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LYMPHSPIRATION

LYMPH, LYMPHOMANIA, LYMPHOTROPHY, AND HIV LYMPHOCYTOPATHY: An Historical Perspective

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ABSTRACT

From 1578-1628, Fabricius and his pupils, Asellius and Harvey, sequentially laid the foundations for the modern sciences of comparative anatomy, lymphology and circulation, as well as a state of lympho-philia or "-mania" which persists to the present time. Lymphomania persists because there remains a fundamental controversy and ignorance about the precise functions of lymph, lymphatics, lymph glands, lymphocytes, and the bursa of Fabricius. In 1778, William Hewson deduced that lymph effluent from lymph glands contains globular particles essential to normal body growth and tissue repair. In 1878, Claude Bernard recognized that lymph is a composite emanating from all body cells which forms the circulating blood plasma in order to sustain homeostasis throughout the internal milieu. From 1890-1960, many observers confirmed older concepts that lymph, lymph glands, and lymphocytes develop to nourish and regulate cell growth throughout the body. However, since 1960 characterization of "T-" and "B-" cells, respectively derived from thymus and the avian bursa, has revolutionized conceptual immunology, almost to the exclusion of older trophic concepts of lymph, lymph gland and lymphocyte functions. Therefore, homeostasis is considered here in terms of lymph circulation from and to respiring cells, as well as in homeostatic "failures" commonly found in persons infected with lymphotropic retroviruses.

The word, *Lymph*, was originally derived from the Greek, *Nymph* connotating a creature generated from or associated with clear limpid streams (1). Modern *lymphomaniacs* are persons "mad" about lymph, lymphatics, lymph glands or lymphocytes. *Lymphomania* might have started 400 years ago, when Hieronymous Fabricius discovered the valves in veins in 1578, and described a cloacal bursa in Leghorn chickens in 1601 (2). Fabricius thought the venous valves regulated the flow of blood from the heart, and that the bursa stored sperm in hens (2). During the latter part of the *Renaissance*, students from many nations flocked to study with him in Padua.

Hieronymous Fabricius had two especially famous pupils, Gaspar Aselli and William Harvey. In 1623, Asellius discovered the lymphatic system after showing that canine and human intestinal lymphatics fill with chyle after a gourmet meal. He likened the production of intestinal lymph to the secretion of breast milk and suggested that the milky lymph from the gut was transformed into red blood by the liver (3). In 1628, Harvey showed by laying hands on Fabrici's drawings of forearm veins that the valves limit venous backflow; and, thus, clarified how human blood actually circulates in his *De motu cordis*

(4). In 1651, Harvey further showed that the liver could not be the source of red blood because blood was formed in all vertebrate embryos before the liver developed (5). Noting that roosters have seminal vesicles, as well as a cloacal bursa, Harvey doubted Fabrici's interpretation of bursal function (2). However, the bursa of Fabricius spawned a new generation of immunologists and *lymphomaniacs* only after 1956.

Mania concerning lymphatic vessels began in 1650 when Olaf Rudbeck, a Swede, and Thomas Bartholinus, a Dane, discovered that lymphatics drain into central veins via the thoracic duct (6). Both agreed with Harvey concerning a negligible role of the liver in blood formation but each had difficulty reconciling their discoveries with older Galenic views involving tidal, as opposed to continuous, circulation from the heart.

In 1778, after comparative dissections in many species of animals of progressive ages, William Hewson concluded that the thymus and lymph glands produce lymph rich in globular particles, now known as lymphocytes, essential to normal growth of the body and repair of the constitution, especially in neonates (7,8). In 1878, Claude Bernard deduced that all body cells contribute to formation of lymph which constitutes the plasma in blood, as well as the common means of nutrient exchange which sustains homeostasis throughout the milieu intérieur (4,8,9). These now ancient conclusions of Hewson and Bernard are fundamental, because *lymphocytes help sustain normal cell growth; while circulation depends on the fluidity of lymph*. Harvey might have quipped that heme and erythrocytes would be useless without fluid lymph and a lymph circulation.

In the aftermath of the Franco-Prussian War of 1870-71, *lymphocytomania* started with the usage of Paul Ehrlich's trichome stains. Along with improved microscopes and tissue sectioning, his staining techniques enabled intense morphologic study of lymph glands, lymphocytes, red blood cells, granulocytes, thrombocytes, Metchnikoff's macrophages, and Ranvier's clasmatocytes, as well as other tissue cells. Almost immediately, Ranvier disagreed with Ehrlich whether lymphocytes are "end cells" or "stem cells" (6). Metchnikoff and Ranvier disputed whether the most important feature of large mononuclear phagocytes is the size of the particles they ingest to provide immunity (10), or the quantity of cytoplasm extruded by *clasmatosis* after digesting foreign particles to feed other cells (11). Such arguments are still germane, but the upshot in 1890-1914 was a flocking of medical scholars to Germany from Western and Eastern Nations.

One receptive scholar was Hal Downey from Minnesota. In 1912, he and his preceptor, Franz Weidenreich (12), concluded that:

1. All kinds of blood cells originate from mesenchymal reticulum cells in definitive lymphopoietic organs in each part of the body when local circulation is established.
2. Definitive kinds of blood cells differentiate directly from local reticulum cells, as well as from partially differentiated stem cells characteristic in each lineage.
3. Basophilic mononuclear cells, including reticulum cells, large phagocytes, monocytes, plasmacytes and lymphocytes normally extrude cytoplasmic fragments (which they termed "hyaline bodies") during successive stages of nuclear chromatin differentiation.
4. As a result, lymphocytes become small cytoplasm-depleted cells with condensed pachychromatic nuclear chromatin.
5. Such cytoplasmic shedding, also called *clasmatosis* (Fr. Greek KLASMA, fragment), is similar to the shedding of platelets by megakaryocytes, except the extruded cell fragments lack chromomeres (13), and become hyaline (depolymerized).

The defeat of Germany in 1918 restored Alsace to France, and displaced the "Golden Days" of hematology to other nations. In the USA, Boston, Massachusetts, came to the fore in 1925 with the discovery of liver extracts capable of curing pernicious anemia. Production of red hemoglobin-filled cells became the theme of hematology.

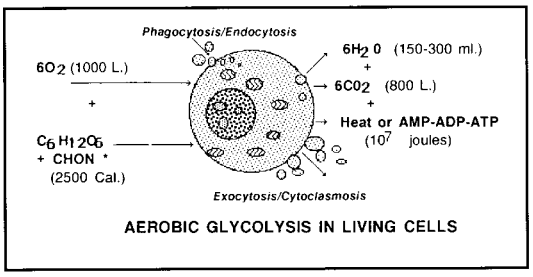

Fig. 1. Aerobic glycolysis in living cells. Each parameter may vary with body activities and ratios of C:H:O:N in foods consumed.

Lymphocytomania paled, but endured with the following chronology:

1. In 1924 Carrel demonstrated that lymphocytes produce substances, he called "trephones," which feed other cells in tissue culture (14). (Fr. Greek TREPEIN, to feed)
2. In 1925 McCutcheon showed that small lymphocytes randomly migrate under their own power at rates of 0-40μm/minute (up to 0.5 times their own diameter/minute) (15).
3. In 1942 Kindred showed that small lymphocytes normally migrate into all interstices, most body tissues, and many secretions; survive 2-4 days as judged by mitotic indices, and ordinarily constitute ±2% of body mass in healthy, well-fed mammals (16).
4. In 1946 Dougherty (a Downey pupil) and White showed that cortisol accelerates the extrusion of nutritive and immune globulins from lymphocytes in the thymus and other lymph glands through lymphocytolysis and cytoplasmic shedding (17).
5. In 1956 Humble et al showed that small lymphocytes characteristically migrate into, through and inside, as well as around or round about other cells by a process called *emperipolesis* (Fr. Greek EM, in; PERI, around; POLESIS, round about wandering) (18).
6. In 1952-58 Trowell showed that lymphocytes normally grow rapidly; require high tissue oxygen concentrations to do so; are the most radiosensitive cells in the body; and that they reutilize large quantities of DNA from circulating lymphocytes during the process (19).

