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Pericapillary collagen in the human thymus: implications for the concept of the 'blood-thymus' barrier

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ABSTRACT

The deposition of collagen in the walls of capillary-size blood vessels was studied in 95 human thymuses with respect to the site of deposition, extent of the change and relation to age and degree of involution. When examined by electron microscopy the collagen was found to be situated between the 2 basement membranes of the so-called 'double-layered' capillaries characteristic of the thymus of many species. This results in the formation of substantial 'collars' of collagen around a proportion of the blood vessels examined. Few such collars are seen before birth, but their number and thickness increase markedly during the 1st year of life. The relationship of these changes to the degree of involution is less apparent. The significance of these changes to thymic structure and function is discussed in relation to cell traffic through the thymus and the postulated 'blood-thymus barrier', the existence of which is seen to be in some doubt.

INTRODUCTION

The pattern of blood vessels in the thymus has been described in the mouse (Smith et al. 1939, 1952; Smith & Ireland, 1941; Weiss, 1963; Ito & Hoshino, 1966; Kramarsky et al. 1967), rat (Murray, 1964; Toro & Olah, 1967; Irino et al. 1981), guinea pig (Olson & Poste, 1973) and human (Kameya & Watanabe, 1965; Kelley, 1966). Kostowiecki (1967*a*), quoting Strandberg (1917) and Smith and Ireland (1941), drew attention to the so-called 'double-walled' blood vessels in the thymus. These possess an inner layer of basement membrane and reticulin derived from the blood vessel wall and a similar outer layer derived from the reticulin framework of the thymic lobule. These layers tend to fuse as the blood vessel is reduced to capillary size. Several authors have commented on the presence of collagen fibres between these 2 layers. During studies on the involution of the human thymus (Henry, 1967; Henry & Anderson, 1987, 1988, 1990), it was observed that many of the blood vessels of capillary size were surrounded by a substantial 'collar' of collagen. A light and electron microscope investigation was therefore undertaken to establish their fine structure and their relation to age and the process of involution.

MATERIALS AND METHODS

Ninety-five thymuses were obtained from male and female cadavers with ages ranging from 20 wk gestation to 65 y. A block from each thymus fixed

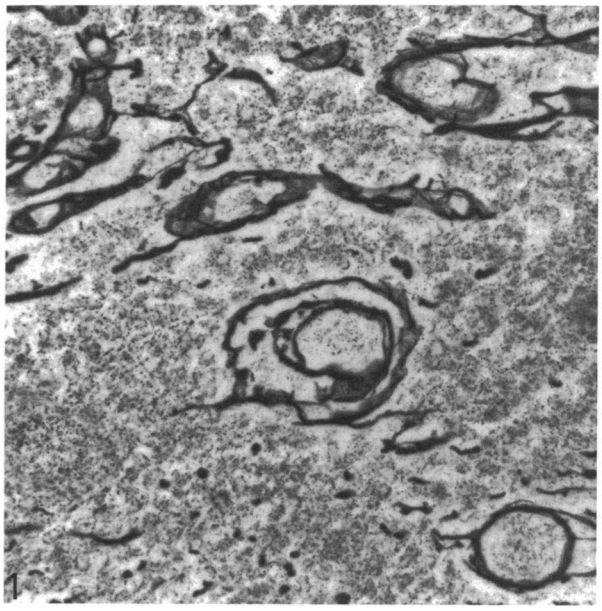

Fig. 1. Double-walled blood vessel in thymic medulla. Reticulin stain. × 160.

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either in 10% formalin or in formol-calcium was processed to paraffin wax. Sections were stained with haematoxylin and eosin, Gomori's reticulin silver impregnation, and Masson's trichome.

For electron microscopy, small blocks of the formalin-fixed tissue were taken from the cortex and medulla of each thymus and postfixed in 1% osmium tetroxide for 1 h. Prestaining was carried out using 1% uranyl acetate in distilled water for 1 h. The tissue was then dehydrated in ascending grades of alcohol to propylene oxide before embedding in Emix resin. Ultrathin sections were mounted on copper grids, stained with lead citrate for 10 min and examined with a Philips EM400 at 60 kV.

