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The Organization of Lymphoid Tissue in Relation to Function

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Summary

Organized lymphoid tissue is found in the thymus, spleen, lymph nodes; lining the respiratory and alimentary tracts; and also occurring at sites of chronic inflammation. Apart from the thymus which is involved in the regulation of T-cell function, the other tissues are organized into T-cell and B-cell areas. Lymphocytes in T-cell areas respond by proliferation in cell-mediated immunity and by the production of suppressor cells and helper cells for antibody formation. B-cell areas are involved in the humoral antibody response. B-cells are segregated into lymph follicles where they form germinal centers and are found at the corticomedullary junction where they differentiate into plasma cells. The role of lymph follicles in becoming germinal centers is poorly understood, but these areas are known to be the site of antigen trapping in primed animals. The particular function of the spleen as a localized area of lymphoid tissue along the course of the blood vascular system is discussed, particularly with respect to its ability to respond to soluble antigen released from sites of localized antigen deposition such as tumors.

Thymus

The function of the thymus in controlling T-lymphocytes has been defined in mice and rats, and to a limited extent, in man. The role of this organ is far less well defined in other species. There are, for instance, major differences between the effect of fetal thymectomy in the lamb and neonatal thymectomy in the mouse (*Morris* 1973). Lambs thymectomized in utero reject skin allografts, although they show impaired (but not absent) delayed hypersensitivity. Despite this, there is evidence to show that thymus deprivation, even in the lamb, results in a reduction in lymphoid tissue.

The thymus itself is dependent on normal pituitary function for its development (*Pierpaoli* et al. 1970). The thymus and thymus-dependent lymphoid tissue atrophy after treatment of mice with antiserum prepared against the pituitary or against bovine somatotrophic hormone. In addition dwarf mice born with pituitary deficiency show similar defects. If such dwarf mice are reconstituted with somatotrophic hormone and thyroxine, they regain T cell function and the ability to reject allogeneic skin grafts. Thyroidectomy of rats in the immediate neonatal period also results in a decrease in thymus weight and significant delay in skin graft survival. It would appear, therefore, that the development of the thymus and the T cell population of lymphocytes is very markedly under the control of thyroxine as well as somatotrophic hormone.

One may next ask the question, how is the structure of the thymus related to T cell control? The thymus has two main regions: a cortex which consists of densely packed small lymphocytes and a medulla in which these same cells are arranged more loosely. The cortex is the area of proliferation. It is presumed that the thymus receives stem cells from the outside, possibly the bone marrow. In animals treated with cyclophosphamide, the cortex of the thymus is rapidly depleted. During the recovery phase, this then becomes the site of large numbers of large pyroninophilic blast cells. One may presume that stem cells enter the thymus through the cortical capillaries; it is likely that they differentiate there in the cortex and acquire thymus-specific antigens and their ability to perform other T-cell functions such as spontaneous rosette formation. These functions all seem to take place in the subcapsular outer region of the thymus cortex; the inner cortex would appear to be

little more than a holding region (*Clark* 1973) in which cellular growth and proliferation is inhibited.

During their passage through the medulla, thymocytes lose some of their thymus-specific antigenicity and become insensitive to corticosteroids. It is also in the medulla that they develop the ability to respond to PHA. Hassall's corpuscles are a distinct feature of the thymic medulla. They are composed of epithelial-like cells arranged concentrically, often around an area of degenerate cells. They have a close relation to capillaries and there are parallels with the vasculature of endocrine organs. They are thought to be derived from the original branchial epithelium. Whether they are in any way involved in the production of thymic humoral factors has not yet been determined. Despite its size, the thymus does not appear to play an important role in most species after birth. In those species in which thymectomy depletes the T cell population after birth, this is possible for only a short time and lasts little longer than the immediate postnatal period. After this there is a period in which T cells can be depleted by a combination of thymectomy and 900 rads irradiation, followed by syngeneic bone marrow replacement.

In adult animals the only way to deplete T cells is by reducing the mobile pool of lymphocytes via chronic thoracic duct drainage or treatment with antilymphocytic serum. In most species the thymus begins to involute after adulthood. It would thus appear that neither the environment of the thymus nor any hormone that it might produce is necessary for the maintenance of a normal T cell population during most of the life of an individual; this organ plays its major role during embryogenesis.