In 1955 my personal *lymphomania* started in Minnesota. Summarily, and in accordance with the foregoing observations, it became apparent that:

1. Proportional to oxygen consumption, all respiring body cells contribute to the formation of lymph which flows between cells to become circulating plasma (20), as depicted in the following equation wherein the overall quantities theoretically involved *daily* in a 70Kg healthy human working, eating and exercising customarily are shown in parentheses *(Fig. 1)*.
2. Lymphatics normally develop with hydraulic flattening of mesenchymal cells proportional to the rate of local lymph formation, filtration and flow to carry lymph emanating from each respiring cell to body cells located progressively distant (21).
3. Lymph glands normally develop proportional to local arterial blood flow to filter and process the lymph which emanates from each peripheral body cell before the effluent central lymph flows via the thoracic and paired cervical lymph ducts into central veins at rates proportional to inspiration of air into the lungs with each breath (21,22).
4. Proportional to the basal metabolic rate, lymphocytes normally develop from periarterial reticulum cells in definitive lymph glands to extrude lymph rich in sundry globulins which circulate, and small cytoplasm depleted lymphocytes which migrate via *emperipolesis* (18,23-25) to carry large molecules, especially DNA, to other cells in order to sustain a constant state of *homeostasis* throughout the milieu intérieur (20,21,23).
5. The nature of the globulins and small emperipoletic lymphocytes produced in each lymph gland depends on lymph input from regional epithelial cells, as well as serial processing of this lymph by adjacent mesenchymal macrophages, monocytes and plasmacytes which also extrude lymph rich in soluble macromolecules (21,26) *(see Fig. 2)*.
6. In phylogenic, as well as temporal sequence, the definitive lymph glands appear as follows:

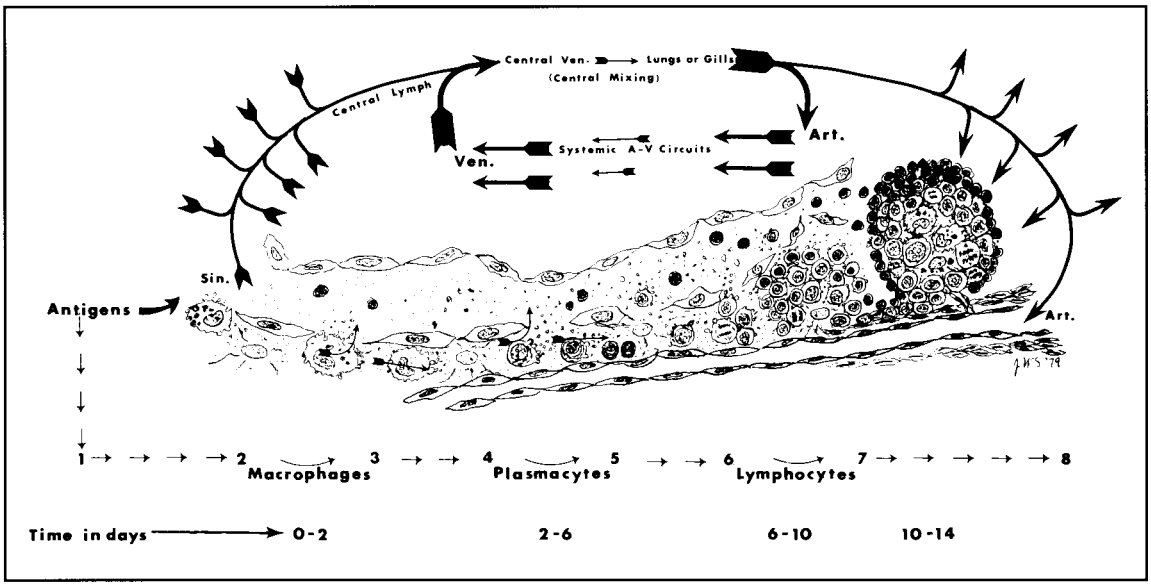

Fig. 2. Normal cell-cell and vascular relations. When myelopoiesis (the formation of granulocytes, thrombocytes and erythrocytes) shifts from extramedullary lymph glands to a microenvironment of low oxygen tension in bone marrow with the establishment of definitive arterio/venous oxygen gradients during embryogenesis, the mononuclear cells (lymphocytes, plasmacytes, monocytes and macrophages) continue to grow in the order shown above with respect to the gradient of arterio-venous blood flow and local oxygen tension, as well as toward lymph sinuses and regional epithelium toward which each lymph gland becomes primarily oriented. Lymph from the sinuses or the epithelium is serially processed through contiguous macrophages, monocytes, plasmacytes and lymphocytes, as depicted above, during primary immunologic responses. Days 1-2: Lysosome-rich macrophages ("clasmatocytes") and monocytes accelerate growth with phagocytosis of antigenic colloids; and excrete the partially digested remains by clasmatosis (fragmentation) to feed receptive cells with combinations of processed antigens, vasoactive, growth-promoting, or growth-inhibiting factors. Days 2-6: Ergastoplasm-rich plasmacytes accelerate growth with endocytosis of partially digested or "processed" antigens and through progressive clasmatosis release soluble mono-reactive immunoglobulins, as well as quanta of immunogenic RNA which can reverse transcribe lymphocytic DNA. Days 6-10: Reticular lymphocyte precursors accelerate growth with reutilization endocytosis of immunogenic RNA and macrophage-processed antigens to produce a variety of trephones (now called lymphokines or interleukins), as well as poly-reactive antibodies capable of neutralizing or opsonizing a variety of old antigens, as well as the new antigen; and secrete these in solution by progressive clasmatosis involving loss of ectoplasm while the nuclear chromatin condenses. Days 10-14: Resulting small cytoplasm-depleted lymphocytes accumulate in periarteriolar nodules, called follicles, whose long axes progressively point away from the arterioles toward sinuses or epithelial cells from where the antigenic colloids were derived. Subsequently, these cytoplasm-poor, but DNA-rich lymphocytes emigrate in effluent blood or lymph relatively devoid of surface-expressed immunoglobulins, but rich in DNA-determined surface receptors capable of recognizing self vs. "foreign" in the genetically inheritable best interests of "self." Many of these lymphocytes recirculate back to follicular germinal centers where lymphocytic DNA reutilization during lymphocytopoiesis perpetuates memory for "foreign" or noxious, along with "self" (see Refs. 19-21,23,26 — drawing from Ref. 26).

a. In animals with and without backbones, the intestinal lymphatic tissue develops to filter the products of intestinal epithelium and produce lymph rich in lipoproteins, globulins and small lymphocytes each time the animal digests a meal (21), as signalled by Asellius (3). In the invertebrates, which characteristically lack erythrocytes, only lymph and suspended white blood cells circulate throughout the body (21).

b. In all vertebrates the capsulated spleen develops in periarterial celiac mesenchyme when the liver and pancreas develop by budding from the intestinal epithelium, and

TABLE 1
Line Computer Survey Showing Numbers of Articles Listed in Index Medicus

	1960	1970	1980	1990
Lymph	33	83	92	79
Lymphatics	129	148	122	162
Lymph nodes	270	298	323	424
Lymphocytes	56	1033	1486	1249
B-lymphocytes	-	-	655	921
T-lymphocytes	-	-	1648	2257
HIV-AIDS caused by lymphotropic retroviruses	-	-	-	3792

hepatic mesenchyme temporarily becomes the major source of erythrocytes in the body. The spleen, then, becomes a major site of storage, as well as destruction of erythrocytes, other cells and complex elements in circulating whole blood, such that the portal effluent can be shuffled by cooperating Kupffer cells and hepatocytes, and returned to the circulation, or be excreted via bile (21).

c. In mammals, encapsulated lymph nodes progressively arise along the course of arteries to filter, process and add lymph to that which normally emanates from peripherally located respiring cells excepting those in the pulp of the capsulated spleen, the bone-encased marrow, the intrasellar pituitary, the adrenal medulla and the pancreatic islets (21). So located, the nodes appear instrumental in peripheral cell surveillance, as well as in immunity to foreign organisms, heterologous transplants and self (21).

d. During metamorphosis of the gill pouches in all vertebrates destined to breathe air, the adenoids and tonsils, derived from the first and second pouches, respectively develop to process inhaled and ingested particles trapped and partially digested by epithelial pinocytes; and grow during infancy to become nodular glands whose primary follicles in birds and secondary follicles in mammals point to the pinocytes (21).

e. More or less proportional to basal metabolic rate at the time of birth in mammals and birds, thymus glands derived from the stranded epithelium of the third gill pouches develop to become massive lymph glands whose epithelial cells produce hormones which accelerate self-oriented lymphocyte production, possibly by catalyzing oxidative chain phosphorylations essential to the sequential combination of nucleotides into lymphocytic DNA (21,27); and whose lymphoid cells are fragmented by adrenal glucocorticoid hormones, especially during stress (such as anoxia, starvation and infection) (17) to release self-oriented globulin- and nucleotide-rich substrates to help sustain *homeostasis* (21).

f. In metameric sequence, the fourth and fifth gill pouches supply the stranded epithelium of the parathyroid and calcitonin-producing glands whose hormonal secretions enable survival on land by adding calcium to the skeleton, making the thorax rigid, and confining the bone marrow (27,28).

