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Corrigendum*

The Human Thymus

A Chimeric Organ Comprised of Central and Peripheral Lymphoid Components

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Abstract

The human thymus is a lymphoepithelial organ in which T cells develop during fetal life. After maturation and selection in the fetal thymic microenvironment, T cells emigrate to peripheral lymphoid tissues such as the spleen, gut, and lymph nodes, and establish the peripheral T cell repertoire. Although the thymus has enormous regenerative capacity during fetal development, the regenerative capacity of the human postnatal thymus decreases over time. With the advent of intensive chemotherapy regimens for a variety of cancer syndromes, and the discovery that infection with the Human Immunodeficiency Virus (HIV) leads to severe loss of $CD4^+$ T cells, has come the need to understand the role of the human thymus in reconstitution of the immune system in adults. During a recent study of the thymus in HIV infection, we observed many $CD8^+$ T cells in AIDS thymuses that had markers consistent with those of mature effector cytotoxic T cells usually found in peripheral immune tissues, and noted these $CD8^+$ effector T cells were predominately located in a thymic zone termed the thymic perivascular space. This article reviews our own work on the thymus in HIV-1 infection, and discusses the work of others that, taken together, suggest that the thymus contains peripheral immune cell components not only in the setting of HIV infection, but also in myasthenia gravis, as well as throughout normal life during the process of thymus involution. Thus, the human thymus can be thought of as a chimeric organ comprised of both central and peripheral lymphoid tissues. These observations have led us to postulate that the thymic epithelial atrophy and decrease in thymopoiesis that occurs in myasthenia gravis, HIV-1 infection, and thymic involution may in part derive from cytokines or other factors produced by peripheral immune cells within the thymic perivascular space.

Key Words

Human
Thymus
T cells
HIV
Myasthenia gravis

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Introduction

The human peripheral T cell pool begins to be established early in fetal development after passage of developing thymocytes through the thymic microenvironment and emigration of mature thymocytes into peripheral sites, such as lymph node and spleen *(1–3)*. Although the thymus is essential for establishing the peripheral T cell pool in early life, recent data have demonstrated an age-dependent decline in thymus function in normal subjects *(4–6)*. Whereas children rapidly constitute their peripheral $CD4^+$ T cell population following cytotoxic chemotherapy, repopulation of the T cell pool following chemotherapy in adults over 20 yr of age is frequently delayed and is thought to be primarily due to proliferation of peripheral T cells in a thymic-independent manner *(4–6)*. Thus, understanding the role of the thymus in reconstitution of the peripheral pool of T cells in the setting of chemotherapy for malignancies and in HIV-1 infection is critical to the development of strategies to restore normal immune function in these settings.

We have recently completed a study of the adult human thymus in HIV-1 infection, with particular attention to analysis of the role that the adult thymus plays in determining the clinical course of HIV infection and in reconstitution of the T cell arm of the immune system *(7)*. In the course of these studies, we observed considerable lymphoid infiltrations exterior to thymic epithelium, and demonstrated that these infiltrations contained $CD8^+$ T cells expressing markers characteristic of peripheral cytotoxic effector T cells.

In this article, we review our recent work on the thymus in HIV infection, and review the work of others regarding the thymus in aging and myasthenia gravis (MG). We present a view of thymic microanatomy and function that may offer insights into the roles the thymus plays in thymic involution and in regeneration of the immune system, and may be important for the development of novel strategies for reconstitution of the immune system in adults. We postulate that the human thymus can be considered a chimeric organ, comprised of both central and peripheral immune cell components. Further, we suggest these two components of the human thymus interact in regulating thymopoiesis in various clinical settings.

The Human Thymus During Normal Fetal Development

The human thymus develops from the third pharyngeal pouch that gives rise to endodermal-derived thymic cortical epithelium and the third pharyngeal cleft that is thought to give rise to ectodermal-derived medullary thymic epithelium (reviewed in refs. *1–3,8*). The thymic epithelial rudiment begins to be colonized by hematopoietic stem cells between 7 and 8 wk of fetal gestation *(9)* (Fig. 1). By 16–20 wk, morphogeneis of the human thymus is complete, and diversification of the T cell repertoire (TCR) is well under way *(10,11)*. During the second and third trimesters of gestation, the thymus increases dramatically in size, with continued diversification of the TCR and emigration of T cells to the periphery, thus establishing the peripheral T cell pool (Fig. 2).

Both thymocytes and thymic epithelium undergo maturation pathways during fetal and postnatal thymus ontogeny. Thymocytes mature from $CD3^-$, $CD4^-$, $CD8^-$ (triple negative, TN) T cell precursors to positively selected $CD3^+$, $CD4^+$, or $CD8^+$ (single positive, SP) naive ($CD45RA^+$) T cells that are ready for export to the periphery (reviewed in refs. *1–3*). In the mouse, only 5% of thymocytes are thought to be positively selected on thymic microenvironment MHC molecules for survival and export. Approximately 95% of human thymocytes express CD45RO isoforms intrathymically and are thought to be those thymocytes that are negatively selected or nonselected for death *(12)*. Thymocytes that

die within the thymus are phagocytosed by mononuclear phagocytes in the cortex, resulting in clusters of macrophages containing pyknotic thymocytes scattered throughout the cortex as well as in the thymic medulla.

Thymic epithelial (TE) cell maturation within the cortex and medulla relies on the presence of developing thymocytes at the respective stages that normally inhabit the cortical and medullary regions *(13)*. $CD1a^+$, $CD4^+$, $CD8^+$ (double positive, DP) immature thymocytes are located within the thymic cortex and give rise to $CD4^+$ or $CD8^+$ SP thymocytes in the medulla. Inhibition of progression of thymocyte maturation from TN to DP thymocytes results in inhibition of development of cortical thymic epithelium. Similarly, lack of development of SP thymocytes from cortical $CD1a^+$, DP thymocytes results in failure of proliferation and expansion of medullary TE cells. TE cells express epidermal growth factor (EGF) receptors, but to date, constitutive production of EGF within human thymus has yet to be documented (Haynes et al., unpublished). Rather, thymic fibroblast and epithelial cells constitutively produce TGF-a, one of several cytokines that bind to EGF receptors, that induces TE cell production of IL-1, IL-6 as well as TGF-a in an autocrine manner *(14)*. The result of proliferation and differentiation of medullary TE cells is terminal differentiation of TE cells to form epithelial swirls termed Hassall's Bodies (HB) *(15–17)*. Located exclusively in the thymic medulla, HB consist of cornified epithelium with crosslinked, high-mol wt keratins otherwise found only in the stratum corneum of skin *(16)*. The presence of HB indicates normal medullary TE cell maturation, which in turn means normal medullary thymocyte maturation to the SP stage. Lack of HB generally is seen in early fetal development before 16 wk of gestation, as well as in congenital immunodeficiency diseases in which thymocyte maturation is disrupted or not normal. The presence of HB calcification represents dystrophic calcification, and likely indicates abnormal or absent thymocyte maturation to the SP medullary thymocyte stage.