An intriguing aspect of thymus function is brought out by the more recent observations of *Pierpaoli* and *Besedovsky* (1975) in which they showed remarkable reductions in levels of thyroxine and gonadal hormones in congenital athymic and neonatally thymectomized mice. This would indicate that the thymus is involved in a complex feedbach mechanism involving the hypothalamic-pituitary axis,

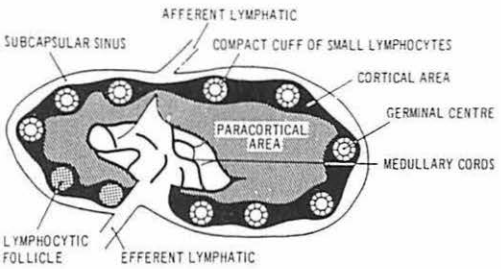

Fig. 1 Diagram of immunologically active lymph node (*Cottier, Turk* and *Sobin* 1973).

which has been poorly defined up to now but which would appear to indicate a far more complicated control of the structure and function of the lymphoreticular system than had been previously envisaged.

Lymph Nodes

T-Cell Areas

The middle and deep areas of the cortex of lymph nodes were shown by *Parrott, de Sousa,* and *East* (1966) to be depleted of small lymphocytes in neonatally thymectomized mice. This is also the area of T-lymphocyte proliferation in cell-mediated immune responses and has been named the "paracortical area" (Fig. 1) (*Oort* and *Turk* 1965). It is characterized by the presence of postcapillary venules with walls of cuboidal endothelial cells. Paracortical distension is a well recognized reaction to the antigenic stimulation and fails to occur in T cell deficient animals. T-lymphocytes are a major part of the mobile pool of lymphocytes. Thus, the paracortical area in life is the site of continuous movement and activity. The only indication of this that can be obtained in two-dimensional studies is from the loosness with which cells are packed in this area, as compared with the denser arrangement of lymphocytes in the lymph follicles and other B cell areas. Another indication is from the rapid way in which these areas are specially depleted by processes that deplete the mobile pool such as treatment with antilymphocytic serum (*Turk* and *Willoughby* 1967) and chronic thoracic duct drainage. These areas are, however, not depleted by treatment with cyclophosphamide that acts preferentially on

those populations of cells with a more rapid rate of turnover (*Turk* and *Poulter* 1972) and depletes B cells preferentially. The cells populating the paracortical area also belong to a more long-lived pool of cells. Following antigenic stimulation however a large proportion rapidly enter the synthesizing phase of the cell cycle and transform into large pyroninophilic blast cells .

Kelly (1975) has demonstrated that, in the rabbit, the paracortical area is not a structureless mass of cells but a series of well defined linear perivenous accumulations of lymphocytes that he terms the "paracortical cords". These cords follow the course of the postcapillary venules. The cords are separated by paracortical sinuses which run from the subcapsular sinus. Cells can, therefore, enter the paracortical area either by migrating through the walls of the postcapillary venules or by passing down the paracortical sinuses from the afferent lymphatics via the subcapsular sinus. During the immune response, the paracortical sinuses become distended after having been plugged by an accumulation of lymphocytes. Paracortical distension similar to that seen during antigenic stimulation can be reproduced by the intralymphatic injection of purified lymphocyte activation products similar to those released by the incubation of specifically sensitized T cells with antigen that inhibit macrophage migration in vitro. This distension is characterized by the appearance of dense aggregates of lymphocytes in the paracortical sinuses. Such aggregates could be due to adhesion of lymphocytes to each other or to the macrophages in the sinus lumen, or more simply to a slowing down of the efferent lymphocyte flow.

In experiments tracing the migration of lymphocytes from the thoracic duct, it can be shown that the T cells localize in this area (*Howard, Hunt* and *Gowans* 1972). It can also be shown that B cells as well as T cells use the postcapillary venule as a route for entering lymphoid tissue. Following their migration through the postcapillary venule, B cells as well as T cells may be found for several hours in close association in the paracortical area. Within 24 hours, however, the two types of cell separate; the T cells remain in the paracortical zone and the B cells move into the perifollicular area and occasionally into the germinal center (*Nieuwenhuis* and *Ford* 1976). This suggests that the paracortical area is not only the site of T cell proliferation in cell-mediated immunity, but also the site of T-B cooperation in humoral antibody production