CURRENT CONCEPTS: T-Cells and B-Cells

Since 1956, the infectious nature of *lymphocytomania* is reflected in the following Med-Line computer survey showing the

numbers of articles listed in the *Index Medicus (Table 1).*

Disproportionate growth of *lympho-cytomania* is partly owing to re-discovery during the 1950's that neonatal thymectomy in mammals impairs normal growth of the body, repair of the constitution and resistance to infection (28-30) — like Hewson predicted in 1775; and discovery in 1956 by Glick, Chang and Jaap (31) that testosterone bursectomy during late incubation causes premature involution of the cloacal bursa of Fabricius and impairs the capacity of newly hatched Leghorn chicks to produce anti-Salmonella antibodies. The outcome was that trophic concepts died and "immunity" was concep-tually (32-34) split into a thymus-derived or thymus-dependent cellular component instrumented by "T-cells", and a bursa-dependent or bursa-equivalent humoral component instrumented by "B-cells".

Retroviral Lymphocytopathy

Such *lymphomanic* ravings might seem obtuse and obscure, were it not for the fact that newly characterized human lymphotropic retroviruses, such as HTLV and HIV, have waxed critically *lymphocytopathic*, as well as pandemic *(see Fig. 3).* By random reverse transcription of lymphocyte DNA, such retroviruses are prone to render secondary lymph follicles neoplastic, hyperplastic or hypoplastic; with respectively resulting lymphoma, autoimmune thrombocytopenia or nephritis, or terminal atrophy in the acquired immune deficiency syndrome (AIDS) (43-46). Worldwide, AIDS now accounts for 1 million infants and 9 million adults with progressive lymphocytopenia who have already died, or are expected to die from severe derangements of internal *homeostasis* characterized by failure to grow normally or wasting away; failure to repair or regulate constituent cells; and poor resistance to neoplasms, as well as sundry infections. Moreover, it seems apparent from comparative searches for cell-free retrovirons in blood, semen, and milk, along with polymerase chain reaction (PCR)-detected integrated proviral DNA in lymphocytes that:

1. Provirus-infected small lymphocytes are prone to vector spread in the body by *emperipolesis* into other cells, as well through the placenta and spinal fluid (44).
2. Provirus-infected *emperipoletic* lymphocytes vector transmission from person to person, especially through blood, semen and colostrum, each of which normally contains 1-5 million emigrant lymphocytes/ml (44-46).

The first sick cohorts out of 10 million of these persons infected with human immuno-deficiency virus, Type 1 (HIV-1), demonstrate more clearly than any man-devised experiment, such as neonatal thymectomy or drugs which inhibit lymphocyte nucleotide synthesis, that William Hewson was surprisingly correct in deducing that lymph effluent from the thymus and other lymph glands is "essential to normal growth of the body and repair of the constitution" (7,8). In AIDS, HIV-1 ultimately induce germinal center and follicular disappearance throughout the lymphatic apparatus, with secondary lymphocytopenia (e.g. <200 CD4+ cells per ml), and tertiary malabsorption; epithelial dysplasia in the mouth, skin and endocervix; profound weight loss and body atrophy; poor resistance to epithelial and endothelial neoplasms, as well as poor resistance to a wide variety of infections, especially those wherein delayed hypersensitivity or lymphocyte killing of foreign micro-organisms are instrumental in defense (44).

In AIDS-related conditions (ARC), including persistent generalized lymphadeno-pathy (PGL), HIV-1 somehow induce a dysplastic form of generalized germinal center hyperplasia without lymphocytopenia, but with hyperglobulinemia and relative increase in CD8+ cells, and secondary auto-immune nephritis or combinations of anemia, granulocytopenia and thrombocytopenia, as well as poor resistance to monilia infections. The above-described tertiary complications of AIDS are not prominent or are absent, at least initially. Usually the dysplastic, as well as

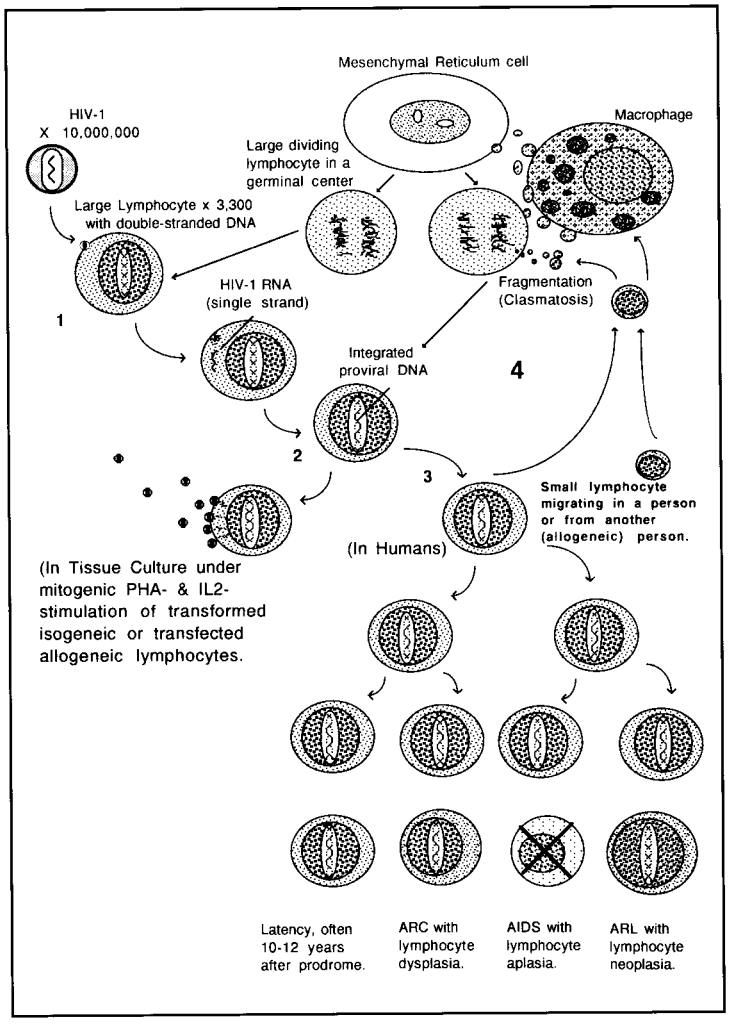

Fig. 3.

1. HIV enters a receptive lymphocyte, presumably having a CD4+ surface receptor.

2. HIV-1 releases its RNA. Single strand RNA reverse transcribes lymphocyte DNA under the influence of virus-formed reverse transcriptase, making a template in double-stranded DNA which can reproduce HIV-1 mRNA.

3. Infected lymphocyte divides into two daughter cells. Cell (left) may express viral RNA to form and shed many HIV-1. HIV-provirus-infected cell (right) may divide to produce two infected daughter cells, each of which may divide again to produce two more, and so on, until billions of infected progeny are generated. In turn, each one out of the billions of daughter cells infected with HIV-1 integrated proviral DNA, termed provirus, may pursue its own destination in a different way, depending on which genes the provirus happens to infect, many co-factors and where the provirus-infected cells happen to wind up during customary emperipoletic migrations. Shown below are some of the results in the germinal centers, when antibodies formed by large germinal center lymphocytes react with HIV-1 related proteins extruded from germinal center cells. Latest concepts of HIV-1 spread within the body and between persons are that it spreads as a complete virus particle, as shown at (1) emanating from cells actually shedding particles (2). However, such cell-free virions have not been identified in body secretions, blood or tissues (excepting the connective tissues in the brain and the germinal centers of hyperplastic lymph glands) in infected humans. Recent evidence suggests that in infected, but healthy humans showing no symptoms or signs of AIDS, approximately 1% of lymphocytes in circulating blood carry provirus. Viral core proteins, e.g., p24 antigen, customarily disappear from the blood with the development of antibodies a few weeks after the AIDS prodrome. Other blood cells, such as red cells, granulocytes and monocytes seldom contain provirus in healthy persons.

