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Immunohistological characterization of lymphoid cell populations in the early human placental bed

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Summary. The distribution of leucocytes in first trimester human decidual tissue has been studied by using a panel of monoclonal antibodies in an indirect immunoperoxidase technique on acetone-fixed cryostat sections. The results indicate that bone marrow-derived cells are abundant in the placental bed and a proportion of these are HLA-DR positive. However, a major leucocyte population in the decidua of early pregnancy is of cells which carry the E-rosette receptor but which do not express peripheral pan-T cell antigens nor HLA-DR. The distribution of these cells suggests that they are endometrial granulocytes. A similar large number of cells express OKT 10, a marker of immature or activated cells. The presence of this unusual T lineage cell raises the possibility that a form of lymphocyte processing is occurring in the decidua in early pregnancy, perhaps in response to foetal antigens presented on trophoblast.

INTRODUCTION

The decidua is the transformed stromal component of the gestational endometrium, and in early human pregnancy two major cell populations have been distinguished morphologically within it. These are the large glycogen-rich decidual cells and the smaller endometrial granulocytes (Körnchenzellen cells), both of which have been claimed to originate from the undifferentiated endometrial stromal cell (Dallenbach-Hellweg, 1981). The endometrial granulocytes are present in large numbers in deciduas throughout the first trimester of pregnancy, but thereafter decline and are virtually absent at term. It has been suggested that these cells secrete relaxin (Dallenbach-Hellweg, 1981), but their origin and function have for long been disputed. However, it has recently been shown that a proportion of endometrial granulocytes express the leucocyte-common antigen and are therefore derived from bone marrow (Bulmer & Sunderland, 1983).

During early human pregnancy foetal trophoblast invades and is intimately associated with maternal cells in the decidua, myometrium and spiral arteries (Boyd & Hamilton, 1970; Pijnenborg *et al.*, 1980; Bulmer, Billington & Johnson, 1984). Although villous trophoblast does not express class 1 antigens of the major histocompatibility complex (MHC) (Sunderland *et al.*, 1981), these antigens are now known to be present on nonvillous trophoblast within the placental bed (Redman, Stirrat & Sunderland, 1983). Despite these abundant genetically alien foetal cells, no classical local maternal cellular inflammatory response is evident, although large numbers of endometrial granulocytes have been reported in areas

Abbreviation: mAb, monoclonal antibody.

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where trophoblast invasion is prominent, particularly around spiral arteries and endometrial glands (Pijnenborg *et al.*, 1980, 1981). Other cell populations have also been described in human decidua. In early pregnancy, lymphocytes and lymphoblasts are sometimes found in close association with decidual cells (Tekelioglu-Uysal, Edwards & Kisnisci, 1975) and, more recently, large numbers of HLA-DR-positive cells have been reported in the decidua of the term placenta (Sutton, Mason & Redman, 1983).

In decidua, therefore, foetal and maternal cells coexist in apparent harmony, yet few studies have been directed towards analysis of its constituent cells and functions. The present study is concerned with further characterization of the bone marrow-derived cells identified in the early human placental bed and with an attempt at a definition of the lineage of the endometrial granulocyte.

MATERIALS AND METHODS

Tissues

Specimens were obtained from five elective aspiration terminations of apparently healthy pregnancy performed at 8–10 weeks gestational age. After a preliminary wash in phosphate-buffered saline, pH 7·2, to remove loose blood, fragments of decidua were identified macroscopically, trimmed to 5–10 mm cubes, snap frozen in liquid nitrogen-cooled isopentane (B.D.H., Poole, U.K.) and stored at $-70°$. Sections (5 μm) were cut in an automatic cryostat (Reichert-Jung), air dried, fixed in acetone for 10 min and air dried overnight at room temperature. Because specimens were from aspiration terminations, orientation was not possible and the distinction between decidua parietalis and decidua basalis was not always made. In each series a number of sections were stained with haematoxylin and eosin to allow morphological examination of the tissues and to identify the presence of trophoblast. In addition, a pregnancy hysterectomy performed at 8 weeks and another at 12 weeks gestational age are included. Sections were taken through the centre of the implantation site to include chorionic villi, cytotrophoblastic shell, decidua basalis and inner myometrium. The tissues were trimmed, frozen and sectioned as described above. A minimum of two tissue blocks from each pregnancy specimen were examined, and immunohistological staining of serial sections allowed comparison of staining patterns obtained with different monoclonal antibodies.

