

AIDS: The Dead-End Of Virus Etiology

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Abstract: The news from AIDS research reveal a totally new angle to the disease. An analysis of data, from extensive research results, establish the disease as a primary stress-precipitated metabolic disorder instead of its proclaimed retroviral infectious origin (9). The initiating factor in this metabolic vicious circle can be argued to be the effect of prolonged reliance on glutamate dominated metabolism and its effect on cysteine functions in the body. Cysteine deficiency and its complex role in the DNA-binding proteins by the formation of "zinc fingers," "zinc clusters" and "zinc twists" seems to precede any HIV replication activity. The imbalance in the amino acid composition of the body for the duration (up to ten years from the recognition of the retrovirus to clinical AIDS) is the cause of a "total system" transition and the precipitating factor for clinical AIDS and the DNA/RNA fragmentation demonstrated and assumed to be the HIV in some cells of the body. It seems, the "HIV particle," a fragment of DNA/RNA of a cell-type in the early process of disintegration, is itself a product of cysteine (and possibly zinc) deficiency in the body. It seems not to be the cause of AIDS, but is itself produced by the severe stress-induced metabolic disorder that AIDS is.

Key Words: AIDS, HIV, Tumor Necrosis Factor, IL-1, IL-6, DNA / RNA fragmentation, CRF, Cysteine, Zinc Fingers, Amino Acid Imbalance.

Current Assumptions

As a result of the direct influence of TNF and IL-6 in the "infected cell" cultures, cell membrane buds identified as HIV are produced by the cell line (1,2). The justification of claims for AIDS having a viral etiology seems to hang on the visual observation of "virions" produced by the infected cells, and that as a result of the direct "inducement" action of IL-6 and TNF (1,2). These laboratory observations form the support argument for the claimed viral etiology of AIDS.

From the same cell culture experiments, it is also apparent that low cysteine concentration in the medium is permissive of a marked rise in the rate of virus replication by HIV inducers, tumor necrosis factor-alpha (TNF - 1,2), interleukin-6 (IL-6 - 2) and phorbol 12-myristate 13-acetate (PMA - 1,2). The addition of N-acetyl-L-cysteine (NAC), Glutathione (GSH) and glutathione monoester (GSE) to the HIV infected cell culture medium, depending on the concentration, strongly suppress the HIV expression at multiple stages of the HIV activation process (2).

Metabolism and AIDS

It has been noticed that AIDS patients are highly deficient of the amino acid cysteine. Dröge and Associates, have shown a markedly decreased cysteine and methionine and an equally disproportionate rise in glutamate concentration in the serum of AIDS patients. (3,4,5). Raised glutamate competitively inhibits the transport of cystine across the cell membrane (3,4). Cystine that passes

through the cell membrane is converted to cysteine in the macrophages and is released (4,5). There is indication that the cysteine deficiency may arise from the raised glutamate's competitive inhibition of cystine transport across the cell membrane, and the consequential decreased conversion of cystine to cysteine. This glutamate inhibition of transport can affect macrophages, fibroblasts and hepatocytes (4). The hepatocytes can biosynthesize cysteine from methionine, but macrophages and other cells can not (5). On the average, the serum of patients with overt AIDS contains markedly reduced concentration of cystine and methionine (3).

The above experimental results indicate that the future research on AIDS should benefit from the wider attention of microphysiologists and the metabolism chemist to fathom the onset and the long-term implications of cysteine, cystine and methionine deficiency and high serum glutamate and arginine seen in AIDS (3,4,5). Further, these statements have a more important transforming impact on the future of medicine as a science-based discipline of thought. Assuming that the virologists who have the attention of the world for a promised solution to AIDS will show prudence, and refrain from presenting the virus as the causative factor for the amino acid imbalance in AIDS, the above research results will prove to have supported the need for adherence to the exposed paradigm change in medicine (6).

It is now possible to further argue in favor of a primary amino acid imbalance as the main factor in the retrovirus formation in AIDS. Depending on the direct impact of the duration and the extent of cysteine, cystine, methionine, and other amino acid deficiencies and unbalanced metabolism, the problem presents itself as an extremely disrupted "system" disturbance (6,8) instead of HIV "particle" effect - a "stress-induced" metabolic disorder instead of a viral disease - a life-style stress-induced metabolic disorder for some special sector of the society (8,9).