Thus, direct cell contact of thymocytes and TE cells appears to be key in regulating both thymocyte and TE cell proliferation and differentiation. Contact between TE and thymocytes is mediated not only by MHC complex-TCR binding, but also by thymocyte CD2, LFA-1, and CD6 molecules binding to TE cell CD58 (LFA-3), CD54 (ICAM-1), and CD165 (ALCAM) molecules, respectively *(18–23)*. Moreover, contact between TE cells and thymocytes has been shown to regulate TE cytokine production *(24)*.

One family of cytokines that trigger TE cell growth likely act via EGF receptors *(14)*, whereas the cytokines that trigger thymocyte growth likely act via numerous receptors (R), including IL-7R, IL-1R, and the receptor for GM-CSF (reviewed in *1–3*). In particular, IL-7 has been demonstrated to induce proliferation and differentiation of immature thymocytes, and to promote thymic reconstitution following lethal irradiation and bone marrow transplantation *(25)*. Children with X-linked severe combined immunodeficiency syndrome have mutations in the γ-chain of the IL-7R and absent T and B cell development *(26,27)*. Mice genetically deficient in the α-chain of the IL-7R have demonstrated that the IL-7R α-chain controls RAG1 and RAG2 expression and initiation of TCR recombination in immature thymocytes *(28)*. Finally, IL-4 transgenic mice were found to have atrophic thymuses *(29)*, implicating this cytokine as a negative regulator of thymic development.

The True Thymic Epithelial Space and the Thymic Perivascular Space

To appreciate the changes that occur in thymus morphology in aging, MG, and in HIV infection, it is important to understand the

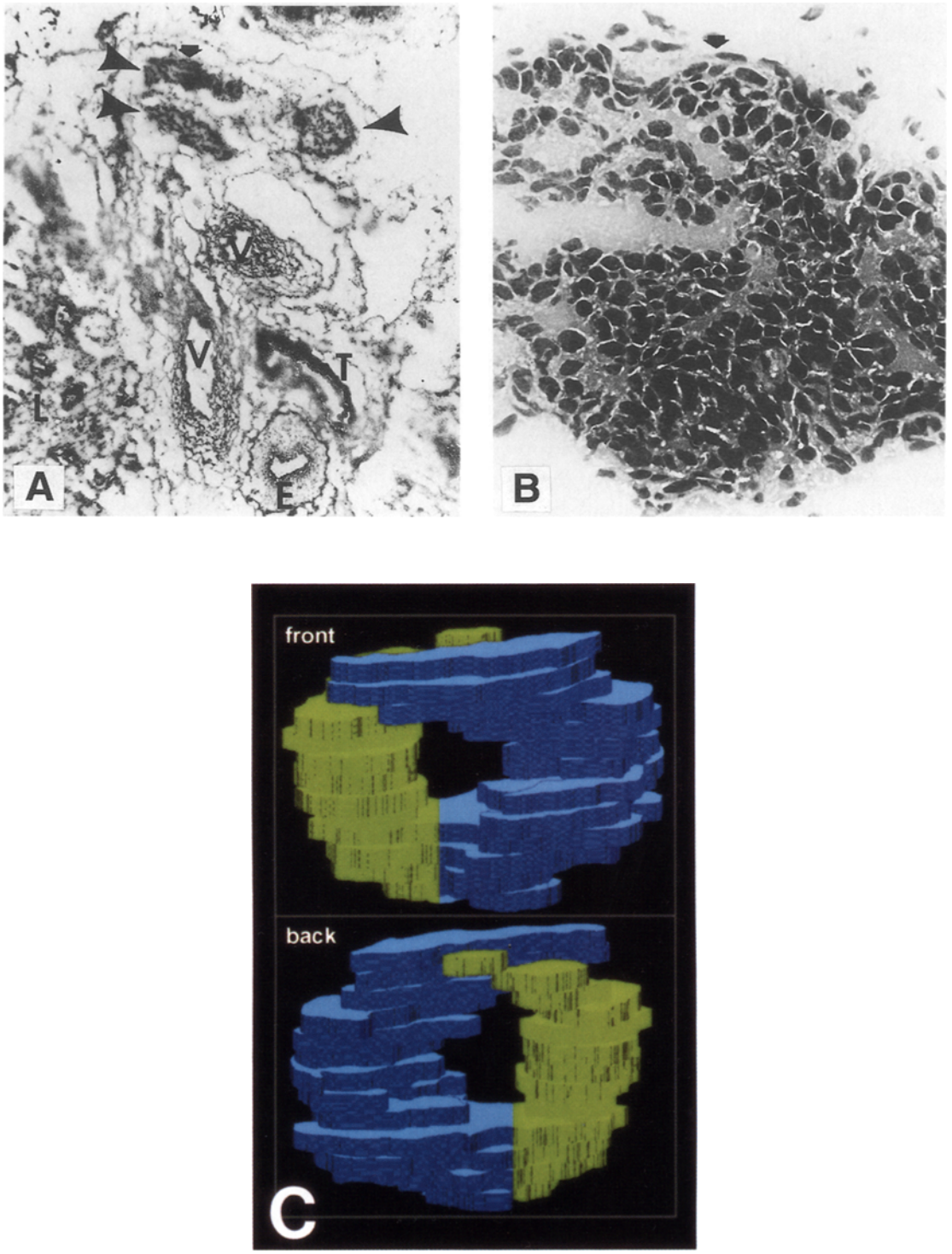

Fig. 1.

relationship of the true thymic epithelial space (TES), where thymopoiesis occurs, to the thymic perivascular space (PVS) (reviewed in *30*). The PVS has been noted by numerous investigators over the years and contains a fine reticular network that is readily identified with silver stains *(31–35)*. Because of the close proximity of the PVS to TES, one cannot distinguish the true TES from adjacent PVS without a special stain of the PVS, such as a silver stain, or by labeling the TES with keratin antibodies. All cells of the PVS are separated from epithelial and lymphoid TES by a basal lamina *(35)*. The PVS contains varying amounts of lymphocytes, granulocytes, mast cells, mononuclear phagocytes, and adipocytes. Several investigators have speculated on the origin of PVS lymphoid cells, with postulates ranging from thymic origin, peripheral origin, or containing recent thymic emigrants *(31–37)*. As will be discussed below, the latter two postulates are the most likely to be the case, depending on the age of the thymus and the clinical setting. The microanatomic relationship of the TES to the PVS in newborn thymus and the adolescent thymus is shown in Figs. 3 and 4.

