

NEUROTRANSMITTER HISTAMINE: AN ALTERNATIVE VIEW POINT

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ABSTRACT: Advances in histamine research show it to be a neurotransmitter, a neuromodulator and an osmoregulator of the body. While thirst sensation is a failing indicator of a now recognized age-dependent state of possible cellular and chronic dehydration of the body to the point that, between the ages of twenty to seventy, the ratio of the extracellular to the intracellular water content of the body has been shown to change from 0.8 to almost 1.1, histamine is demonstrating responsibility for the essential osmoregulatory and central dipsogenic functions in the body. Histamine is involved in the initiation of cellular cation exchange that seems to be supplemental to the role of water in cellular metabolic mechanisms (1). Histamine is also a modulator of lymphocyte biology and function; through H₁ or H₂ activation of the different lymphocyte subpopulations that have nonrandom distribution of histamine receptors, their functions are integrated (2). Histaminergic drive for body water regulation and intake brings about the release of vasopressin (3,1) which, in turn, by possible production of "shower head" cluster perforations of 2 Angstrom units, allowing the single file entry of one water molecule at a time through the membrane, promotes increased flow of water through the cell membrane (4). This function is particularly important for the maintenance of the low viscosity, microtubule directed, microstream flow of the axonal transport system (5,6). Vasopressin also acts as a modulating cortisone release factor (7) when continuous and increased ACTH secretion can be implicated in the general inhibition of the immune system's functions (1,8); histamine may be involved in modulation of

neuroendocrine systems, possibly when ACTH feedback mechanism is broken (9). Next to oxygen, water is the single most essential substance for the survival of the body, recognizing also that dry mouth is not the sole indicator of free water deficiency of the body, but a symptom producing excess histaminergic activity, including chronic pain production, and should also be judged to be an indicator of body water metabolism imbalance (1). The natural primary physiological drives of the histaminergic, the serotonergic neurotransmission (another system involved in the body water regulation, as well as pain threshold alteration) and the angiotensin II for water intake of the body should be acknowledged and satisfied before and during evaluation of the clinical application of antihistamines in treatment procedures, particularly as increased water intake may be the only natural process for the regulation and inhibition of histamine's over-production and release (1). The prolonged use of antihistamines in gastroenterological, psychiatric (10,11) - the seasonal allergic conditions - as analgesics (12) or anti-inflammatory agents without very strict attention to the body water intake regulatory functions of histamine by masking signals of dehydration, may eventually be the cause of cell membrane receptor down-regulation (1) and disturb the integration and balance and, possibly, shift the immune system in an opposite dominant direction and, therefore, be responsible for the production of new and continuing change of physiological steady-state situations, incompatible with total and prolonged well-being of the patient.

Key Words: *histamine, pain, inflammation, AIDS, Kaposi's sarcoma, immunomodulation, stress, thirst, water, asthma, rheumatoid joint, leukemia, lymphoma, aplastic anemia, apoptosis, transglutaminase, senescence.*

It has been shown that increased water intake under severe emotional and environmental stress reverses the clinical picture and relieves the severe abdominal pain associated with peptic ulcer disease (PUD) (13,14); a condition that at present is being treated with H₂ blocking agents. Because of the neurotransmitter status of histamine and its involvement in water regulation of the body, an associated thirst pain signal to water metabolism disturbance is indicated, including the epigastric pain seen in dyspepsia and peptic ulcer disease, chronic back pain, anginal pain, pain of intermittent claudication (1).

NEUROTRANSMITTER HISTAMINE AND WATER REGULATION OF THE BODY

Histamine is a neurotransmitter/neuromodulator (15,16,17,18,19, 143) with a specific neuronal system of its own (18,143), particularly represented in the upper intestinal tract (19); also, according to Enerback, mucosal mast cells that show a different set of characteristics to the connective tissue mast cells and are extensively distributed in the whole of the intestinal tract, seem to be closely associated to nerve fibers of the lamina propria (20).

Histamine is an osmoregulator (21) involved in body water intake by its direct central nervous action (22,23,24,25,26,27,28 - *Fig 1*) and through activation of the renin-angiotensin II-aldosterone system (29,1) which is another pathway for the central regulation of the water intake of the body (30,31). Histamine is a strong stimulant of the antidiuretic hormone (ADH)

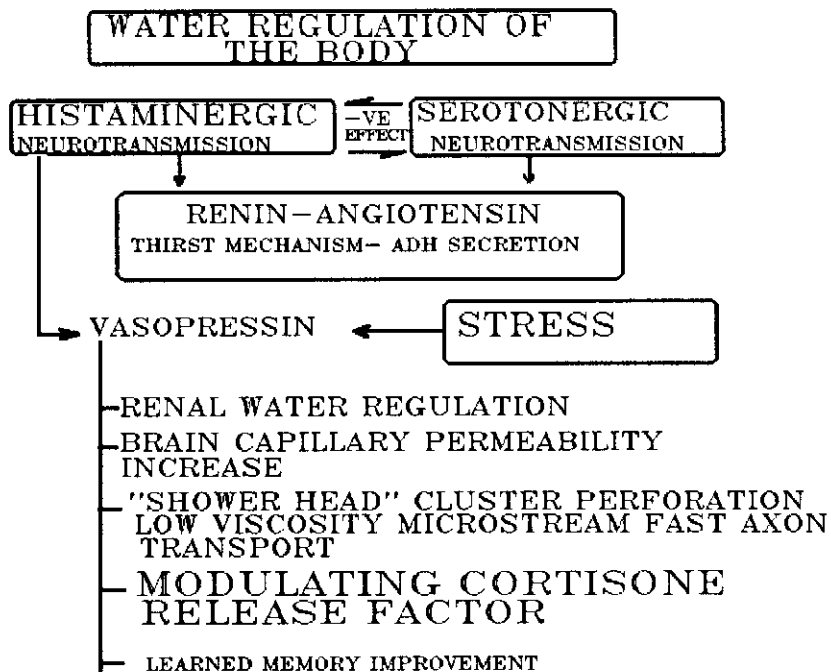


Fig 1: The central water regulatory mechanisms

release (3), again a water regulatory action for all the ADH-dependent systems. The "fine-tune", histamine facilitated, flow modulation of the circulation to a system is further regulated by prostaglandins kinins platelet activating factor (PAF) and other down-stream products, *Fig 2*; kinins can be released by the action of mineralocorticoids, angiotensin II and PGE₂ (32). Kinins and histamine release also promote the secretion of PAF; kinins, prostaglandins, as well as histamine itself, are algescic humoral factors (33); PAF is now being researched as an agent of pain induction. Among the mast cell mediators, PAF and

lymphokine, histamine-induced suppressor factor (HSF) (H₂ receptor and interleukin-I dependent action - when interleukin-I is also a neurotransmitter -136). The subsequent effect of HSF on monocytes results in the production of prostaglandins (PGE) which, in turn, brings about the suppression of lymphocyte proliferation. The production of HSF may be the way histamine brings about its inhibitory action on some cells involved in the body immune system (34) *Fig 6*, although it seems that histamine can inhibit human T cell interleukin-2 and interferon-gamma production initially and directly (149). H₂ receptor activation has

