AIDS -- INDICATORS OF A STRESS-INDUCED METABOLIC DISORDER

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***ABSTRACT**: Although the total attention of AIDS research is directed toward its predicted viral etiology, the intestinal stress and tissue cortisone release factor induced physiology of the body, over a long period of time, and dependent on the mode and frequency of homosexual practice, can possibly be the precipitating cause of this condition. It is proposed that in homosexuals, AIDS is an intestinal stress induced metabolic disorder and, opioid peptides being markers of stress to the regulatory systems of the body, excessive use of opiates can possibly cause an indirect promotion of stress physiology that can bring about the associated immune system inhibition and disturbance.*

***KEY WORDS**: AIDS, intestinal stress, amino-acid metabolism, glutamate, histamine, retrovirus, homosexuality, transglutaminase, prostaglandin, hypercalcemia.*

PRESENT STATUS: The media treatment of an immune system dysfunction among homosexuals and drug addicts has served notice on the scientists in medicine for a very speedy solution to the problem, lest the human race would soon become extinct. The doom's day predictions that the unknown precipitating factor would affect large sectors of the population of the world precipitously, prompted researchers to concentrate on the identification of a viral causative factor. Upon the prediction that the disease could only be caused by a virus, when a virus was seen in some of the cells of the affected persons, without least hesitation, it has been assumed that the virus is the cause of the disease. Accordingly, the presence of the antibody has become the marker for the presence of the disease, further complemented by an abnormality in the number and the ratio of the T4/T8 lymphocytes. The presence of the virus genetic markers is sought in the host's DNA as a confirmation of the disease.

Based upon these summary assumptions, the presence of the antibody to the HIV in the blood of individuals, even heterosexuals, has become a social stigma and a sentence of slow and painful death. As the diagnostic tests have been developed and made available in increasing quantities, so has the number of antibody positive people among the general population. The disproportionate number of deaths to viral presence in the body of the tested people, who show no apparent sickness, has disproved the predictions of a worldwide rise in AIDS deaths. There has not been any sign of AIDS epidemic among heterosexual virus antibody positive people either. Now the advocates who still consider AIDS to be caused by retroviruses claim the disease to be a slowly developing phenomenon. The consideration that the virus is the primary cause of AIDS pathology and eventually death has been based on an assumption and a jump of faith; it has not been proven accurate, even when so much research has been conducted within this approach to the problem. The proposed viral etiology

needs to be revised and other views given a chance to emerge and be tested.

DISCUSSION

The arguments against the virus etiology by the lucid explanation are; a) the HIV's genetic structure is incapable of causing so much damage and such variation of pathology classified within the AIDS syndrome; b) that the presence of antibody to the virus is an indicator of host's defense system function and not a sign of the disease progression in the distant future when a fully established death inducing pathology will emerge (1); c) during many years of research for the etiology of cancer transformation of tissues in the body, the same retroviruses have been extensively investigated as a causative factor, that the same retrovirus would cause cancer in some and AIDS in others and yet remain silent in a vast majority of cases is in itself a very strong indication that the virus is not the initiating cause of these diseases (1). An extensive review of AIDS research seems also to expose the weaknesses in the argument in favor of a Viral etiology of AIDS (2). The same viruses that have been implicated in less serious conditions, that are now being proposed as the cause in AIDS, have been presented as opportunistic infections (3); and the ratio of T4 to T8 can change in any other type of prolonged infection or antigenic stimulation without it being solely an AIDS marker (3). Kaposi's sarcoma (KS), although seen in older age persons of Ashkenazi Jewish ancestry, and in the elderly men throughout eastern Europe, and among people of Mediterranean descent, and eventually recognized as a very common condition in Africa, also seen in renal transplant recipients, has now been classified as a component of AIDS condition because its epidemic form is seen in homosexual men but, less so in drug users (4). Since the retrovirus DNA sequence is not necessarily found in this condition (5), the proposed primary viral etiology of this condition must also be considered to be unlikely. Zolla-Pazner and Edelman have proposed that there is an active immune suppression as a primary factor prior to the HIV's effect on the T cells and the precipitation of the immune system dysregulation subsequent to immune system stimulation, rather than immune deficiency (6). This observation seems to find its explanation in the function of PGE-induced tissue transglutaminase activity of the macrophages, particularly in the bone marrow (in this volume). Levy and Zeigler (3) are of the opinion that KS results from secondary immune stimulation.