The Thymus in Aging

In aging, the thymus undergoes changes of involution that originally were thought to commence at puberty. Confusion on this point arose because early investigators did not appreciate the presence of the PVS in addition to the TES in human thymus. Steinmann and colleagues have clarified this point, and in 1986 summarized their work and the work of others *(36,37)*. It is now appreciated that the true TES begins to involute beginning at the first year of life, whereas the PVS involutes at a different pace, increasing in size from the age of 1 yr until young adulthood, and then decreasing in size thereafter. Thus, the human TES reaches its maximum size at age 1, whereas the lymphoid volume of the PVS is only a potential space at birth, peaks in volume between ages 10 and 25, and decreases in volume thereafter *(36–38)*. It is also important to note that the human thymus, in contrast to the mouse thymus, does not lose its volume during aging *(36)*. Rather, the human thymus retains its size and volume during life, and by processes and stimuli that are poorly understood, the TES involutes whereas the PVS lymphoid component initially increases, and then eventually decreases in volume. Beginning at age 1, the adipocyte component of the PVS increases over time to comprise over 80% of the overall thymic volume by age 50 (Fig. 5) *(36–38)*.

As mentioned above, the presence of noncalcified HB indicates healthy growth and differentiation of medullary thymic epithelial cells *(15,17)*. During aging, the volume and size of HB decrease by over 60%, likely representing slowing down in TE cell maturation and function *(37)*.

Although the overall volume of the thymus remains the same during life and the TES volume diminishes, thymopoiesis has been seen

Fig. 1. The human thymus at the time of colonization with hematopoietic stem cells. **(A,B)** Hematoxylin and eosin stained sections of an 8.2-wk human fetal thymus. (A) Single right and double left thymus lobes (arrowheads), trachea (T), esophagus (E), ascending and decending aorta (V), and left lung (L) (×50). (B) Left thymus lobe. Small arrowhead on upper thymus left lobe in panel A shows the same point at small arrowhead of magnified left thymus lobe in B (×800). **(C)** A three-dimensional reconstruction of the 8.2-wk thymus in A and B. Computer-assisted reconstruction of the thymus was performed via overlay of hematoxylin and eosin-stained serial sections taken every 50 μ. The right and left lobes of the thymus are fused at the bottom and appear to be intertwining at the top. The left lobe has just begun to be lobulated by invasion of blood vessels, and the right lobe is nonlobulated. Actual thymus size in vivo was 1 mm high × 1 mm wide × 0.25 mm deep. (A and B adapted from ref. *9* with permission. C adapted from ref. *3* with permission.)

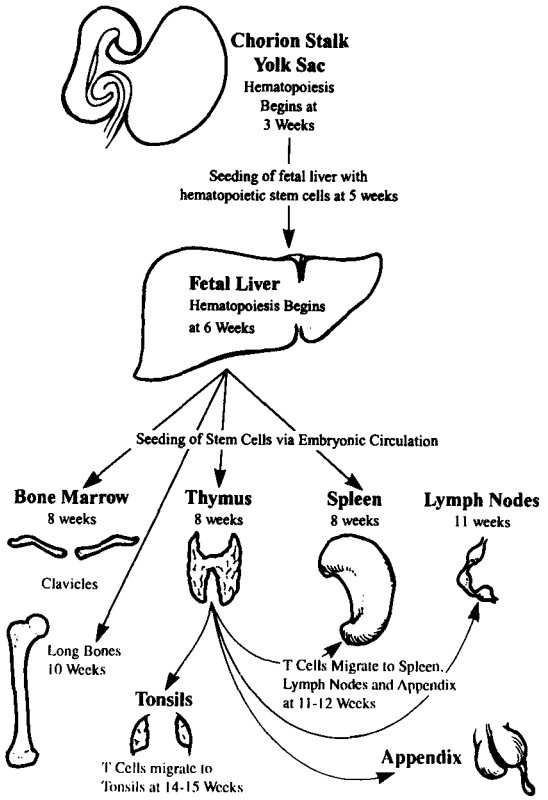

Fig. 2. Time-course of seeding peripheral immune microenvironment during normal fetal development. (Used with permission from ref. 11a.)

in thymus tissues of normal persons >60 yr old *(38,39)*. Thus, immature T cell precursors are present in the human thymus throughout adult life, and thymopoiesis continues to occur, although at a reduced rate compared to fetal development. However, whether the adult thymus with its reduced thymopoietic rate is capable of reconstitution of the adult peripheral immune system remains an open question *(40,41)*.

Whereas in children it is generally agreed that naive T cells (recent thymic emigrants or emigrants that have yet to see antigen in the periphery) express high levels of CD45RA isoforms and memory T cells express high levels of CD45RO isoforms *(42)*, data are accumulating that these markers may not always identify naive and memory T cells in adults. Specifically, recent data suggest that CD45RO memory cells can "revert" back to CD45RA "memory" cells *(43–45)*. Therefore, in adults, T cells that are CD45RA$^+$ may be heterogeneous and contain T cells capable of immunologic memory as well as contain naive T cells *(45)*.

Kong and colleagues have recently described a monoclonal antibody (MAb) against recent thymic emigrants that allows the monitoring of thymic function in vivo in chickens *(46)*. In addition, determination of excised TCR δ DNA circles in peripheral T cells as a measure of recent thymic emigrants has been suggested, but T cells containing excised TCR δ DNA circles can be long lived *(46)*. Until new technology is available, the quantitation of thymic function in and kinetics adult humans remains an open question.

Thus, in aging, TES involution begins at age 1 yr coincident with the increase in infiltration of the thymus PVS by T, B, mononuclear phagocyte, and myeloid cells. Although qualitatively thymopoiesis can be seen in TES islands in geriatic involuted thymuses, as yet, we have no data in adult humans regarding the quantitative contribution of the adult thymus to the peripheral T cell pool.