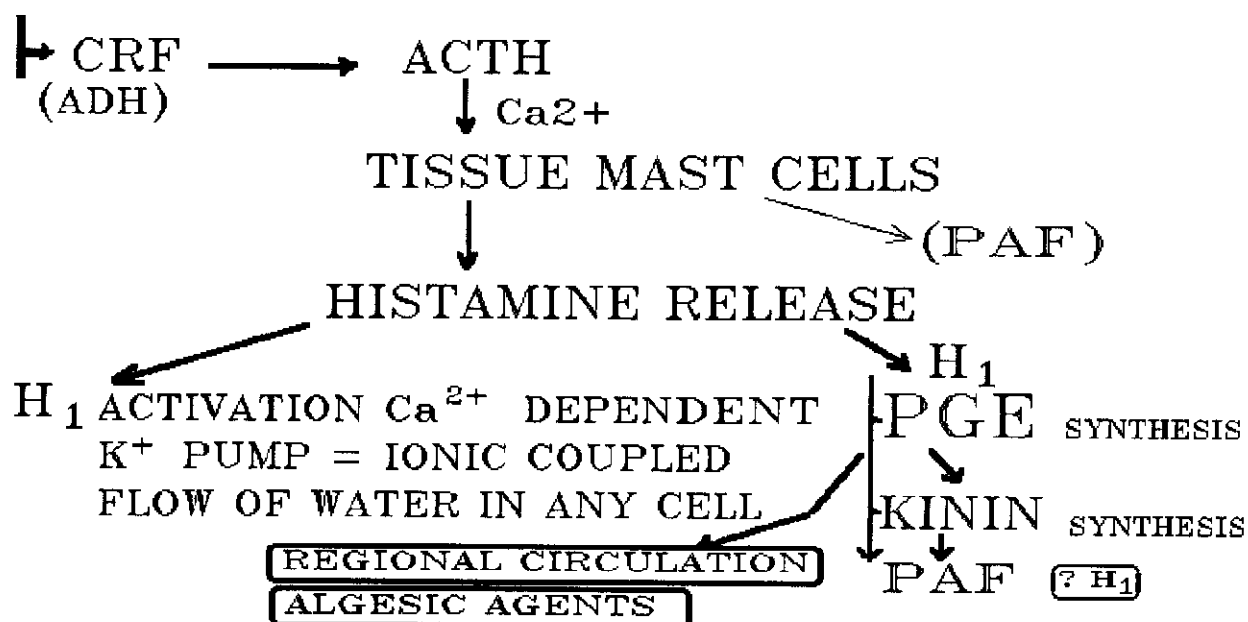


Fig 2: A proposed model of the down-stream histamine-induced water regulatory mechanisms

the slow reacting substance (SRS) have prolonged spasmogenic activity; human mast cells do not contain serotonin, while the rodent mast cells also secrete serotonin (111).

Another major pathway of prostaglandin formation, other than the direct effect of histamine (H₁) on some tissues (the vascular wall in particular) bringing about the release of arachidonic acid (2), is mediated through T cell stimulation by histamine and production of the

been reported to suppress inter alia lymphocyte transformation, the cytotoxic activity of T cells, antibody formation, and interleukin (IL)-2 production. In monocyte-dependent in vitro experimentation, histamine (H₂) has been shown to stimulate the natural killer cell activity (75). Prostaglandins also "fine-tune" the regulation of host defense response to stress; cAMP augments the biosynthesis of PGE₂ (many folds). PGE₂ induces the inhibition of tumor cell replication by 80-90% (*in*

vitro study); prostaglandins bring about cellular events leading to cell differentiation of tumor cells; indomethacin, a suppressor of PGE formation, results in consistent and significant stimulation of replication (in *vitro* study and in *vivo* indication). Prostaglandins seem to be involved in the restoration of immunoresponsiveness, maturation of T lymphocytes from stem cells, and many other functions in the body (51,35). Chronic (*in vivo*) exposure of lymphocytes to circulating histamine seems to produce an atopic form of lymphocytes that do not demonstrate H₂ (not H₁) receptor membrane markings; thus, a "desensitization" or receptor "down-regulation" and the subsequent reduction in HSF production (34). H₁ activation and Ca²⁺ release over a long period of time (through activation of Ca²⁺-dependent membrane proteases -- 52) can be implicated in the cell membrane receptor protein down-regulation (43), particularly as PGE can cause bone resorption and bring about hypercalcemia (51), a possible mechanism of atopic lymphocyte formation.

MUCOSAL MAST CELLS - SINGLE CELL NEURONES

It seems to become evident that the conclusion to the studies carried out in the rodent peritoneal mast cell is not necessarily applicable to the basophils and mast cell population of other species (120); however, it seems logical to expect a close functional relationship, given the fact that it is the physiological role and function of histamine itself that allocates a position to the cells that contain it.

Schwartz, et al., (15) have shown that the histaminergic neuronal system and the tissue mast cells have different characteristics for the release of their histamine granules; compound 48/80 releases the tissue mast cell histamine and does not release the neuronal system's histamine. K⁺ depolarization releases the neuronal histamine granules (16) and not the tissue mast cells' histamine (15,1). Mucosal mast cells, shown to have different final

characteristics to tissue mast cells, are of bone marrow stem cell origin (20, 35). Although the basophils mature in the microenvironment of the stem cells in the marrow, mast cells do not, even if they have the same stem cell origin. The committed precursors to mast cells leave the hematopoietic microenvironment, migrate in the peripheral circulation and, by an as yet unclear humoral stimulation of the homing receptor mechanism (63), enter the particular "home" tissue (35). In the case of mucosal mast cells, the Peyer's patches have been shown to be such a site for precursor replication and adoption of secondary characteristics *Fig 3* (36,37). They enter the lymphatics and become distributed to the mucosal "home tissue" in the gut, via intestinal systemic circulation. In the gut mucosa, the mast cells, seem to home toward nerve terminals of the lamina propria, to which they may become directly connected; they further differentiate and establish the final characteristics of a mucosal mast cell, different from its sister cell in other tissues for its mode of histamine release.

