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# Prenatal Development of The Post-Capillary Venules in Human Lymphatic Tissue

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**Summary**

Lymph nodes, Peyer's patches and tonsils from 19 human fetuses or stillborn babies between 13 and 40 weeks of pregnancy were collected, and their post-capillary venules (PCV) were subjected to direct morphometric measurements. The aims were to gain information about their development as well as about the circumstances of lymphocyte recirculation during the fetal period.

First PCV:s detectable in fetuses aged 15 weeks had a low endothelium (2.3 to 3.2 $\mu$m), which increases in heigth thereafter, up to 10.1 $\mu$m in full-term pregnancies. This increase was not directly related to gestational age, however, but correlated most closely with the state of supposed lymphocyte traffic, as defined on morphological grounds.

The results suggest that active lymphocyte recirculation is established in fetal period, and because of absence of external antigenic stimuli it must be an inherent property of lymphocytes acquired by them during the second trimester.

## *Introduction*

Post-capillary venules located in the thymus-dependent areas of the lymphatic tissue are known to be the sites where recirculating lymphocytes pass from blood to lymphatic tissues (1, 5, 9, 10, 18, 20, 22, 30, 32). The route utilized by the lymphocytes in their passage is through small intercellular gaps in the PCV endothelium, and not through the endothelial cells proper as previously thought (8, 16, 18, 20, 22, 32, 33). The factors regulating the passage of lymphocytes through the PCV are not fully elucidated, but recently, such properties were attributed to IgG found to be present in the PCV endothelium (21, 23, 25, 27, 28, 29, 30). Such a molecule could recognize T- and B-cells by their surface antigens and Fc-receptors, respectively (30).

It is well established that PCV endothelium is subject to changes related to the current activity of the lymphocyte traffic, i.e. to either immunosuppression or antigenic stimulation (2, 4, 6, 7, 11, 12, 13, 14, 30). These morphological changes have been utilized in the evaluation of the lymphocyte recirculation under a variety of experimental conditions (11, 12, 13, 14, 23, 26, 27, 28, 29, 30). One of the factors influencing the PCV morphology is age (15), but no attempts have been made so far to evaluate the lymphocyte recirculation on these grounds, albeit the post-natal development of the vessel has been studied in some species including man (17, 19, 31). The prenatal development of PCV is more poorly understood, and the extent of lymphocyte recirculation in human fetus is totally unknown (3, 19, 31).

The present communication describes the morphology of the PCV:s in the lymphatic tissues of human fetus with reference to their development as well as to the recirculatory circumstances of the small lymphocytes.

## *Material and Methods*

A total of 17 human fetuses varying from 13 to 25 weeks of gestation, provided by means of legal abortions instituted at Kuopio University Central Hospital during 1980, were included in the study. In addition, two newborn infants (38 and 40 weeks of gestation) who died im-

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**Tab. 1** The dimensions of the post-capillary venules (PCV) in fetal lymphatic tissues

