

## COMMENTARY

## IGNORANCE IN AIDS, KS AND SEPTICEMIAS

Your timely article on Ignorance in AIDS, KS and Lymphology (1) is truly "lymphspirational" and deserves comment:

*In the Abstract*, you might have stated that "These questions are placed in the context of general ignorance about infectious diseases and the relationship of 'germ' to the tissues which 'lymph, lymphocyte and blood loops' have developed to nourish, coordinately regulate and provide immunity throughout the life-span of all living animals." (2)

*In AIDS and Ignorance*: "It's the virus, stupid," David Ho (37) and "Le germe n'est rien: c'est le terrain (*ou le milieu*) qui est tout." (The germ is nothing, the terrain or *medium* is everything.) Louis Pasteur (38)" These two statements \_ 100 years apart are crucial in our current knowledge, ignorance and "ignore-ance" in HIV/AIDS, as well as bacterial septicemias because: (a) The "main stream" of HIV/AIDS research continues to contend that cell-free HIV-1 is the primary cause of AIDS and the entity which carries this devastating retroviral infection worldwide via infected blood, semen, uterine secretions and maternal milk. (b) Investigators of the origins, structure, propulsion and functions of the lymph stream and migrating lymphocytes contend that provirus-infected lymphocytes are the cause and the motile vectors of AIDS in humans, as well as other species (2,3). I'd like to emphasize that *randomly* integrated provirus in lymphocytes fulfills Koch's postulates as follows:

1. In AIDS, proviral DNA variably integrated into lymphocyte nuclear DNA is uniformly demonstrable in humans and other species, along with variable quantities of retroviral RNA in lymphocyte cytoplasm and

in circulating blood plasma (3-5), derived from lymph (3).

2. Variably integrated proviral DNA can be isolated in pure form, identified by PCR (polymerase chain reaction) technology, by culturing infected lymphocytes with genetically foreign lymphoblastoid or other kinds of genetically receptive cells when stimulated by phytohemagglutinin (PHA) and Interleukin-2 (IL-2) in mixed cell cultures (5). The receptive genetically foreign cells bearing nucleotide sequences resembling those in the inoculated provirus-infected lymphocytes may, in turn, proceed to shed plasmalemma-encased retroviral particles lacking DNA (4,5).

3. Supernates containing such encapsulated retroviral particles and/or the soluble products of DNA disintegration (apoptosis) in human mixed cell cultures, when inoculated into other animals, usually elicit the temporary production of antibodies from the lymphoid tissues characteristic of species. However, practically none develop AIDS or infected cells.

4. In naturally transmitted AIDS, most notably resulting from blood injection (6), retroviral RNA nucleotide sequences resembling those in the primary host are often identified by PCR nucleotide sequencing in the DNA of lymphocytes of the secondary host (5). It is doubtful that a retrovirus lacking DNA could transmit this much genetic information.

It should be added that lymphocytes are especially prone to undergo cytolysis with mechanical injury, hypotonicity or with adrenal glucocorticoids, thus giving rise to appreciable concentrations of soluble DNA and/or component nucleotide sequences (3).

Therefore, it seems likely that soluble cell-free DNA containing HIV-1 provirus is a more likely cause of AIDS than encapsulated cell-free retrovirus in hemophiliacs receiving multiple intravenous injections of mechanically processed "cell-free" plasma products (3).

Encapsulated cell-free HIV-1 fails to fulfill Koch's postulates, because:

1. Encapsulated cell-free HIV-1 are sometimes found budding from the plasma-lemma of large germinal center lymphocytes (LGCL) in spleen or nodes of infected individuals (5,7). However, encapsulated cell-free HIV-1 remain to be identified via electron microscopy in the blood, semen, uterine endocervical or mammary secretions of infected humans (3-5).