The mucosal mast cells also contain 5HT and collect dopamine (20) in the rat - the human mast cell does not contain serotonin. The mucosal mast cells demonstrate the same response to compound 48/80 as the histaminergic neurones; namely, they do not degranulate as a result of stimulation with this compound (20,36). Although the tissue of origin may be the bone marrow stem cell, because of its acquired characteristics and possession of at least three realizable neurotransmitters, the logical conclusion would be that the mucosal mast cell may have to be recognized as a type of a single cell neurone *Fig 4*, involved in the maintenance of homeostasis in the microenvironment of the tissue it serves, with the downstream involvement of prostaglandins and kinins. Its primary function in the gut seems to be the regulation of the cation exchange, its coupled transport systems and the regulation of the water intake of the body (1). This aspect of its function must be very com-

plex because the metabolic processes and the intestinal absorption involve so many compli-

cated transmission mechanisms (83). There is a suggested possibility that the mucosal mast

THE MAST CELL

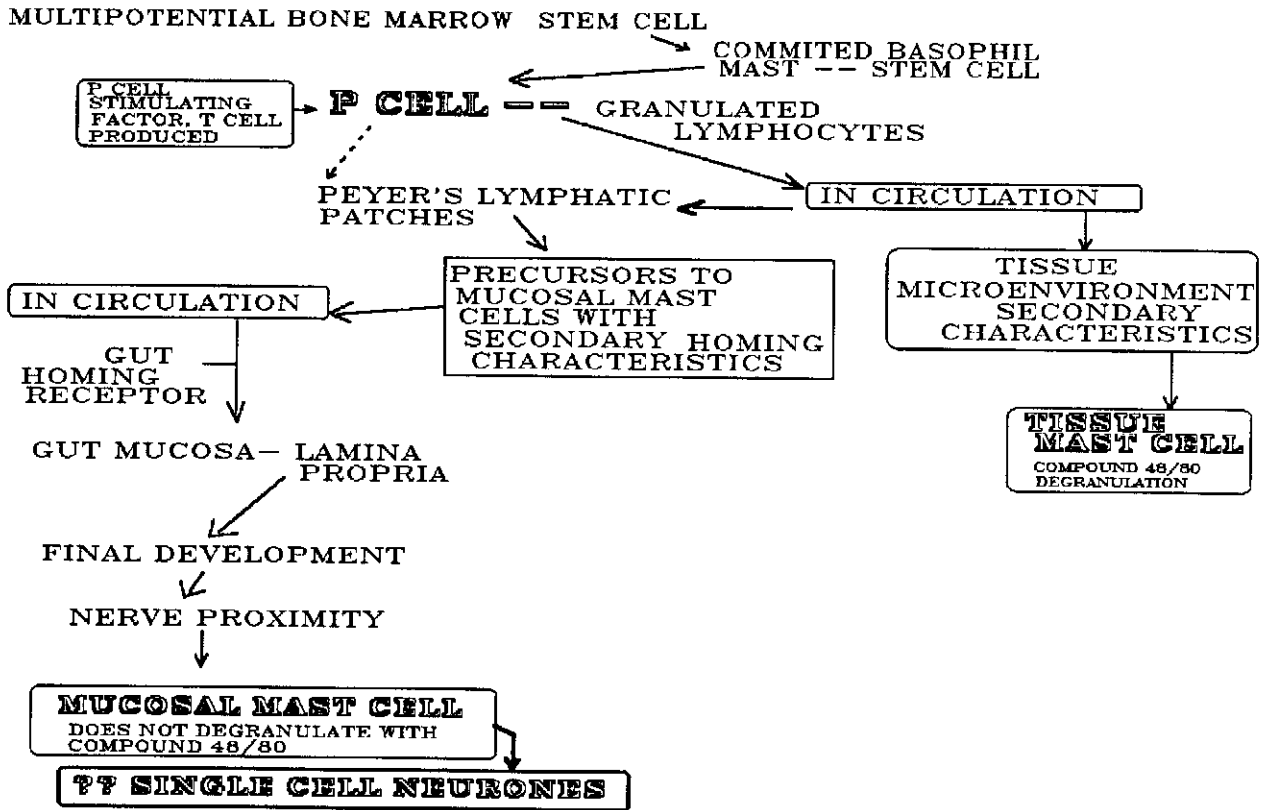


Fig 3: Model of the stages of development of the mucosal mast cell and the tissue mast cell from the multipotential bone marrow stem cell, exposing a circulating mast cell precursor to the white cell composition of the blood

cells do not proliferate at the stimulated tissue (35). Mucosal mast cells and also basophils possess immune globulin E receptors on their membranes (53). The basophils and mast cells are capable of manufacturing histamine granules after secretion of the amine. Basophils seem also to possess a transport system for a gradual secretion of histamine; there seems to be a complementary regulation for the secretion rate between the mast cell and the basophil cell (120).

The gradual loss of thirst sensation (that would

water to extracellular water would change drastically (41). This disturbance in water metabolism of the body can become symptom producing (1,13,14). When the "free water" intake mechanisms of the body become deregulated, in effect, the water intake by the process of free diffusion through the membrane into the cells becomes inadequate. Under such circumstances, it seems, water intake will become coupled to ion movement across the cell membrane through an H₁ cyclical activation of Ca²⁺ dependent K⁺ pump (42). It again seems

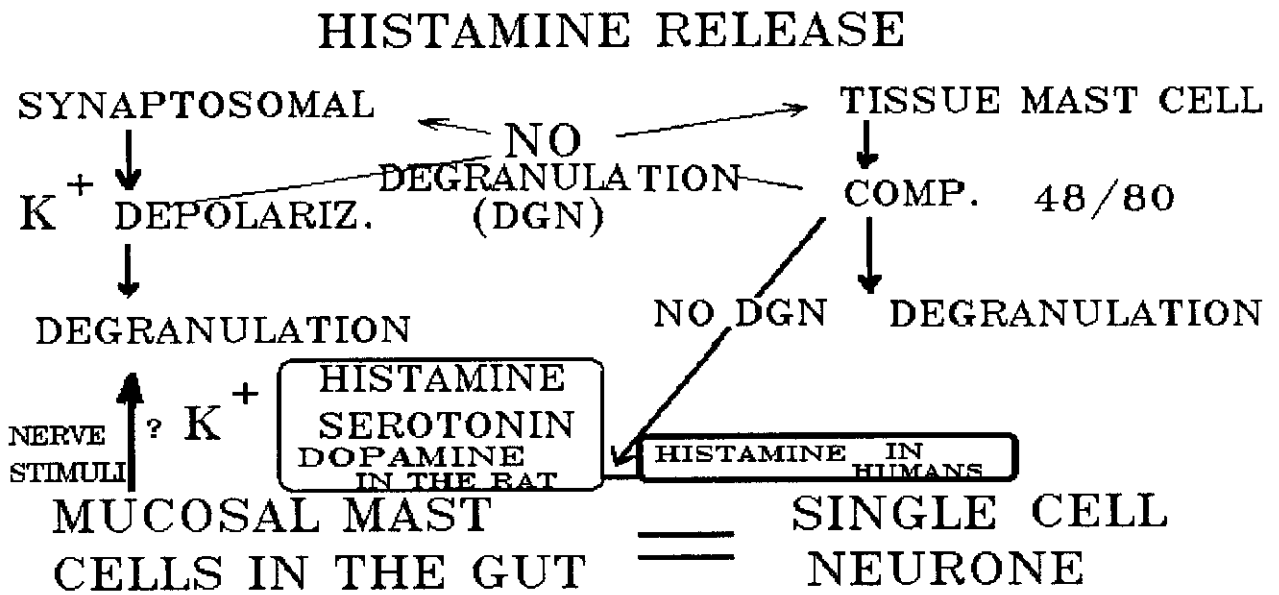


Fig 4: A proposed histaminergic neurone status for the mucosal mast cell

prompt one to drink water by itself) establishing an incipient and gradually increasing chronic dehydration of the body in the elderly is now a recognized fact (38,39,40,1), to the point that the ratio of the intracellular

that histamine regulates this aspect of water intake of the body as a whole, as well as that of the individual cells (since other cation exchanges across the membrane follow the lead of Na⁺-K⁺ exchange -- 1); hence, all the as-

sociated water retaining mechanisms coupled to sodium retention of histamine-renin-angiotensin II-angiotensin III-aldosterone system.