If the number of people who are HIV antibody positive is increasing and yet the number of AIDS deaths is not demonstrating the same rate of increase (1), and if KS is not a new disease, the DNA sequence of HIV is not seen in some of the KS conditions (5), and KS, in its epidemic form, is seen in homosexuals, then, the common factor to all these conditions is a very rapidly deteriorating physiological steady-state situation precipitated by the habits of the homosexuals and drug users, further embarrassed by the associated infections, for which the virus has caught the limelight;

whereas, the deaths are actually a direct consequence of other gross infections.

Batmanghelidj has proposed that AIDS research should take into consideration that to *a homosexual act* there is an element of intestinal stress; that the physiology of stress, Fig.1, in the body is the background to the immune dysregulation in the group of conditions now classified as AIDS (7). It is true that homosexuality has existed throughout history, but it had never been an openly practiced, exaggerated and socially accepted form of life. The frequency of insults to the intestine, in the way described in the book by Adams (2), is not the understanding of the average scientist in the field of research from the word "homosexuality." It is certain, if the modes and frequency of such practices, with or without the intake of the recreational drugs for their pleasure enhancing effects, become fully investigated within the concept of the disease, the effect of the probable gross intestinal traumatization will dictate its investigation instead of the magnified effect of the virus.

Other than the normally recognized neural or hypothalamic pathway for cortisone release factor (CRF) release, there is "a" form of tissue cortisone release factor that has a delayed, strong and prolonged ACTH releasing effect (8,9,10,11). Brodish (9) has shown that stressing the intestine, by its limited handling in the rat, produces a delayed long acting tissue CRF. Logically, to the repeated insults and traumatization of the intestine in homosexual practices, by the introduction of a fist, an arm or other objects, there is a stress component and a continuous long acting tissue CRF release should be anticipated. Depending on the frequency and the type of insults involved in the relationship, the drive on the body's steroid production and release will undoubtedly establish the physiology associated with the effect of high steroid imposed metabolism, Fig. 2. There is a direct thymus-adrenal connection. Glucocorticoids have immunomodulatory effects, a high concentration of which can induce thymic involution, reduce mitotic activity in T cells and phagocytic activity of leukocytes. Lower concentration of glucocorticoids can enhance their activity (12). The effect of continuous and increased production of steroids in induction of tryptophan oxygenase and tyrosine aminotransferase in the liver can possibly deplete the body's reserve of these amino acids (13). Central to the chemistry of gluconeogenesis in the body, brought about by glucocorticoids, is the increased metabolism of amino acids; the pathway to such metabolism involves glutamate and its secondary products, glutamine, gamma- aminobutyrate (GABA, a central nervous system inhibitory neurotransmitter and an inhibitor to cells possessing its receptors), proline (in plants it accumulates as an adaptive phenomenon to drought, it is involved in osmoregulation and in energy requirement of muscle), and among other metabolic pathways, glutamate's interconversion from and to arginine production (13). The composition of the amino acid pool and the transport system across the cell membrane determines the rate and the quality of protein production in the cell (14). Tryptophan is central to the requirements for

protein production (13) and DNA synthesis and repair (7), a depletion of this amino acid in the body would be disruptive to the deprived cells' normal functions. Accordingly, prolonged periods of steroid induced gluconeogenesis can alter the amino acid pool composition with a decrease in tryptophan and tyrosine reserves of the pool (and most probably other amino acids that cannot easily be reassembled) and an increase in glutamate and arginine content of the pool.

Dröge, et al. (15,32) have presented evidence that in serum samples from AIDS and AIDS associated conditions, such as lymphadenopathy syndrome (LAS), AIDS-related complex (ARC), on the average, contain significantly elevated levels of arginine and glutamate, and significantly reduced concentrations of methionine and cystine. Their *in vitro* experiments show that elevation of extracellular glutamate concentration (comparable to that seen in AIDS cases) inhibits T cell thymidine incorporation whereas, addition of cystine augments the T cell protein synthesis. The analysis of the sera from these patients demonstrate a metabolic disturbance (15). Thus, an indication that the composition of the amino acid pool available to T cells, particularly cysteine produced by the macrophages, is implicated in the impaired function of the lymphocytes in AIDS and its associated conditions (15,31,32). Such drastic change can only establish from prolonged periods of indiscriminate protein breakdown in gluconeogenesis. Prolonged activation of CRF and ACTH release can decrease the sensitivity to the negative feedback effect of corticosteroids, so that the level of ACTH and corticosteroid secretion can be maintained throughout the period of stress (16).