4. Based on observations in mammalian germinal centers, I suggest:

a. Migrant small lymphocytes from another person may disintegrate in germinal centers, along with isogeneic small lymphocytes to yield DNA fragments which are partially digested in macrophages or are reutilized in reticulum cells from which large dividing lymphocytes are derived.

b. If this DNA is infected with provirus, integrated proviral DNA will be reproduced in successive generations of daughter lymphocytes (3), along with other genes inherited and transfected similarly.

c. In humans, the perpetual reutilization of proviral DNA from emperipoletic daughter cells spreads the infection to all lymph glands containing germinal centers, as well as throughout the body and through body secretions normally rich in small lymphocytes. Provirus-infected small lymphocytes in such secretions, in turn, serve as emperipoletic vectors for the spread of HIV infection between persons, as well as within a person.

hypertrophic primary and secondary lymph follicles in various lymph glands lose their characteristic polar orientation toward peripheral epithelia, as well as peripheral and central lymph sinuses or sinusoids, and point instead toward internal structures, especially hyperplastic or disorganized collections of endothelial cells. Because ARC and PGL frequently appear to be transitory stages in the evolution of HIV-1 infections into AIDS or into AIDS-related lymphoma (ARL), it is not clear whether such retroviruses actually kill infected lymphocytes or induce follicular pathology through auto-immune mechanisms.

In ARL, HIV-1 appear prone to induce neoplasms comprised of cells like those in the germinal centers (GC) of secondary lymph follicles. Neoplasms comprising cells like those in the juxta-arterial, dark-staining lymphocytopoietic poles are often classified as "undifferentiated B-cell lymphomas, immunoblastomas, or immunocytomas." Neoplasms comprising cells like those in the abarterial, pale-staining reactive poles are often classified as Hodgkin's lymphomas, owing to admixture of multinucleate histiocytes and dysplastic macrophages. ARL often occur in unusual sites, especially in the brain. ARL are prone to occur, either as an end-stage in the evolution of ARC or a terminal event in the progression of AIDS. ARL seldom contain demonstrable integrated HIV-1 proviral DNA, but are prone to contain integrated EBV, as in Burkitt lymphoma. Like "undifferentiated" lymphomas prone to occur in allograft recipients given lymphocytolytic steroids and drugs which inhibit lymphocytic DNA synthesis, ARL may be owing to inadequate "feed-back" of normal *emperipoletic* lymphocytes to modulate growth of large dividing precursors (21).

The situation may be analogous with respect to development of capillary endothelial sarcomas and epitheliomas in individuals whose circulating *emperipoletic* lymphocytes are insufficient and, thus, inadequate to feed-back information and *trephones* to other rapid-growing cells (21,23) through which they normally migrate or into which they transfect DNA (21,23). However, ARL and KS seldom regress spontaneously in AIDS.

Signal studies by Racz et al (47) indicated that many infected large GC lymphocytes produce HIV-1 mRNA in quantity during the early stages of human AIDS. Subsequently, others (48,49), using advanced PCR (polymerase chain reaction) technology, showed that GC lymphocytes contain relatively large quantities of HIV-1 integrated proviral DNA essential to the expression of this mRNA, at least until the GC and surrounding periarteriolar lymphocytes finally disappear in most, if not all, lymphocyte-depleted individuals with AIDS. When it is generally recognized, after Downey (12), that rapidly dividing GC lymphocytes (now called B-cells) normally produce myriad small cytoplasm-depleted lymphocytes (now called T-cells) following the cytoplasmic shedding of soluble globulins and lymphokines (12,21,42), another chapter will open in the Annals of *Lymphomania*. Moreover, a new chapter will open in the study of morbid conditions wherein germinal center cells progressively become allergic to their own products. For instances:

a. The AIDS Prodrome (AP): Assuming HIV-1 provirus infected *emperipoletic* lymphocytes are the most common vectors of AIDS, the AP usually commences 3-6 weeks after infected lymphocytes in blood, semen or endocervical secretions have entered the milieu intérieur by intravenous injection or migration through single layers of epithelial cells. Many of those injected into the blood stream customarily terminate their migrations in the liver, spleen and lymph nodes. Those gaining entry via single layers of epithelial cells customarily migrate to regional lymph nodes. Like many isogeneic small lymphocytes, many allogeneic migrating lymphocytes may be trapped in germinal center macrophages *(see Fig. 4)* which present partially digested macromolecules to adjacent rapidly dividing large GC lymphocytes, or disintegrate within reticulum cells from whence the large germinal center lymphocytes are derived (21). In turn, the macrophages or reticulum

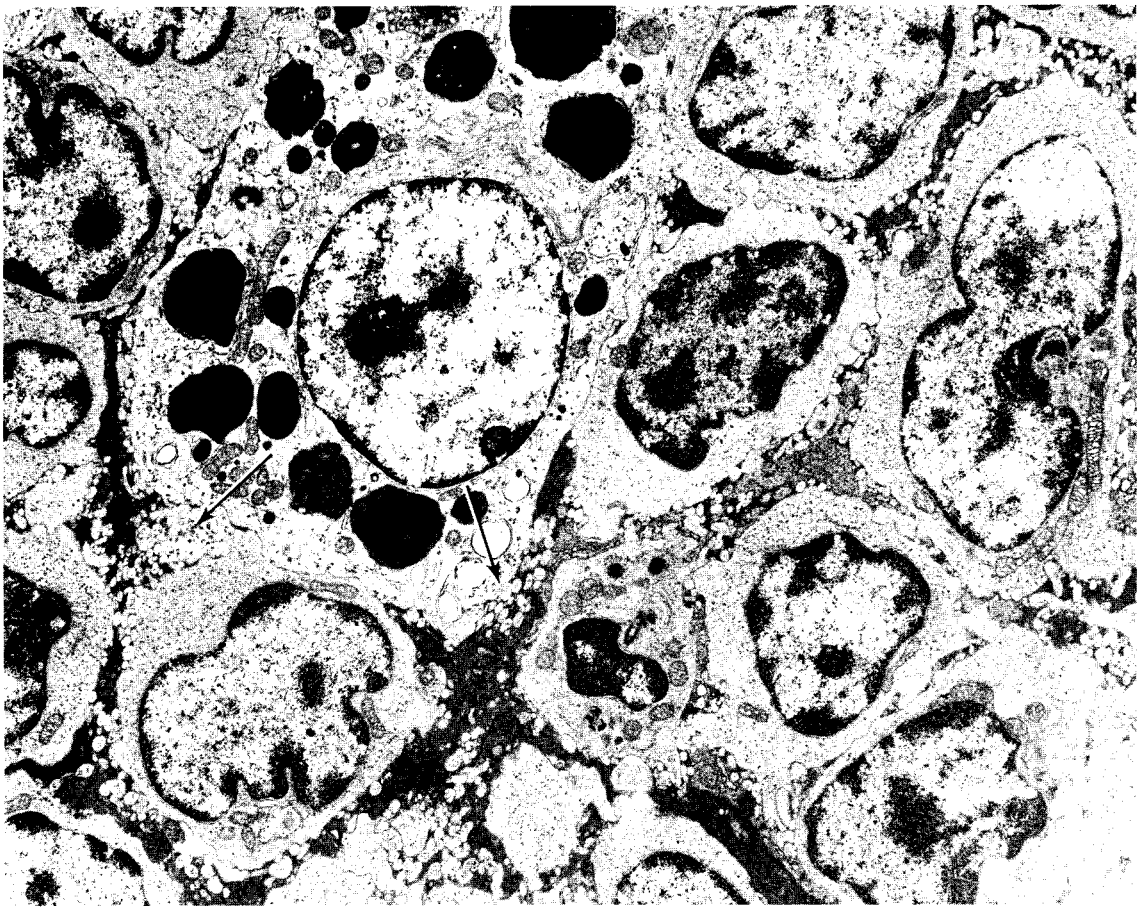

Fig. 4. Ultrastructure of a normal rat germinal center macrophage. The macrophage contains 20 visible fragments of small lymphocytes in advancing stages of disintegration. Such fragments are sometimes called tingible bodies. Arrows point to clasmatosis (fragmentation) in the form of extruded globules or "buds" on the lower surface of the germinal center macrophage. Note similar shedding of cytoplasmic globules from surfaces of surrounding large germinal center lymphocytes. (x3,300) [Reprinted from Lymphology 12 (1979), 49-58]

cells transfected with HIV-1 proviral DNA carried by allogeneic migratory lymphocytes may reutilize the transfected proviral DNA, along with DNA transfected from isogeneic lymphocytes especially during mitosis when cell chromosomes are most unstable (21).