When the two natural physiological products of body function, IL-6 and TNF can induce virus replication and a recognized amino acid can prevent the *in vitro* replication of the same virus, and this process could represent a normal body activity, logic seems to point to a natural mechanism for the retrovirus replication in the body's complicated immune system. It has been proposed that the retrovirus replication in the lymphocyte is a natural phenomenon within the memory bank of the immune system of the human body (7). Even a means of "batching" of the antigen stimulation of the immune system memory bank seems to exist (8).

Although it is now known that cysteine can arrest HIV replication in chronically HIV infected cells, the more significant importance of cysteine to cell function is its role in DNA assembly. Cysteine is essential to DNA-binding protein domain because of its almost unique functional role in the formation of "zinc fingers," "zinc clusters" and "zinc twists." Zinc clusters and zinc twists are distinctive motifs in DNA-binding proteins containing multiple zinc atoms (10). Many proteins and enzymes depend on the zinc binding property of cysteine for their normal function. The family of receptor proteins that bind glucocorticoid hormone, thyroid hormone, retinoic acid, mineralocorticoids, androgen, progesterone and others, possess repeats of four, six, eight, nine to ten conserved cysteines and one or two zinc residues in their amino acid sequence. The zinc-nucleic acid binding domain is said to consist of repeats of four or more cysteines (some times with histidine) attached to the zinc in a sequence of other amino acid spacers that constitute the binding protein (10).

If the steroid hormones directed metabolism of the body is dependent on the efficiency of their respective receptors' function, the level of cysteine and zinc incorporation into the receptor protein production could become a limiting factor in conditions predisposed to cysteine metabolism

disturbance. The mineralocorticoid, progesterone and *androgen receptors'* efficient functional activity is essential to normal sex differentiation and growth. The loss of sexual dominance and participation in the life-style that predisposes to AIDS may be the consequence of an initiating disturbed amino acid metabolism that also includes cysteine and possibly zinc loss. Thus, cysteine deficiency in AIDS patients is the tip of the iceberg of a protracted stress-induced metabolic "system disturbance." It may be responsible for the attraction to homosexual life-style, with the consequential precipitation of progressive immunodeficiency complications.

On the average, the "incubation period" from the time of initial serum conversion to AIDS manifestation seems to be about 10-11 years. This lag-time between the identification of the viral antibody to the clinical stages of AIDS is a further indication that the initial cause of the condition is not the virus. The associated amino acid imbalance can more easily cause death in AIDS than the virus. Thus, the assumption that the retrovirus is directly responsible for AIDS, particularly when the addition of even one of the deficient amino acids can efficiently suppress its *in vitro* replication, proves to be devoid of scientific logic.

The Natural Role of Cytokines TNF, IL-1 and IL-6

The assumption that TNF and IL-6 are HIV replication inducers in the HIV infected cell line cultures (1,2), and the particular extrusion particle these inducers are producing in a cysteine deficient culture medium is the agent that causes AIDS does not seem to be accurate. This premise does not reflect on the known functions of TNF, even if less is known about IL-6 as a regulator of an intracellular messenger mechanism.

Trauma by itself causes a release of a certain group of cytokines into the wound. Interleukin-1

(IL-1), IL-6, macrophage colony stimulating factor and TNF are secreted into the wound to promote repair and remodelling of the site of trauma. Wound fluid inhibits interleukin-2-dependent cell lines - inhibitory to thymic lymphocytes mitogenesis (11,17). Sepsis in the wound augments TNF production even at the same time there is an elevated rate of Prostaglandin-E2 (PGE2) production (12). PGE2 does not inhibit TNF production by the monocytes, even if PGE2 is known to inhibit the immune system (12). TNF induces an enhanced production of PGE2 by some cells (14).

The patients suffering from AIDS and the associated conditions have high levels of endogenous TNF/cachectin in their serum compared to those with asymptomatic HIV infection. Mixed infections seem to further promote TNF production (13). It must also be presumed, in the routine act of homosexual gratification, the established pattern of frequently produced local tears and tissue injury - the result of *permissive intestinal pumping (lacking acute nociception)*, fisting and other forms of homosexual behavior of the vast majority with AIDS - predisposes to the production of TNF and the other cytokines for the establishment and integration of the tissue repair system at the site of the digestive tract damage. The unavoidable superimposition of infection at the damaged site will further enhance the cytokines production.

Cachectin and TNF factor seem to be homologous molecules with identical properties (14). They have the same bioactivities that are derived from the same protein. They seem to promote a wasting of tissues; and in mice, at certain microgram concentrations can even kill within days or even hours (14). Cachectin/TNF and lymphotoxin share a common receptor. These receptors are involved in the process of cellular DNA fragmentation, demonstrated by the *in vitro* cytolytic property of both cachectin and lymphotoxin (14, and the references therein).

