

## ***AIDS: IS TRANSGLUTAMINASE THE PRIMARY PERMISSIVE FACTOR FOR HIV ESTABLISHMENT AND SPREAD?***

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The Science policy forum articles on the primary role of HIV in AIDS disease (1) discloses one *major scientific error* on the part of Blattner and colleagues. If Duesberg (1a) claims that the virus is not capable of causing AIDS, he is considering the role of the virus itself. When Blattner and colleagues (1b) claim the virus to be the primary cause of AIDS, they are disregarding any primary permissive physiological state of the body that would allow the virus to infect some lymphocytes or even macrophages. In continuation of these assumptions, in their view, the antibody to HIV becomes a marker of disease progression; a claim that has become confusing to the understanding of the very fundamentals of the immune systems of the body. However, it seems that anti-p24 antibody from healthy individuals with high antibody titre and antigen neutralizing capacity, given to very sick patients, for the duration of its presence in the serum, does clear the antigenemia (2). This reported fact indicates that the presence of antibody to the virus is not a sign of disease progression, *it should not be so pushed, it also becomes confusing to non-AIDS/VIRUS researchers, and is misleading to the public at large.*

Since in the West, AIDS is primarily a disease of an "at-risk" section of the population, with clearly established and con-

tinuously participating "life-style" patterns (3), the physiological influence of the perpetuation of the "life-style" should also become a factor for consideration in this disease. The body has normal physiological shut-down mechanisms for the immune system, for the establishment of which humoral and enzyme factors are manufactured. Otherwise, how will the body survive in its stressful environment of antigens? Within this normal physiological activity of the body, immunosuppressive or immune permissive factors are produced, the very permissive factors that Blattner and colleagues (1b), in their stand on the solely viral etiology of AIDS, have not taken into consideration. They do not entertain the idea that the ongoing "stressful" life-style of the at-risk group may be an important factor in immunosuppression, they only acknowledge a long-term role for the virus in establishment of AIDS. This is where good reasoning and speculation part company.

The following are some proposed physiologically induced permissive common factors that need to be considered when the etiology of AIDS is being researched. For evaluation of any disease condition, a detailed all-encompassing attention to the role of the *milieu interieur* is still important, more so in chronic viral infections. From this angle of view, it

may even be possible to rationalize the diversity of disease conditions for which HIV seems to be made responsible, including the forms seen in hotter climates and poorer countries.

The semen, that contains uteroglobin (UG)-like protein (SV-IV - 4) and transglutaminase (TGE), that seem to render the allograft sperm non-antigenic to the recipient uterus, in all stages of its intrauterine life, (5,4), could possibly also render the antigenic virus non-antigenic to the same immune system that would otherwise have established an immune response to the sperm. TGE is highly immunosuppressive and anti-inflammatory(4,6), *even the glucocorticoid's induced thymic involution seems to be mediated through the activation of the TGE in this gland* (7); lymphocyte proliferation is arrested by TGE (6); TGE seems to transform a non-species specific protein from the seminal vesicle (SV-IV - demonstrated in the rat) that is highly suppressive to the lymphocyte proliferation (4). It has been proposed that TGE is involved in the biochemical pathway of programmed cell death (7); it has been implicated in apoptosis of the cell (demonstrated in the liver cell), altering the cell structure and rendering it "insoluble"(8); these apoptotic cells undergo phagocytosis(7), when phagocytosis of several of the "insoluble" cells must temporarily render the "host cell" multinucleated. This may be the more logical explanation for the mechanism of syncytia formation seen in AIDS, and explained as a virus induced phenomenon (15) In view of the foregoing explanations, it becomes

logical that the vertical transfer of the virus from the mother to the immune-naive fetus - that should inherit immunity from the already immunosuppressed mother, with the same amino acid pool available to the fetus as the composition of the pool in the mother (see below) - will establish without any form of resistance in a similar manner, not because of the aggressive properties of the virus but, because of the permissive state of the naturally suppressed immune system in the mother and the child.

Semen introduced into the mouth or the lower part of the intestine will probably have the same immunosuppressive impact on the lymphatic system as it is naturally designed to do in the reproductive organs of the male and the female of the species (4). Thus, if the use of a condom seems prudent, the reason for its use should clearly identify the immunosuppressive property of the semen!

In hemophiliacs who receive factor VIII concentrate, containing factor XIII, which is a TGE, the same TGE-induced immunosuppression seems to be indicated (9,10,11,12), even before the perceived viral suppression of the host's immune system. HIV seropositive hemophiliacs who die, also have liver disease with AIDS, some of them die from liver disease alone (13).