As depicted in *Fig. 3*, some daughter cells and successive generations of lymphocytes in the host GC may code for the production of HIV-1 mRNA, along with other kinds of mRNA customarily produced. Partially under the influence of cytokines, interleukins and soluble globulins generated shed by large rapidly dividing GC lymphocytes (12,21), large quantities of HIV-1 virions, core proteins or envelope proteins may be expressed *(see Fig. 6)*, along with soluble globulins normally extruded by clasmatosis *(see Figs, 4,7)*, during the normal course of cytoplasmic volume reduction and chromatin condensation which results in the production of myriad small cytoplasm-depleted lymphocytes within and surrounding the GC (21) *(see Figs. 4,5)*. Migration of many of these via blood or lymph

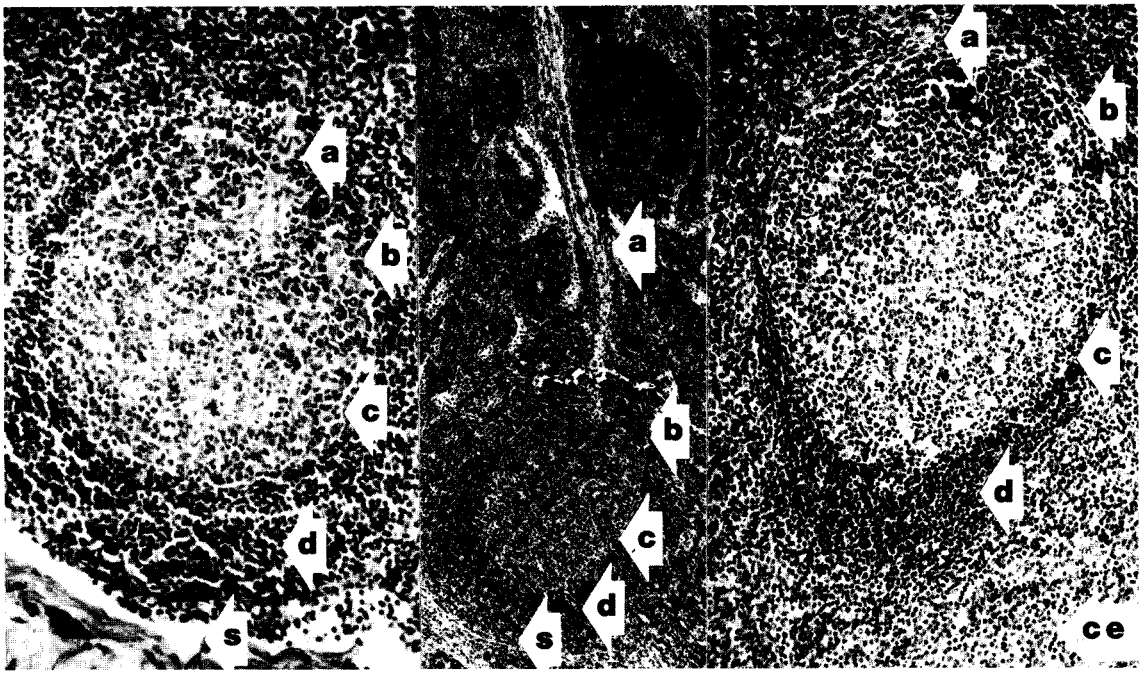

Fig. 5. Normal human germinal centers in a node (left x100), (center x40) and in a tonsil (right x100). Note characteristic zonation: a. Afferent arteriole to germinal center. b. Dark lymphocytopoietic pole. c. Pale reactive pole. d. Cap of mantle zone. s. Sinus. ce. Surface epithelium. Note: The bulk of small lymphocyte fragments shown in Fig. 4 are found in the dark lymphocyto-poietic poles (b) of normal germinal centers where mitoses are most frequent and Feulgen staining for DNA is densest. Also, the bulk of integrated proviral HIV-1 during the latent stages of AIDS seems to be in the nuclei of the large lymphocytes in these dark poles.

effluent from splenic or regional nodal GC to GC in remaining lymph glands will temporarily magnify proviral DNA reutilization and re-expression in the remainder (21). As combined results, the new host passes through an acute self-limited viremic illness, somewhat like infectious mononucleosis or measles, wherein many circulating lymphocytes temporarily display viral HIV-1 mRNA, and many lymph glands are transiently enlarged (50). However, the AP usually subsides with lymphocytic recognition, after sequential processing in macrophages and plasmacytes (*see Figs. 2,4*), that cell-free retrovirus and HIV-1 core proteins (e.g., p24 antigens) shed into lymph are substantially foreign. However, antibodies against HIV-1 surface proteins (e.g., gp120) which usually appear after subsidence of the AP do not disappear, partially because (a) some large GC lymphocytes continually reutilize HIV-1 proviral DNA from circulating small lymphocytes, along with DNA from small thymic lymphocytes and small lymphocytes "primed" after first encounter with other antigens *(see Fig. 2)*; (b) partly because the envelopes of cell-free HIV-1 are supplied by the plasmalemma of large dividing lymphocytes during the process of virus "shedding", along with other globular particles (12,21), originally called "globulines" by Donné (51) or "hyaline bodies" by Downey (12); and (c) possibly because *reverse transcriptase* production induced by HIV-1 proviral DNA during replication in large dividing lymphocytes induces random, instead of constant gene site insertion into the chromosomes of large lymphocytes (52), especially during mitosis when the

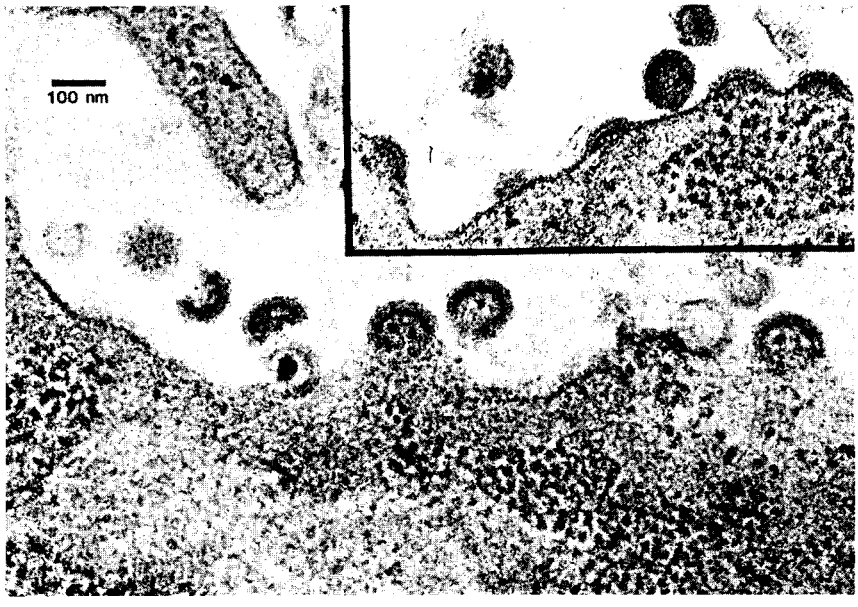

Fig. 6. Transmission electron microscopy of ultra-thin sections of retrovirus-producing cord blood lymphocytes (under PHA and interleukin-2 stimulation in tissue culture). (Magnification ±10^7). Note, especially in the inset, that the lymphocyte surface plasmalemma contributes to form the capsule of the 100nm retrovirus. [Courtesy F. Barré-Sinoussi et al in Science 200 (1983) 868-871]. Copyright 1983 by the AAAS.

chromosomes are most unstable with respect to reverse transcription, as well as DNA reutilization (21,26). As combined results, we may observe a rapid rate of mutation of HIV-1 proviral DNA and mRNA, even though circulating antibodies to HIV-1 envelope proteins, such as gp120 sharing plasmalemmal origins with CD4+ T-cell receptors, usually persist throughout the prolonged latent course of HIV-infections following the AIDS prodrome (AP).