The process of DNA/RNA fragmentation by

lymphotoxin/TNF receptor stimulation involves an endonuclease that cleaves the DNA at regular intervals (15). The process lacks antigen specificity and does not require Ca^{2+} (15). The process of fragmentation results in the release of discretely sized DNA fragments from the cell (15). Even recombinant-derived TNF can cause DNA release from the target cells. The fragmentation seems to begin by nuclear membrane breakdown (15). Another aspect to the action of TNF in the process of DNA and RNA fragmentation seems to point to the initiation of oxidative attacks and release of lysosomal proteases (16). The apparent antioxidant action of cysteine in the cytosol seems to point to a reduction of TNF toxicity (17).

Although not much is known about the role of IL-6 as an intracellular messenger with receptors on the nucleus, there seems to be indication that it can cause DNA depletion or damage (18). Culture of pancreatic islet cells in the presence of (5000 picogram/ml) of IL-6 for 48 hours decreased the DNA content of the islet cells (18). This DNA depleting property of IL-6 seems to be time-dependent. No such damage seems to occur for the first 18 or so hours. The damage to DNA, in this *in vitro* experiment on the rat pancreatic islet cell line, seems to become measurable after a set period of time (18). The pancreatic islet cells in culture lose DNA substance and are not able to secrete insulin. Although IL-1 also has an effect on pancreatic B cells directly; however, it is now considered that its main action is mediated through IL-6 activation (18).

IL-6 and TNF have complementary effects on one another (22). They seem to have an autocrine/paracrine mode of function. IL-6 seems to enhance its own production, a function needed for immunoglobulin production (22).

According to Hasselgren and associates (25), the current concepts on amino acid turnover in times of stress is that IL-1 and TNF (in turn IL-6 stimulated by the latter cytokines) are involved in bringing about a breakdown of muscle mass and

the delivery of its amino acid products to the liver - a catabolic process for the large muscle mass and an anabolic process for the liver - for the production of new enzymes and protein products. It has been proposed that a split product of IL-1 is able to promote the breakdown of muscle proteins (25).

Trauma and β -Endorphin

IL-1 promotes the production of cortisone release factor (CRF); at the same time, cortisone release factor promotes the secretion of IL-1. The process seems to reflect a magnifying effect of one mediator on the release of the other - an autocrine/paracrine process (24,23). A very important by-product of the sequence of events between CRF and IL-1 is the IL-1 activation of B lymphocytes to secrete β -endorphins into the mesenteric lymph nodes and the spleen (24). This relationship between the traumatization of the lower intestinal tract and the secretion of cytokines, among them IL-1, and eventually the endorphin production may well be the addictive lure to the homosexual life-style. It begins with a simple rectal intercourse and graduates to the more advanced stages of damage by the introduction of the fist or the arm through the rectum.

So far, by presenting AIDS as a viral disease, although it is so obviously prevalent in homosexuals and drug addicts, the extreme burden of finding an urgent magical and medical solution to AIDS has been passed on to society. To justify the concentrated attention of research of a virus in AIDS, the cardinal rules of immunology have been twisted 180 degrees. Now and only in AIDS, the presence of HIV antibody is pushed as a sign of the eventual clinical disease. The same assumption, that the recognition of HIV antibody in heterosexuals is also a sign of future AIDS, exposes a large sector of the population to the devastation of anxiety stress. The homosexuals and the drug addicts have been further exposed by the belief that it is the virus and not the primary impact of their life-style that contributes to the various clin-

ical manifestations of AIDS.

Now, even boxers and football players, who become traumatized in the process of sports, and because some blood is passed from their cuts and bruises, are not exempt from having to be tested for HIV lest they become infective! Whereas, the tissue products of the local trauma will naturally bring about the secretion of some cytokines, including TNF, IL-1, IL-6 and TGF. The natural effect of these agents will encompass some DNA/RNA fragmentation in the process of tissue repair and its remodelling. Naturally and quite possibly, some of these people can test positive for HIV, if the *in vitro* effect of TNF and IL-6 is judged (1,2) to be HIV replication.