The Thymus in MG

MG is an autoimmune disease characterized by the production of antibodies against acetylcholine receptors that block neuromuscular signals, resulting in clinical weakness and muscle dysfunction. Most patients with MG have pathologic changes in the thymus with 60% of patients having enlarged, hyperplastic thymuses containing B cell germinal centers, and 10% of patients having a thymoma *(35,47)*. It was noted early on that thymectomy in MG was frequently associated with clinical improvement in muscle weakness, thus implicating the thymus in the pathogenesis of MG.

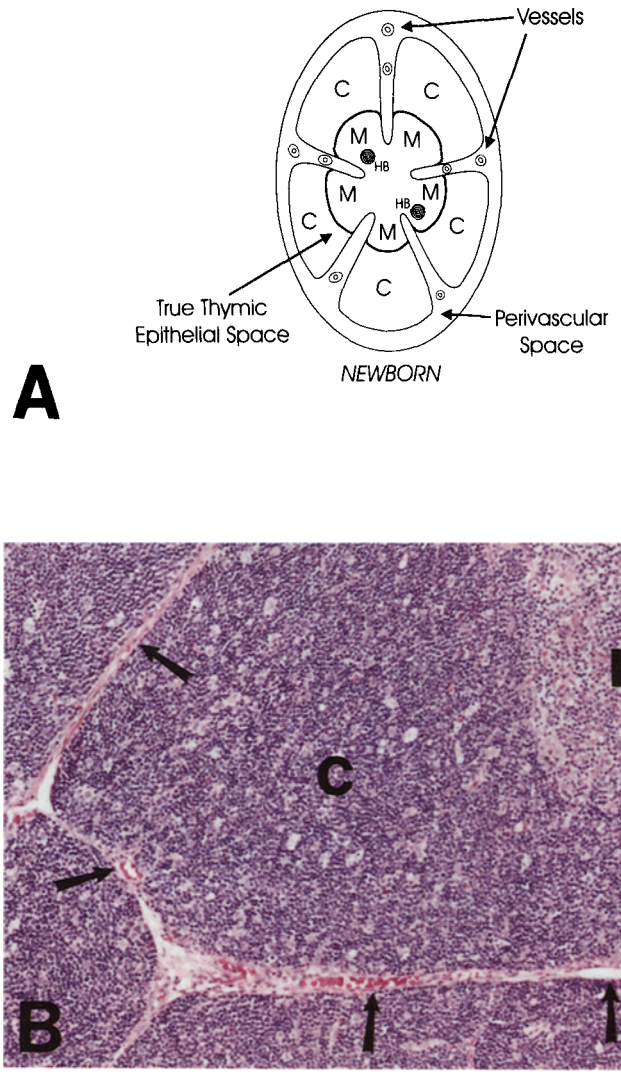

Fig. 3. The newborn human thymus. **(A)** A representative neonatal thymic lobule in schematic form. **(B)** A hematoxylin and eosin stained section of a thymus from a 1 mo old. At this age, the perivascular space (arrows) is only a potential space, containing primarily vessels and connective tissue of the thymic lobule capsules. M shows the thymic medulla, and C points out the cortex (×33).

The initial studies of the MG thymus by modern pathologists suggested that B cell germinal centers were located within the medulla of the thymus *(48)*. This was understandable, since by light microscopy, B cell germinal centers frequently are located next to HB *(48)*. In 1971, Tamaoki et al. used silver stains to identify the PVS of MG thymuses, and demonstrated that most of the B cell infiltration in MG thymuses was not in the TES, but rather was in the PVS *(31)*. Moreover, they showed the presence of postcapillary venules around MG germinal centers that were similar to those found in normal lymph node. They also dem-

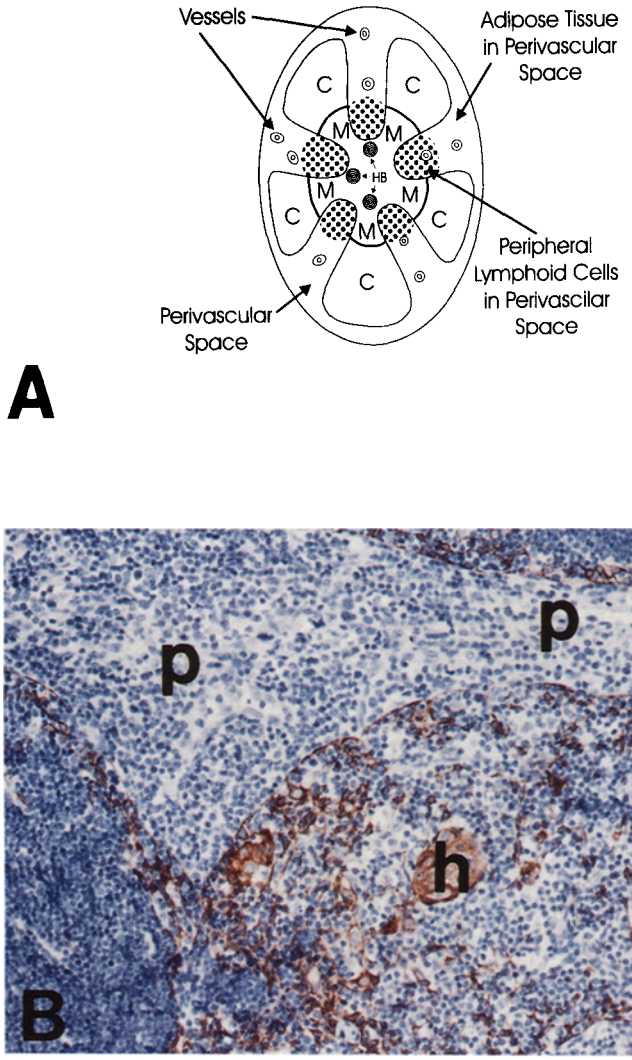

Fig. 4. The adolescent human thymus. **(A)** A representative adolescent thymic lobule in schematic form. **(B)** A hematolylin and eosin-stained section of a thymus from a 7-yr-old. During adolescence, the perivascular space (P) begins to be infiltrated with lymphoid and other peripheral cells, and adipose cells begin to appear in the perivascular space. **(B)** Immunohistologic analysis of a 7-yr-old thymus using MAbs that bind to human keratins. Brown areas are thymic epithelium within the thymic epithelial space, H points out a Hassall's body. P points out the lymphoid infiltration in the perivascular space (×40).

onstrated with immunohistologic stains that PVS lymphocytes around germinal centers expressed enzymes with the characteristics of lymph node cells rather than with characteristics of thymocytes *(31)*. Tamaoki et al. postulated that the influx of cells in the PVS was from the periphery, although these authors could not rule out PVS cell derivation from thymocytes *(31)*. Others have noted the presence of true high endothelial venules in the PVS of germinal center infiltrations in MG thymus, and commented on their similarity to those found in lymph nodes and other sites of peripheral migration in the periphery *(35,49)*.