| Weeks of Gestation | Lymphatic Organ | Diameter of the PCV (μm, M ± SE) $D_{pcv}$ | Diameter of the PCV lumen $D_{lu}$ | Height of the PCV endothelium $H_{end}$ | Number of Lymphocytes in the area |
|---|---|---|---|---|---|
| 13 | LN | ND | ND | ND | very low |
| | PP | ND | ND | ND | very low |
| | TS | ND | ND | ND | very low |
| 14 | LN | ND | ND | ND | very low |
| | PP | ND | ND | ND | very low |
| | TS | ND | ND | ND | very low |
| 14 | LN | ND | ND | ND v | very low |
| | PP | ND | ND | ND | very low |
| | TS | ND | ND | ND | very low |
| 15 | LN | 12.81 ± 1.30 | 6.40 ± 1.24 | 3.20 ±0.32 | low |
| | PP | ND | ND | ND | very low |
| | TS | 5.78 ± 0.39 | 1.11 ± 0.19 | 2.33 ± 0,09 | low |
| 16 | LN | 13.52 ± 1.33 | 7.12 ± 1.08 | 3.20 ± 0.25 | low |
| | PP | 14.24 ± 1.49 | 8.54 ± 1,90 | 2.84 ± 0.43 | low |
| | TS | ND | ND | ND | very low |
| 17 | LN | 15.66 ± 2.66 | 6.05 ± 2.22 | 4.80 ± 0.45 | moderate |
| | PP | 12.46 ± 1.86 | 6.40 ± 2.15 | 3.02 ± 0.21 | low |
| | TS | ND | ND | ND | very low |
| 19 | LN | 12.46 ± 3.56 | 4.62 ± 2.43 | 3.91 ± 0.77 | low |
| | PP | 15.66 ± 2.06 | 9.25 ± 2.28 | 3.20 ±0.21 | low |
| | TS | 16.02 ± 1.04 | 7.65 ± 1.70 | 4.71 ± 0.26 | low |
| 19 | LN | 11.03 ± 1.04 | 5.51 ± 0.43 | 2.75 ± 0.35 | low |
| | PP | ND | ND | ND | very low |
| | TS | 9.25 ± 1.53 | 4.62 ± 1.90 | 2.31 ± 0.25 | low |
| 20 | LN | 18.86 ± 1.33 | 8.18 ± 1.33 | 5.34 ± 0.00 | moderate |
| | PP | 14.95 ± 1.44 | 8.72 ± 0.90 | 3.11 ± 0.39 | low |
| | TS | 25.98 ± 2.61 | 16.19 ± 2.76 | 4.89 ± 0.27 | moderate |
| 20 | LN | 18.86 ± 1.55 | 9.79 ± 1.05 | 4.53 ± 0.45 | low |
| | PP | 13.88 ± 1.04 | 6.58 ± 0.77 | 3.64 ± 0.49 | low |
| | TS | 20.64 ± 3.31 | 8.54 ± 2.84 | 6.05 ±1.10 | high |
| 22 | LN | 12.81 ± 1.72 | 4.98 ± 1.21 | 3.91 ± 0.38 | low |
| | PP | 9.96 ± 0.43 | 3.02 ± 0.35 | 3.47 ± 0.29 | low |
| | TS | 11.21 ± 0.95 | 4.80 ± 0.35 | 3.02 ± 0.21 | low |
| 22 | LN | 16.37 ± 2.78 | 4.45 ± 1.84 | 5.96 ± 0.66 | moderate |
| | PP | 14.59 ± 1.30 | 6.05 ± 1.20 | 4.27 ± 0.17 | low |
| | TS | 23.85 ± 1.65 | 12.99 ± 1.04 | 5.42 ± 0.53 | moderate |
| 23 | LN | 21.36 ± 2.52 | 6.58 ± 2.95 | 7.38 ± 0.33 | high |
| | PP | 20.29 ± 0.43 | 12.28 ± 0.71 | 4.00 ± 0.28 | low |
| | TS | 17.08 ± 1.20 | 5.34 ± 1.40 | 5.87 ± 0.65 | moderate |
| 23 | LN | 16.02 ± 2.93 | 8.18 ± 3.01 | 3.91 ± 0.35 | low |
| | PP | 13.75 ± 2.00 | 6.76 ± 2.52 | 3.20 ± 0.38 | low |
| | TS | 11.74 ± 1.65 | 4.62 ± 0.90 | 3.56 ± 0.56 | low |
| 24 | LN | 21.00 ± 3.00 | 4.98 ± 2.60 | 8.01 ± 0.39 | high |
| | PP | 17.44 ± 2.89 | 9.61 ± 1.65 | 4.80 ± 0.21 | moderate |
| | TS | 19.93 ± 2.06 | 7.47 ± 2.35 | 6.23 ± 0.48 | moderate |
| 25 | LN | 17.08 ± 1.44 | 7.47 ± 1.42 | 4.80 ± 0.21 | moderate |
| | PP | 9.25 ± 1.18 | 2.31 ± 0.53 | 3.47 ± 0.45 | low |
| | TS | 12.10 ± 2.32 | 5.69 ± 0.66 | 3.20 ± 0.45 | low |

| Weeks of Gestation | Lymphatic Organ | Diameter of the PCV | Diameter of the PCV Lumen | Height of the PCV endothelium | Number of Lymphocytes in the area |
|---|---|---|---|---|---|
| 25 | LN | 15.30 ± 0.90 | 7.47 ± 0.66 | 3.91 ± 0.21 | moderate |
| | PP | 10.14 ± 1.94 | 5.34 ± 1.73 | 2.39 ± 0.33 | low |
| | TS | 19.22 ± 2.36 | 5.69 ± 1.53 | 6.76 ± 1.34 | moderate |
| 38 | LN | 25.27 ± 2.06 | 6.05 ± 0.90 | 9.61 ± 0.59 | high |
| | PP | 21.00 ± 2.64 | 5.69 ± 1.90 | 7.65 ± 0.53 | high |
| | TS | 29.19 ± 3.31 | 8.90 ± 3.13 | 10.14 ±0.45 | high |
| 40 | LN | 28.48 ± 3.60 | 9.96 ± 3.50 | 9.25 ± 0.21 | high |
| | PP | 23.85 ± 2.96 | 7.12 ± 2.03 | 8.36 ± 0.66 | high |
| | TS | 28.48 ± 3.73 | 11.39 ± 4.20 | 8.54 ± 0.77 | high |

Explanation of the symbols: LN, lymph node; PP, Peyer's patch; TS, tonsils; ND, not detectable

mediately after birth were studied for comparison. All fetuses were subjected to thorough necropsy, whereby segments of intestines, tonsils and all detectable lymph nodes were removed. The specimens were fixed in neutral formalin and processed for light microscopical study according to routine procedures. The 4 micron sections were stained with hematoxylin eosin and methyl green-pyronin stains.

