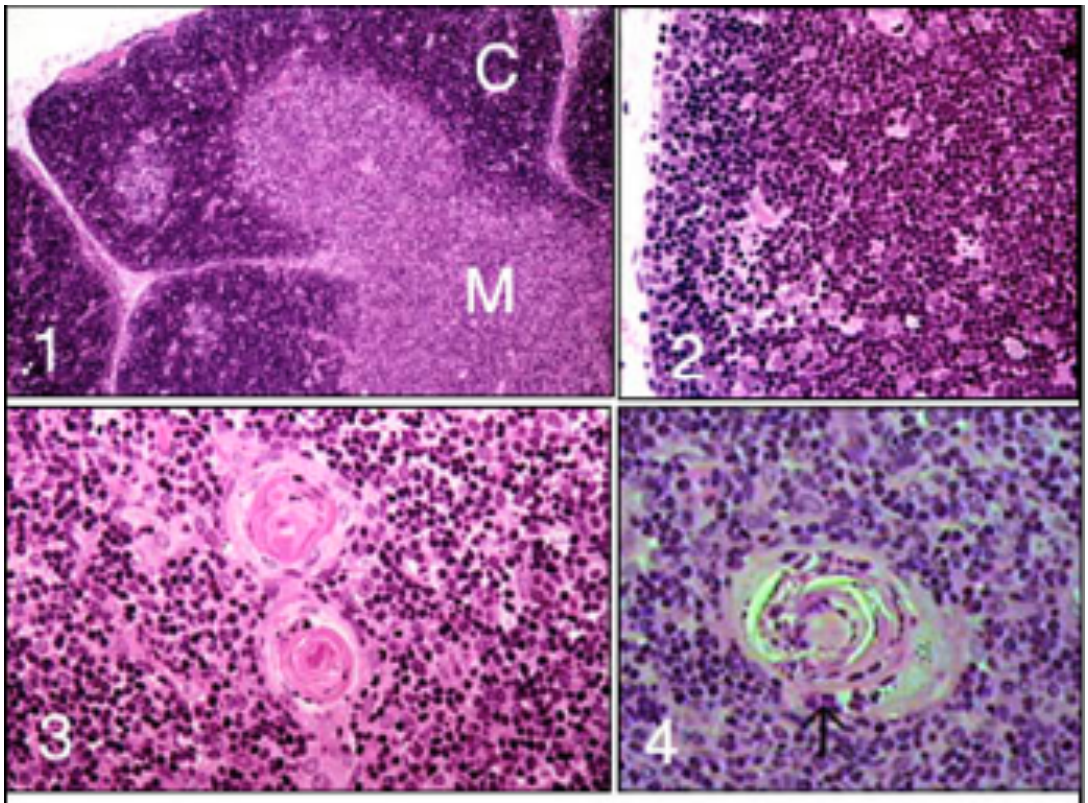
Thymus



1. A region of juvenile thymus illustrating its dark cortex (C) and light medulla (M).
2. A region of thymic cortex. Note that the least mature, light staining lymphocytes lie beneath the capsule at the left.
3. Two thymic (Hassall's) corpuscles within the medulla of the thymus.
4. Increased magnification of a larger thymic (Hassall's) corpuscle.

The thymus is a bilobed, encapsulated lymphatic organ situated in the superior mediastinum dorsal to the sternum and anterior to the great vessels that emerge from the heart. The thymus is the only primary lymphatic organ and is the first organ of the embryo to become lymphoid. Unlike the spleen and lymph nodes, it is well developed and relatively large at birth. The greatest weight (30 to 40 g) is achieved at puberty, after which the organ undergoes progressive involution and is partially replaced by fat and connective tissue.

Structure

The thymus consists of two lobes closely applied and joined by connective tissue. Each lobe arises from a separate primordium, and there is no continuity of thymic tissue from one lobe to the other. A thin capsule of loosely woven connective tissue surrounds each lobe and provides septa that extend into the thymus, subdividing each lobe into a number of irregular lobules. Each lobule consists of a cortex and medulla. In the usual sections, the medulla may appear as isolated, pale areas completely surrounded by denser cortical tissue. However, serial sections show that the lobules are not isolated by the septa; the medullary areas are

continuous with one another throughout each lobule. The free cells of the thymus are contained within the meshes of a reticular network, which, however, differs from that of other lymphatic tissues. In the thymus the reticular cells take origin from endoderm rather than mesenchyme and are not associated with reticular fibers. These epithelial reticular cells are stellate in shape with greatly branched cytoplasm that contains few organelles. The large, round or oval euchromatic nuclei show one or more small but prominent nucleoli. The cytoplasmic processes are in contact with the processes of other reticular cells and at their points of contact are united by desmosomes. Thus, the stroma of the thymus consists of a cytoreticulum composed of epithelial cells. Reticular fibers are found only in relation to blood vessels.