There seem to be three feedback inhibitory pathways between corticosteroids and the corticotrophic response, fast, intermediate and delayed; the former two are involved in the normal physiological responses of the body, while the latter is said to be sensitive to the level of corticosteroids involved in response to stress and the demand for its continued secretion. The serotonergic neuronal system is said to be responsible for modulating the delayed feedback inhibition (16). Opioids manipulate the serotonergic neuronal system (7) and possibly inhibit the delayed feedback inhibitory pathways to ACTH secretion, although the immediate direct effect of opiates is inhibition of ACTH secretion (16); through the action of opiates from a continuous stimulation of the serotonergic neuronal system that, by and large, promotes CRF and ACTH secretion, a swing toward a prolonged disinhibitory mechanism of ACTH secretion may establish, particularly as opioid peptides are secreted in response to stress, Fig 1. Thus exogenous opiates may give a similar signal of continuous stress that could promote a prolonged establishment of a stress response by the body, possibly when the direct inhibitory effect on ACTH, through continuous stimulation that can establish a receptor down-regulation ("fatigue"), becomes less effective.

In stress and the induction of pituitary adrenal axis a direct stimulation and release of CRF, vasopressin, angiotensin II, opioid

peptides, and other neuropeptides results (16). Vasopressin, apart for its body water regulatory role, is considered to be a modulating cortisone release factor (27,17,7). Angiotensin II (AGII) also has both water and thirst mechanism controlling properties (7), as well as the ACTH releasing effect (16). ACTH in presence of Ca^{+2} degranulates the mast cell of its histamine (7). Histamine is a neurotransmitter amine that is primarily involved in water regulation of the body (7, 17). Histamine is a very strong stimulant of vasopressin and AGII production (7), and both are strong CRF secretion stimulants (16); histamine and AGII are central hypothermia inducing