The primary role of the virus in suppression of the immune system in AIDS is being openly and clearly questioned (14,1a), particularly as the limited number of T cells affected by the retrovirus could not explain the extreme immunosuppression (14,15,19). At the same time, the serum from AIDS patients show consistently (many fold) raised extracellular glutamate

and arginine, and low concentration of methionine and cystine (17). It seems that raised extracellular glutamate concentration can be damaging to the T4 cells (16,17,18). At the same time, the low levels of serum cystine, when conversion of cystine to cysteine by the macrophages is essential to the lymphocyte metabolism (16), signifies an obvious disturbed amino acid metabolism of the body that can constitute a primary cause of the lymphocyte mal-function in AIDS. Unless the AIDS/HIV advocating virologists (1b) can expose a role for the retrovirus in establishment of - a) the abnormal serum amino acid composition and metabolism in AIDS (16,17,18), b) the consistently increased prostaglandin (PGE) production seen in the asymptomatic, as well as in the clinically established AIDS patients (19) - when PGE can stimulate TGE production (20) - when the macrophages of the bone marrow possess "tissue" TGE, while in the presence of raised  $Ca^{2+}$  (PGE induced osteolysis - 22), "tissue" TGE of macrophage origin in the bone marrow (21) is capable of suppressing the immune system at its primary site of the stem cell production, it becomes essential to seriously investigate the "life-style" promotion of stress induced physiology and metabolism in AIDS cases (23). Because, in adventuresome homosexual participation of the introduction of a fist or an arm into the lower intestinal tract, the proposed (23) intestinal stress-induced "tissue cortisone release factor" release could be better reasoned to be effectively capable of establishing all these physiological steps in the direction of the immune system suppression, rather than the imaginatively per-

ceived (1b) role of the virus in immunosuppression in AIDS - and only in the "at-risk" group at that!

One very important issue in AIDS research seems to be the small number of lymphocytes that are infected by the retrovirus at any one time (14,15). Although the trigger mechanism for virus replication is not understood, it seems to be associated with the direct activation of the infected cell; whereas, the virus by itself does not seem to activate the cell into virion production (15). It is naturally understood that the lymphocytic activation is tightly coupled to the immune system activation. Therefore, virion production is also coupled to a generalized immune system activation. Since one of the most important components of the immune system build-up is the simultaneous development of an immune system memory-bank, logically, the immune system education for the newly manufactured cells must also be a part and parcel of the process. The mechanism and the process of virion production by a comparatively small number of lymphocytes seems to find better explanation as a natural component of the mechanisms involved in the immune system memory-bank build-up than a source of immune suppression in AIDS. Extending this explanation, when the immune system becomes gradually suppressed in the group of conditions associated with AIDS, what should be an "educational" antigenemia becomes exaggerated and exposed. Although a tunnel vision concentration on HIV seems to be the vogue, the above logic for the possession of a mechanism of virion production to maintain the memory-bank of the immune sys-

tems of the body could also apply to other viral disease recurrences seen in AIDS.

In drug addicts, the recognition of opiates by the central regulatory mechanism of the body as markers of stress physiology in place of opioid peptides, manipulating the serotonergic system that permissively regulates the delayed feedback inhibition between ACTH and CRF (24), can possibly also promote an uninhibited release of CRF. Since glucocorticoids seem to promote TGE production for their role in thymic involution, the common factor between the permissive state of physiology of AIDS in homosexuals, drug addicts and hemophiliacs seems logically to be the immunosuppressive role of transglutaminase, rather than the direct action of HIV in AIDS.

Since disturbed and excess glutamate metabolism and its neurotoxicity seem to be implicated in some of the more serious neurological disorders (25,26), AIDS-related neurological manifestations could also find a possible and a simpler explanation in the high serum glutamate seen in AIDS patients (16,17,18). As stated, to present the presence of HIV antibody as the marker of the progress of AIDS is inaccurate, all seropositive cases do not develop the clinical disease. To present The AIDS associated Kaposi's sarcoma (KS) as a virally caused clinical stage of the disease is inaccurate too. Delli Bovi and associates (27) report of AIDS-associated KS cases that presented chromosomal abnormalities and yet did not demonstrate the presence of HIV's DNA sequence in their KS cells. Both the sporadic KS and

the AIDS-associated KS cells are dependent on platelet derived growth factor (PDGF - 28). When there is no HIV genetic marker in the KS cells of some patients, and the KS cells demonstrate a dependence on the paracrine influence of PDGF, then, other operative factors than the direct immunosuppressive influence of HIV as the primary cause of KS should be investigated. In hemophiliacs who are thrombocytopenic (13), KS does not seem to be a form of presentation of AIDS.