In 1985, Bofill et al. similarly noted the infiltration of the PVS with germinal centers

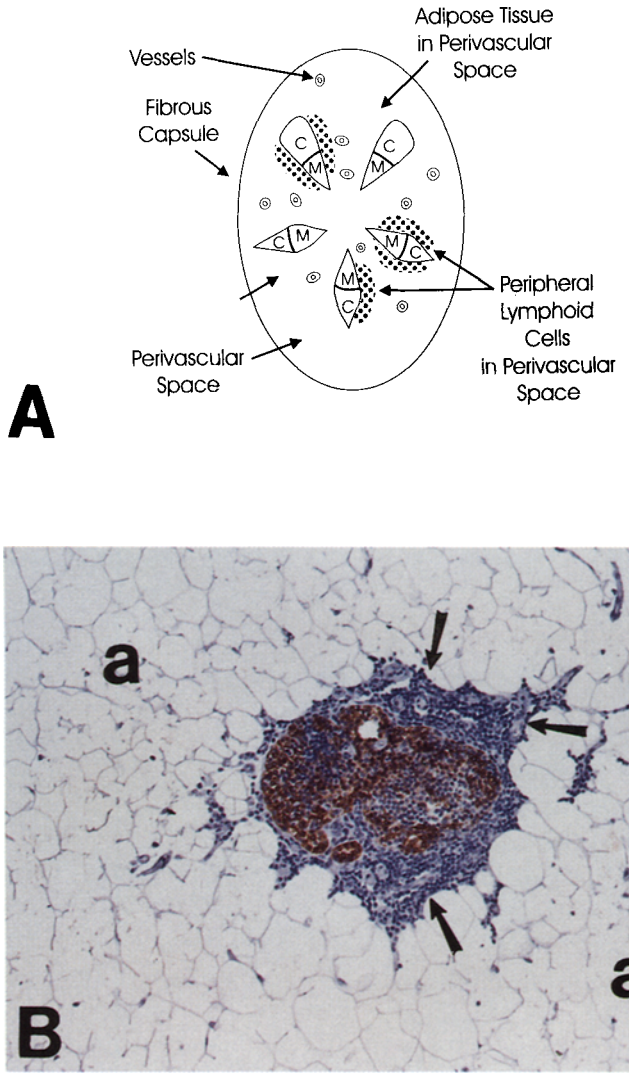

Fig. 5. The involuted geriatric human thymus. **(A)** A representative geriatric thymic lobule in schematic form. **(B)** A hematolylin and eosin stained section of a thymus from a 49-yr-old male. During aging, the perivascular space continues to contain lymphoid and other peripheral cells surrounding thymic epithelial spaces, and adipose cells predominate in the perivascular space. **(B)** Immunohistologic analysis of a 49-yr-old thymus using MAbs that bind to human keratins. Brown areas are thymic epithelium within the thymic epithelial space; arrows points out the lymphoid infiltration in the perivascular space. The lower-case letter "a" points out adipose cells in the perivascular space (×40).

in MG, and described the orientation of the pale zone of the germinal center toward the thymic medulla and epithelial HB *(35)*. At this site, they also noted the frequent breakdown of the the basal lamina that normally separates the PVS from the TES, resulting in mixing of cells from the PVS with the TES *(35)*. Wekerle and Muller-Hermelink noted that in the "hyperplastic" MG thymus, it is only that the PVS is "hyperplastic," but the TES of the thymus is actually hypoplastic, collapsed in on itself, and frequently devoid of developing thymocytes *(47)* (Figs. 6 and 7).

Thus, the prominent PVS observed in the hyperplastic MG thymus is an exaggerated form of the normal histology that is seen in the adolescent thymus (Fig. 4), since primary B cell follicles and germinal centers, though rare, can be seen in normal thymuses. When present in normal subjects, primary follicles and germinal centers are located in the PVS, just as they are in MG thymuses (Hale and Haynes, unpublished observations). One view of the immunopathology in MG is that peripheral T and B cells activated by antigen have migrated to the thymic PVS and proliferated there. Wekerle has drawn attention to the fact that the MG thymus looks very similar to the morphology of gut-associated lymphoid tissue, such as tonsils, with close approximation of peripheral germinal centers to tonsillar epithelium *(49)*. It should be pointed out that the thymic medulla of the TES normally contains a resident population of B cells *(50)*, even though thymic germinal centers form only in the PVS. Figure 8 illustrates this point, showing normal thymus TES tissue with medullary B cells, and PVS germinal center formation in adjacent hyperplastic areas of a MG thymus. These observations suggest that B cells reside in both the TES and PVS. Whether the same or different B cell subsets migrate to the TES and PVS is unknown.

The appearance of B cell germinal centers in thymus tissue of MG patients has prompted discussion regarding the possibility that the inciting antigen in MG is located in the thymus. Given the pathogenic role of antiacetylcholine receptor antibodies in MG and the presence in thymus of striated "myoid" cells that contain acetylcholine receptors, there has been considerable enthusiasm for the concept that MG is an autoimmune disease triggered by an antimyoid cell antibody response *(35,47)*. However, myoid cells are not increased in MG compared to normal thymuses *(57)*, and the

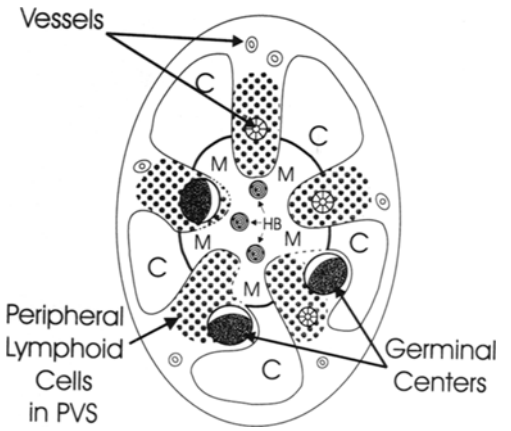

Fig. 6. Schematic representation of the thymus in MG. Figure shows a representative lobule in schematic form of a hyperplastic MG thymus. Germinal centers frequently are located near to medullary HBs, with the germinal center pale zone next to the HB. The basic lamina between the PVS and TES is frequently disrupted in this region (broken line). Vessels within the perivascular space near the germinal centers frequently are high endothelial venules similar to those found in normal lymph node.

histology of "thymitis" in MG can be seen in a number of other autoimmune and infectious diseases, including early HIV-1 infection. Thus, it remains an open question concerning whether MG is an autoimmune disease that occurs in the thymus owing to a thymic autoantigen or is a systemic autoimmune disease with peripheral immune cell trafficking to the thymus.