ASSESSMENT OF INVOLUTION

The stage of thymic involution was assessed by examination of the reticulin pattern (Henry, 1967). Thymuses assigned to group I showed no histological evidence of involution, the lobules being outlined by a single strand of reticulin which also encompassed the transcortical blood vessels. As involution proceeds, there is the development of a reticulin network surrounding these blood vessels and the formation of reticulin fibre networks at the corticomedullary junction (groups II and III). In advancing involution (group IV) the lobule begins to shrink, the cortex being mainly affected (Henry and Anderson, 1987). In group V the reticulin pattern becomes increasingly condensed and both the cortical and medullary blood vessels become more closely approximated. When involution is almost complete (group V) the perivascular networks are no longer apparent and the distinction between cortical and medullary blood vessels is obscured. In group VI involution is complete and little thymic tissue remains. The reticulin fibres outline closely packed blood vessels but the lobular structure is lost.

RESULTS

Light microscopy

On examination by light microscopy the presence of double-walled blood vessels was confirmed (Fig. 1). Using Masson's stain, 70 (74%) of the thymuses showed evidence of pericapillary collagen, the remaining 25 (26%) showing none. When these results were correlated with age, 24% (5/21) stillborn fetuses showed pericapillary collagen. After birth 88% (65/74) thymuses were positive, the changes being more pronounced after the 1st week of life. Thereafter the proportion of positive cases remained broadly similar at each age group, varying between 100% at ages 5–9 y and 83% at ages over 10 y. The lower figure in the older cases reflected the difficulty of assessment in thymuses showing extensive involution.

When correlated with the degree of involution the relationship was less apparent. In thymuses showing

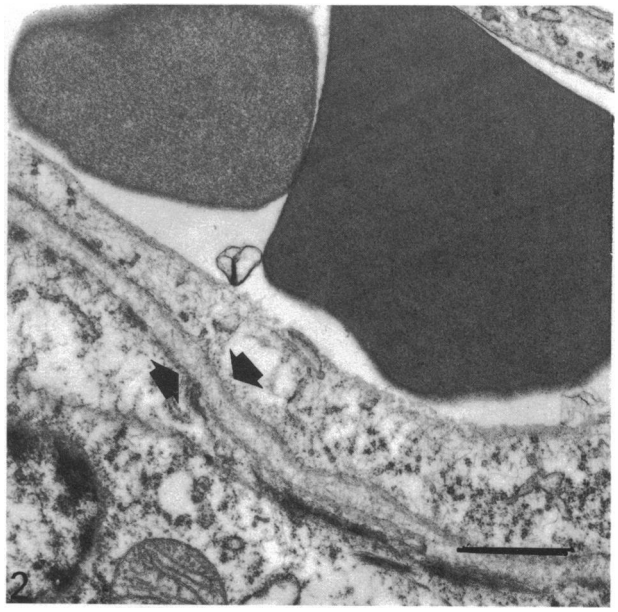

Fig. 2. Electron micrograph. Thymic capillary showing 2 distinct basement membranes. × 10000.
Calibration bar on electron micrographs = 1 μm.

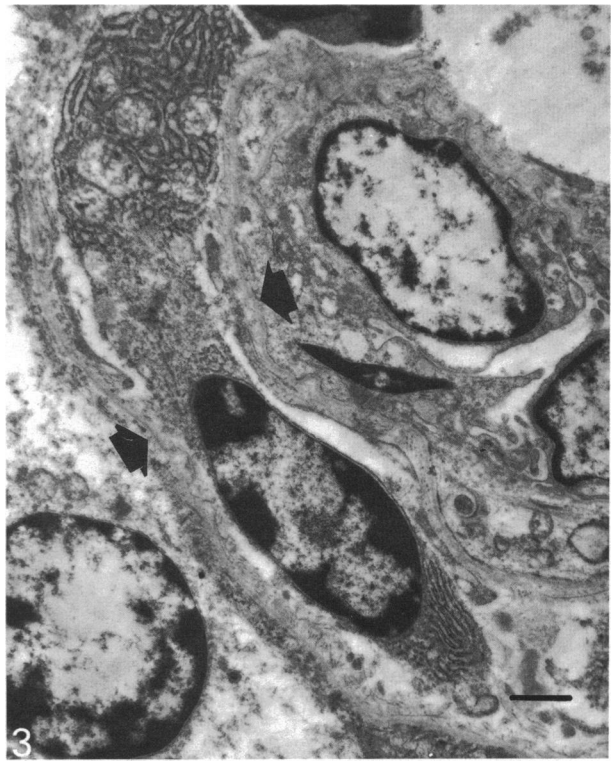

Fig. 3. Electron micrograph. Two basement membranes are identifiable (arrows). The intervening space contains a few collagen fibrils and a plasma cell. × 6000.