Discussion

According to the above discussion, both TNF and IL-6 have been demonstrated to attack and damage the DNA structure of cell line in *in vitro* experiments. To present DNA fragmentation and fragment extrusion in similar *in vitro* experiments as indicators of virus replication, in the process of scientific inquiry by well placed scientists, whose words can affect the lives and the fears of people all over the world, leaves much to be desired.

The sooner the need for a shift of research from its viral "dead-end" is accepted, the sooner the vast ramifications of AIDS can be addressed as a physiological/metabolic disorder (6,8,9). It should now be possible to address the issue of life-style as a probable primary cause of AIDS in the at-risk sector of the society (6,7,8,9). This fact stares us in the eye, we need to acknowledge it and admit a failure of virus research in AIDS. It also becomes academic who first discovered the "HIV," or even who has the right to its patent and the test-kit rewards. An argument that the retrovirus is a fragmented portion of a replicating gene that replicates incomplete products because of cysteine and possibly zinc deficiency, and can break in more ways than one is now possible.

It is even possible that the mechanism of fragmentation or cleavage of DNA material may involve the messenger RNA. If we consider the action of a mRNA is a form of reverse transcription, then the "AIDS retrovirus" produced by TNF or IL-6 in cell cultures may be a segment of cleaved mRNA, or even an incomplete product of DNA manufacture because of cysteine deficiency. The idea that viruses are "jumping genes" is not new. It is also interesting to note that IL-1 produces a depression of serum zinc and iron levels in addition to causing the catabolism of peripheral proteins (21).

Thus, the process of zinc absorption and its incorporation into the DNA binding proteins, as well as steroid receptor proteins, including the androgen receptors, becomes depressed. The consequences of protein breakdown and the decreased manufacture of receptor proteins will gradually - and in time - produce a "system" imbalance that will eventually become irreversible, if the human body is continuously exposed to the extremely drastic and brutal stresses of the particular life-style of homosexual behavior, or even drug addiction.

It is now becoming clear that different sub-set of lymphocytic cell population in blood circulation are also capable of manufacturing and secreting of some of the recognized neurotransmitters, among them IL-1 and histamine (19, 9, 26). The production of these neurotransmitters and active peptides by the single cells in blood circulation must be a part of a natural design that can deliver the same neuropeptides and cell function regulators at the sealed-off site of local inflammation, septic or sterile.

It is also worthy of note that vasopressin action depends on its cysteine residues. Also, a component of antigenic epitope of HIV and T-cell leukemia viruses have common factors to the rat and human hormone vasopressin-neurophysin (20). This close antigenic similarity makes the production of a viral vaccine difficult (20). At the same

time, is it at all possible that DNA/RNA fragmentation, in the so called HIV infected cell lines, is in effect taking place on a segment of mRNA for vasopressin manufacture; or alternatively, the stimulus for vasopressin production results in an incomplete manufacture of cysteine deficient products? This in effect may be the reason for "HIV" "replication" in a cysteine deficient culture medium. Whereas, if cysteine is added to the culture, HIV is not replicated. It would be interesting to find what happens to the cysteine; does it become incorporated into another primary protein product of the cell in culture?

What seems to become more clear than ever before is that HIV as a primary cause of AIDS seems to be no more than a myth of science. The amino acid metabolism disturbance of the body seems to precede the virus as a primary cause of the disease. Although some scientists in AIDS research are now proposing to market some amino acid products for release of cysteine with which to treat AIDS patients, they must also be aware that one single amino acid taken in capsule form will not alter the gross problems associated with the total amino acid pool imbalance, even if the condition presents itself with the deficiency of one or another amino acid that one sees in AIDS.

The accent in the presentation of information on AIDS seems to be on the transfer of HIV through blood or blood products transfusion. If cysteine is the stabilizing factor in HIV replication, then what becomes transferred may be another "split product" that regulates the stress-induced amino acid metabolism of the body. It could not be HIV itself when in the presence of cysteine it is not "replicated." *The "HIV" itself is a "product" of cysteine deficiency.* What we need to find is what causes the amino acid imbalance to the extent that "HIV" particle is produced. The sum total effect of TNF, IL-1, IL-6, CRF, ACTH, histamine, Ca²⁺-dependent proteases, and more, all of them "stress-induced, if constantly invoked, can bring about an ever-expanding "system" malfunction that will

result in a group of clinical conditions now identified as AIDS. The more bizarre, "it" is now considered to be caused by one of the products of the system disorder itself.