Monoclonal antibodies

Fourteen monoclonal antibodies (mAbs) to leucocyte surface antigens were included in the present study; dilutions and references are detailed in Table 1. F-10-89-4 reacts with the leucocyte-common antigen and it can be concluded that cells which bind this mAb are bone marrow-derived. NFK-1 was used to detect HLA-DR locus products and therby localize B lymphocytes, macrophages, interdigitating cells and activated T cells. F-8-11-13 reacts strongly with B cells but is also weakly expressed on all OKT 8-positive lymphocytes and 1/3 of OKT 4-positive lymphocytes. TU71 reacts with peripheral T cells and TU102 binds to T cells of suppressor-cytotoxic subset; TU71 and TU102 have been shown biochemically to be equivalent to OKT 1 and OKT 8 respectively. In selected specimens the commercial peripheral pan-T cell reagents OKT 3 and anti-leu-1 were used to confirm results obtained with TU71. Similarly, staining patterns observed with anti-leu-2, which reacts with the suppressor-cytotoxic subset of T cells, were compared with those seen with TU102. TO15 is a marker for B lineage cells and stains centrocytes and centroblasts in addition to peripheral B cells.

In addition to peripheral T and B cell markers, a mAb which is reactive with natural killer (NK) and killer (K) cells (anti-leu-7) was employed, as well as a cortical thymocyte marker (NA1/34). Also included were anti-leu-5, which is reactive with the E-rosette receptor, and OKT 10, a marker for myeloid and lymphoid precursors, thymocytes and activated T and B cells. Selected specimens were stained with OKT 11 which also reacts with the E-rosette receptor to confirm results obtained with anti-leu-5.

Immunohistology

Sections were stained using an indirect immunoperoxidase technique. After a preliminary short wash in 0·15 M NaCl, 0·05 M Tris-HCl, pH 7·6 (TBS), sections were overlain with mAb at the appropriate dilution (Table 1) for 45 min. Following two 1 min washes, tissues were incubated with peroxidase-conjugated rabbit anti-mouse immunoglobulins (Dakopatts, A/S, Denmark) diluted 1:50 in TBS containing 10% normal human serum. After two further TBS washes, the dye reaction was developed with 0·5 mg/ml diaminobenzidine (Sigma Chemical Co., Poole, U.K.) containing 0·01% hydrogen peroxide for 5–10 min. Finally the sections were plunged into excess water and lightly counterstained with Mayer's haematoxylin. Appropriate negative controls were employed and included

Table 1. Monoclonal antibodies

Monoclonal antibody	Antigen/cells detected	Reference and commercial source	Dilution
F-10-89-4	Human leucocyte-common antigen	Dalchau, Kirkley & Fabre (1980)	1:100 (PE)
NFK-1	HLA-DR	Fuggle *et al.* (1983)	1:200 (PE)
F-8-11-13	B cells, OKT 8-positive T cells, 1/3 of OKT 4-positive T cells	Dalchau & Fabre (1981) Dalchau & Fabre (1984)	1:100 (PE)
TU71	Peripheral T cells	Shi *et al.* (in preparation)	1:1 (CS)
Anti-leu-1	Peripheral T cells	Engleman *et al.* (1981) (Becton Dickinson, CA, U.S.A.)	1:10 (Ig)
OKT3	Peripheral T cells	Kung *et al.* (1979) (Ortho Diagnostics, Slough, U.K.)	1:10 (Ig)
TU102	Suppressor-cytotoxic T cells	Shi *et al.* (in preparation)	1:1 (CS)
Anti-leu-2	Suppressor-cytotoxic T cells	Ledbetter *et al.* (1981) (Becton Dickinson, CA, U.S.A.)	1:10 (Ig)
TO15	B lineage cells	Stein, Gerdes & Mason (1982)	1:1 (CS)
Anti-leu-7	NK and K cells	Abo & Balch (1981) (Becton Dickinson, CA, U.S.A.)	1:10 (Ig)
NA1/34	Human thymus antigen (HTA1)	McMichael *et al.* (1979) (Seralab, Crawley, U.K.)	1:1 (CS)
Anti-leu-5	E-rosette receptor	Howard *et al.* (1981) (Becton Dickinson, CA, U.S.A.)	1:10 (Ig)
OKT 11	E-rosette receptor	Verbi *et al.* (1982) (Ortho Diagnostics, Slough, U.K.)	1:10 (Ig)
OKT 10	Myeloid and lymphoid precursors, thymocytes, activated T and B lymphocytes	Terhorst *et al.* (1981) (Ortho Diagnostics, Slough, U.K.)	1:10 (Ig)