Since the function of cation exchange is energy dependent, histamine also liberates energy for this function (1,43). Histamine binds the stimulatory nucleotide regulatory component (Ns) of GTP and the complex then binds the adenylate cyclase and activates it (11) to liberate the energy for the function of cation transport (1,43). No histamine receptor has been shown to couple to the inhibitory protein (Ni) of GTP (11); thus, histamine is involved in the amplificatory functions of GTP and the energy release for a particular function. cAMP production by histamine stimulation is an H₂ receptor dependent function (16,11,1). The cyclic GMP mediated component of this amplification depends on an influx of Ca²⁺ which is brought about by H₁ receptor activation (11). Since Ca²⁺ ATPase serves to transport calcium with the stoichiometric coupling ratio of 2 mol of Ca²⁺ for each mol of ATP (48), it may be reasonable to assume that when calcium is being released from its stores, for every two mol of Ca²⁺ released, energy for the formation of one mol of ATP is also being freed (43). It is an inherent property of calcium to "precipitate" with heat. The ATP driven cation pumps that depend on the conversion of ATP to cAMP for their function, relying on the presence of "free water" (osmotically active water), can reverse the process and, instead of ATP breakdown, can generate ATP (44,1). The structure of the cell membrane is such that in the presence of osmotically active or "free water," high heat of activation can be generated (45,46,47).

IMMUNOSUPPRESSION

The bone marrow pluripotent stem cells, that give rise to the committed precursors to the T and B lymphocytes, erythrocytes, platelets, granulocytes, eosinophils and

monocytes/macrophages, basophil-mast cell precursor depend on the bone marrow microenvironment for their differentiation and maturation. According to Hempling, maturation of the proliferating and differentiating stem cells depends on the availability of free water in their bone marrow microenvironment; they are dependent on the heat of activation generated by "free" or "osmotically active" water for their maturation; as the cells increase in size, the ratio of osmotically active water within the cells increases (46,47). E-type prostaglandins are also essential for the process of maturation, as well as other humoral factors (49). It becomes a logical conclusion that with the loss of thirst sensation, and therefore free water diffusion decrease, the generation of high heat of activation will become less pronounced (43) and, therefore, a decrease in ATP production from the energy of solvation, hydration or tightly coupled hydrolysis will result (43), with its direct consequential effect of slower bone marrow stem cell maturation and generation of the different final cell lines.

BONE MARROW CELLS: HISTAMINE AND STRESS

The bone marrow cells consist of 2% lymphocytes; the ratio of suppressor cells to helper cells is 2:1 (49). The bone marrow has very high levels of histamine generating enzyme histidine decarboxylase activity; cytochemical studies suggest that histamine occurs in immature granulocytes; persisting (P) cells of the bone marrow have a very extensive regenerating capacity and they are considered to be the precursors to mast cells, with histamine producing ability, thus becoming involved in the growth regulation within its microenvironment (50). Prostaglandins in the microenvironment of the bone marrow seem to be able to produce osteolysis and bring about hypercalcemia (51). Raised Ca²⁺ availability to the tissues can promote repair, angiogenesis and capillary formation (76); a possible mechanism

for the early Kaposi's sarcoma (KS) tissue formation in AIDS.

In vitro experiments indicate that approximately 45% of the human T cells, 75% of the bone marrow, lymph nodes and spleen lymphocytes and 90-100% of the mononuclear cells possess histamine (H₁ and H₂) receptors. T helper cells have the highest histamine binding capacity for their H₁ receptors per cell, followed by B cells and then T suppressor cells, although the number of receptors per cell are in the reverse order (2). H₂ receptor stimulation, through its cAMP production, promotes activation and increased production of the suppressor T Lymphocytes; suppressor T cells are more responsive to H₂ stimulation than the helper/inducer or cytotoxic lymphocyte subset (2, a critical review).

The hypothalamic histaminergic neurones (mainly H₂, but H₁ receptors are also involved) seem to be directly involved in the stress-induced release of pro-opiomelanocortin-derived peptides, demonstrated in the rat (112). Endorphins also have water intake regulatory properties (113).

Stress causes a release of cortisone release factor (CRF), opioid peptides vasopressin and angiotensin II. The central effect of angiotensin II on CRF release can also be the cause of a dose related release of ACTH. These release mechanisms are cAMP independent, but cytosolic Ca²⁺ and phospholipid turnover dependent (54). ACTH in presence of Ca²⁺ degranulates up to 90% of the histamine of the tissue mast cell (1), and ACTH can also depress the immune system and inhibit antibody production independently (8,54). There is also a thymus adrenal connection. Excess action of cortisone can cause thymus involution; transglutaminase(s) (TGE) are considered to be involved in bringing about programmed cell death (apoptosis); during glucocorticoid-induced thymus involution (apoptosis) in the rat, transglutaminase activity increases substantially (92); thymus is also implicated in tissue cortisone release factor

production (7,8). There are three levels of feedback inhibition of cortisone on ACTH secretion: fast, intermediate and delayed or slower inhibitory systems. Histaminergic activity seems to become involved when this feedback mechanism is broken (9); the serotonergic neuronal system seems to be involved in the delayed feedback component to stress stimulation of ACTH release. Beta-endorphins or their agonists manipulate the serotonergic neuronal system, possibly affecting the delayed feedback component of ACTH release in stress (54). Since opioid peptides are involved in stress regulatory mechanism of the body, the use of opiates must also manipulate the same pathways of action as opioid peptides, registering a stress situation and establishing the physiological response of the body to stress; namely, a drive on the CRF-release-associated metabolism of the body (although the direct action of opiates on ACTH release seems to be inhibitory -54)

Fig 5.

The serotonergic neuronal system is also extensively involved in the regulation of growth and metabolism -- food, water, sodium intake,... (1). Its functions seem to regulate histaminergic activity through the stabilization of the calcium current across the cell membrane. It inhibits the action of histamine in its acid secretory capacity of the stomach, through a certain osmotic range (1). Serotonin also (like histamine H₂ receptor, 74) regulates the human natural killer cell activity (62). If the activity of the natural killer cells is essential for the recognition and destruction of the transformed or infected cells then, the depletion of tryptophan reserves of the body and conversion of histamine to N-N-dimethylcasein, by the action of transglutaminase, in prolonged periods of stress must also affect the efficiency of the natural killer cell activity. The degranulation of mast cells also releases serotonin in the microenvironment, in the rat; serotonin also brings about mobilization of calcium followed by calcium retention (spike followed by a plateau) in the cell.