While the above arguments are presented against the virus as the primary causative factor in AIDS, and the wealth of information seems to point in that direction, there is a remote possibility that the particle labeled as HIV may be an active component of the vasopressin hormone. Since the amino acid sequence of the DNA/RNA fragment known or labeled as "HIV" has an antigenic similarity to vasopressin (20), and vasopressin has strong CRF properties (6,8,9), it may be possible that the "fragment" in question may retain the CRF properties recognized in vasopressin.

However, even if this "particle" has CRF properties, nothing changes. It is still the amino acid imbalance that produces the clinical picture of AIDS; and it is still the life-style that brings about the drastic changes in the amino acid pool composition that permit the production of the DNA/RNA fragments that may retain some physiological activity.

The mutually activating and enhancing relationship of IL-1 and CRF (see Receptor Down-Regulation in this volume), and eventually the promotion of IL-6 production, which has a self-perpetuating property, may well be implicated in the production of a strong and "long-acting CRF." Brodish and Lymangrove (27,28) demonstrated that a form of "long-acting tissue CRF" is produced in the rat after one minute's "stressing of its intestines." This "long acting tissue CRF" is transferable through blood or serum (27,28). Thus, in an already "stressed" person, with some amino acid metabolism disturbance, the transfer of a long-acting tissue-CRF through blood or serum products, until the "cascade" is turned off physiologically, may produce a series of "one-way" *catabolic* processes that can possibly and eventually result in cysteine and methionine deficiency.

The positive HIV test may well become an indi-

cator of amino acid metabolism disturbance in the body, particularly cysteine, cystine and methionine, rather than the present indicator of a viral disease.

Recently, the media are reporting on the infection of patients by an HIV positive dentist. The above rationalization of AIDS can still apply.

Dental "work" is a most traumatic routine procedure on the jaw bones. If carried out repeatedly and in a short span of time, the remodelling of the bone will produce the necessary stimulus for secretion of the "repair cytokines." If the patient is already stressed by other social and emotional factors, and has already established an ongoing catabolic pattern of metabolism, the net catabolic action of the "repair cytokines" will superimpose, and there will be an enhanced run on the amino acid pool of the body. If the patient is unfortunate and has developed an aberrant subpopulation of post-trauma monocytes with an autocrine/paracrine sensitivity for the secretion of IL-6, TNF, TGF and PGE₂ (26), the cycle of events will continue to produce a breakdown run on the protein pool in the body. The final blow is the news that the dentist dies of AIDS and the patients are advised to test for HIV infection. Since the DNA/RNA fragmentation under the physiological influence of IL-6, IL-1, TNF and CRF is a part and a parcel of protein recycling processes in the body, and the HIV test that is designed to demonstrate the presence of the DNA/RNA fragments known as HIV, the test may show a positive reaction.

Under the influence of all the misinformation that has been generated on the primary role of *HIV as an agent of death*, even in the heterosexuals, the news of the positive HIV test will become the last emotional straw that will break the back of any defense the body may have had until the "news." Under these possible situations, the underlying physiological state of the body, and its already stretched protein metabolism will predispose to the ultimate consequences of extreme

stress-induced metabolic disorder that AIDS seems to be.

It seems, IL-4 is able to break the autocrine/paracrine cycle of cytokines production by the aberrant post-trauma monocyte subpopulation (26). This method of treatment should be investigated in AIDS patients. It may prove to be a more naturally effective way of treatment for AIDS, particularly in the heterosexuals.

Conclusion

The primary cause of AIDS epidemic in our advanced society, where there is sufficient food and shelter - particularly for the social stratum now afflicted - is a "stress-induced metabolic system disorder," brought about by the life-style of the AIDS patients (6,7,8,9). The only way to deal with the problem is through education and life-style change. To perpetuate any other approach to this national and international problem so as to secure easier funding or to support socio/political aims will expose the public to further unnecessary anxiety and fear. It will render those predisposed to substance abuse, or to succumb to the lure of the homosexual life-style more vulnerable and prevent them from becoming responsible for their own ultimate care.

For the sector of any society where the level of real-life stresses are high, with shelter and food deprivation, when other infectious diseases are prevalent, the stress-induced amino acid imbalance can similarly produce the type of damage that one sees in AIDS. To postpone the address of this issue until a viral vaccine is discovered may not be a long-term humanitarian measure.

Thus, a simpler way to deal with AIDS would be the establishment of a physiological turnaround of body metabolism from a catabolic to an anabolic mode of protein metabolism. *It seems, it is the continuous body proteins' breakdown that*

constitutes the disease we have labeled as AIDS (6,7,8,9).

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