The Thymus in HIV Infection

HIV-1 infection leads to progressive loss of $CD4^+$ T cells, and results in immune cell deficiency and opportunistic infections. The mechanisms of $CD4^+$ T cell loss in HIV-1 infection have been attributed to viral-induced $CD4^+$ T cell destruction, and to damage of central and peripheral generative immune microenvironments (reviewed in *52*). Combination antiretroviral therapy leads to rises in $CD4^+$, $CD45RO^+$ (putative memory) T cells, and

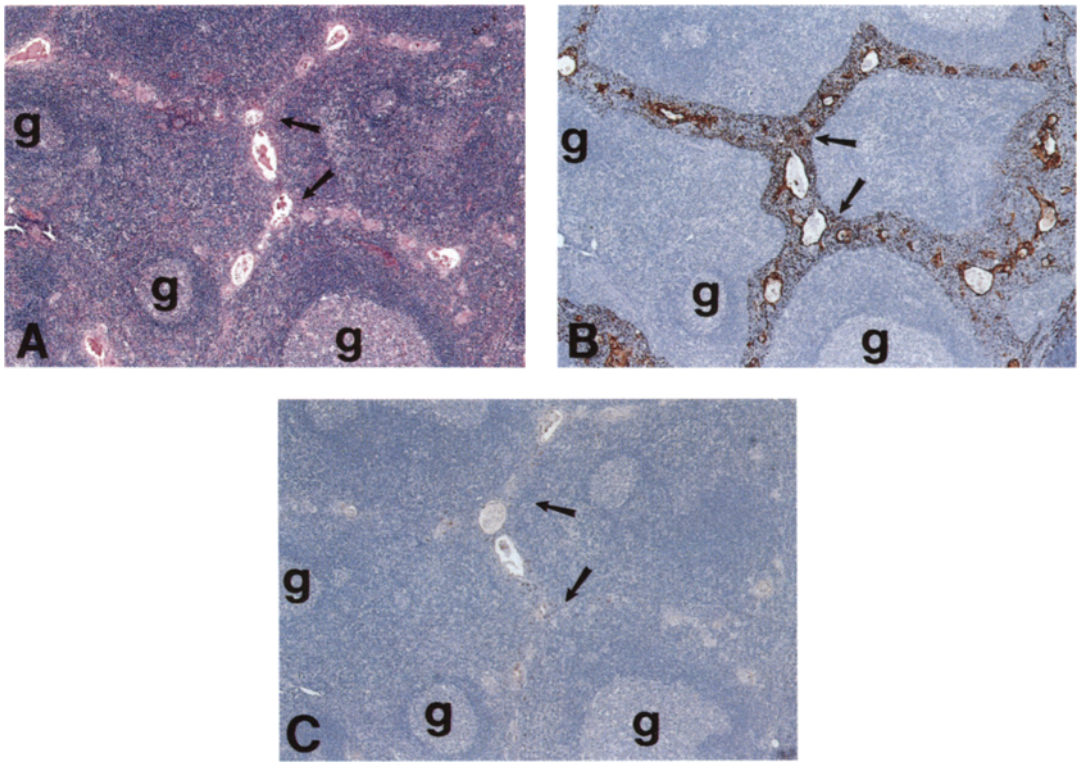

Fig. 7. The thymus in MG. **(A–C)** Equential sections of the same area of a hyperplastic myasthenia gravis thymus. (A) Hematoxylin and eosin-stained section. (B) Reacted with antikeratin antibodies to show (brown areas, arrows) the thymic epithelial space. (C) Lack of any $CD1a^+$ immature cortical thymocytes (i.e., no brown stain), demonstrating that thymopoiesis is actually suppressed in this "hyperplastic" myasthenic thymus. None of the (g) germinal centers are within the true thymic epithelial space (all panels ×13).

to rises in $CD4^+$, $CD45RA^+$ (putative naive) T cells *(53–55)*. However, antiretroviral therapy-induced CD4+ T cell rises do not usually reach normal pre-HIV-1 infection levels. Therefore, a question for understanding how the immune system reconstitutes following an injury, such as HIV infection, is whether the adult thymus contributes to the immune reconstitution of peripheral T cells in AIDS.

The first reports of thymus pathology in HIV-1 infection described premature thymic involution, calcification, and loss of HB, as well as loss of normal thymic architecture *(56–59)*. Subsequent reports have described selective loss of cortical thymic epithelium, expansion of the perivascular areas of thymus, and increased numbers of $CD8^+$ T cells, particularly in perivascular areas *(60,61)*. Interestingly, several reports have described extensive germinal center formation in the thymus of patients with early HIV-1 infections, with morphologies nearly identical to those seen in MG thymuses *(62,63)*. As in lymph node, in HIV-1-infected thymuses with germinal centers, HIV-1 has been detected in lymphocytes and follicular dendritic cells within germinal centers and in paracortical areas around germinal centers *(62,63)*. Others have reported HIV-1-infected cells in cells in the thymic epithelial space as well as in the PVS *(7,60)*.