CS, culture supernatant.
PE, peritoneal exudate.
Ig, purified immunoglobulin.

the use of irrelevant hybridoma supernatants and omission of primary and/or secondary antisera.

RESULTS

In all areas of decidua, considerable numbers of bone marrow-derived cells were demonstrated by staining with F-10-89-4, a mAb to the leucocyte common antigen. Attempts were made to characterize this leucocytic infiltrate using a panel of mAbs and the results showed two main areas with distinct staining patterns. Approximate counts were made of various cell types in serial sections of several blocks. Consistent results were obtained and the percentages given derive from these values.

In regions in which infiltration of decidua by trophoblast was prominent, and in the absence of degenerate glands or spiral arteries, 70–90% of the leucocytes could be accounted for by the numbers of cells staining with NFK-1, a mAb to HLA-DR locus products. Many of these DR positive cells were irregular in shape but others were smaller and rounded and may represent either B cells or activated T cells. Approximately 10–30% of the leucocytes stained with T or B cell reagents. Of these, the majority of peripheral T cells defined by TU71, anti-leu-1 or OKT3 expressed the suppressor phenotype and reacted with TU102 and anti-leu-2. The number of cells staining with the peripheral pan-T cell markers was essentially similar to those staining with antbidodies to the E-rosette receptor (anti-leu-5, OKT 11). In these areas, and in comparable areas in formalin-fixed paraffin-embedded sections stained with phloxine-tartrazine, endometrial granulocytes were relatively scarce.

In contrast, areas in which trophoblast invasion was not prominent or where it was associated with residual