To continue to allocate a dominant role to HIV in all pathological conditions that, at some time or another, in some cases, have also demonstrated markers of having come across the virus is also a marker of bankruptcy of scientific reasoning, particularly when the majority of the "at-risk" group so openly belong to a "life-style" participating sector of the society. How can it be justified that the disparity of the chemistry of the constantly determined "life-style" practitioners should not be investigated and yet the investigation of a viral causative factor, in so many different conditions, be so conclusively advocated? After all, if the camel had a back-breaking point to the weight of the last straw, surely the human body must also have a breaking point to being "life-stylishly" loaded. *Do we measure the straw or the inherent structural/physiological limitations?*

**Key words:** AIDS, Transglutaminase, Stress.

**References:**

- 1) Policy Forum, a) Duesberg, P.; HIV Is Not The Cause Of AIDS, PP.514- 516; b) Blattner, W.; Gallow, R.C., and Temin, H.M.; HIV Causes AIDS, PP. 515,517; Science, Vol. 241, 29 July 1988.
- 2) Jackson, G.G.; Rubins, M.; Knigge, M.; Perkins, J.T.; Paul, D.A.; Despotos, J.C. and Spencer, P.; Passive Immunoneutralisation Of Human Immunodeficiency Virus in Patients With Advanced AIDS; The Lancet, PP. 647- 652, September 17, 1988.
- 3) Fischl, M.A.; Dickinson, G.M.; Scott, G.B.; Klimas, N.; Fletcher, M.A.; and Parks, W.; Evaluation Of Heterosexual Partners, Children, and Household Contacts Of Adults With AIDS; JAMA, Vol, 257, No. 5, Feb. 6, 1987.
- 4) Metafora, S.; Peluso, G.; Persico, P.; Ravagnan, G.; Esposito, C. and Porta, R.; Immunosuppressive And Anti-Inflammatory Properties Of A Major Protein Secreted From The Epithelium Of The Seminal Vesicles; Biochemical Pharmacology, Vol. 38, No. 1, PP. 121-131, 1989.
- 5) Mukherjee, A. B.; Cordella-Miele, E.; Kikukawa, T. and Miele, L.; Modulation Of Cellular Response To Antigens By Uteroglobulin And Transglutaminase; Adv. Exp. Med. Biol, 231, PP 135-152, 1988.
- 6) Porta, R.; Esposito, C.; Persico, P.; Peluso, G. and Metafora, S.; Transglutaminase-catalyzed Crosslinking Of An Immunosuppressive And Anti-inflammatory Protein Secreted From The Rat Seminal Vesicles; Adv. Exp. Med. Biol, 231, PP. 153-160, 1988.
- 7) Fesus, L. and Thomazy, V.; Searching For The Functions Of Tissue Transglutaminase: Its Possible Involvement In The Biochemical Pathway Of Programmed Cell Death; Adv. Exp. Med. Biol, 231, PP 119-134, 1988.
- 8) Fesus, L.; Thomazy, V.; Autuori, F.; Ceru, M.P., et.al.; Apoptotic Hepatocytes Become Insoluble In Detergents And Chaotropic Agents As A Result Of Transglutaminase Action; FEBS Lett. 245, 1-2: 150-4, March 13, 1989.
- 9) Ablin, R.; Transglutaminase: Co-factor In Aetiology Of AIDS; The Lancet, PP. 813-4, April 6, 1985.
- 10) Ablin, R.; AIDS: A Noncommunicable Cofactor: Jama, Vol.253, No. 23, PP.3398-9, June 21, 1985.
- 11) Ablin, R.J. and Bartkus, J. M.; Impaired Cell-Mediated Immunity In Hemophilia: Suppression Of Natural Killer Activity By Factor VIII; The Journal Of Laboratory And Clinical Medicine, Vol. 107, No. 4. PP. 396, 1986.
- 12) Lederman, M. M. and Ratnoff, O. D.; letter, The Journal Of Laboratory And Clinical Medicine, Vol. 107, No. 4. PP. 396-7, 1986.
- 13) Eyster, M.E.; Gail, M.H.; Ballard, J.O.; Al-Mondhiry, H., and Goedert, J.J.; Natural History Of Human Immunodeficiency Virus Infection In Hemophiliacs: Effect Of T-Cell Subsets, Platelet Count, And Age; Annals Of Internal Medicine, 107 (1): 1-6, July 1987.