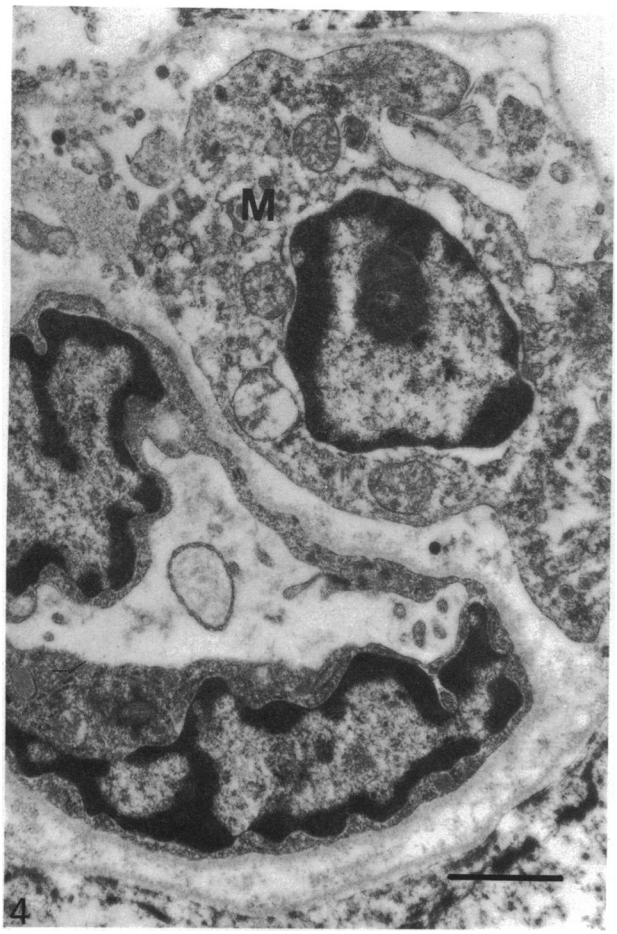

Fig. 4. Electron micrograph. A macrophage (*M*) lies between the 2 basement membranes. × 10000.

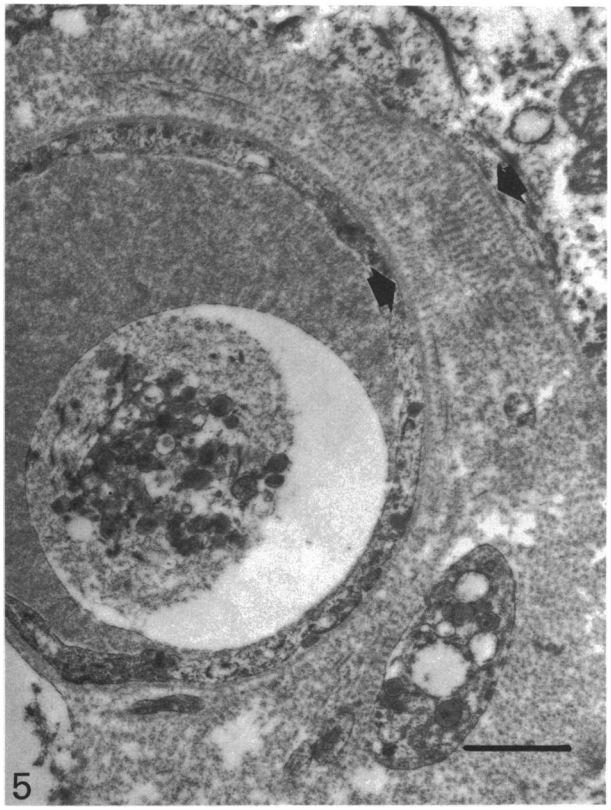

Fig. 5. Electron micrograph. Two basement membranes are identifiable (arrows). The intervening space contains a substantial amount of banded collagen. × 6000.

