

LYMPHSPARATION**LYMPHOCYTE EMPERIPOLESIS IN AIDS****J.W. Shields**

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ABSTRACT

Excepting sperm, lymphocytes are the most motile cells within and outside of the body in mammals. In the body, lymphocytes are the primary victims of the Acquired Immune Deficiency Syndrome (AIDS). This photo-essay illustrates that migrant lymphocytes outside of the body are the primary vectors of AIDS spread.

BACKGROUND

In 1924 McCutcheon (1) observed that small cytoplasm-poor lymphocytes migrate at the rate of 0-40 μ m/minute in tissue cultures maintained near 37°C. Lewis (2) emphasized the extraordinary motility of lymphocytes in tissue cultures and described a characteristic "hand mirror" configuration during migration. Studying lymphocytopoiesis and lymphocyte migration in the body, Kindred (3) showed that small lymphocytes normally migrate into and through most, if not all body tissues and into many body secretions. He calculated that migrating small lymphocytes, circulating lymphocytes and their larger precursors in lymph glands, normally constitute 1-2% of the total body mass in healthy well-fed mammals. Observing that small lymphocytes commonly migrate into, as well as through other kinds of cells, Humble, Jayne, and Pulvertaft (4) coined the term, *emperipolesis* (Gr. EM, in - PERI, around - PO-

LESIS, wandering about), to describe this unique form of migration peculiar to lymphocytes. Subsequently, others confirmed in tissue cultures that small lymphocytes actively migrate into and through, as well as around other cells, such as endothelial cells, fibroblasts, reticulum cells, macrophages, and single layers of epithelial cells (5-8). During the course of migration, the small lymphocytes may lyse other cells, undergo lysis to release their substance, or wander about without causing apparent reactions (4-8).

OBSERVATIONS

Studying lymphocyte *emperipolesis* in healthy humans through oil immersion light microscopy (1000x) of freshly fixed thin tissue sections (6 μ), we found that "intraepithelial" lymphocytes within and between epithelial cells are roughly proportional to the rate of cell renewal in selected tissues (9,10). For instance, in single layered jejunal, bronchial and endometrial epithelium, and in the basal layer of uterine exocervical and corneal epithelium, we found a mean of 75, 47, 35, 87, and 25 intraepithelial lymphocytes, respectively, per 1000 individual epithelial cells counted consecutively. More than half of these lymphocytes within or between the epithelial cells showed progressive degenerative changes, such as cloudy swelling, nuclear pyknosis or almost complete lysis with dispersion of chromatin

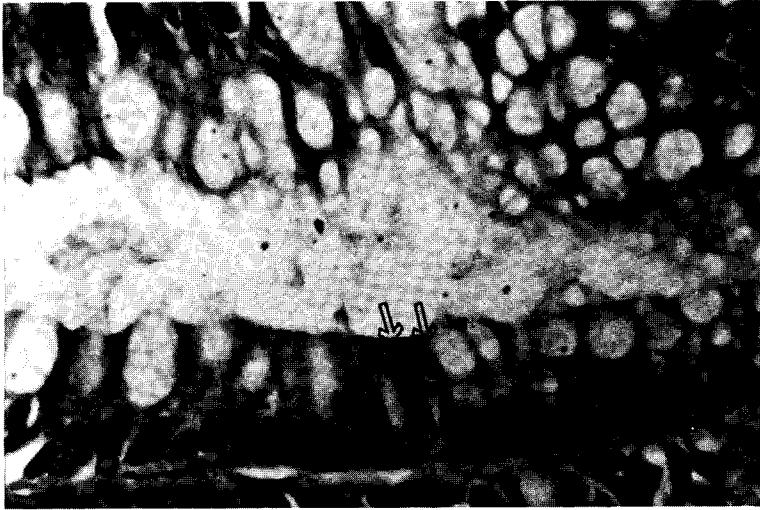


Fig. 1. A section of rectal mucosa in a healthy human (x1000). Arrows point to small cytoplasm-poor emperipoletic lymphocytes migrating between or within the epithelial cells which form this vulnerable monolayer, especially in homosexual men sharing anal sex.

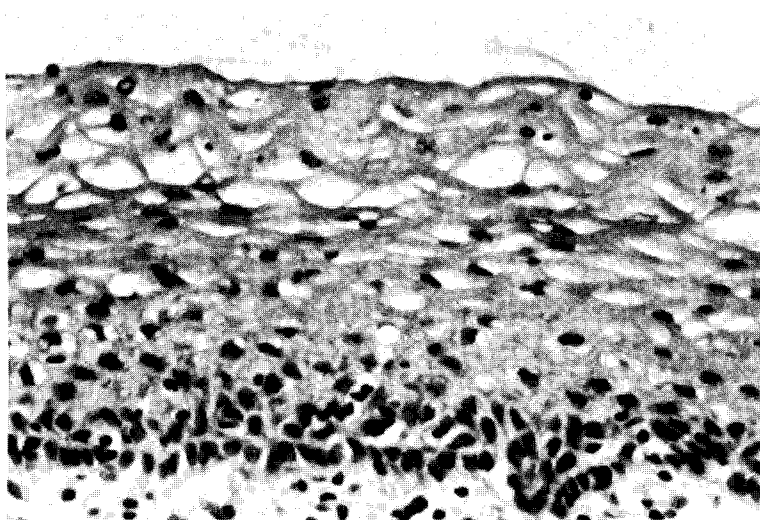


Fig. 2. A section of the multilayered squamous mucosa which normally lines the female vagina and exocervix (x250). Note the absence of emperipoletic lymphocytes in the superficial mucosal layers which usually prevent the transmission of many kinds of infections during conventional heterosexual intercourse.