b. Latent HIV Infections (LHIVI): Following the AP, LHIVI persist without symptoms in most HIV-1 infected persons for extremely variable periods of time (44-47). During LHIVI the GC in all lymph glands, except the thymus which lacks GC under normal homeostatic conditions (21), show subtle changes in persons whose circulating blood contains demonstrable neutralizing antibodies against HIV-1 surface envelopes. Such subtle changes include the precipitation of antigen-antibody complexes between the plasmalemma of large GC lymphocytes and follicular dendritic cells which mechanically support the former (47,48), suggesting that cell-free viruses presumably shed from large GC lymphocytes are immediately precipitated by corresponding antibodies against HIV-1 envelope proteins during LHIVI wherein the cell-free HIV-1 blood burden is low (49). However, it should be interjected and added that: (a) HIV-1 shedding from any kind of lymphocyte remains to be demonstrated *in vivo*. (b) Cell-free HIV-1 with characteristic nucleoids have been observed in the meshes of follicular dendritic cells lacking PCR demonstrable HIV-1 proviral DNA (47,48), but remain to be demonstrated microscopically in blood, semen, endocervical secretions and colostrum during the course of HIV-1 infection. (c) Plentiful circulating antibodies and adequate numbers of recirculating small lymphocytes, sometimes with increased CD8+/CD4+ ratios are found during LHIVI. However, ±1% of small circulating lymphocytes usually contain HIV-1 proviral DNA (50), a few of which may contain HIV-1 RNA (49,50).

c. Persistent Generalized Adenopathy (PGL): Following prodrome, the average human adult with HIV-1 infection, detectable by demonstration of circulating antibodies against envelope proteins, is usually free from

major symptoms for ±10-12 years. However, in some, palpable enlargement of superficial lymph glands persist, partly owing to very hyperplastic GC surrounded by thick paracortices containing densely packed medium-sized and small lymphocytes. Presumably, this GC hyperplasia in PGL is owing to persistent stimulation by HIV-1 related antigens or co-factors which serve as adjuvants. In individuals with PGL, no diagnostic alterations in circulating lymphocytes are evident. However, many individuals have non-specific polyvalent hypergammaglobulinemia, and often suffer from recurring fevers of unknown origin before ARC, ARL or AIDS ensue.

d. AIDS Related Complexes (ARC): The inexorable progression of HIV-1 infections is so subtle that less than 50% of infected individuals recall an AP. Persons with PGL seldom recall the onset, but usually fear the outcome sufficiently to avoid ELISA and Western blot testing for HIV-1. Partly depending on inherent genetic constitution and exogenous cofactors, many persons with or without preceding PGL go on to develop ARC wherein customary polar orientation of extremely hyperplastic GC toward sources of exogenous and endogenous antigens emanating from lymph sinuses or adjacent epithelia becomes disoriented, as well as dysplastic. The GC sectioned in polar axes generally point in no definitive direction from afferent arteries toward definitive epithelial or endothelial structures *(see Fig. 5)*. Common consequences are the precipitation of retroviral proteins together with corresponding antibodies on the plasmalemmal surfaces of GC lymphocytes to form insoluble "antigen-antibody" or "immune complexes" (47,48). The most common symptomatic results are "auto-immune" fatal nephritis or "auto-immune" life threatening thrombocytopenia, hemolytic anemia or granulocytopenia, singly or in combination (44). It should be emphasized, again, that plenty of circulating "polyclonal" or polyvalent antibodies and plenty of circulating lymphocytes, often with increased CD8+/CD4+ ratios are common during this stage of HIV-1 infestation.

e. AIDS Related Lymphoma (ARL): Prolonged cellular hyperplasia or dysplasia being harbingers of neoplasia, it should not be surprising that 10-15% of persons with or without obvious preceding PGL or ARC go on to develop aggressive malignant lymphomas whose cellular constituents resemble GC cells gone awry with reversion to anerobic respiration (21).

f. Kaposi Sarcoma (KS) and Epithelial Neoplasms: Kaposi endothelial sarcomas and rectal epithelial neoplasms are common in gay men accustomed to receptive anal intercourse; while endocervical dysplasia and endocervical epithelial neoplasms have become common among heterosexual women, especially those frequently exposed to other cell-borne sexually transmitted diseases which may serve as cogent co-factors during the prolonged latent period of HIV-1 infections. For qualitative, as well as quantitative observations on *emperipoletic* lymphocyte traffic through endothelia and such epithelia, please see Refs. 21-25,43-45.

g. AIDS Related Dementia (ARD): ±30% of individuals develop ARD during the course of HIV-1 proviral infections. Such progressive dementias, as well as transient forms of meningo-encephalitis prone to occur during AP, can be partially explained by the fact that small lymphocytes are the only circulating blood cells which normally migrate through the "blood-brain" barrier and through glial cells to appear in cerebrospinal fluid (21,44). During migration, some small *emperipoletic* lymphocytes may transfect HIV-1 proviral DNA to the rapidly dividing glial cells which customarily support neurones. Transfected glial cells, in turn, may demonstrate HIV-1 shedding under the microscope (53), possibly because the concentration of blood borne neutralizing antibodies is characteristically low in cerebrospinal fluid. If mesenchymal glial cells, like GC cells, are prone to become hyperplastic, dysplastic or neoplastic as a

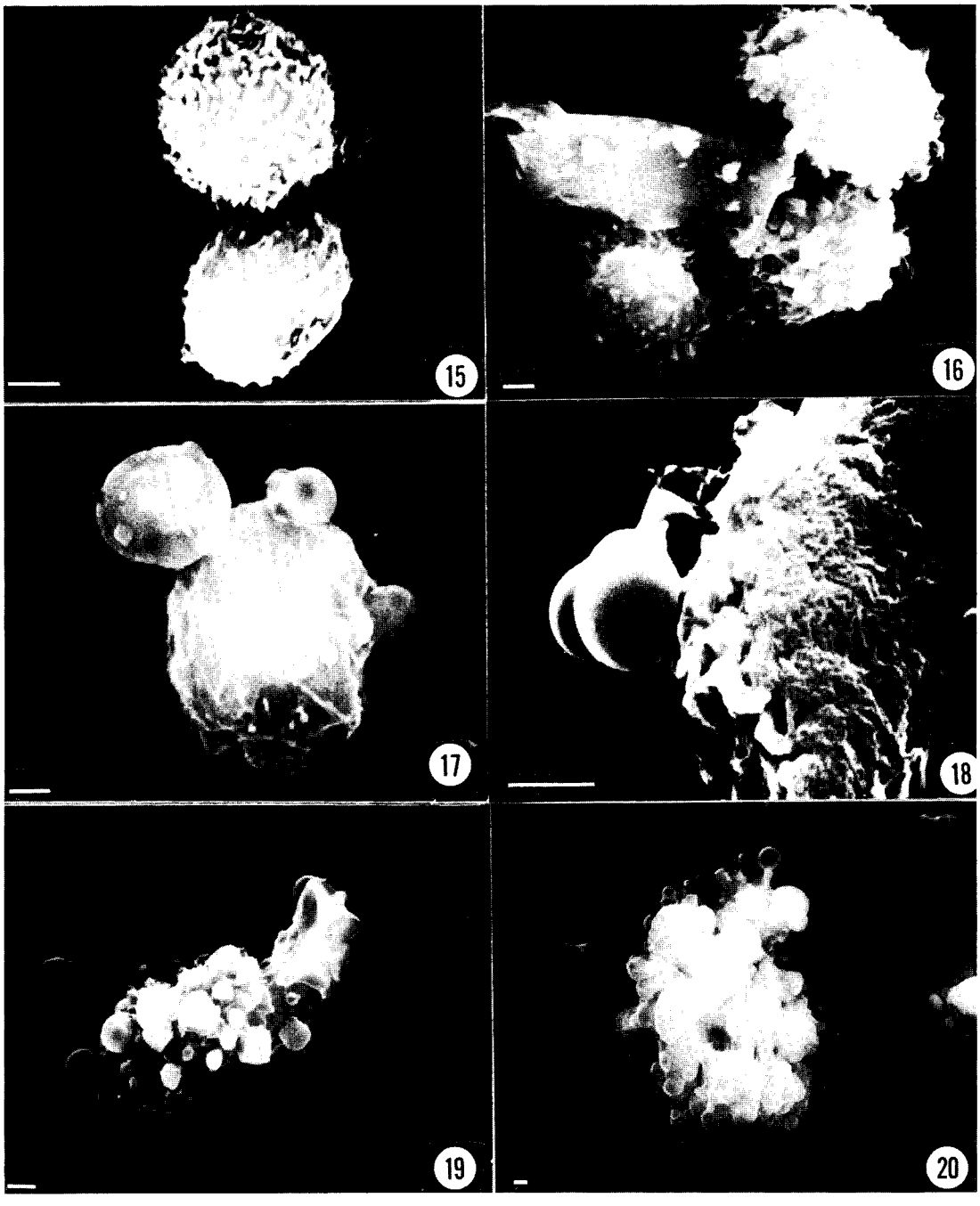

Fig. 7. Scanning electron microscopy of healthy human peripheral blood lymphocytes under PHA-stimulation in tissue culture. (Magnification ±3x10^3— Markers=5μ). Note, especially in frames 16-20 and in Fig. 4 (under transmission electron microscopy) that during clasmatosis, the cell plasmalemma contributes to the formation of globules up to 5μ in diameter which disperse and dissolve into the surrounding medium. As shown in frame 15, "unstimulated" small lymphocytes usually have surfaces studded with blunt microvilli. As shown in frame 16, when "stimulated" by a foreign object, some of the microvilli extend to contact the object; while others may swell to form tiny globules.