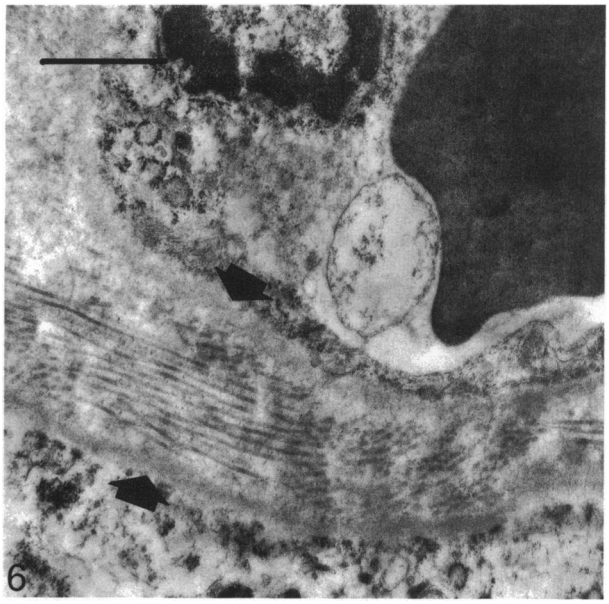

Fig. 6. Electron micrograph showing close relationship between the 2 basement membranes (arrows) and the collagen in the intervening space. × 13000.

no involution (group I), 48% (14/29) showed pericapillary collagen. As involution proceeded this figure rose in group II to 76% (25/33); III, 92% (12/13); IV, 100% (5/5); V, 89% (8/9); and VI, 100% (6/6). However, individual thymuses showed deviations from these trends. Considerable pericapillary collagen could be demonstrated in a few stillbirth cases and in thymuses that showed no involution. Likewise, no such collagen could be demonstrated in some older cases and in some showing varying degrees of involution. No sex difference was observed.

Electron microscopy

The degree of the changes seen varied between specimens. Some thymuses showed no excessive deposition of collagen, and even where such changes were apparent in some blood vessels, other capillaries on the same grid were unaffected. However, the degree of change seen was broadly similar to that demonstrated by light microscopy. The presence of the double-layered capillary wall was confirmed (Fig. 2), consisting of an endothelial cell and inner and outer basement membranes. A few collagen fibrils could be seen in the space between the 2 membranes which sometimes also contained plasma cells (Fig. 3) and macrophages (Fig. 4). Increased amounts of collagen