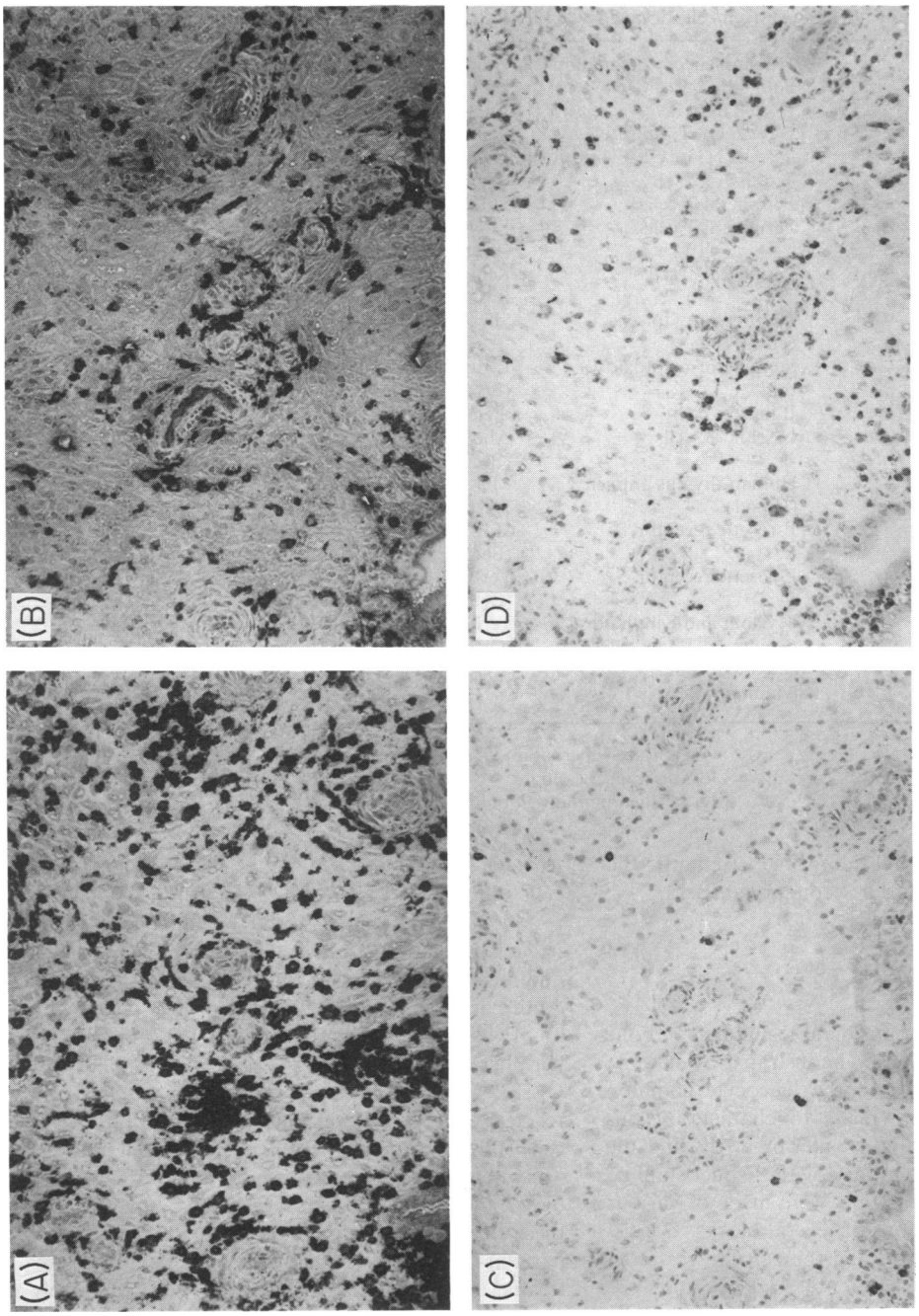

Figure 1. Serial sections of first trimester decidual tissue were stained with monoclonal antibodies using an indirect immunoperoxidase technique. Tissue nuclei were counterstained with haematoxylin. (Magnification × 76.) mAb specificities were as follows.

(a) Leucocyte-common antigen, mAb F10-89-4: large numbers of leucocytes are shown to be present and are found in particularly dense aggregates near spiral arteries and glands.

(b) HLA DR antigens, mAb NFK-1: a proportion of the leucocytes stain intensely for HLA DR; particularly prominent are irregularly shaped cells around the spiral arteries.

(c) All peripheral T cells, mAb TU 71: only a very few scattered cells are positive.

(d) E-rosette receptor, mAb anti-leu-5: a major population of the leucocytes carry the E-rosette receptor, approximately 10-fold more cells than stain with peripheral T cell markers.