2. During the latent phase of HIV/AIDS, when soluble serum HIV-1 RNA levels are characteristically less than  $10^3$  copies per mL, anticapsular antibodies, presumably produced by LGCL, precipitate the viral capsular gp120 antigens to form amorphous antigen-antibody precipitates loaded with HIV-1-RNA between the surfaces of LGCL and follicular dendritic cells (7). Thus, relatively little retroviral RNA circulates in blood, until the terminal stages of AIDS when most, if not all germinal centers and their small cytoplasm-depleted progeny, currently called B-cells and T-cells are destroyed, probably as a result of random, repetitive and progressive reverse transcription of retroviral RNA into the DNA of LGCL during mitosis when the chromosomes divide and the component genes in the DNA of LGCL are most unstable (4). Coupled with the normal reutilization of DNA from isologous SCDL in LGCL during mitosis to sustain homeostasis (3,4), the LGCL may reutilize and replicate variably integrated proviral DNA from the migrating SCDL of another person until DNA from the latter is recognized as foreign. Because the variably integrated HIV-1 RNA reverse transcribes at random into the LGCL genes (4,5), more than one of  $\pm 70,000$  genes may be functionally altered or incapacitated beyond the means of

natural DNA repair. The progressive results are genetic chaos in the nuclear DNA, depletion of functional genes, depletion of LGCL and homeostatically effective SCDL, and emergence of mutant clades of HIV insensitive to medications or vaccines (4,5).

During the prodrome and latent phase of human AIDS,  $\pm 0.5\%$  of  $\pm 5 \times 10^6$  SCDL per mL in  $\pm 5L$  of whole blood circulating in the body are found to contain variably integrated HIV-1 RNA (4,8). During late stages, when serum viral RNA loads are high, highly active anti-retroviral therapy may reduce RNA loads drastically, but does not significantly reduce the numbers of provirus-infected lymphocytes in blood or organized lymphatic tissues (8).

3. From a practical point of view, it should be added that HIV-1 RNA contains genes for production of reverse transcriptases and proteases which may become active when integrated into the DNA of dividing LGCL (4,5). However, the retrovirions lack DNA and inherent capacities of SCDL for emperipoletic motility between and within other cells (9); and the power to recognize and coordinate functions of endogenous cells, as well as destroy foreign cells and antigenic matter for convenient reuse as non-toxic food (10), after appropriate sensitization with sequential help from endothelium, macrophages, plasmacytes and reticulum cells in the spleen and other lymph-producing glands of mammals (3,4,10).

*AIDS Questions in Tables 1-3.* Nearly all questions remain cogent in the year 2000, along with the documented enormity of the worldwide AIDS pandemic. The crux herein probably lies in dogma versus "ignore-ance" in fundamental aspects of Lymphology, as the science evolved after the signal observations of Gaspar Aselli, almost 400 years ago. Rediscovery of the bursa of Fabricius in 1956 and the recognized advent of HIV in 1981 have been recent events spurring focus on B- cells, T-cells and CD - subclasses, instead of the "lymphatic apparatus" as a whole, as defined by Drinker,

Yoffey and Courtice. Insofar as AIDS is concerned:

*“The random reverse transcription of HIV-1 RNA into the genes of large dividing lymphocytes (LGCL) and transport of integrated proviral DNA within and between persons via migratory small cytoplasm depleted lymphocytes (SCDL) derived therefrom causes deterioration of the entire lymphopoietic system. Secondary results are progressive failure in homeostasis, loss of sensitivity to potentially therapeutic drugs, and inability to produce preventive vaccines. The world-wide prevention of HIV-1 sickness and other lymphopathic retroviral diseases will depend on greater individual cooperation, especially with respect to minimizing the number of infected lymphocytes which migrate between persons through blood, semen, uterine endocervical secretions and maternal colostrum.”* (4).

Among contemporary contributors to this concept, I should like to thank Françoise Barré-Sinoussi, Paul and Klara Tenner Rác, and Ashley T. Haase. I was pleased to see that the first three were included among your acknowledged “ignorant experts”.