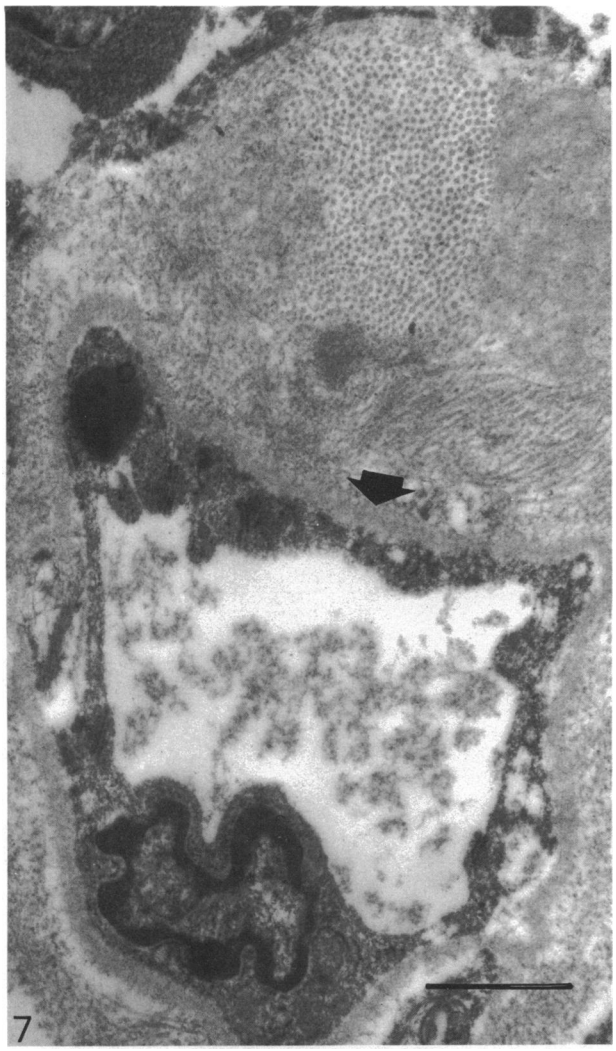

Fig. 7. Electron micrograph showing pericapillary collagen deposition. The inner basement membrane is clearly seen (arrow) but the outer basement membrane is not identifiable. × 6000.

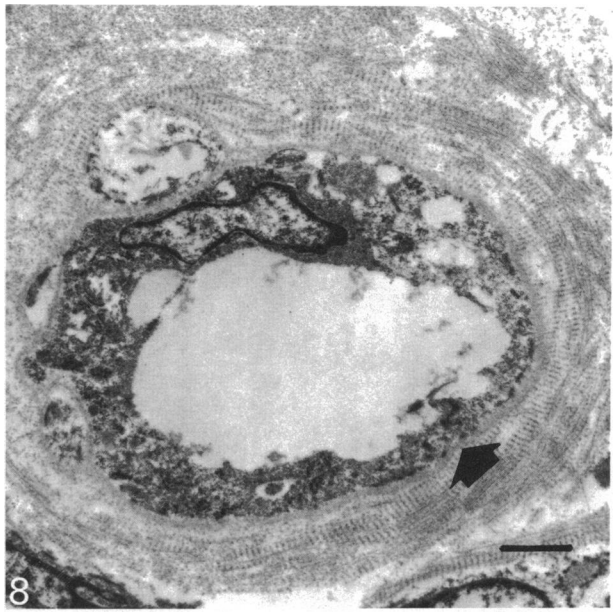

Fig. 8. Electron micrograph showing pericapillary collagen deposition. The outer basement membrane cannot be identified. The inner basement membrane is only partially complete (arrow). × 6000.

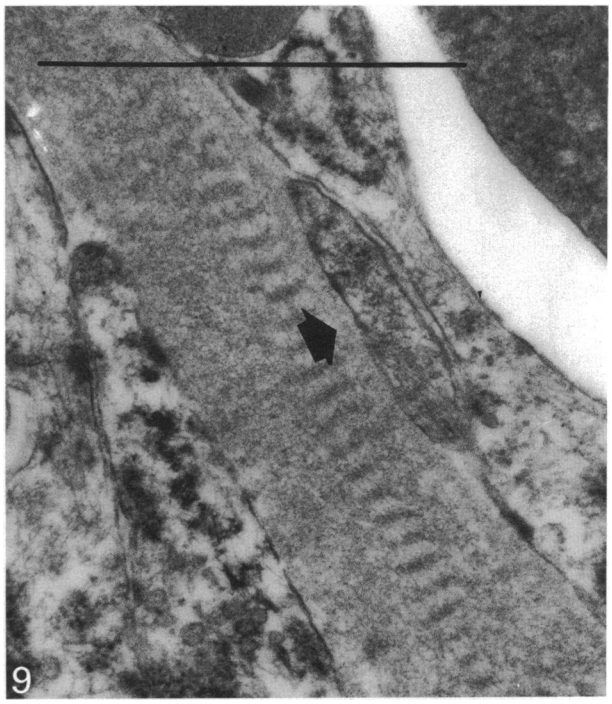

Fig. 9. Electron micrograph showing pericapillary collagen deposition. The outer basement membrane is absent. The inner basement membrane is barely identifiable (arrow). × 48000.