These changes and population movements can be assessed in relation to the development of a cell-mediated immune response. In the guinea pig, it can be shown that the peak of T cell proliferation is on the fourth day after the application of a chemical sensitizer to the skin. This is the day before sensitization can be regularly demonstrated as a peripheral event. In addition to cytological evidence of massive T cell proliferation in the paracortical area, there is a generalized increase in lymph node weight and in the area of the paracortical zone, which also reaches its peak at this time. The outburst of T cell proliferation is more than can be explained by the expansion of a single clone or group of clones and could be related to local release of a mitogen into the area. At the peak of the response on the fourth day, as many as 20% of the cells are large pyroninophilic blast cells (*Turk* and *Oort* 1970). The relation of these changes to function can be assessed by experiments in which the draining chain of lymph nodes are removed at various days after sensitization and transplanted into syngeneic recipients. The ability to transfer sensitivity is developed in most cases only by the fourth day. This would indicate that it takes this time for the clone to expand and differentiate sufficiently to maintain itself in the new environment. If the draining lymph nodes are removed after the fourth day, it is still possible to demonstrate sensitivity. Excision before this time blocks the development of sensitivity. This would indicate that, after the fourth day, the active clone is no longer confined to the draining lymph nodes (*Turk* and *Stone* 1963). It would also indicate that the efferent lymphatic "shutdown" caused by the aggregation of cells in the paracortical sinuses has been overcome, and there is a return to a free flow through the paracortical area. This is associated with the beginning of a decrease

in lymph node and paracortical area with return to normal size.

The role of the afferent lymphatics in the stimulus to T cell proliferation was indicated by the classical work of *Frey* and *Wenk* (1957) who inhibited the development of contact sensitivity when application of the sensitizer was applied to islands of skin from which the afferent lymphatics had been cut. This prevents both soluble antigen and lymphocytes triggered by antigen in the periphery from passing down to the paracortical areas.

In man the areas of the lymph node with the character of the paracortical area as demonstrated in other species, has been shown to be the site of T cells with membrane receptors for sheep erythrocytes (E rosettes). B cells demonstrated by the ability to form EAC rosettes localize in thymus-independent areas (*Silveira, Mendes* and *Tolnai* 1972).

When lymph nodes are depleted of T lymphocytes from whatever cause, the background structure of the paracortical area is exposed. It can then be seen that the lymphocytes in this area are supported by an interlocking web of cytoplasmic processes derived from mesenchymal cells of a wide variety of structure (*Carr, Turk* and *Poulter* 1975). These cells include macrophages and reticulum cells. Some of these cells are intermediate between macrophages and reticulum cells and have prominent cytoplasmic microfibrils arranged in aggregates. These cells can be regarded as the framework on which the node is built. Changes in the cells of this framework are a feature of an number of chronic granulomatous diseases. In lepromatous leprosy the whole paracortical area may be replaced by macrophages packed with globi of *M. leprae* with an almost complete absence of T lymphocytes (*Turk* and *Waters* 1968). The B-lymphocyte areas are unaffected and often show marked hyperplasia with germinal center formation and plasma cell proliferation. Similar granulomatous infiltration of the paracortical area may also be seen in secondary syphilis (*Levene* et al. 1971). The appearance of lymph nodes in patients with lepromatous leprosy is consistent with a drainage of parasitized macrophages from peripheral lesions down afferent lymphatics. Similar infiltration with macrophages may be observed in experimental animals following the induction of a histiocytic infiltration in the skin by injecting BCG vaccine, colloidal aluminium or silica (*Gaafar* and *Turk* 1970). Here only the lymph node immediately draining the affected piece of skin is involved. The paracortical area of the lymph node may also be found to be the site of granulomatous infiltration in sarcoidosis. In addition in Hodgkin's disease, infiltration in minimally affected lymph nodes may be localized to the paracortical area (*Turk* and *Oort* 1970).