STRESSORS

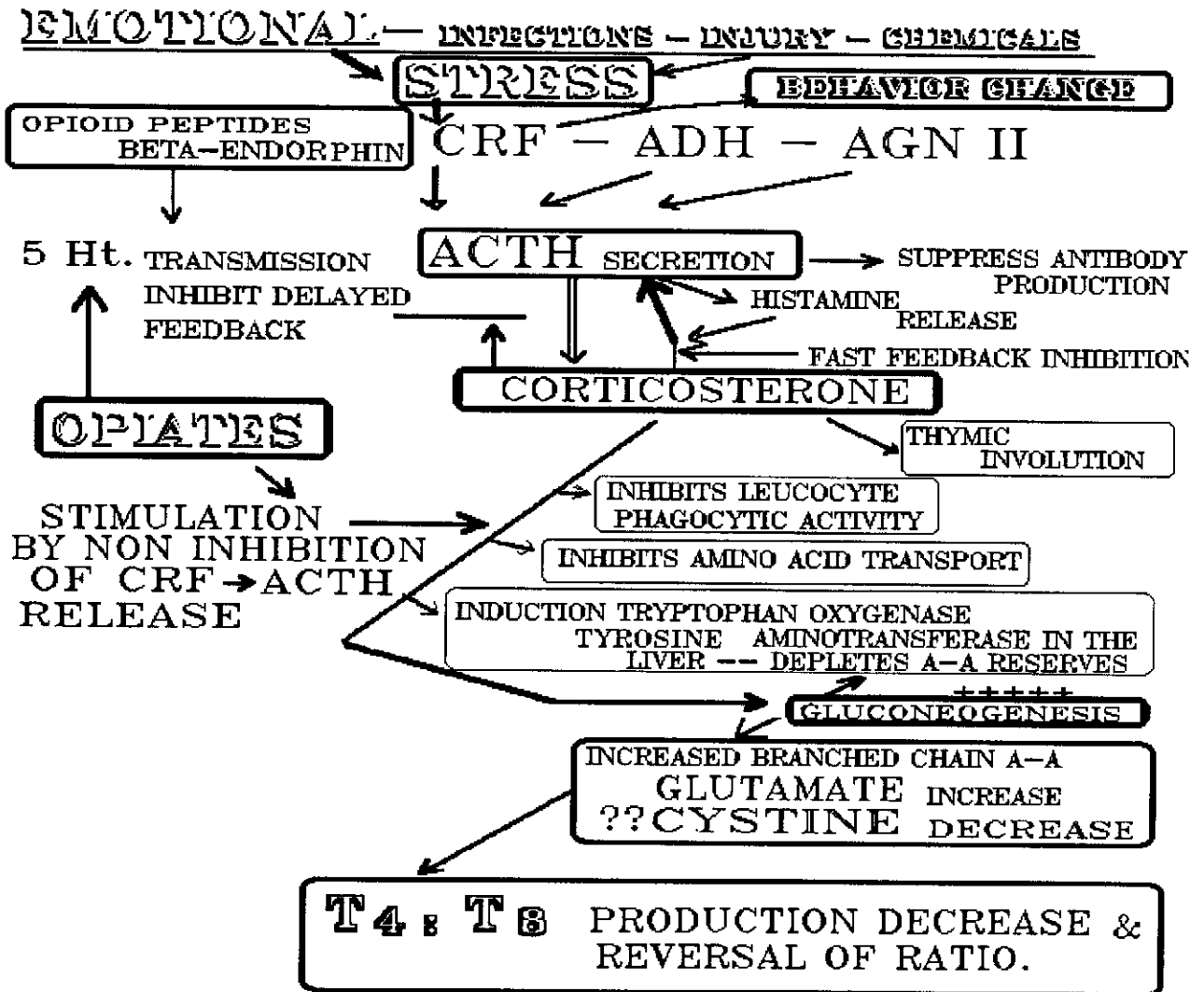


Fig 5: A schematic model of the proposed stress-induced major endocrinological events, leading to immune system suppression and the reversal of the T4:T8 ratio. Also the role of opiates in immune system suppression.

MANIPULATION OF THE HISTAMINE RECEPTORS

In isolation, histamine receptors may be manipulated in different symptom producing disease conditions. In disorders of the immune system, just because the different subset of lymphocytes demonstrate a particular

receptor, *Fig 6*, they either register a dominance of cAMP turnover (H_2), or phosphatidyl-inositol turnover (H_1) and, because the ratio of H_2/H_1 membrane receptor population in different cell subset is unbalanced (2), the manipulation of these cells may become a short cut to treatment of disease conditions. Since conversion of ATP to cAMP means energy release and Ca^{2+} release also means