were seen between the 2 basement membranes in some capillaries (Fig. 5), the collagen coming into close relationship with the membranes (Fig. 6). With increasing collagen deposition the outer membrane was no longer detectable (Fig. 7). The inner basement membrane became only partially complete (Fig. 8), then barely identifiable (Fig. 9) and finally disappeared. The capillary was then surrounded by a broad collar of banded collagen in which neither the inner nor the outer basement membranes could be seen (Fig. 10). A few high-endothelial venules were seen. These usually had a single basement membrane but one showed a moderate deposition of perivenular collagen (Fig. 11). Lymphocytes could be seen between the endothelial cells of these venules (Fig. 12). No single-walled capillaries were seen. The minimum distance between the basement membranes was 190 nm. The maximum distance between 2 identifiable basement membranes separated by collagen was 3476 nm. The maximum observed thickness of pericapillary collagen was 6666 nm. The periodicity of the collagen banding was 78 nm, identifying this as wide-banded (fibrous long-spacing) collagen. No cells were

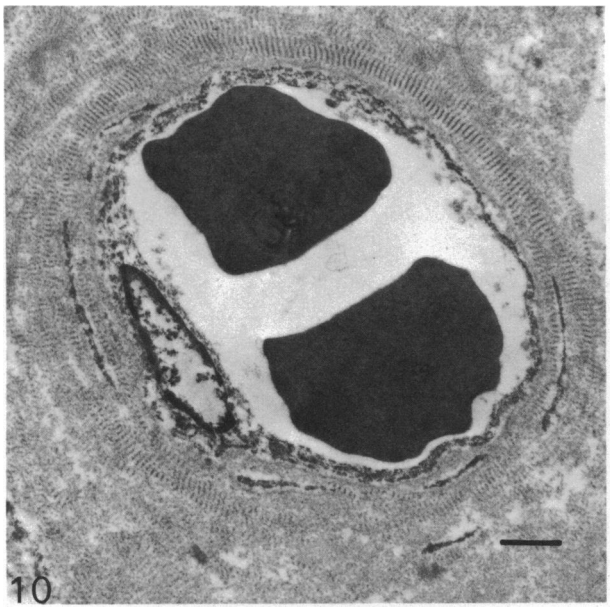

Fig. 10. Electron micrograph showing pericapillary collagen deposition. Neither the inner nor the outer basement membranes can be identified. ×4000.

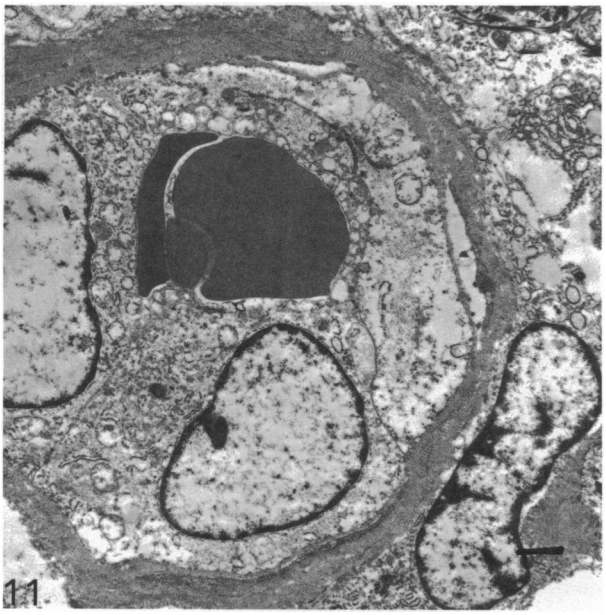

Fig. 11. Electron micrograph showing a high-endothelial venule at the corticomedullary junction. A little perivenular collagen is present but 2 basement membranes cannot be identified. ×4000.

seen in the walls of capillaries surrounded by a wide collar of pericapillary collagen.

At no stage were deposits seen in relation to the blood vessels which could be interpreted as antigen-antibody complexes. No fenestrated blood vessels were seen, but the subcapsular blood vessels were not specifically examined. No tight junctions were observed between adjacent endothelial cells, but as this was postmortem material, they may not have been detectable.