(9,10). Such observations support the conclusion that lymphocyte *emperipolesis* is an important mechanism whereby migrant lymphocytes normally nourish, control growth and carry immunologic protection to other cells in the body (10).

Recently, we counted in hemocytometers the numbers of small cytoplasm-poor lymphocytes migrating through body sections of healthy humans (11,12). Blood colostrum, semen pre-vasectomy, semen post-vasectomy, vaginal pools, saliva and



Fig. 3. A section of the monolayered epithelial cells which normally line the female endocervix, uterus and Fallopian tubes (x1000). Arrows point to small emperipoletic lymphocytes which, if infected with lymphocytopathic retroviruses, are prone to transmit infection from male semen to the female or from female blood to the male penis during coitus, especially in sexually promiscuous persons, female partners of male bi-sexuals, drug-shooting heterosexual persons and in women inseminated through the artificial placement of male ejaculate in the cervical canal.

spinal fluid, respectively, contained $1-3 \times 10^6$, $1-2 \times 10^6$, 2.5×10^6 , 2.5×10^5 , $1-5 \times 10^5$, $1-2 \times 10^5$, and $1-5 \times 10^3$ per ml. We noted that the small lymphocytes commonly migrate into and through single layers of epithelial cells, such as endocervical and rectal epithelium; but seldom do so through superficial layers of stratified epithelia, such as skin, oral mucosa, and vaginal epithelium (see Figs. 1-3). We noted that small lymphocytes are the only cells which normally migrate through the "blood-brain barrier" and brain substance to show up in spinal fluid. Others have demonstrated that many maternal, as well as fetal lymphocytes normally cross the placental barrier during pregnancy (13). Such observations, in addition, support the consideration that *emperipolesis* is an important mechanism whereby lymphocytes can carry virus infections into other body tissues, as well as between individuals sharing body secretions, especially blood, semen and colostrum (12).

AIDS: PATHOGENESIS

AIDS is caused by retroviruses which integrate their RNA into lymphocyte DNA under the influence of viral reverse transcriptase (14). The integrated proviral DNA propagates through replication of infected lymphocytes and reutilization of infected lymphocyte DNA (7,10,12), as well as by transfection via migrating lymphocytes to other replicating cells, such as macrophages and glial cells supporting neurones (14). Expression of the proviral DNA in the form of viral RNA or virus shedding usually occurs at extremely low levels, such that the infection usually appears latent for months or years. In tissue cultures re-expression of proviral DNA in permissive cells can be stimulated by combinations of plant mitogens and interleukins derived from rapidly dividing lymphocytes (14). In the body the large and small lymphocytes in lymph glands, the small lymphocytes in circulation, and the

tiny lymphocytes migrating in tissues are ultimately destroyed by the retrovirus infection, or by coinfection with other viruses capable of integrating into lymphocyte nuclear DNA. With reduction of all these lymphocytes below a critical mass in the body, normal tissue nutrition, regulation of cell growth and immunologic protection of diverse tissues usually fail—more or less like that seen in athymic newborn mammals (10,12). Consequently, the infected individual develops combinations of emaciation (as seen in Slim Disease), defective regulation of cell growth and function (as seen in Kaposi's sarcomas, poorly differentiated lymphomas, epithelial carcinoma, or AIDS-related dementia), and decreased resistance to opportunistic, as well as common infections ordinarily kept in check by cell-mediated immunity (12).

AIDS: TRANSMISSION

AIDS spreads between human adults mostly by means of shared secretions rich in *emperipoletic* small lymphocytes, especially semen and blood (15). In infants, spread is most likely via infected maternal lymphocytes which normally migrate through the placenta or colostrum. Semen, colostrum, vaginal secretions, saliva and tears from persons whose blood contains evidence of human immunodeficiency virus or human leukemia virus infection have been shown to contain infected lymphocytes but seldom any retroviruses which can be cultured from the cell-free fluid (15). Therefore, it would appear that the small *emperipoletic* lymphocytes in such body secretions are the primary vectors for transmission of integrated proviral DNA or viral RNA between individuals, as well as within the body.

COMMENT

1. Fig. 1 illustrates why "receptive anal intercourse" is very risky.
2. Fig. 2 illustrates why conventional vaginal intercourse is less risky.
3. Fig. 3 illustrates why artificial insemination, effaced endocervices and intercourse with male bisexuals or intraven-

ous drug users are not without risk.

4. Because the skin and most mucous membranes are normally lined by stratified epithelia somewhat like that shown in Fig. 2, the "casual" transmission of AIDS via *emperipoletic* lymphocytes is practically nil.

5. Although circulating lymphocytes seem to "home" to specific tissues and cells, especially cells in mitosis; small lymphocyte *emperipolesis* is universal, bi-directional, indiscriminate, and at random around, into, within, and through other cells, benign and malignant (1-12). Therefore, lymphocyte spread of retroviruses causing AIDS does not, necessarily, depend entirely on specific surface CD4 molecules, receptors, or the reproduction of free retrovirus particles lacking the power to move independently.

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