From each lymphatic organ studied (lymph nodes, Peyer's patches and tonsils) five PCV:s were randomly selected and subjected to direct measurements using an eye-piece graticule ($E_{17}$, Graticules Ltd., England) and a 63x objective in Leitz Laborlux 12 light microscope. The dimensions measured were; $D_{pcv}$, the diameter of the PCV as a distance between the basement membranes of two opposing sites, and $D_{lu}$, the diameter of the PCV lumen as a distance between the apices of the two opposing endothelial cells. The height of the endothelium, $H_{end}$, was calculated from the formula;

$$(1) \qquad H_{end} = \frac{D_{pcv} - D_{lu}}{2}$$

whereby a more exact average value for the endothelium could be obtained than if only a few single cells had been measured.

For the evaluation of the lymphocyte traffic across the PCV endothelium, the criteria described previously were used (23, 26, 30).

*Results*

The values of the parameters measured in the PCV:s of the lymph nodes (LN), Peyer's patches (PP) and tonsils (TS) are summarized in Table 1. It is evident from these figures that $D_{pcv}$ varies within wide limits, as does $D_{lu}$ in all tissues studied. As to $H_{end}$, no clear-cut correlation seems to exist between its values and the gestational age of the fetus, except that the highest values were obtained in those of the full-term pregnancies. More critically than with the gestational age, $H_{end}$ seems to correlate with the activity of lymphocyte recirculation, i.e. the number of cells within the PCV lumen, passing through their wall and aggregated around these vessels (Table 1, Number of lymphocytes in the area). $H_{end}$ was low in organs with scanty lymphocytes, and high in tissues where lymphocytes were present in abundance. Values between the two extremes were measured in organs moderately populated with lymphocytes (Figs. 1–3).

*Discussion*

In the present work an approach is made to assess the development of the PCV:s by direct measurements of their dimensions in the lymphatic tissues of human fetuses. This is the first attempt made to evaluate morphologically the circumstances of lymphocyte recirculation during the human fetal development. Not much more is known about this process even in the fetal period of experimental animals, albeit a recent study showed a vivid lymphocyte circu-

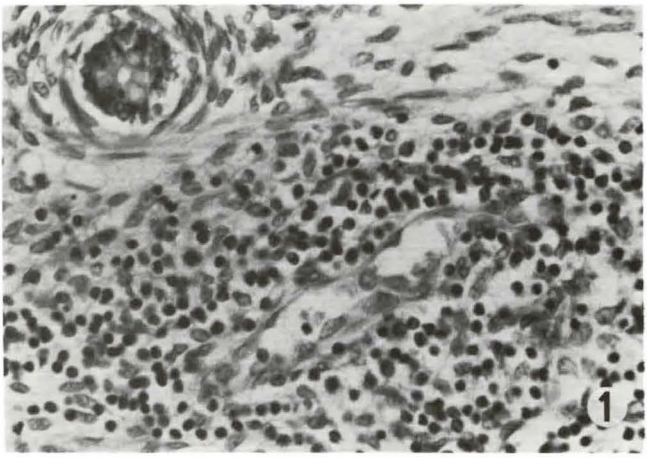


**Fig. 1** A PCV from the Peyer's patch of a 20 week fetus showing an endothelium made up of low cuboidal cells ($H_{end}$ 3.64 ± 0.49). (H and E, original magnification x 400)

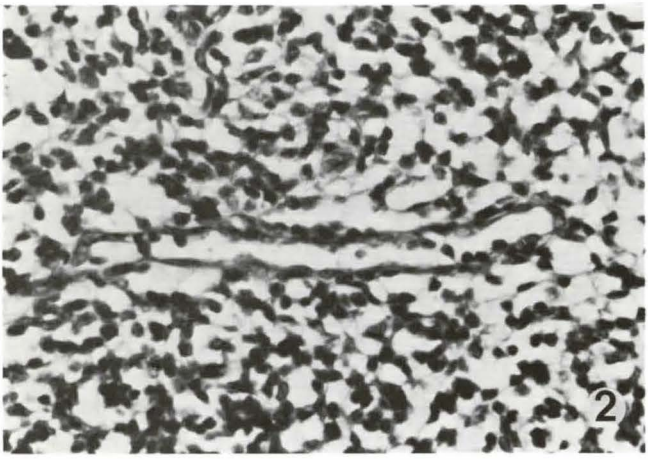


**Fig. 2** Part of a tonsil in a 15-week fetus showing low content of lymphocytes and a PCV with flat endothelium ($H_{end}$ 2.33 ± 0.09). (H. and E, original magnification x 400)