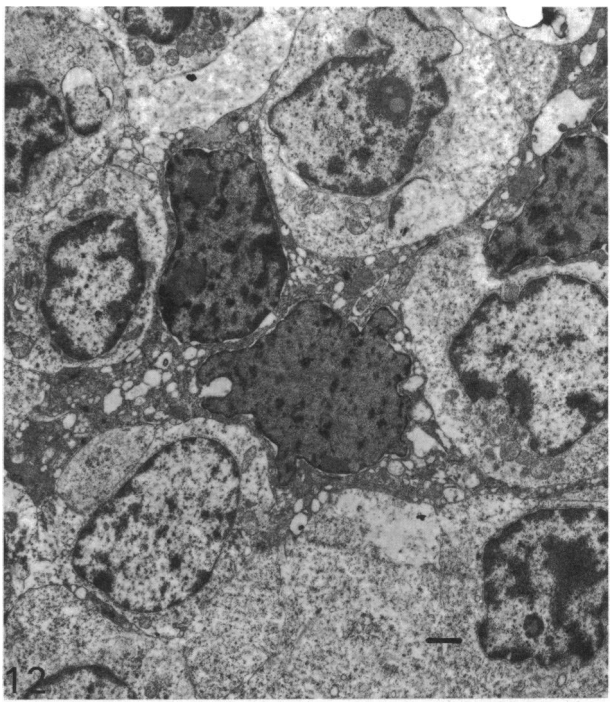

Fig. 12. Electron micrograph showing a high endothelial venule at the corticomedullary junction. Two lymphocytes are passing through the wall of the venule between the endothelial cells. × 5000.

DISCUSSION

As the human thymus undergoes 'age' involution there is an increase in reticulin fibre formation, particularly in relation to the transcapsular blood vessels and at the corticomedullary junction. As involution proceeds, collagen is laid down in these areas forming broad bands of fibrous tissue continuous with the collagen of the septa. The blood vessels have their own basement membrane and reticulin fibre envelope, but as they penetrate the cortex and enter the medulla, the transcapsular arteries carry with them a second envelope derived from the reticulin fibres which outline the septal surface of the thymic lobules. This double layer of reticulin is carried down to blood vessels of capillary size and an outer basement membrane is also developed (Strandberg, 1917; Smith & Ireland, 1941; Kostowiecki, 1967*a*). The normal structure of these capillaries therefore comprises an inner layer of endothelial cells, a capillary basement membrane, a pericapillary space and an outer basement membrane with associated reticulin. The outer layer comes into contact with a closely adherent sheath of thymic epithelial cells. A few collagen fibres are present in the pericapillary space and these may be intimately associated with the inner basement membrane (Kameya & Watanabe, 1965; Kelley, 1966). Similar findings have been documented in the mouse thymus

(Clark, 1961, 1962; Weiss, 1963; Ito & Hoshino, 1966), the rat (Murray, 1964; Toro & Olah, 1967) and guinea pig (Toro & Olah, 1967). Since all these authors comment on the 'double-layered' blood vessels, this structural complex extends over a variety of species and may well be unique to the thymus in contradistinction to the structure of capillary blood vessels in other organs (Palade, 1961). No fenestrated blood vessels were seen, although these have been described in the peripheral cortex and capsule (Raviola & Karnovsky, 1972).

The observations described here confirm these findings but indicate that the collagen normally present between the inner and outer basement membranes may increase to such an extent that the capillary is surrounded by a broad 'collar' of dense collagen. This fuses with both of the basement membranes and eventually these structures cease to be identifiable. The development of this collagen component bears some relation to the degree of involution but shows a stronger correlation with age, the greatest increase occurring during the postnatal period and the 1st year of life. These dense accumulations of pericapillary collagen may have a bearing on the concept of a 'blood-thymus barrier' postulated by Marshall & White (1961). If soluble antigen is injected intravenously, the thymus does not react by forming lymphoid follicles and producing humoral antibody. However, if the same antigen is injected directly into the thymus, lymphoid follicles develop and antibody is produced. A conclusion was derived that the thymus contains the necessary immunological components to mount a humoral reaction but that a 'blood-thymus barrier' exists, denying entry of circulating antigen into the thymic parenchyma. This experiment is questionable because the physical act of injection may have traumatised the blood vessels of the thymus at that site, allowing ingress of nonthymic immunocompetent cells from the bloodstream. There is, however, a normal traffic of cells through the thymus (Scollay & Shortman, 1985). Cells of various types, macrophages, plasma cells and lymphocytes have been demonstrated passing through high-endothelial venules at the corticomedullary junction and through the double-walled capillaries (Clark, 1961, 1964*a*; Ito & Hoshino, 1966; Toro & Olah, 1967; Irino et al. 1981). The present study confirms these findings in the human. However, no cells were seen passing through capillaries with increased perivascular collagen and it may be that this constitutes an obstacle to cellular traffic. There is a considerable production of lymphocytes in the thymic cortex (Bryant, 1972). Rather than the majority of these cells dying, it has been postulated that migration to the medulla takes place, where the cells pass into the peripheral blood through the walls of the medullary blood vessels (Sainte-Marie & Leblond, 1958; Bryant et al. 1975). However, effector T lymphocytes can also pass into the thymus (Naparstek et al. 1982), with a tendency to accumulate at the corticomedullary junction (Galton & Reed, 1966), suggesting passage through the high-endothelial venules as shown by Irino et al. (1981).