*KS and Ignorance* — Good show! I admired your Figs. 5 and 6.

*Hospital Acquired Septicemias* – Bypassing the nodes as shown in Fig. 5, septicemic side-effects of AIDS ignorance are now killing more Americans annually than AIDS (11,12).

## CONCLUSION

“Ignore-ance” in infectious diseases is delaying prevention and killing too many people. Moreover, ignorance fosters complacency.

*More thoughts on “Ignore-ance” and a BIQ:*

Ignorance in and “ignore-ance of Lymphology is a shame, because the lymphatic system of each species with or without

backbones develops under the impetus of DNA, unique in each species and each member of the species, to maintain homeostasis throughout the milieu intérieure, and respond appropriately to each morsel of food, each germ, and each part of another living creature entering the body by any route from the milieu extérieure (See William Hewson and Claude Bernard, as cited in Reference 3). Moreover, the lymphatic system characteristic of species develops in extent and complexity proportional to the amount of oxygen required to assimilate all forms of food essential to normal growth and customary activities of the body as a whole (10,13).

Fundamentally, the system works through the sequential cooperation of mononuclear cells, including endothelium, macrophages, plasmacytes and reticulum cells continually derived from mesenchyme which grows to absorb, filter and modify the products of each cell in the body for the production of lymph which flows centrally to constitute the circulating hemal lymph of invertebrates lacking red blood cells, and the liquid plasma in the recirculating blood of vertebrates (3,10). During the normal course of differentiation, each cell type plays essential roles during the sequential filtration, processing and formation of lymph, as outlined previously (3,4,10). The BIQ here is what forces enable the DNA of lymphocytes, the most concentrated and labile reservoirs of DNA in the body of most species, to produce a wide variety of soluble nutritive and immune globulins during maturation in lymphoid tissues and, then, migrate actively via lymph and blood to carry DNA-rich substrates which feed, coordinate growth and supply immunity to remaining body tissue characteristic of species?

*An Answer to the Big Important Question — Plasmacyte RNA*

Probably, the answer is that, following the sequential filtration and processing of exogenous, as well as exogenous antigens in

sinus endothelial cells and macrophages, the plasmacytes of each species initially produce "monoclonal" antibodies and, later, release soluble immunogenic RNA during cytolysis (10). Some of the RNA, initially responsible for plasmacyte production of "monoclonal" antibodies is released by plasmacytolysis and, subsequently, reutilized in large lymphocytes during the S-Phase of DNA synthesis before mitosis to reverse transcribe additional recognition codes into the DNA of large lymphocytes (14). As results, along with other soluble globulins normally produced by large lymphocytes, the progeny of the large dividing lymphocytes extrude soluble polyvalent antibodies reactive toward the new endogenous or exogenous antigen during early stages of maturation. In turn, with nuclear condensation and cytoplasmic depletion migratory "sensitized" SCDL are released to circulate and migrate with their DNA coded for recognition of the new endogenous or exogenous antigen, as well as self. Memory for self, as well as memory for the new antigen is sustained by reutilization of SCDL DNA throughout the lymphatic system characteristic of species *ad infinitum* via the lymph circulation and emperipoletic SCDL which constantly migrate from thence to serve regional and remaining tissues (3,10).

Normally, along with self-serving globulins and SCDL sustained in circulation, the quantities of specifically reacting antibodies and "sensitized" SCDL sustained at given times depend on the potency and persistence of new endogenous or exogenous antigen. If a new endogenous or exogenous source of a noxious antigen (or substance noxious to the inherited genes of the host) persists, high levels of specific antibodies and "sensitized" SCDL are normally sustained in circulation. However, when the noxious antigen source is destroyed or modified, the levels decline to a steady homeostatic state wherein specific antibodies may not be detectable, but  $\pm 1\%$  of circulating SCDL can be shown to reproduce specific antibodies with artificial stimulation *in vitro*; and in *in vivo*

during secondary immune reactions wherein subsequent encounters with the same antigen are greatly accelerated through reutilization of sensitized lymphocytic DNA (10).