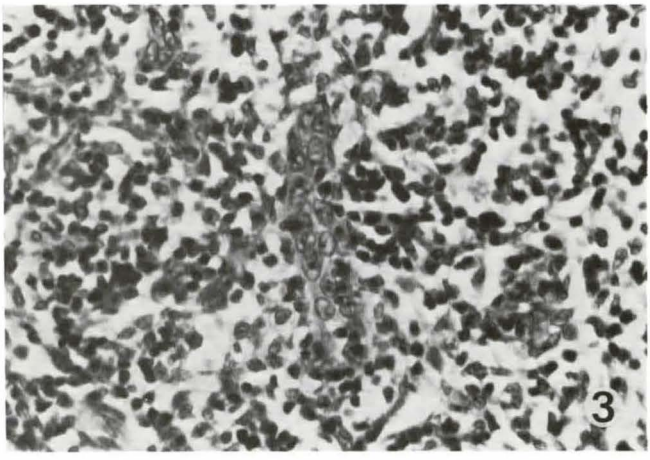


**Fig. 3** A well developed PCV in a lymph node of a 24-week fetus. Lymphocyte content is high, and PCV endothelium is made up of high cuboidal cells ($H_{end}$ 8.01 ± 0.39). (H and E, original magnification x 400)

lation in these fetuses was evaluated more rapid than exists in their adult counterparts (3). Formerly it was believed that the T-cells, exclusively, have circulatory capability, but recent data unequivocally show that also the B-cells do recirculate between blood and lymph (6, 10, 22, 30). The tempo of their circulation is more slow, however, and the circulating B-cell pool is probably more limited than that of T-cells (6, 10, 22). In any case, both the circulating B- and T-cells seem to utilize the PCV as their route of passage from blood to lymphatic tissues (1, 4, 5, 6, 8, 9, 10, 13, 16, 18, 20, 21, 22, 30, 32, 33). Despite considerable pain and effort, the mechanisms regulating the passage of circulating lymphocytes through the PCV wall are not understood (30). This is probably due to the fact that most studies are focused on the circulatory cells proper, and the PCV endothelium as a subject of study has been largely neglected (6, 16, 18, 20, 30). There is evidence emerging, however, that suggests the role of this vessel to be probably mandatory in this process of mutual recognition between the circulating lymphocyte and the endothelial cells (14, 21, 23, 24, 27, 28, 29, 30). The full elucidation of these factors would be of utmost importance for the understanding of a diversity of immunological reactions, including the important co-operations between the lymphatic cells involved in these complex responses (30).

In previous works, PCV:s have been described to appear in human lymphatic tissues concomitantly with the lymphatic follicles (19). Their role as a basic structural unit in the development of lymphoglandular tissue has been previously emphasized (31). It is well known that the height of the PCV endothelial cells is subject to alterations according to the current activity of lymphocyte circulation (2, 4, 7, 11, 12, 13, 14, 23, 30). Thus, both hypertrophy and flattening of the endothelium is seen under appropriate immunomanipulations. Furthermore, the full height of the endothelium does not seem to be apparent before 12 years of age, and in old individuals the endothelium is lower (15, 19). These facts in mind the present study was undertaken to initiate the assessment of how these vessels develop and to what extent lymphocytes do recirculate during the fetal development in man.

The present results show that first vessels identifiable as PCV:s according to their topography appear in the lymphatic tissues of human fetuses aged 15 weeks. Thereafter their development proceeds rapidly, and they gain more width and endothelial height. This development seems not, however, to run parallel with the gestational age in all respects, as shown by the measurements in Table 1. More critically than with gestational age, $H_{end}$ seems to correlate with the density of the lymphocyte population in the thymus-dependent areas (LN paracortex and the interfollicular zone of PP and TS). This is in full agreement with the findings in adult animals or in man under situations where lymphocyte circulation is altered (2, 4, 7, 11, 12, 13, 14, 23, 26, 29, 30). The findings suggest that lymphocyte recirculation of varying activity exists in human fetus starting from the second trimester. In the absense of any evident antigenic stimuli from outside the fetus, this possible recirculation must be an inherent property of the individual's lymphocytes acquired by that time (3). As evidenced by the divergent results in fetuses of equal age, wide individual variations seem to exist in the activity of the recirculatory process. The factors responsible for these variations remain obscure in the present work, but in future studies attempts will be made to evaluate the role of factors such as intrauterine infections, hormonal imbalances as well as immunological abnormalities.

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