- 14) Duesberg, P. H.; Retroviruses As Carcinogens And Pathogens: Expectations And Reality; *Cancer Research* 47, 1199-1220, March 1, 1987.
- 15) Fauci, A. S.; The Human Immunodeficiency Virus: Infectivity And Mechanism Of Pathogenesis; *Science*, Vol. 239, PP. 617-622, February 5, 1988.
- 16) Droge, W.; Eck, H-P.; Naher, H.; Peker, U. and Daniel, V.; Abnormal Amino-Acid Concentration In The Blood Of Patients With Acquired Immunodeficiency Syndrome (AIDS) May Contribute To The Immunological Deficit; *Biol. Chem. Hoppe-Seyler*, Vol. 369, PP. 143-148, March 1988.
- 17) Eck, H-P.; Gmunder, H.; Hartmann, M.; Petzoldt, D.; Daniel, V. and Droge, W.; Low Concentrations Of Acid-Soluble Thiol (Cysteine) In The Blood Plasma Of HIV-1-Infected Patients; *Biol. Chem. Hoppe-Seyler*, Vol. 370, PP. 101-108, February 1989.
- 18) Eck, H-P. and Droge, W.; Influence Of The Extracellular Glutamate Concentration On The Intracellular Cyst(e)ine Concentration In Macrophages And On The Capacity To Release Cysteine; *Biol. Chem. Hoppe-Seyler*, Vol. 370, PP. 109-113, February 1989.
- 19) Edelman, A.S., And Zolla-Pazner, S.; AIDS: A Syndrome Of Immune Dysregulation, Dysfunction, And Deficiency; *FASEB J.*, 3: 22-30, 1989.
- 20) Ishitani, K.; Ogawa, S., And Suzuki, M.; Influence Of Arachidonic Metabolism On Enhancement Of Intracellular Transglutaminase Activity In Mouse Peritoneal Macrophages; *J. Biochem.* 104, PP. 397-402, 1988.
- 21) Roth, W.J.; Il Chung, S.; Raju, L. And Janoff, A.; Macrophage Transglutaminase; Characterization Of Molecular Species And Measurement Of Enzymatic Modification By Cigarette Smoke Components; *Adv. Exp. Med. Biol.* 231, PP. 161-173, 1988.
- 22) Jaffe, B.M.; LaRosa, C., And Kimura K.; Prostaglandin And Surgical Diseases: Part I and II, *Curr. Probl. Surg.*, 25 (10), PP. 673-747, Year Book Medical Publishers, Inc. 1988.
- 23) Batmanghelidj, F.; Pain: A Need For Paradigm Change; *Anticancer Research* 7, 971-990, 1987.
- 24) Gailard, Rolf-C. And Al-Damlugi, S.; Stress And The Pituitary Adrenal Axis; *Ballier's Clinical Endocrinology And Metabolism*, Vol. 1, No. 2, PP. 319-354, 1987.
- 25) Pearce, R. B.; Palmer, A. M.; Bowen, D. M.; Wilcock, G. K.; Esiri, M. M. And Davison, A. N.; Neurotransmitter Dysfunction And Atrophy Of The Caudate Nucleus In Alzheimer's Disease; *Neurochemical Pathology*, Vol. 2, PP. 221-232, 1984.
- 26) Olney, J. W. And Taisija de Gubareff; Glutamate Neurotoxicity And Huntingtons's Chorea; *Nature*, Vol. 271, PP. 557-559, 9 February 1978.
- 27) Bovi, D.P; Donti, E.; Knowles II, D.M.; Friedman-kien, A.; Luciw, P.A.; Dina, D.; Dalla-Favera, R., And Basilico, C.: Presence Of Chromosomal Abnormalities And Lack Of AIDS

Retrovirus DNA Sequence In AIDS-Associated Kaposi's Sarcoma; *Cancer Research*, 46, 6333-6338, December 1986.

28) Roth, W.K.; Werner, S.; Schirren, C.G. And Hofschneider, P.H.; Depletion Of PDGF From Serum Inhibits Growth Of

AIDS-Related And Sporadic Kaposi's Sarcoma Cells In Culture; *Oncogene*, 4, 483-487, 1989.