
Schematic diagrams of various types of lymphoid tissue

- Diffuse
- Solitary follicle
- Aggregated follicle
- Lymph Node
- Spleen
- Thymus
Lymphoid follicle

Germinal Centers
• Are formed when activated B cells enter lymphoid follicles and proliferate
• Somatic hypermutation
• Affinity maturation
• Isotype switching
• Selected B cells will mature to plasma cells or become memory cells
Follicle with germinal center

- **Germinal Center**
  - **Mantle Zone**: resting cells
  - **Light zone**: more mature, smaller centrocytes contact follicular dendritic cells
  - **Dark zone**: closely packed, rapidly dividing centroblasts
Encapsulated peripheral lymphoid organs

- **Lymph nodes**
  - filter Ag from lymph
  - Receive Ags and APCs from local sites

- **Spleen**
  - filters Ag from blood
  - Ags from systemic infections
The Lymph Node: filters lymph

- Filters lymph
- Filtering stations interposed in the lymphatic vessels
- Varying sizes (pinhead to walnut)
- Present everywhere, but large and numerous ones are found in certain sites: axillary, groin (inguinal LNs), near the abdominal aorta (coeliac LNs), in the neck (cervical LNs) and in the mesentery (mesenteric LNs)
- Regional nodes: draining particular regions or organs
Lymph nodes filter lymph

Lymphatic vessels

Lymph node
Figure 2-16b
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HEVs

- Lymphocyte
- Afferent lymphatic vessels
- Germinal centers
- Postcapillary venule
- B lymphocytes
- Valve
- Extravasating lymphocyte
- Primary lymphoid follicle
- Capsule
- Cross section postcapillary venule
- Bloodstream
- Capsule
- Lymphatic artery
- Lymphatic vein
- Efferent lymphatic vessel
- Lymphocyte
- Valve
Follicular reticular cell conduit system

Figure 2-9b part 1
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The Spleen: filters blood

• In contrast to lymph nodes, which are inserted in the lymph circulation, the spleen is inserted in the blood circulation.

• Oblong, purplish body the size of a fist, on the left side

• Smooth surfaced except for hilus, where blood vessels enter and leave

* There are no lymphatics leading to the spleen.
The Spleen has 2 major regions

• **White Pulp: lymphatic**
  – Small arterioles surrounded by sheaths of lymphocytes = Peri-Arteriole Lymphoid Sheaths (PALS- human arrangement slightly different)
  – Surrounded by marginal zone

• **Red Pulp: clears RBCs**
  – “Cords” of cells: Erythrocytes, macrophages, dendritic cells, few lymphocytes and plasma cells
  – Also contains venous Sinusoids
Spleen- surface of a fresh cut appears stippled due to red and white pulp.
White pulp: two components

1. PALS- T cells
   • periarteriole lymphoid sheath

2. Lymphoid follicles- B cells
   • spherical structures Scattered throughout PALS
   • Visible to the naked eye on the surface of a freshly cut spleen as white spots.
Spleen- human

capsule

Red pulp

Central artery

trabeculae

White pulp
Spleen: Red Pulp and Sinusoids

Reticular fibers and endothelial cells
Function of the spleen cont.

- Erythrocytes enter the red pulp, push through the masses of macrophages filling the splenic cords and enter the sinuses.
  - Macrophages engulf old rbcs and antigens in blood
- Lymphocytes are brought into the spleen by the arteries and arterioles; they enter the marginal sinus and then migrate to their respective domains
  - B cells to the follicles, T cells to the PALS
Spleen - Red pulp

Red pulp cord

Sinusoid

M
Mucosal Immune System
MALT- Mucosal Associated Lymphoid Tissue

- Mucosal surfaces of mouth, respiratory and reproductive tracts are colonized by lymphocytes and accessory cells
- Respond to ingested, inhaled antigens
- BALT (bronchial):
- GALT (gut):
  - Tonsils
  - Peyer’s Patches
  - Appendix
Solitary lymphoid follicles

- Surrounded by a network of draining lymphatic capillaries
- Do not occupy fixed positions; they come and go depending on the conditions in a given organ at a given time.
- Found in the same place as diffuse lymphoid tissue - submucosa under epithelium
- Particularly abundant in the digestive (esp intestine), respiratory and genital tracts
Tonsils

- Latin *tonsar* (stake set up on the shore)
- At entrance to GI tract:
  - 1 pharangeal = "adenoids"
  - 2 tubal
  - 2 palatine = "tonsils" (from pouch 2)
  - 1 lingual
Diagram of the Tonsil

- **Aggregated lymphoid follicles**
- Corrugated surface with cracks and pits CRYPTS lined with *stratified squamous epithelium*
- become filled with sloughed off cells, dead lymphocytes and fluid
- good culture medium for bacteria
Peyer’s Patches (~30) are found in the ileum (small intestine) in the wall opposite the mesentery.

Each is a collection of many individual lymphoid follicles (pink) scattered between the microvilli “like puffballs on a lawn”.

X-section showing the follicles in the submucosa.
Plane of cross section shown in next slide
Identify the lymphoid organ indicated by the green arrows.
M cell (microfold cell) in the surface of the Peyer’s patch is the cell specialized to uptake Ag from the gut.
M cells do not have microvilli, but have a flat smooth surface. They have a deep pocket under them containing B cells, T cells and APC’s, including DCs. They endocytose Ags from the gut and transport them across the cell to deliver them to the area of the immune cells. Leads to activation of B cells– become plasma cells and release Abs into the gut.
Appendix

• Worm-like projection of the human large intestine, 10-15 cm long and up to 8mm in diameter.

• The lamina propria contains dense, diffuse lymphoid tissue packed with some 200 lymphoid follicles.
There is a network of lymphatics surrounding each follicle.
Summary

- The immune system is composed of many cells, tissues and organs
- The anatomical arrangement of the immune system facilitates interactions between antigens and cells at appropriate times
- If you understand the anatomy, you will be able to better understand the context of these interactions... (see gut animation)
http://www.nature.com/ni/multimedia/mucosal/animation/index.html

• The gut mucosa is the largest and most dynamic immunological environment of the body. It's often the first point of pathogen exposure and many microbes use it as a beachhead into the rest of the body. The gut immune system therefore needs to be ready to respond to pathogens but at the same time it is constantly exposed to innocuous environmental antigens, food particles and commensal microflora which need to be tolerated. Misdirected immune responses to harmless antigens are the underlying cause of food allergies and debilitating conditions such as inflammatory bowel disease.

• This animation introduces the key cells and molecular players involved in gut immunohomeostasis and disease.

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