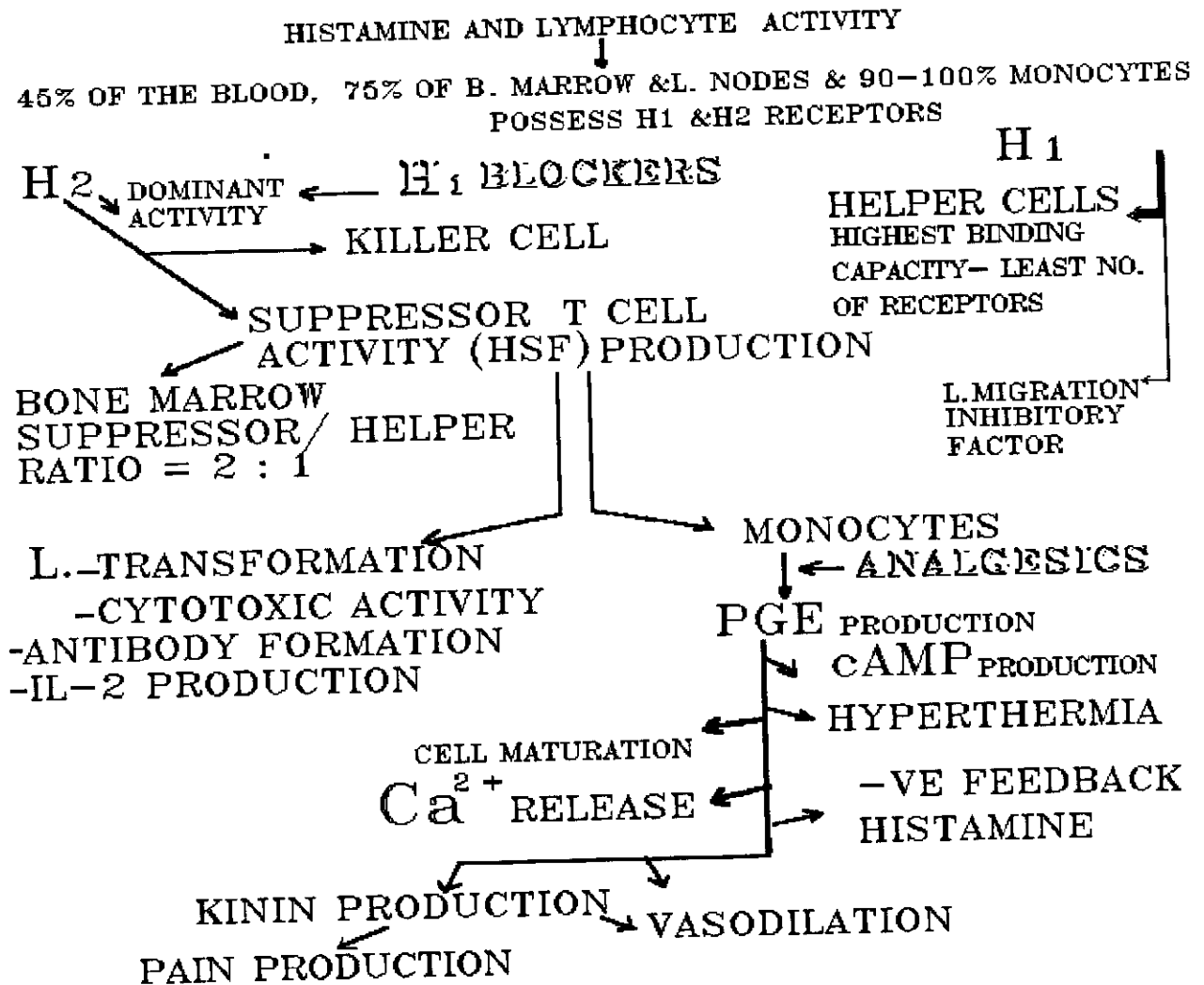


Fig 6: A schematic model of the histamine receptor distribution and function in the lymphocyte sub-population; a proposed possible imbalance that can be caused in their respective functions by prolonged use of known and unknown antihistamines (since most of the antidepressant drugs are strong antihistamines).

energy release involving GTP intermediary pathway, then histamine is involved in mobilization of energy for a particular integrated function of the cell that would involve its growth or its normal functions. The production of cAMP and the released calcium are then post energy release markers. This function of histamine caters to many different systems regulating the functions of the total body; its activity is not exclusive to the immune system, gastroenterological, or even psychiatric disorders. In the case of the neurotransmission system, it is involved in the cation exchange. At the level of the internal membranes in the cell, histamine may be involved in the oscillatory activation of calcium-dependent K^+ channels, an H_1 receptor dependent function (42). An H_1 receptor blocker used in treatment of certain conditions would also block this regulatory role of histamine in the maintenance of the microenvironment as well as the cation exchange at the inner cellular membranes.

Histamine by itself is a promoter of growth (55-59,1). Bender (60) considers histidine to become an essential amino acid for growing children and in the elderly, because the rate of its production and intake does not keep up with the needs of the body during these periods of life. During the growing period of the life of children, when the actual process of cell growth places an increased demand on the water intake of the body, there will be a natural physiological drive on the histaminergic system to populate the gut with mast cells to regulate the process of food metabolism involving the Na^+ exchange coupled transport system at the basal membrane of the cells of the intestinal tract and the associated ionic coupled water intake of the body.

THE POSSIBLE PRIMARY INFLUENCE OF WATER METABOLISM DISTURBANCE AND SOME ASPECTS OF THE IMMUNE SYSTEM PATHOLOGY

The effect of histamine as an agent of growth, supplemented by the actual effect of the growth hormone when the lymphocyte population may as yet be "uneducated", immature and naturally non-inhibitory, and, if coupled to the social and environmental stresses associated with the process of growth in children causing further histamine release from mast cells, an uninhibited drive on the bone marrow stem cells in the microenvironment of the marrow or secondary "home" tissue will undoubtedly ensue. If the views of Guy-Grand (37) that precursors to mast cells may even be a type of gut lymphocyte are taken into consideration, then a drive on the histaminergic neuronal system for increased water intake in children will have a gut lymphocyte proliferation component. If at this phase of the mast cell precursor proliferation when the final characteristics are not yet established but, nonetheless, its lymphocytic properties expose it to antigenic stimulation (possibly retroviral), causing a down-regulation of the homing receptors (61), a leukemic/lymphoma clinical picture to a natural drive for increased water intake of the body may become established, *Fig. 7*.

The same process may become operative during the later periods of life, when severe stress and/or chronic dehydration places the same drive on the stem cells for production of mast cells, except that a preliminary depressed bone marrow may be an initial outcome. A drive on the histaminergic neurotransmission system for water intake and also with concomitant stress, because of the 2:1 ratio of suppressor (H_2) to helper T lymphocytes presence in the bone marrow (49), a predominance of H_2 receptor activation can possibly become the causative factor in some cases of bone marrow depression. Lipton (49)