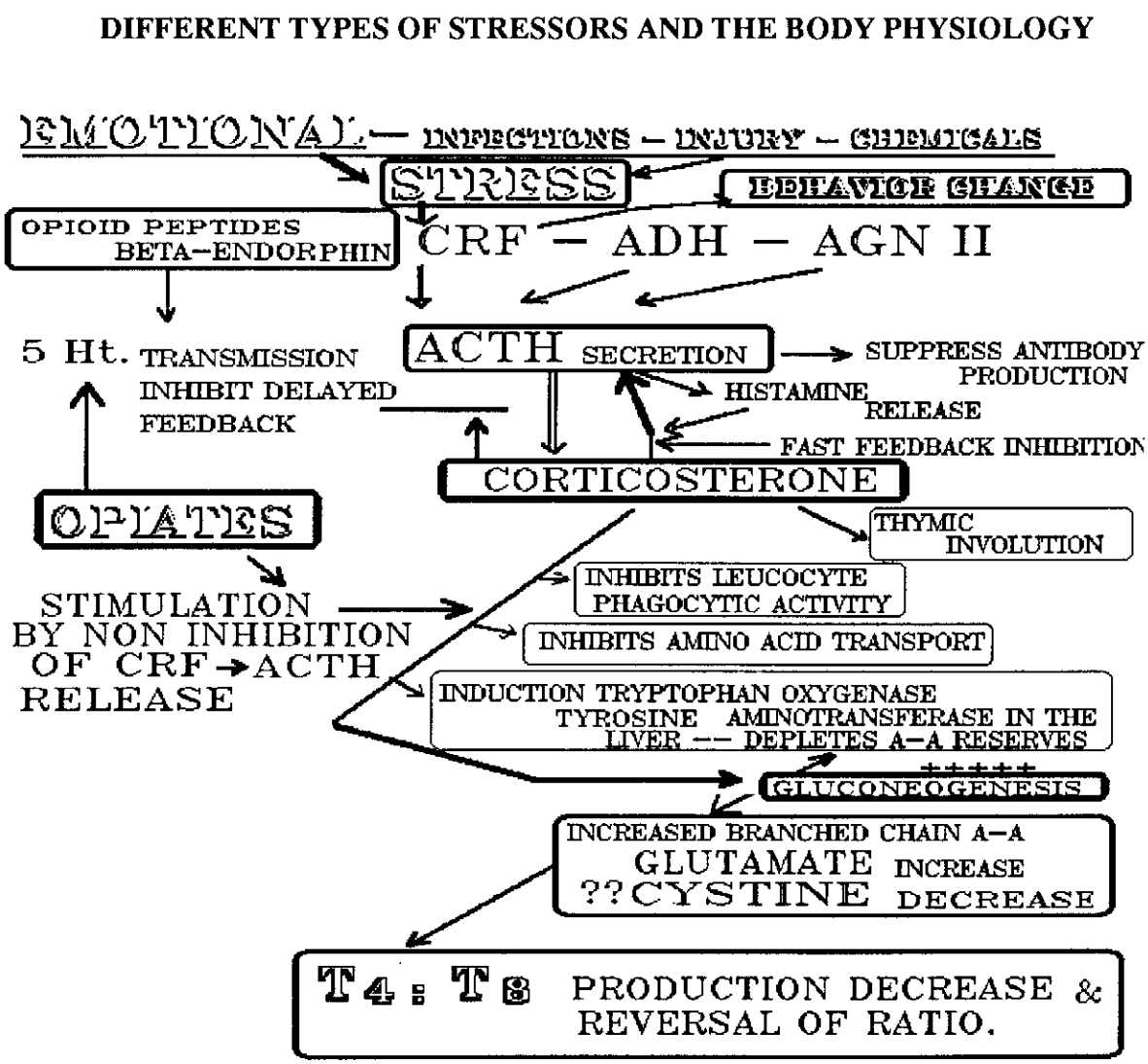

Fig. 1, A proposed schematic model of stress-induced major endocrinological events, leading to immune system suppression and the reversal of the T4:T8 ratio. Also the role of opiates in immune system suppression, from ref. No. 17.

transmitters (18,19). Thus the regulation of water metabolism of the body in hot regions of the world with possible food shortages can also establish a type of physiology in the body that strongly resembles a stress physiology, indicating that stressors to the body need not be chemicals, injury, infectious or even emotional - *adaptation to environment could also induce a stress physiology*. The relationship between AIDS in the West to the history of the disease in Africa or the Caribbean region can thus be explained by viewing these related conditions as stress induced metabolic disorders, and would also include the body's immune system disturbance resulting from the irregularities in its metabolism of water (7,17).

High histamine turnover in the body, stress or water metabolism disturbance induced (including the body temperature regulation through the sweat glands stimulation in the skin) will promote prostaglandin E (PGE) production as a subordinate system for regional water and flow regulation (17). Edelman and Zolla-Pazner (6) have shown that in the asymptomatic, as well as the symptomatic stages of LAS/ARC and AIDS, prostaglandin production is consistently raised. Continuous PGE production can cause osteolysis and increased Ca^{2+} release (20). Increased Ca^{2+} made available to the tissues in the body can cause angiogenesis (21). Since a component of the clinical picture in AIDS is raised calcium levels in circulation (22,23), the generalized angiogenesis seen in KS (24) and its epidemic form seen in AIDS (25) may also need to be viewed as a stress-induced paracrine-dependent (platelet derived growth factor -33) metabolic disorder Fig. 2. During the phase of high histamine turnover in the body, because of the nonrandom possession of H_1 or H_2 receptors in the different subpopulation of lymphocytes (28), particularly in the bone marrow where the ratio of suppressor to helper cells is 2:1 (29) and the suppressor cells have a dominance of H_2 receptors (28), and in the presence of high cortisone levels in circulation, lymphocytes sequester in the bone marrow (30), their biology and functions are affected non-uniformly. The use of analgesics or drugs with antihistaminic properties could swing the immune system in an opposite direction and establish an imbalance (17). Thus, by their frequent use, recreational drugs, possibly possessing antihistaminic properties, can impose their possible added inhibitory effects on the immune system. The effect of recreational drugs on the immune system, at the same time as the metabolic effect of the severe and unceasing "injury" stress imposed on the intestinal tract should become an important issue in the understanding of AIDS in the homosexual way of life and practice, all the time keeping in mind the effect of severe emotional stress that must also be associated with the behavior.