The thymus arises as a pair of endodermal outgrowths from the third pharyngeal pouch, with some contribution from the fourth also. Each outgrowth extends caudally and medially and by the eight week lies in the midline beneath the upper part of the sternum. Initially, each outgrowth has a slitlike lumen surrounded by several layers of tall cuboidal or columnar cells. As the cells proliferate, the lumina disappear. Centrally, the cells become stellate and loosely arranged but retain their cytoplasmic connections with one another. These form the epithelial reticular cells of the thymic cytoreticulum. At about 8 weeks, the thymic rudiment is seeded by blood-borne stem cells that originate in the yolk sac and fetal liver; lymphoid stem cells capable of repopulating the thymus are present in the bone marrow also. The migration of stem cells appears to be guided by chemotactic agents liberated by the thymic reticular cells. The stem cells give rise to the thymic lymphocytes, which, by the fourteenth week of gestation, are arranged into cortex and medulla

Cortex

The cortex consists of a thick, deeply stained layer extending beneath the capsule and along the septa. Most of the cells in the cortex are lymphocytes that are closely packed with little intervening material between them. Because of mutual compression, the cells appear polyhedral in shape. Large, medium, and small lymphocytes are present, the latter being the most abundant; they are indistinguishable from small lymphocytes found elsewhere. Large lymphocytes tend to concentrate in the outer cortex beneath the capsule and represent stem cells that have newly emigrated from the bone marrow. They form only a small part of the cell population. Small lymphocytes become increasingly more numerous toward the deeper cortex, where degenerating cells with pyknotic nuclei also are found. Unlike lymph nodes, there are no lymphatic nodules in the cortex of the thymus, nor is there an internal sinus system. Reticular cells in the cortex are highly branched, but their processes are obscured by the mass of lymphocytes. They form a continuous layer at the periphery of the cortex, separating it from the capsule and septa. These epithelial reticular cells contain tonofilaments and membrane-bound structures that appear to be secretion granules. Macrophages are consistently present in small numbers, scattered throughout the cortex. They are difficult to distinguish from reticular cells by light microscopy unless phagocytosed material can be seen in their cytoplasm. In electron micrographs they are distinguished from epithelial reticular cells by the lack of desmosomes. Macrophages that have engulfed degenerating cells can be found scattered throughout the thymus and tend to increase in number toward the junction of the cortex and medulla.

Medulla

The medulla occupies the central region of the thymus, where it forms a broad, pale band of tissue that is continuous throughout each lobule. Often, however, in histologic sections it appears to be isolated within a lobule, surrounded by a complete layer of cortex. Lymphocytes are less numerous than in the cortex, and the epithelial reticular cells are not as widely dispersed or as highly branched. The reticular cells tend to be pleomorphic and vary from stellate cells with long processes to rounded or flattened cells with many desmosomes and abundant tonofilaments. Dendritic interdigitating cells are found in the medulla and cortico medullary region. They act as antigen-presenting cells for more mature T-lymphocytes. The free cells of the medulla are mainly small lymphocytes, but a small and variable number of macrophages are present. Plasma cells, mast cells, and eosinophil granulocytes can be found. Mitotic figures are rare. Collagen and reticular fibers extend for short distances from blood vessels and wind between the epithelial cells. Rounded or ovoid epithelial structures, the thymic corpuscles, are a prominent feature of the medulla. These bodies vary in size from 10 to 100 μm or more in diameter and consist of flattened epithelial reticular cells, wrapped about one another in concentric lamellations that are joined by numerous desmosomes. Many contain granules of keratohyalin. The cells at the center of the structure undergo hyalinization or necrosis and may become lysed to leave a cystic structure. Some of the cells at the periphery of the corpuscle retain their connections with the surrounding cytoreticulum. The function of the thymic corpuscles is unknown; they have been regarded purely as degenerated structures, but there is evidence that they may be secretory bodies.