CHILDREN - GROWTH & STRESS

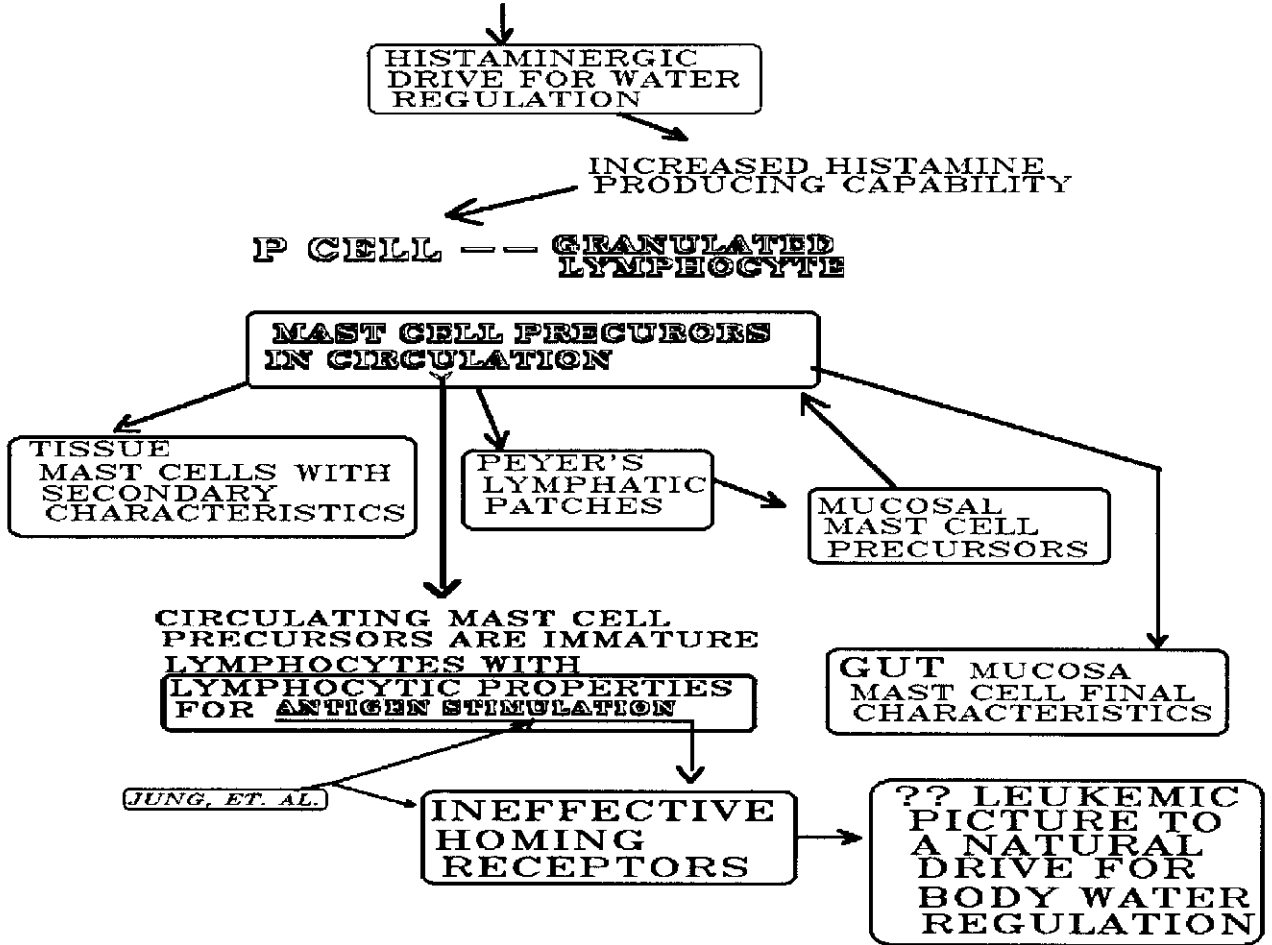


Fig 7: A Schematic model of possible events leading to a leukemic picture in children

presents supportive discussion on the involvement of suppressor T cells in "autoimmune" bone marrow depression; also Abdou, et al. (63), Fauci, et al. (64), and Bacigalupo, et al. (65) present confirmatory evidence in favor of T cell involvement in suppression of bone marrow in aplastic anemias. Fauci, et al., cite experiments showing that in certain disease conditions and also with corticosteroid therapy (a physiologic by-product of continued stress/dehydration) mature T lymphocytes from the peripheral blood home and sequester in the bone marrow, these T cells can function as potential killer cells (64). According to Abdou and associates, the role of prostaglandins, Fig 8, and the microenvironment of the bone marrow become deciding factors in the pathogenesis of aplastic anemia, or preleukemic bone marrow depressions (63). At a later phase of continued drive directed at the bone marrow for mast cell production, even though effectively suppressed, and

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since mast cells do not have a long half-life, and histamine (H₂) receptor down-regulation

may render the suppressor T cells ineffective (34), an uninhibited generation of stem cell

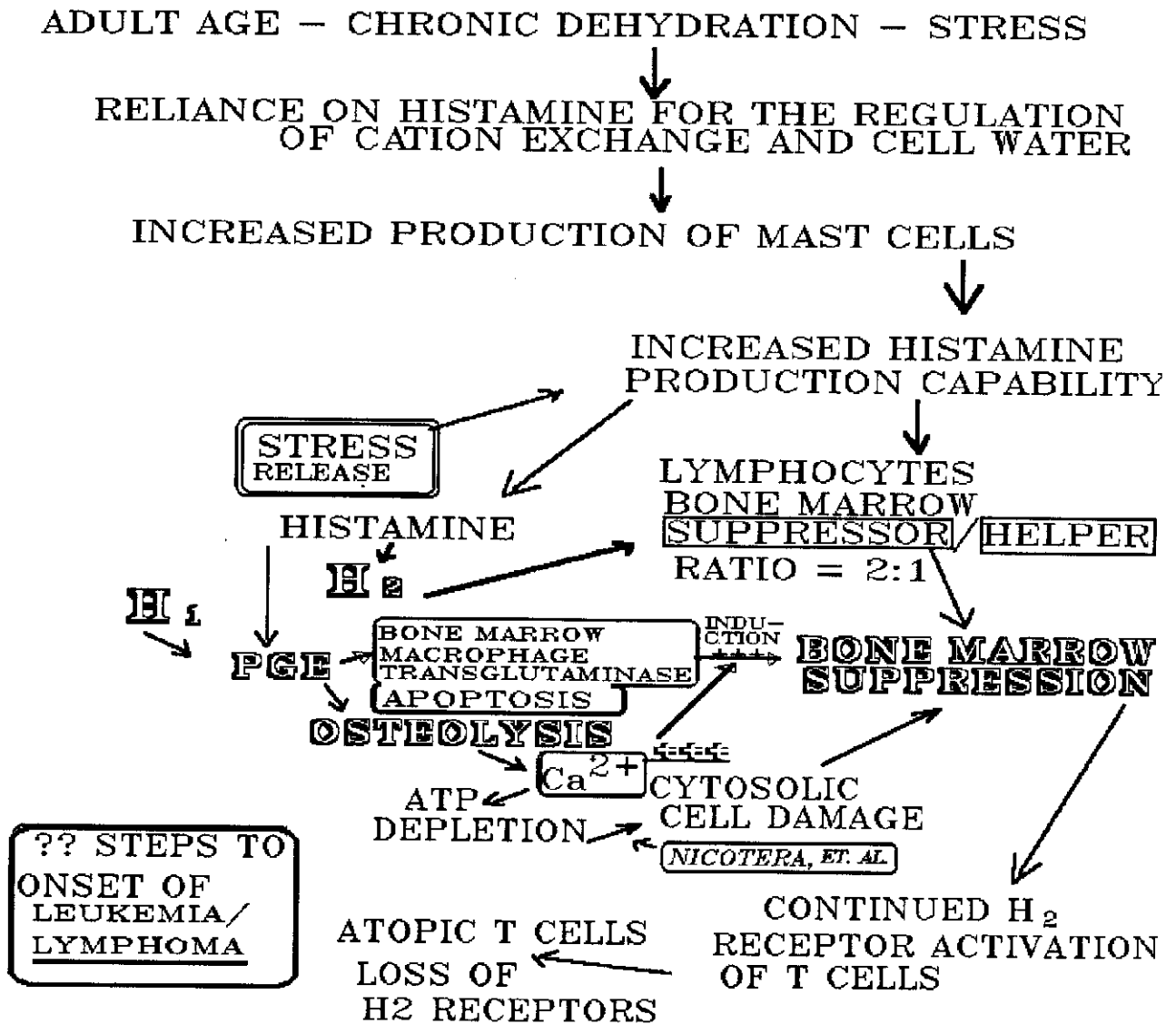


Fig 8: A Schematic model of a possible water metabolism disturbance-induced bone marrow suppression in adults, eventually leading to the development of a leukemia / lymphoma clinical picture.

progeny will possibly ensue; more so by the suitability of the microenvironment and ready availability of Ca^{2+} released by PGE_2 ; particularly if circulation to the area can not increase much (a function of histamine induced prostaglandins release). Because of the sphincter effect of the foramina and the Haversian and the Volkmann's canal systems (0.05-0.12 mm.) that dictate the size of the vessels that go through the bone structure (a constriction of the vessels within the same confined canal space is possible and should be studied in rheumatoid arthritic joints that show structural deficiency of cartilage regeneration). The effect of the Ca^{2+} -dependent "tissue" transglutaminase activity of the macrophages of the bone marrow (further explained below) in bringing about a possible apoptotic bone marrow suppression also needs serious consideration.