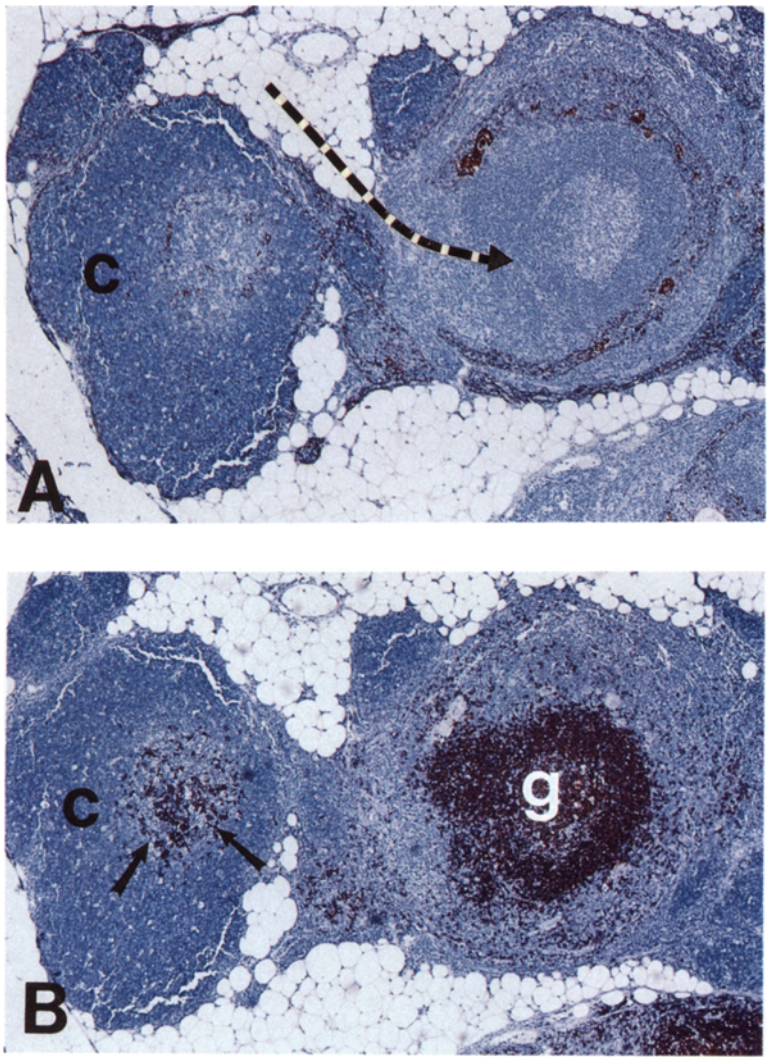

Fig. 8. B cells are present in the normal thymus medulla and within germinal centers in the thymic perivascular space. **(A)** Normal thymus tissue in a hyperplastic MG thymus pointed out by the C within the normal cortex. On the right side of the field, a large germinal center within the perivascular space (P) compresses the true thymic epithelial space stained brown with antikeratin antibody. One can follow the dotted line that leads from the adipose-infiltrated perivascular space into the germinal center-containing perivascular space in the hyperplastic thymus area. **(B)** The same area in (A) reacted with MAb L-26 that binds to human B cells, and shows a resident B cell population in the normal thymus medulla area on the left side of the figure in brown (arrows), as well as within the large germinal center in the hyperplastic area on the right side of the figure (g) (×13).

We have performed mediastinal dissections at autopsy in adult patients who died of complications of HIV-1 infection. We found that thymuses had inflammatory infiltrates within the perivascular space surrounding lympho-depleted thymic epithelium. The PVS infiltra-

tions were comprised of macrophages, B cells, and $CD8^+$ T cells, many of which had markers of $CD8^+$, cytotoxic effector cells *(7,64)*. The presence of CD8+ CTL effectors in the PVS demonstrated to us the peripheral nature of the cellular infiltrate in the PVS in HIV-1 infected thymuses *(7)*. Figures 9 and 10 demonstrate the typical morphologies of the thymus in early and late HIV-1 infection.

If the thymus were adding to the peripheral pool in adults in the setting of HIV infection, the T cell Vβ CDR3 repertoire could change toward more diverse TCR usage. Connors et al. demonstrated few changes in TCR repertoires over time in nonthymectomized HIV-1+ patients on combination antiretroviral therapy *(54)*. Gorochov et al. recently have found partial normalization of the $CD4^+$ T cell repertoire in select patients after long-term (>6 mo) treatment with antiretroviral therapy *(65)*. Interestingly, Zhang et al. have demonstrated "repair" of peripheral lymph node architecture and restoration of lymph node $CD4^+$ T cell populations over time on antiretroviral therapy *(66)*. Thus, repairs in the peripheral T cell repertoire can occur in patients on antiretroviral therapy over time and may be owing to repairs in the peripheral generative microenvironments, such as lymph node, or be owing to repairs in the central generative microenviroment in the thymus. The status of the thymus in this latter setting in HIV-1+ adults remains unknown; however, since no opportunity to observe the thymus in the setting of long-term treatment of a HIV-1-infected adult patient on antiretroviral therapy has arisen.

It is important to note that our comments above only apply to HIV-1 infection in older adults and not to HIV-1 infection in children. HIV-1-infected infants with T cell lymphopenia within the first 6 mo of life were more likely to progress rapidly to AIDS than were those with normal T cell levels *(67)*. Thus, in children and young adults, disruption of the thymus by HIV-1 may result in reduced postthymic T cell pools *(67–69)*.

A Unifying Hypothesis and Future Studies

Taken together, the data reviewed in this article suggest that the human thymus can be thought of as a chimeric organ comprised of a peripheral lymphoid component (the peripheral vascular space) and a central lymphoid component (the true lymphoepithelial thymus). In normal neonatal thymus, the PVS is only a potentia l space, with few peripheral cells present. The cellularity of the normal PVS increases up to approximately age 25 as the cellularity of the normal TES decreases. After age 25, the cellularity of both the normal PVS and TES decreases *(37)*. The true thymus neither fills up with adipose tissue during aging nor fills up with inflammatory cells during MG. Rather, in aging and in MG, cellular infiltrates and adipose tissue fill the PVS around the true thymus lobules, with collapse of the medullary epithelial component of the thymus and loss of cortical epithelium *(37)*. The thymus in early HIV-1 infection is similar in appearance to the thymus in MG, with PVS germinal centers and collapse and atrophy of the TES *(62,63)*. The thymus in late HIV-1 infection is an accelerated version of the thymus in older adults, with extensive PVS infiltrates and a largely lympho-depleted TES *(7,60)*. Therefore, the changes seen in MG and HIV-1 can be thought of as exaggerated variations of the changes that are seen normally in the aging thymus, resulting in atrophy of the true TES and decrease in thymopoiesis.