It should be emphasized that the plasmacyte role in neoformation of antibodies and sensitized lymphocytes through accurate reverse transcription of DNA in dividing lymphocytes is applicable to all invertebrates, as well as vertebrates, whether or not the latter develop thymus glands, cloacal bursae of Fabricius or bone marrow. Moreover, the plasmacytic role in adding recognition codes to lymphocytes would seem relatively efficient compared with current theories based on antigen selection from randomly mutating genes in inherited lymphocyte DNA characteristic of species. Being dedicated toward diverse homeostatic functions, along with humoral and cellular immunity, one lymphatic system would seem more efficient than separate B- and T- cell systems concerned exclusively with humoral and cellular immunity, respectively; and with each system producing lymphocytes useful for only one defined purpose, even though the inherited DNA of each cell contains 50,000 to 100,000 genes capable of coding for an infinite variety of functional products. AIDS, KS and the CNS

Poor control of diverse infections and control of coordinate cell growth in tissues, along with tissue malnutrition are common findings when genes in the DNA of lymphocytes are randomly and progressively altered by the reverse transcription of HIV-1 RNA into proviral DNA. The spectrum of manifest signs and symptoms vary widely during the acute, latent and terminal stages of HIV-1 disease, probably because of cofactors and the randomness and extent of HIV-1 RNA insertion into the nucleotide sequences of multiple genes contained in lymphocyte DNA over extended periods of time (4).

In terminal stages, malnutrition is commonly reflected in the characteristic wasting of all tissues in infected children and adults. In latent stages before SCDL

depletion, poor control of coordinate cell growth is commonly reflected in dyskeratoses of the skin, Kaposi sarcomas (KS), "B-cell" lymphomas or uterine cervical dysplasias followed by cancer. In the last three, HHV8, EBV and HPV appear to be co-factors, respectively (1), even though HIV-1 RNA is seldom found in the DNA of the tumor cells. It seems relevant that in KS, associated with the use of nucleoside analog inhibitors of nucleic acid synthesis in lymphocytes and adrenal glucocorticoids which lyse SCDL in circulation and in organized lymphoid tissues, the endothelial tumors simply disappear with dosage reduction. During the latent phase, when circulating SCDL are not significantly reduced, but germinal center structures becomes dysplastic (3,4), we may see variety of homeostatic disorders, including nephritis, myocarditis, or failure of marrow to sustain customary output.

The situation in the central nervous system (CNS) seems unique in that during the acute prodromal phase of AIDS, a transient, self-limited form of encephalitis is common wherein glial cells have been observed to produce viral particles. Later, during the latent phase, "B-cell" lymphomas are prone to occur in the periaxonal leptomeninges which normally lack lymphatics, as well as organized lymphoid tissue. However, blood-borne SCDL are normally the only blood cells which invade through the "blood-brain barrier and brain substance to gain access to cerebrospinal fluid. Currently, it seems likely that too many instances of AIDS dementia are being caused by transfection of infected or defective lymphocyte DNA to rapidly dividing glial cells which structurally support and nourish neurons, along with communicating dendrites (3,4,15).

#### *Ignorance vs "Ignore-ance" in the Future*

Basic biologic ignorance persists in the Science of Lymphology. Basic biologic "ignore-ance" persists even more in the Science of Immunology. Therefore, I hope

that your Curriculum on Medical Ignorance (1) will prove infectious, as well as pervasive into the "mainstream" of Medical Science in the near future.

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**Jack W Shields MD, MS, FACP**  
**1950 Las Tunas Road**  
**Santa Barbara, CA 93103**  
**805-965-1638; E-m pgs99jws@aol.com**