With respect to the penetration into the thymus of circulating antigens or particulate material, recent studies have shown that the 'blood-thymus barrier' is far from complete. Evans blue passes readily into the medulla from the bloodstream (Blau & Veall, 1967) as does circulating protein (Kouvalainen & Gitlin, 1967). Intravenously injected ferritin passes into the thymic parenchyma (Clark, 1964*b*) with a concentration in the subcapsular region and medulla (Abe & Ito, 1974). Circulating pneumococcal polysaccharide is subsequently found principally in macrophages surrounding the transcortical blood vessels (Kaplan et al. 1950), as are bacterial agents (Kostowiecki, 1967*b*; Gaugas et al. 1970). Using carbon particles, Blau (1971) suggested a continual exchange of macrophages between the thymus and the circulation. Green & Bloch (1963) suggested that the thymic vasculature is more permeable in newborn mice than in the adult. Kyewski et al. (1986) showed that a number of circulating antigens of different molecular weights can cross the walls of the medullary blood vessels and thus be exposed to processing by the medullary dendritic cells. However, these studies have been carried out in animal thymuses apparently showing no involution. It is probable that the transport of such materials across the vessel wall will be seriously impaired by the deposition of pericapillary collagen.

There is, however, an alternative route for antigenic material to enter the thymus, namely from the mediastinum by the transcapsular route. Protein injected into the mediastinum permeates into the thymic cortex, possibly by way of the perivascular channels (Sainte-Marie, 1963; Stet et al. 1987; Niewenhuis et al. 1988). Particulate material injected intraperitoneally may be taken up by macrophages (Koelsch, 1968), transmitted via lymphatic channels to the mediastinum and thence into the thymic parenchyma (Hess et al. 1985; Eggli et al. 1986). Transport of material into the thymus across the capsule appears to be more readily accomplished than that through the blood vessels, particularly in respect of the thymic cortex. It is clear, then, that there are adequate mechanisms for the transport of antigens into the thymic parenchyma by a variety of routes.

The normal thymus contains all the cell populations necessary to mount an immunological response, including macrophages (Kostowiecki, 1963; Barclay & Mayrhofer, 1981; Duijvestijn et al. 1983), some of which can present antigens (Modabber, 1973; Beller & Unanue, 1980; Kyewski et al. 1986), including self-antigens (Lorenz & Allen, 1989). There are also populations of immunocompetent T lymphocytes (Leckband & Boyse, 1971), B lymphocytes (Isaacson et al. 1987) and immunoglobulin-producing cells (Henry & Anderson, 1988). The immunological responsiveness of the thymus does not therefore result from the failure of antigen entry or a lack of responsive cells. Nevertheless, the profound changes in the walls of the thymic capillaries described in this study cannot fail to have an effect both on the cell traffic and the nutrition of the thymus in the human and should be taken into account when considering both the function and involution of the organ.

Most accounts in the literature of thymic structure and function make reference to animal models. The present study gives no indication in the human thymus as to whether the collagen deposition described is a cause or an effect of the involutional process. The absence of antigen-antibody complexes would exclude a humoral reaction but the walls of small blood vessels may provide a critical site of interaction between antigenic material and immunocompetent cells, both of which may be present at this site. Such an interaction could result in the liberation of factors stimulating the formation of collagen. The development of these vascular changes in the early weeks or months of life may therefore be related to the development of immunocompetence during this period.

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