From our observations in HIV-1-infected thymuses and from studies by others of aging and MG thymuses, we postulate that the atrophy in TES and decreased thymopoietic activity may in some manner derive from changes that occur in the PVS during aging, MG, and HIV-1 infection. The common event in each

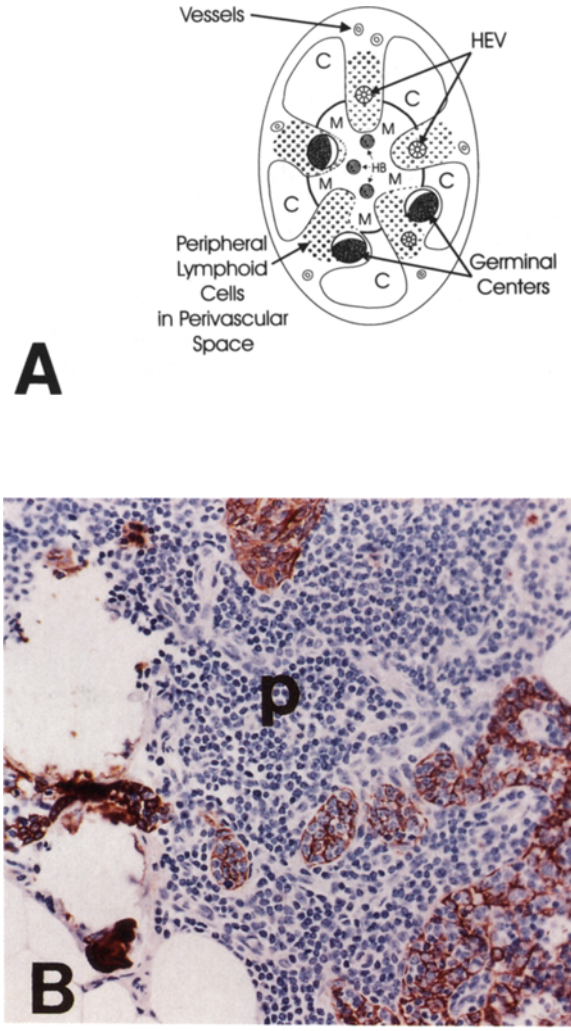

Fig. 9. The human thymus in early AIDS. **(A)** A representative thymic lobule in schematic form demonstrating that in some patients, the histology of early AIDS in the thymus is indistinguishable from that seen in hyperplastic MG thymus. **(B)** Immunohistologic analysis of a thymus from a HIV+ patient, who at autopsy had many areas of thymopoiesis present, using MAbs that bind to human keratins. There were many CD1a$^+$ thymocytes (shown here only as the blue cells, arrows) scattered within the normal thymic epithelial space. Brown areas are thymic epithelium within the thymic epithelial space; P points out the lymphoid infiltration in the perivascular space. In this photomicrograph, there are no germinal centers present. H points out HB (×13).

case is infiltration of the PVS with peripheral cells that resemble the phenotype of peripheral lymph node cells. In addition, in each case, the PVS also contains large numbers of adipocytes. It is known that thymocyte and thymic epithelial cell maturation is highly dependent on a rich milieu of appropriate cytokines for normal function (reviewed in refs. *1–3,8*). Moreover, it is also known that certain cytokines (such as IL-4) are inhibitory for either thymocyte or thymic epithelial cell function *(29)*. Thus, one unifying hypothesis to explain the atrophy seen in the TES in aging, MG, and HIV-1 is that the presence of lymph

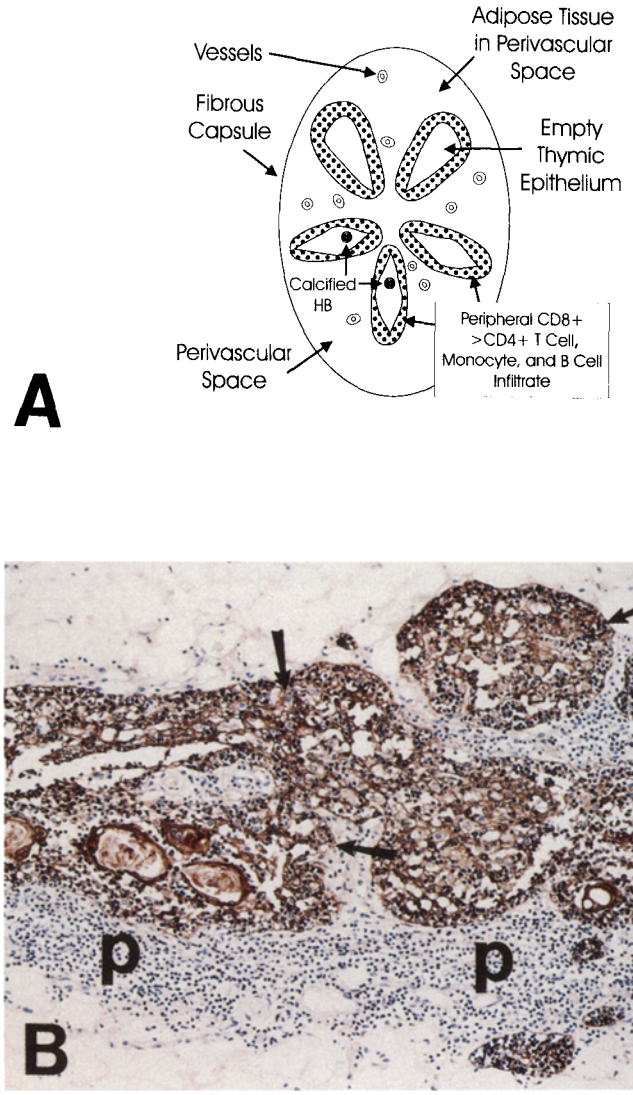

Fig. 10. The human thymus in late AIDS. (A) A representative thymic lobule in schematic form. (B) A keratin-labeled section of a thymus from an HIV+ patient who had no areas of active thymopoiesis present at autopsy. **(A)** shows that in some patients, the histology of late AIDS in the thymus is an exaggerated pattern of that seen in the normal aged involuted thymus (*see* Fig. 5). **(B)** shows immunohistologic analysis of a thymus from an HIV + AIDS patient, using MAbs that bind to human keratins. In other sections, there were no CD1a$^+$ thymocytes within the normal thymic epithelial space. Brown areas (arrows) are keratin + thymic epithelium within the thymic epithelial space; P points out the peripheral lymphoid infiltration in the perivascular space (×33).

node-like infiltrations of peripheral immune cells in the thymic PVS leads to either loss of critical trophic cytokines or production of cytokines inhibitory for normal TES function. Interestingly, it has been shown that transgenic mice expressing leukemia inhibitory factor have thymuses with numerous germinal centers with a morphology identical to that seen in MG and early HIV-1 infection *(70)*.

Thus, future studies on the roles that cytokines play in regulating TES and PVS formation and function should prove invauable in providing new insights into normal thymus function and thymus function in a variety of disease syndromes. It is critical to understand how to drive the postnatal thymus and peripheral lymphoid tissues to regenerate damaged immune systems to function normally in the setting of autoimmune diseasese, such as MG, and in the settings of infections that damage the immune system, such as HIV-1-induced AIDS.

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