B-Cell Areas

B-cell areas of lymph nodes may be defined as those areas which are not depleted by procedures that reduce the T cell population. The B cells that remain are found in the lymph follicles, the narrow rim of the cortex under the capsule and at the corticomedullary junction. After T-cell depletion, B cells can still respond to antigens by proliferation and thereby form germinal centers at the corticomedulary junction and in the medullary cords where the B cells frequently differentiate into plasma cells. B-cell areas of lymph nodes are specifically depleted of lymphocytes three days after the injection of 300 mg/kg cyclophosphamide; this spares most of the T cells in the paracortical areas (*Turk* and *Poulter* 1972). In human lymph nodes, the distribution of B cells has been demonstrated by making use of their receptors for EAC rosettes (*Silveira* et al. 1972). Much less is known about the structure of B cell areas than about T cell areas. Lymph follicles are characterized by dendritic reticular cells that have long processes and trap antigen (*Nossal* et al. 1963). The bone marrow origin of B cells in lymphoid tissue has been demonstrated in thymectomized irradiated mice. The migration of these cells prepared from thoracic duct lymph or directly from the bone marrow has been followed; the cells have been shown to migrate to follicular areas around the germinal centers (*Howard* et al. 1972). B cells enter the lymph through the paracortical area to localize eventually in the follicular area of lymphoid tissue (*Nieuwenhuis*

and *Ford* 1976). Lymphocytes in the medullary cords are also of bone marrow origin (*de Sousa* 1971). In the primary antibody response, antigen is localized within 6 hours in the medulla where it is taken up by the macrophages in this area. In primed animals there is also a heavy localization of antigen in the lymph follicles. Localization of antigen in lymph follicles occurs only in animals where a circulating antibody is present (*Humphrey* and *Frank* 1967). The relation of the trapping of antigen by lymph follicles and germinal centers to the presence of antibody has been studied by *Brown* et al. (1970). They found that aggregated immunoglobulin and immune complexes are concentrated in the germinal centers by the dendritic reticular cells. Germinal centers are areas of massive cell proliferation and also considerable cell death. In addition to consisting of large dividing cells, they are also the site of large macrophages containing recently ingested pyknotic nuclei.

There are two views regarding the role that germinal centers play in the immune response (*Celada* 1971). The classical view connects these structures with the generation of IgG immunological memory. Three reasons are given for this: 1) germinal centers appear phylogenetically with the development of IgG memory; 2) both immunological memory and germinal centers are destroyed by colchicine and X-rays; 3) germinal centers appear in the primary immune response just after the peak of antibody formation and the development of "primed cells".

An opposing view regards the development of the germinal centers as a proliferative response to soluble immune complexes trapped by the dendritic cells in the lymph follicles. The localization of immune complexes with fixation of complement in lymph follicles would be enough to stimulate B lymphocytes into a state of intense proliferation that would result in formation of germinal centers. Labeled studies (*Turk*, unpublished observations) indicate little evidence of migration of cell progeny from germinal centers. Twenty-four hours after the intravenous injection of ^{3}H-thymidine, the labeling material is still confined within the germinal center and the labeled cells outside can easily be accounted for by proliferation of T cells in the paracortical area. Much of the data suggesting migration of labeled cells from germinal centers comes from an era before B-cells could be differentiated from T cells. There has been no recent data which might indicate that germinal centres actually produce memory cells.

Although the appearance of germinal centers could be the result of an intrafollicular immune reaction, the role of the dentritic cells in trapping antigen within the follicles is not clear. It could be that they play a regulatory role in controlling the flow of antigen down to the B cells at the corticomedullary junction. Restriction of the amount of antigen passing down during the secondary response might allow a smoother production of antibody and prevent the swamping of the immune response by excess antigen or immune complexes in the medulla.

Spleen

Lymphocytes in the spleen are concentrated in the periarterial lymphatic sheaths which form the white pulp. The T cell area is that part of the white pulp immediately sorrounding the central arteriole. The outer area of the white pulp is formed by B cells which aggregate in lymph follicles. These contain dendritic reticular cells and expand into germinal centers at the peak of antibody production as in lymph nodes. Both T and B cells enter the spleen through the arterial circulation by way of the penicillary arterioles initially, into the marginal zone between the white pulp and the red pulp (*Mitchell* 1973). Some enter the white pulp while others pass to the red pulp. B cells localize then in the follicular region while T cells pass to the periarterial region. The periarteriolar region is generally deficient of lymphocytes in neonatally thymectomized mice (*Parrot, de Sousa* and *East* 1966). The particular role of a discrete lymphoid organ positioned in the blood vascular system must be considered as other than that of the lymphatic system. It may be that the role of the spleen is in relation to antigens that enter the circulation, especially to soluble antigens.