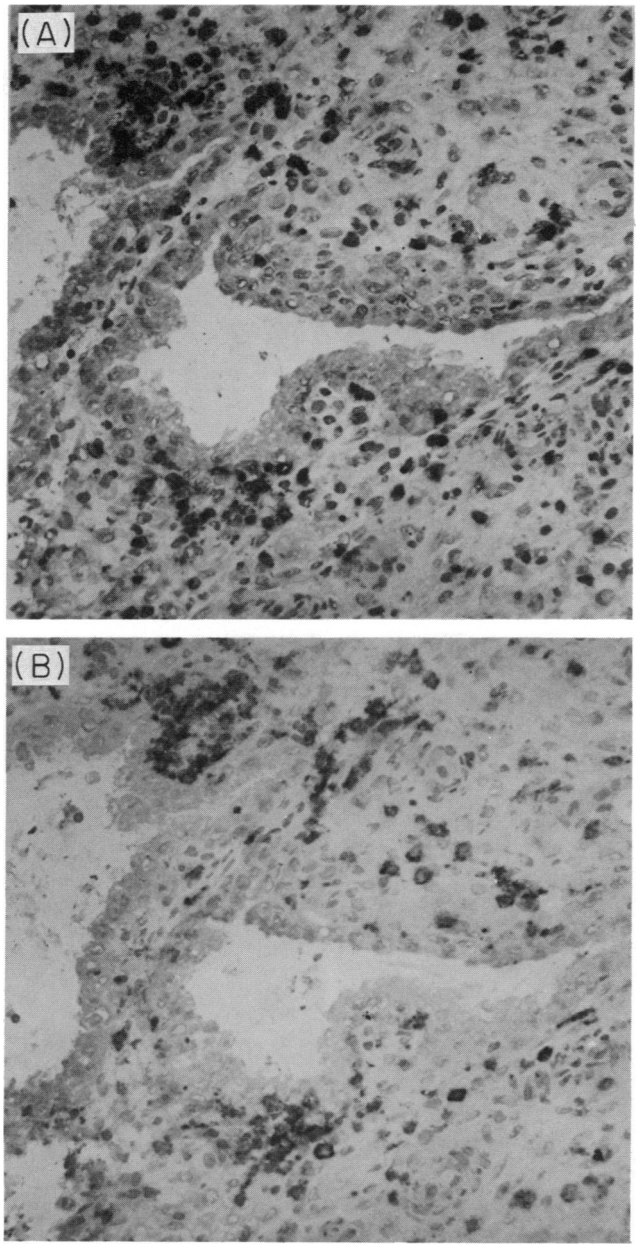

Figure 2. (a) E-rosette receptor, mAb anti-leu-5: aggregates of leucocytes near decidual glands express the E-rosette receptor.
(b) Lymphoid and myeloid precursor cells, thymocytes, activated lymphocytes, mAb OKT 10: these same leucocyte aggregates express OKT 10.
(Magnification × 140.) Otherwise as Fig. 1.