CONCLUSION

While it is not possible to rationalize the proposed relationship of the retrovirus to so many different conditions that are now included in AIDS syndrome, a look at these conditions from the angle of physiology of stress can possibly offer a more logical

RECTAL AND INTESTINAL STRESS

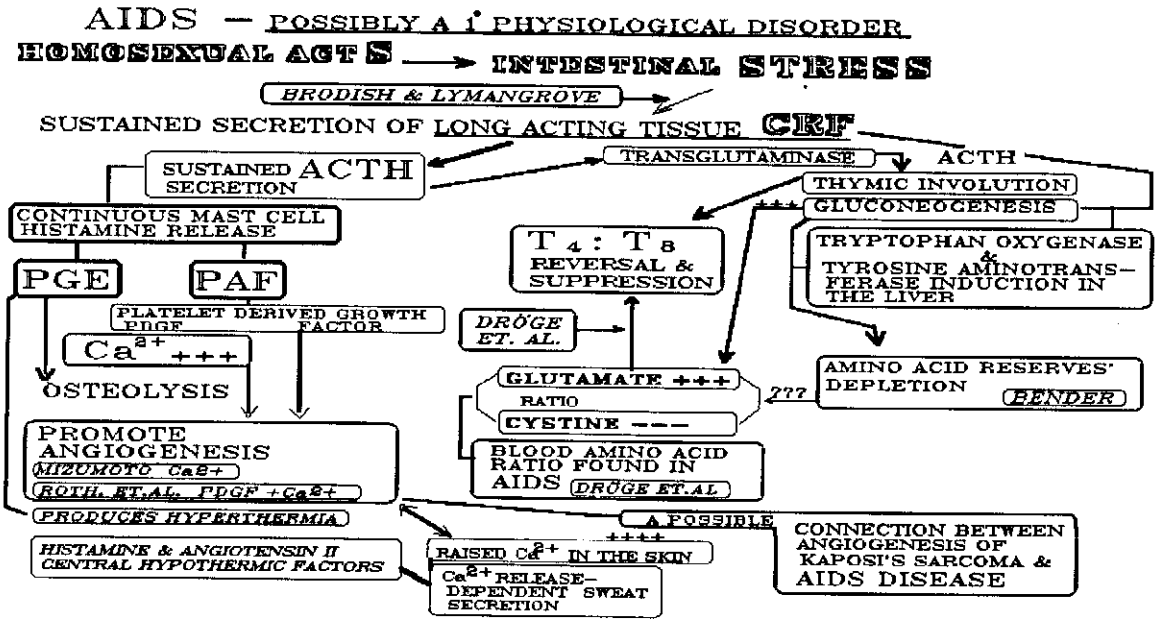

Fig. 2, A proposed schematic model of events leading to AIDS and its associated conditions caused by continuous intestinal stress in homosexuals, from ref. 17.

direction to the future research of these disparate conditions. The above arguments are presented to provoke a discussion of the subject at the level of scientists who also believe that the retrovirus probably has as long a history as humans, if not more, if it had the power to cause all the ills that are attributed to it, man would not have sur-

vived beyond a few generations. We should recognize that there are certain *naturally installed* inherent laws that govern the functions of the body, the misuse of the anatomical structures of the body outside their intended purpose may direct the whole system along a *physiological dead-end.* It may be credulous to think that one can repeatedly injure the intestinal tract in pursuit of physical gratification and blame the outcome on a virus that knows it can not survive if that body is not surviving. *It is even more bizarre to present the presence of the antibodies to the virus in the serum as a sign of progress of the disease.* It is possible that the antibody production under the direct and potent inhibitory influence of ACTH (16) is insufficient to completely neutralize the virus or the other pathogenic bacteria that eventually cause the death of the patient. Interferon production is also inhibited by ACTH - in vitro finding (16). Assuming that, during development in early life, adaptation to the environment, on and off, establishes a stress response in the body, resulting in CRF and ACTH production, it seems high levels of CRF can influence the learning capacity, motivation, sensitivity, and behavior. These central effects of CRF on the behavior pattern have been demonstrated in rats (26). In the rhesus monkey, high doses of CRF injected directly into the brain, among other disruptive behavior patterns produced, suppresses the normal sexual behavior (26). Is it remotely possible that the consequence of an inability to adjust and surmount the stresses associated with early development in childhood, in some, step by step, leads the child to the physiological ending of immune deficiency syndrome in early adult life and sexual aberrations are steps in the process?

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