There are a number of situations where the major part of the immune response will normally occur in the draining lymph nodes. These include responses to fixed antigens such as with solid tissue and organ allograft, tumors, and contact sensitivity. In all these situations, there may be a parallel response to soluble antigen released from the site of antigen deposition. This is especially important in tumor immunology where soluble tumor-specific transplantation antigens are released into the circulation. The response to soluble antigens may be mainly a B cell response and much of this may occur in the spleen. There are many examples of the modulation of a T cell response by a B cell response to the same antigen (*Voisin* 1971). In some of these systems, an increased T cell response can be demonstrated after B cells have been reduced by treatment with cyclophosphamide (*Turk, Polak* and *Parker* 1976). The B cells responsible for the modulating effect may be restored by transfering spleen cells from normally sensitized animals. Occasionally, it is possible to reproduce the increased reactivity by splenectomy performed after sensitization. Tumor models showing a particular role of the spleen can also be designed (*Chang* and *Turk* 1977). For instance it has been found that prior splenectomy increases the resistance of BALB/c mice to a syngeneic, methylcholanthrene-induced ascitic tumor inoculated intraperitoneally. The survival rate of the splenectomized mice is 80% while that of normal and sham operated mice is 20%. This effect however, is only seen within the dose range of 10^3 to 10^4 tumor cells. Normal spleen cells reverse the effect of splenectomy if given immediately after tumor inoculation, as does serum from tumor-bearing mice. This suggests that, in this tumor system, the spleen may be the site of an antibody which modulating that part of the immune response is responsible for host resistance.

The periarteriolar region of the spleen is generally regarded as the thymus-dependent area; it is populated almost entirely by T cells. In neonatally thymectomized mice, however this area has been occasionally found to be replaced by cells of the plasma cells series (*Parrott, de Sousa* and *East* 1966). A similar phenomenon is found in mice infected with the malaria parasites *Plasmodium berghei* and *Plasmodium yoelii;* this could account for the temporary state of immunosuppression occurring in this disease (*Salaman* et al. 1969). At the height of the parasitemia at the time that nonspecific immunosuppression occurs, the thymus-dependent area is replaced by proliferating lymphoid cells, many of which are IgG-containing plasmablasts (*Moran* et al. 1973). It would appear, therefore, that the antigenic stimulus in malaria is so great that an abnormal proliferation of both T and B cells is induced in the thymus-dependent area to the exclusion of all but malarial antigens.

Gut-Associated Lymphoid Tissue

A large proportion of the organized lymphoid tissue of the body may be found associated with the gut. Lymphocytes are found scattered throughout the subepithelial lymphoid tissue and also in collections forming Peyer's patches. Peyer's patches have thymus-dependent and nonthymus-dependent areas. In the newborn all lymphocytes in Peyer's patches are T cells. In older animals, however the porportion of B cells increases to 75%. The thymus-dependent areas can be identified as those areas depleted of lymphocytes in neonatally thymectomized mice (*Ferguson* and *Parrott* 1972a, *Parrott* and *Ferguson* 1974). In Peyer's patches lymph follicles and germinal centers can be identified in the thymus-independent areas; the T cell areas are characterized by the presence of post-capillary venules similar to those seen in lymph nodes and other areas of organized lymphoid tissue. Both T and B cells enter Peyer's patches through the postcapillary venules and leave through the efferent lymphatics. Germinal centers fail to develop in fetal tissues kept in a germ-free position; this indicates that gut-associated lymphoid tissue responds immunologically to antigens within the lumen of the bowel (*Ferguson* and *Parrott* 1972b). Much of the B cell response of this tissue is probably involved in the production of IgA. IgA-containing plasma cells, however, are rarely found in Peyer's patches. These cells are found mainly in the lamina propria of the intestine.

How much of the body's total lymphoid tissue is gut associated is not known. There is no doubt, however, that a major area of organized lymphoid tissue is involved in cell-mediated immunity as well as humoral antibody production. This tissue is involved in host resistance to ingested pathogens and probably also with gastro-intestinal allergies. It is of interest that, in experiments in which lymphocytes labeled by incorporating ^{3}H-thymidine are transfused, large numbers of these cells are found in the lamina propria of the intestines rather than in organized areas of lymphoid tissue. The role of these cells is not known, although it is clear that this localization is not mediated by antigens (*Ford* (1975). The function of gut-associated lymphoid tissue is still not completely clear. This is particularly the case in relation to its role as the mammalian equivalent of the bursa of Fabricius and its role in the sequestration of excess lymphocytes. It is also not clear why the gut is the preferential homing area for activated lymphocytes.

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