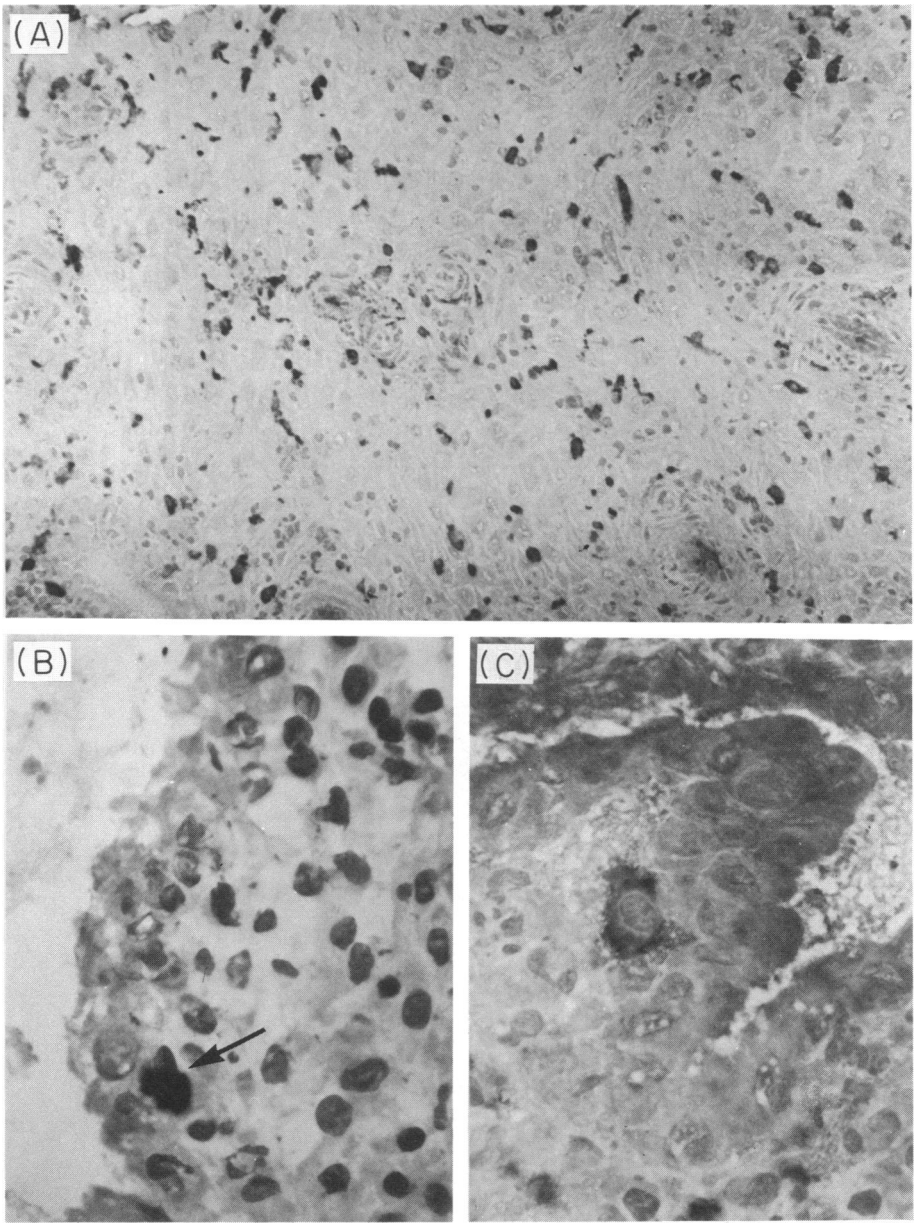

Figure 3. (a) B lineage cells, mAb TO15: positive cells include both small lymphocytes and larger cells which may be lymphoblasts.

(b) NK and K cells, mAb anti-leu-7: an isolated positive cell close to glandular epithelium. (Magnification ×405.)

(c) Cortical thymocytes, Langerhans cells, mAb NA1/34: a single positive cell lying beneath the glandular epithelium. (Magnification ×405.)

Otherwise as Fig. 1.

endometrial glands or spiral arteries showed a different leucocyte content. Leucocytes were abundant and were frequently aggregated adjacent to degenerate endometrial glands or to spiral arteries (Fig. 1a). This distribution is similar to that of endometrial granulocytes which are demonstrated by phloxine-tartrazine staining (Pijnenborg *et al.*, 1980; Bulmer & Sunderland, 1983). Only approximately 40–50% of leucocytes were HLA-DR-positive and these cells were often irregular in shape and prominent around spiral arteries, although scattered small rounded cells were found in other areas (Fig. 1b). Cells of a similar number, distribution and irregular morphology were stained by anti-leu-M3, a mAb reactive with tissue macrophages (Dimitriu-Bona *et al.*, 1983) and are the subject of a separate study (Bulmer & Johnson, 1984). The peripheral pan-T lymphocyte markers (TU71, anti-leu-1, OKT 3) stained less than 5% of the leucocytes in all such areas examined (Fig. 1c) whilst mAbs reactive with the suppressor-cytotoxic T cell subset stained a similar but possibly slightly greater number of cells. However, two mAbs to the E-rosette receptor (anti-leu-5, OKT 11) reacted with approximately 10-fold more cells than were detected by peripheral pan-T cell markers (Fig. 1d). The E-rosette receptor is present on cortical and medullary thymocytes as well as on peripheral T cells, whilst TU71, anti-leu-1 and OKT 3 are present only on peripheral T cells. Thus, a major cell population in the early human decidua appears to be of unusual or immature T lineage cells. This possibility was strengthened by use of OKT 10, a marker of myeloid and lymphoid precursors, thymocytes and activated T and B cells, but which does not react with mature peripheral T or B cells (Terhorst *et al.*, 1981). This mAb stained a large population of cells in these areas. The distribution of positive cells was similar to that seen with E-rosette receptor markers, but the number of cells staining was greater (Fig. 2a, b). This is probably accounted for by the wider spectrum of OKT 10 which reacts with both immature T and B cells. A mAb specific to peripheral B cells was not available, but TO15 is reported to react with most B lineage cells including centroblasts, centrocytes and peripheral B cells. Approximately 20–30% of leucocytes stained with this mAb, some of which had typical small lymphocyte morphology, while others were large and may represent immature blast cells (Fig. 3a).

Using the mAb anti-leu-7, which is reactive with NK and K cells, occasional cells stained, often in association with residual endometrial glands (Fig. 3b). A cortical thymocyte marker (NA1/34) which does not react with peripheral T cells gave variable results, but in a few sections many weakly positive cells were seen around spiral arteries. In addition, in most specimens very occasional intensely positive cells were seen immediately beneath the endometrial gland epithelium (Fig. 3c). This result compares with a recent report of similar cells in a similar position which react with a mAb to the cell surface receptor for transferrin (Johnson & Bulmer, 1984).