Normally during PHA-stimulation, large numbers of small lymphocytes disintegrate in the culture medium through "potocytosis" (swelling and bursting with water imbibition) or "apoptosis" (premature death) associated with eventual nucleolysis, in proportion to the numbers which transform into large rapidly-dividing lymphocytes resembling "stem cells" or "lymphoblasts". Like tumor cells, these survive via anerobic glycolysis.

This globular form of "exocytosis", called "clasmatosis" or "cytoclasmosisis", is instrumental in the cellular secretion of soluble or dissolved globulins; and is characteristic of mesenchymal mononuclear cells, especially reticulum cells, macrophages, plasmacytes and lymphocytes, in vitro and in lymph glands. However, lymphocytes differ in that "endocytosis" of organic particles other than elemental carbon and mycoplasma remains to be demonstrated. Moreover, small and large lymphocytes have not been shown to form endocytic vesicles; or to possess intracellular organelles, such as lysosomes, essential to the digestion of macromolecules or retroviruses gaining internal access between mitoses. [From J. Shields SBMFC Proc. 1 (1983), 34-46].

result of provirus transfection, ectodermal neurones which they support cannot be expected to function well.

h. Acquired Immunodeficiency Syndrome (AIDS): At a median of ±12 years after the initial critical exposure to allogeneic infected lymphocytes, most HIV-1 provirus infected human adults surviving the former complications develop AIDS, and die as a result of opportunistic infections 1-3 years later. At this stage, the most common denominators are the disappearance of GC and loss of cortex in all lymph glands, along with disappearance of nearly all small cytoplasm-depleted circulating lymphocytes, especially those designated as CD4+ T-cells (48). Out of the CD4+ lymphocytes remaining in circulation, 1-10% commonly contain HIV-1 proviral DNA (48,50). Simultaneously, the cell-free HIV-1 or circulating p24 antigen burden in circulating blood may increase (48,49), possibly in proportion to deficient or defective antibody production in the few polarized germinal centers which remain. It is not certain why successive genetic mutations in integrated proviral DNA, possibly resulting from repetitive aberrant RNA insertion under influence of HIV-1 reverse transcriptase (52), should result in aplasia, instead of hyperplasia, dysplasia or neoplasia in GC cells. However, it seems certain that disappearance of GC and paracortices in most, if not all lymph glands — not just circulating CD4+ T-cells are critical.

i. Pediatric AIDS (PAIDS): PAIDS differs from adult AIDS partly because infants lack GC at birth. After weaning they progressively develop GC with thick paracortices in the gut, spleen and in all extrathymic lymph glands during childhood and adolescence (21,38), provided that their thymus glands develop and function normally during customary age and stress involution (21). The infants are commonly infected by small maternal lymphocytes which migrate through the placenta or through colostrum of a HIV-1+ mother (44,45) characteristically having a low cell-free HIV-1 burden in circulating blood (possibly owing to the presence of circulating antibodies vs. HIV-1 envelope proteins). The onset of symptoms and signs in PAIDS tends to be delayed until circulating maternal antibodies disappear and the GC, periarteriolar paracortices and customary infantile circulating lymphocytosis become well-developed. However, after onset, the signs of prodrome, PGL, ARC, ARL an ARD tend to be more fulminant, until the germinal centers, nodal paracortices and circulating lymphocytes mostly disappear. With disappearance of the GC, paracortices and most of the lymphocytes in the body, the infant or child ceases to "thrive" and approaches a state commonly seen in athymic newborn wherein body wasting, weakness, poor resistance to sundry infections and disintegration of "the constitution" are the end results (21,44), again as foretold by William Hewson (7).

j. Closely Related Phenomena: Because mammalian GC and their soluble, as well as *emperipoletic* cellular products develop to serve every respiring cell in the body of a mammal throughout the course of a natural life span (21,23), service is frequently impaired when their soluble products now called

immunoglobulins, interleukins and lymphokines, and their cellular products now called B-cells or T-cells are morbid, especially during early stages of HIV-1 infections when circulating antibodies may be abnormal; and during later states when proviral DNA is transfected to other body cells, especially those prone to divide frequently. Therefore, the most common secondary ill-effects are prone to occur in the skin, gut, bronchi and genito-urinary tract wherein the local epithelial cells are usually replaced every 4-21 days (21,24).

k. Koch's Postulates: Currently there remains considerable difference of opinion whether cell-free HIV or integrated HIV-1 proviral DNA causes AIDS (54), partly because cell-free HIV-1 are seldom demonstrable microscopically in tissues or in body secretions; and are not demonstrable in all stages of this progressive disease. In terms of integrated HIV-1 proviral DNA, Koch's postulates can be satisfied as follows:

1. After prodrome, integrated proviral HIV-1 DNA can be found in germinal center, blood, seminal, endocervical and colostral lymphocytes in most, if not all infected persons during latency and successive stages of AIDS, as outlined above.

2. Integrated proviral HIV-1 DNA almost always can be isolated in cultures of lymphocytes obtained from an infected person during the latent and symptomatic stages of AIDS.

3. Pure integrated proviral HIV-1 DNA has not been experimentally inoculated into a susceptible person, and found to reproduce AIDS. However: (a) Purified proviral SIV_{MAC} has been extracted from cultured lymphocytes and, after injection, has been found to produce simian AIDS in macaque monkeys (55). (b) Unpurified and probably cell-free integrated proviral HIV-1 DNA in Factor VIII concentrates obtained from pooled human plasma, when infused into veins, is a common cause of AIDS in hemophiliacs (46,54). (c) Proviral HIV-1 integrated into the DNA of circulating lymphocytes, when transfused therapeutically in ±250 ml units of packed cells, almost uniformly produces AIDS in susceptible transfusion recipients (54).

4. As opposed to cell-free HIV-1, integrated proviral DNA is uniformly found in, and recovered from circulating lymphocytes of said injected monkeys and from said infused or transfused humans who developed AIDS or an AIDS-related condition.

In partial summary, then, it seems reasonable to conclude that *fluid lymph* is essential to circulation and that circulating *emperipoletic* lymphocytes are essential to *homeostasis* in humans. HIV-1 can ultimately destroy *homeostasis* by eliminating the germinal centers from whence many small cytoplasm-depleted lymphocytes migrate, along with a variety of soluble globulins responsive to many kinds of exogenous antigens.

MORE REFLECTIONS ON HUMAN BEINGS: "To B-, or not to B-?"

Although a continuum in structure and function among lymphocytes of decreasing size and cytoplasmic content is discernable by tracing PCR-labeled elements during the course of HIV-1 infections, current concepts of B-cells and T-cells still remain dogmatic. To wit, if Fabricius, Asellius, Harvey, Hewson or Bernard were still alive today, one of them might have mused:

1. Like puberty, injected testosterone induces involution of the avian thymus and the bursa of Fabricius (27,28,35). At 17 days of incubation in chicks, "testosterone bursectomy" also induces thymic atrophy (37).

2. Surgical bursectomy at 7 days of incubation does not impair the capacity of newly hatched chicks to produce antibodies toward injected Salmonella antigens (37). What happens when the precocial newly hatched bursectomized chicks promptly start feeding on the ground among the flock, and become prone to encounter live Salmonella in the excreta of others is another bursal question.

3. In the secluded nest, altricial avian

hatchlings, such as squabs, hawks and songbirds, customarily feed on cropsac milk which is regurgitated from the cropsac of one or both parents into the gullet of the hatchling (56). The cropsac or "pigeon's milk" is a mixture of ingested food, saliva and mucus, along with lymphocytes and antibodies which emanate from the parental tonsils (38,56). The lympho-epithelial cloacal bursae remain atrophic in most, if not all altricial hatchlings until they are well-feathered and ready to fly (38). At fledgling, then, the bursae of Fabricius in altricial birds becomes comparable in mass and development with that in the cloacal bursae of precocial birds (38).