Blood Supply

The arteries to the thymus penetrate the organ within the connective tissue of the septa. Arteriolar branches from these vessels run along the cortico medullary junction and provide arterioles and capillaries to the medulla and capillaries to the cortex; vessels larger than capillaries are not found in the cortex. Within the cortex, the capillaries run toward the capsule, where they form branching arcades before passing back through the cortex to drain into venules and thence into veins that accompany the arterioles in the cortico medullary region and medulla. The veins leave via the septa and ultimately unite to form a single thymic vein. A collar of connective tissue that forms part of the blood-thymic barrier envelops the cortical capillaries. A continuous layer of epithelial reticular cells in turn surrounds this envelope. The perivascular connective tissue space varies in width and is traversed by reticular fibers that accompany the vessel. Within the perivascular space are granular leukocytes, plasma cells, macrophages, and lymphocytes. The blood-thymic barrier in the cortex thus consists of the capillary endothelium and its basal lamina, the perivascular connective tissue sheath, and the layer of epithelial reticular cells and their associated basal lamina. There is little movement of macromolecules across this barrier, and cortical lymphocytes develop in relative isolation from antigens in a privileged environment. Vessels of the medulla and cortico medullary junction are permeable to circulating macromolecules. As T-lymphocytes differentiate in the cortex of the thymus, they acquire surface marker molecules of major histocompatibility complex (MHCI and MHCII,) and synthesize receptors for recognition of foreign antigens. Those lymphocytes which recognize self MHC are destroyed in the thymus, whereas those T-lymphocytes capable of reacting to nonself go on to form clones of cells that mature and are released as immunocompetent T-lymphocytes. Lymphocytes leave the thymus by entering postcapillary venules located in the medulla and near the cortico medullary junction.

Involution

Growth of the thymus during fetal life is very rapid, and the organ attains its greatest relative size by the time of birth. It continues to grow, at a lesser rate, until puberty, after which it undergoes progressive involution. The organ decreases in weight, loses cortical lymphocytes, and shows an increase in the size and number of thymic corpuscles. The septa also increase in width. The cortical areas become infiltrated by fat cells, and the replacement may become extensive. By the time involution commences, T-cells have disseminated into the secondary lymphatic tissue throughout the body. The thymic parenchyma does not disappear completely even in old age, and the thymus maintains some activity in the adult.

Other Constituents

The thymus frequently shows a number of peculiar structural elements, the significance of which is not known. Among these structures are cyst-like spaces lined by cells with brush borders, cilia, or mucus-producing cells or by reticular cells that contain microvillus-lined vacuoles. Most peculiar are the "myoid" cells, which have an imperfect resemblance to striated muscle. These cells may resemble embryonal or adult muscle fibers complete with typical banding patterns: Z lines and A, I, and M lines have been described. It is not known whether these various inclusions have functional significance or represent aberrant differentiation of embryonal elements.

Dendritic (Antigen-Presenting) Cells

Dendritic (antigen-presenting) cells arise in the bone marrow but, unlike monocytes (macrophages), have low levels of lysosomal enzymes. In contrast, they have high levels of class II major histocompatibility complex (MHC) molecules essential for presenting new antigens to T-lymphocytes. Dendritic cells have the capacity to ingest foreign proteins, process (partially digest) the antigens, and insert selected portions of an antigen into their cell membrane, thereby retaining the product for long periods of time. Dendritic cells are found in lymph nodes, spleen, thymus, mesenteries, and skin (Langerhans' cells) and under mucosal surfaces. Despite the morphologic similarities of exhibiting fine ramifying cytoplasmic processes and containing relatively few lysosomes, each dendritic antigen-presenting cell appears to have developed specialized surface receptors for a given specific microenvironment at the site in which it is found. After a period of time, they leave the specific environment (skin, for example), make their way to lymphoid tissue, and gradually present the antigens collected in a specific environment to T-lymphocytes. Thus, the dendritic antigen-presenting cells play a very important role in the immune system by monitoring a number of different environments.

The thymus is essential for production of T-cells, lymphocytes that are involved in cell-mediated immune responses such as rejection of foreign grafts and immunologic responses to fungi, viruses, and certain bacteria. Although not directly involved in elaborating conventional antibodies, T-cells do cooperate with B-cells in producing antibodies against antigens such as foreign red cells. All these responses are impaired in animals that have been thymectomized at birth. There is a marked decrease in the number of circulating small lymphocytes, and the deep cortex of lymph nodes and the periarterial lymphatic sheaths of the spleen fail to develop. Most of the lymphocytes in the thymus seem to be inert and acquire immunologic capabilities

after passage through the spleen. T-cells have a long life span and re-circulate between lymphatic organs (except for the thymus), lymph, and blood. Thymic lymphocytes show a high rate of mitotic activity, but many die within the thymus or emigrate to other organs. Thymic tissue contained in diffusion chambers and transplanted into thymectomized newborn animals partly prevents or reverses the effects of thymectomy. Permeable molecules but not whole cells diffuse from the chamber, indicating the presence of a thymic-produced humoral factor. Several peptides have been isolated from thymic extracts and appear to have some regulatory and stimulating effects on the thymus. The best characterized of these is thymosin, an agent that restores T-cell deficiencies in thymectomized mice; it is regarded as a hormone that induces T-cell differentiation. Other agents have been described: thymopoietin, which induces T-cell maturation; thymic humoral factor, which enhances T-cell mediated graft rejection; and serum thymic factor, which induces development of surface markers on T-cells. The agents appear to be produced locally in the thymus, possibly by the reticular epithelial cells, and to have local effects on the lymphocyte population in the thymus.