DISCUSSION

In this study an unusual population of lymphocytes has been demonstrated in the early human placental bed. These cells are of the T lymphocyte lineage as defined by the presence of the E-rosette receptor, but do not carry the peripheral T cell antigens recognized by TU71, anti-leu-1 or OKT 3, nor the suppressor subset antigens recognized by TU102 or anti-leu-2. They do not express HLA-DR and are therefore distinct from the population of DR-positive cells described recently in term decidua (Sutton *et al.*, 1983), and they do not stain with a mAb reactive with NK or K cells. They do, however, express OKT 10, a marker of immature myeloid and lymphoid precursors and activated T and B lymphocytes. The numbers of cells which stain with OKT 10 together with the number reactive with the B lineage marker TO15 suggests that, in addition to this unusual T lineage population, other immature or activated cell populations may be found in early human decidua. The population of T lineage cells predominates in areas where endometrial granulocytes are prominent (Pijnenborg *et al.*, 1980; Bulmer & Sunderland, 1983), although it is not possible to demonstrate endometrial granulocytes in cryostat sections, as the granules are disrupted by freezing. It may be concluded, however, that a high proportion of endometrial granulocytes are T lineage cells which carry the E-rosette receptor but do not express peripheral T cell markers.

Several hypotheses can be forwarded to account for the presence of these cells in early human decidua. They may arise directly from the bone marrow without thymic processing, further maturation and differentiation occurring within the decidua itself or in uterine draining lymph nodes or even in response to foetal thymic hormones. It has been suggested that the granulated metrial gland cells of rats and mice, which may be analogous to the endometrial granulocytes,

differentiate *in situ* within decidua from a lymphocyte-like precursor (Peel & Bulmer, 1977; Stewart & Peel, 1977). Recent studies employing transplantation of rat bone marrow into irradiated mouse recipients have confirmed a bone marrow origin of these cells in murine deciduomata and support the former hypothesis (Peel, Stewart & Bulmer, 1983).

Alternatively, the cells may arise by leakage of immature cells from the thymus, perhaps in a specific response to pregnancy under hormonal influences or cellular contacts or even at a particular stage of the menstrual cycle. In this situation, the decidua or foetal thymus would be responsible for post-thymic maturation of the cells. Our studies do, however, indicate that the T lineage cells of decidua are not identical to immature cortical thymocytes in that the decidual cells lack the NA1/34 and suppressor-cytotoxic markers, both of which are found on cortical thymocytes (Janossy *et al.*, 1981).

Finally, unusual antigen expression of these cells could result from further processing of mature T lymphocytes in the placental bed, perhaps in response to foetal antigens or as a component of the decidual reaction, so that immature markers are re-expressed and mature markers lost. This may occur as a result of activation and it is known that mitogen-activated T lymphocytes can re-express OKT 10 which is not present on resting T cells (Terhorst *et al.*, 1981). However, the cells do not express HLA-DR which can be expressed by activated T cells (Moretta *et al.*, 1982).

Whatever their origin, it is possible that these cells represent a functionally distinct population of T cells which is confined to the highly specialized environment of the decidua. This decidual lymphocyte population may be analogous to the small granular lymphocytes described in murine pregnancy which are responsible for non-specific suppression of cytotoxic T lymphocyte generation. These cells are found specifically in the decidua and uterine draining lymph nodes (Slapsys & Clark, 1982) and do not carry mature peripheral T cell markers (Slapsys & Clark, 1983). In human pregnancy, no comparable cell population has so far been identified, although immunosuppressive activity has been demonstrated in a soluble factor released from explants of early human decidual tissue (Golander *et al.*, 1981). In addition, in the guinea-pig, it has been suggested that the Kurloff cell, a granulated cell abundant in the placental labyrinth, is a modified thymic lymphocyte which donates to trophoblast various mucopolysaccharides capable of killing macrophages (Marshall *et al.*, 1971).

This T lymphocyte lineage population appears to be specific for early placentation since endometrial granulocytes are virtually absent in term decidua, and preliminary studies of term placental bed tissue have not revealed any discrepancy between numbers of E-rosette-bearing cells and those possessing peripheral pan-T cell markers, nor are any OKT 10-positive cells identified (Bulmer, unpublished results). Since immune acceptance of the semi-allogeneic conceptus must be established very early in pregnancy, these unusual T lineage cells may be of fundamental importance in this process.

Current studies are directed towards analysis of the cell populations throughout the menstrual cycle, since endometrial granulocytes can be detected in the mid and late secretory phase. Examination of decidua from disorders such as hydatidiform mole and recurrent spontaneous abortion may provide valuable information and further our understanding of their underlying pathology.

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