4. How, when and why the unique avian bursa of Fabricius traps and processes liquid urine, feces and, sometimes, sperm, as well as enteric flora throughout the post-natal life of birds are other cogent bursal questions. Nevertheless, it seems likely that the bursa, sometimes called the "cloacal thymus" (36), plays essential homeostatic roles supplementary or complementary to those of the 5-6 paired thymus glands which normally become stranded from vestigial gill pouches to reside on each side of the trachea in the long necks of birds. Gill derivation and inspiratory synchrony are clues (38).

5. In mammals, which characteristically lack cloacae and cloacal bursae, colostrum rich in lymphocytes, antibodies, proteins, sugars and, later, in fats appears functionally similar to the cropsac milk in newly-hatched altricial birds, such as pigeons, hawks and song-birds; and similar to the lymphatic effluent from the well-developed lympho-epithelial cloacal bursae in newly hatched precocial birds, such as chicks, ducklings and plovers (38).

6. Some species of aquatic turtles develop homologous cloacal bursae (36) which serve as cloacal gills during submersion (39-41). These bursae are structurally and functionally analogous with the cervical gill pouches from which the adenoids, tonsils, thymus, parathyroid and calcitonin-producing glands are sequentially derived during thyroxin-induced metamorphosis in all vertebrate embryos destined to breathe air; and crawl, slide, hop, walk, or fly on land (27). However, in such aquatic turtles the pinocytic epithelium remains convoluted, as in gills; and does not invaginate to form epithelial reticula surrounded by proliferating lymphocytes, like we see in the thymus and bursa (36,38).

7. In most, if not all organized lymphatic tissues, the progressive development of "B-, D- (B+T), T- and Null-lymphocytes" from mesenchymal reticular cells can be explained simply by continual shedding of surface cytoplasm during the normal course of gene switching/expression, as larger lymphocytes transform into pachychromatic small cytoplasm-deleted *emperipoletic* cells destined to feed, regulate or kill other cells, as well as invading microorganisms (21). As a result, toxic antigens are opsonized, and noxious cells or microorganisms are lysed to be re-cycled as food for diverse genetically tolerable host cells (21).

8. Humoral immunity to a given soluble or macrophage-processed antigen normally precedes cellular immunity to its living source, partly because lymphocytes shed much of their cytoplasm in the form of dissolved antibodies, as well as soluble *lymphokines* or *"trephones"*. Subsequently, many cytoplasm-depleted "T- or Null cells" still retaining T-cell receptors may proceed to recognize "self", as well as "non-self", among a veritable sea of competing "selves" whose DNA differs genetically.

9. Sequentially coordinate *(see Fig. 2)*, "humoral" immunity depends on the diffusion of macromolecules dissolved in circulating lymph (42); while "cellular" immunity depends on the random, but *emperipoletic* migration of small cytoplasm-depleted lymphocytes through endothelium, interstices, cells, cell layers, lymph glands and external, as well as internal secretions (21).

10. William Hewson, "Thymicologist: Father of Hematology?" (7) might have deduced further that the thymus glands not only produce "lymph containing numberless

particles essential to normal growth of the body and repair of the constitution", but also many oriented toward "self", especially during neonatal life. Because the thymus normally contains concentrations of DNA-bound phosphate (DNAP) 5-10 times greater than remaining body organs, excepting the lymph nodes, spleen and intestinal lymphatic tissue (21,23), one might surmise that the DNAP which is exported by small cytoplasm-poor thymic lymphocytes, which is reutilized in other cells (21,23-26) or which breaks down with stress-induced lymphocytolysis (17,21) is essential in such orientation toward "self". For instances:

a. Throughout adult life in all forms of vertebrates, internal *homeostasis* depends on the formation of chylous lymph as a result of gut epithelial and lymphatic tissue hypertrophy and hyperplasia (57) with each ingested meal (3). During infancy in mammals, the thymus supplies relatively large quantities of lymphocytic DNAP which is reutilized by rapid growing intestinal epithelial and lymphatic tissue cells (58). Without thymus glands, mammalian neonates not only fail to develop adequate intestinal lymphatic tissue, but also fail to grow or "thrive" and lack resistance to many kinds of gut infections, as is commonly seen in adults with HIV-related "Slim Disease".

b. During all forms of severe stress, including anoxia, cold exposure and systemic infections, adrenal glucocorticoid mediated lymphocytolysis (17) suddenly releases relatively large quantities of information-rich DNA, water soluble high energy phosphate and sundry globulins essential to self-preservation until *homeostasis* is restored (21).

c. Throughout infancy and adult life, all kinds of mammals depend on a capacity to destroy, as well as feed on living organisms which enter the body by parenteral routes. A given mammal's capacity to do so is greatly enhanced by the development of lymphopoietic germinal centers in all lymph glands, except the thymus which continues to export extraordinary quantities of thymocyte-borne DNAP (21) under the impetus of pressure changes occurring with each breath of air into the lungs (20-22). Reutilization of this energy and information directed toward self, probably from thymocyte or small lymphocyte nuclear remnants, called "tingible bodies", found in germinal center macrophages or between large dividing germinal center lymphocytes perpetuates the recognition of "self" during the sequential chain of cellular reactions *(see Fig. 2)* which enables the body to destroy and reutilize matter recognized to be genetically foreign.

d. It is essential to recognize, in accordance with standard principles of mass/energy conservation, that matter is neither created nor destroyed, but changes into another form. Therefore, one must account for the origins and dispositions of "B-cells" and "T-cells", along with the foreign matter which they or their products destroy in order to sustain *homeostasis*, as defined by Claude Bernard (8,21). Normally, the "clasmatocytes", as described by Ranvier (11) enable the body to ingest cells and macromolecules; to digest that which is ingested by phagocytosis, as described by Metchnikoff (10); and extrude the partially digested remains by *clasmatosis* in soluble forms which can be reutilized by other adjacent cells, be altered in the spleen and liver, or be excreted via the kidneys (21).

e. Current theory with respect to the pathogenesis and treatment of the human AIDS pandemic has reverted to the consideration that thymus-derived Th2 CD4+ lymphocytes controlling B-cell development might switch with AIDS progression to Th1 CD4+ lymphocyte populations (59). Because many cells, especially thymocytes and lymphocytes normally decrease in volume and organelle content in synchrony with nucleolar changes and chromatin condensation during a customary life span (12,21), we can expect their surface structures and products to change accordingly.

Therefore, after Fabricius, Asellius and Harvey we might still ask, "To B- or not to B-?". This question was probably best posed by

their English contemporary, William Shakespeare in *Hamlet* (Act III, Sc. 1, 56-69 & 86-89); and best answered in his *As You Like It* (Act II, Sc. 7, 139-142 & 143-166). In paraphrase:

Hamlet:
Ham. To B-, or not to B- — that is the question:
Whether 'tis nobler of the mind to suffer
The slings and arrows of outrageous fortune
Or to take arms against a sea of T-B-L's
And by opposing end them. To die — to sleep —

And enterprises of great pith and moment
With this regard their currents turn awry
And lose the name of action. Soft you now!
The fair Lymph'thelia! — Nymph, in thy orisons
Be all my sins rememb'red.

As You Like It:

Jaq. All the bod's a stage,
And all the lymphocytes merely players.
They have their exits and their entrances;
And one lymph in its time plays many parts.

(Lines 143-166 can be paraphrased similarly, but not so easily for the lymphocytes wherein the seven stages are 1. Birth in the matricial reticulum. 2. Growth and instruction in germinal centers. 3. Prolific shedding of ectoplasm. 4. Migration into lymphatics. 5. Transport in circulation. 6. Emperipoletic migration into tissues. 7. Final oblivion through loss of all surfaces and markers, and terminal disintegration of the DNA core within other cells or secretions.

CONCLUSION

Perhaps Fabricius, Asellius, Harvey, Hewson, Bernard and Shakespeare were more prescient than contemporary scientists acknowledge. Nevertheless, pursuing in their footsteps, myriad modern *lymphomaniacs* might generate a better understanding of human *homeostasis*, as well as help to minimize *homeostatic* failures caused by the pandemic spread of HIV-1 within and between people via provirus-infested *emperipoletic* lymphocytes (44-46,49).

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