In AIDS, the main thrust of research is being directed toward identification of viral causative factors. Viruses that are known and recognized for their involvement in other less serious conditions are being considered as causative factors in the development of AIDS (66). Even when the retrovirus DNA sequence is not seen in the abnormal chromosomes of patients with AIDS associated Kaposi's sarcoma (67), still no physiological approach to research of this condition seems to emerge (it is now being shown that KS tumor development is a paracrine-dependent phenomenon - 93). The ratio of T4/T8 seems to be a criterion of the presence and the progress of the disease; the same pattern may be seen in many common infections (66). Although the predominance of the disease is seen among homosexuals and drug users, no association with the habits and the life-style of these people and the clinical manifestation of the disease is entertained; the criterion has become the presence of the viral antibody in the serum of the suspected "AIDS" sufferers, even when the patient may become clear of the viral infection and antibody markings (68) and even when the anti-p24 antibody from healthy in-

dividuals with high antibody titres and antigen neutralizing capacity, given to very sick patients, for the duration of its presence in the serum, does clear the antigenemia (144,145). Still the presence of HIV antibody in healthy people is being "pushed" as a sign of the presence of the disease. The retrovirus genetic apparatus is limited to its own survival. Duesberg (88) has extensively argued that the retrovirus is incapable of bringing about so many conditions in the body for which it is being blamed, causing AIDS in some, remaining silent in a vast majority of healthy and virus antibody positive people, and yet be capable also of cancer transformation of some cells in others since, for many years, this deed has also been blamed on the retrovirus. The presence of the virus antibody in the serum is a sign of an effective defense system and not immune deficiency (88,94) that is being symbolized when considering seroconversion as an indication of the progress of the disease. The lymphocytes that are involved in virus replication constitute a very small percentage of the total number, clearly indicating that factors other than the virus must be responsible for the gross immune suppression of AIDS (88, 89). Adams (95) has also reviewed the literature on AIDS and has presented the primary role of the retrovirus in the group of conditions classified under AIDS as a scientific myth. This book defines some of the patterns of gross homosexual insults to the lower intestine and the rectum while, simultaneously, recreational and pleasure enhancing drugs are extensively used.

AIDS: INDICATORS OF A STRESS-INDUCED METABOLIC DISORDER

A simple alternative approach to the understanding of AIDS may become apparent by an evaluation of the physiological components of homosexual acts, frequent as opposed to isolated (77), proposed by Batmanghelidj (1), with full exposure and involvement of recreational drugs that can also inhibit the im-

immune system. Animal experiments have shown that simple manipulation and even limited handling and stressing of the intestines can induce a sustained secretion of a long acting tissue cortisone release factor, transferable through blood or plasma (69,70,71,126,1). Assuming that to a rectal homosexual act there is also a "stress" component for the lower part of the intestine, particularly with the extensive liberty taken in homosexual practice of the introduction of the fist and the arm and other objects into the delicate intestinal tract in the process of achieving physical gratification, (now prevalent and openly advertised in the bathhouse system of facilitated encounters among the homosexuals) then, the production of a similar long acting cortisone release factor is not out of the question (1). The initial consistently raised cortisone levels not only depress the immune system and bring about thymic involution (8, 92) directly, but will also alter the percentage composition of the amino acids in circulation (1), which will include tryptophan and tyrosine that can become depleted from the continuous glucocorticoid induction of the enzymes tryptophan oxygenase and tyrosine aminotransferase in the liver (60). Since the efficiency of the amino acids' metabolism and their incorporation into proteins is in a very sensitive interdependent balance (60), then, with prolonged periods of induced gluconeogenesis, protein breakdown and increased metabolism of one as opposed to another amino acid can cause a disturbance in the dependent systems (1). Central to the chemistry of gluconeogenesis in the body, brought about by glucocorticoids, is the metabolism of glutamate and its secondary products, glutamine, gamma-aminobutyrate (GABA, a central nervous system inhibitory neurotransmitter and an inhibitor to cells possessing its receptors), proline and among other metabolic pathways, glutamate's interconversion from and to arginine production (in plants proline accumulates as an adaptive phenomenon to drought and in animals it

is involved in osmoregulation and in the energy requirement of the muscle - 60). 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 (85). Tryptophan is central to the requirements for protein production (60) and DNA synthesis and repair (1). 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, *Fig 9*.

SERUM GLUTAMATE AND T₄:T₈ RATIO IN AIDS

It is now becoming apparent that T₄-T₈ lymphocytes in AIDS patients may possibly be demonstrating inhibited sensitivity because of an abnormally high concentration of glutamate and arginine, and a decrease in cysteine and methionine (the blood amino acid picture seen in AIDS conditions - 72). The situation becomes further complicated by the central inhibitory effect of serotonergic neuronal system on insulin secretion (84) when, in effect, sensory stimulation of the rectum and the intestines and during drug use is registered through the serotonergic neuronal system. In such a physiological situation the much needed insulin's effect on anabolic and protein synthesis mechanisms will also become deficient, further complicating the amino acid pool composition (85). At the extreme of this situation, even the insulin receptors must be assumed to be down-regulated and damaged by the continuous action of tyrosine aminotransferase on their exposed tyrosine residue. The insulin receptor action depends on the autophosphorylation of at least five tyrosine residues by the activated kinase, a cysteine-rich domain is involved (146).

In vitro studies have shown that addition of cystine can bring about an increase in the proliferative activity of lymphocytes, while the addition of glutamate to the medium will inhibit their proliferation (72,87,86). If this amino acid imbalance is responsible for lymphocytes' inhibition, T4 more than T8, then prolonged cortisone release factor secretion and the activity of vasopressin secretion in stress or dehydration may warrant serious investigation in all cases of immune system depressions, irrespective of disease classification. Opiates, through their effect on serotonergic neuronal system and ACTH release, may possibly bring about a similar physiological picture seen in AIDS. The physical stimulation of the serotonergic system in the gut could also have a possible effect on the delayed feedback inhibition of ACTH on CRF release, also a possible reason for the increased occurrence of AIDS in homosexuals as opposed to drug users (a double jeopardy effect-another major factor must be the immune suppressive effect of transglutaminase of the semen that must act on the level of the lymphatic system of the lower gut - the secretion of the transglutaminase of semen into the lower gut may also have a local keratinizing effect on the mucosa of the large bowel that should normally function as a water absorbing membrane and, thus, may be the primary cause of the non-infectious diarrhea - the gay-bowel syndrome - seen in AIDS). In AIDS, its associated KS and its hall mark of wide spread angiogenesis, the early precipitating factor may be the osteolysis and excess calcium release (76) brought about by PGE₂. Edelman and Zolla-Pazner (79) have shown that in AIDS cases, prostaglandin levels in the serum is consistently increased in the asymptomatic as well as the fully blown cases; the early physiological events are further complicated by the central hypothermic effect of histamine (15 - the central H₁ receptor activation lowers the core temperature and H₂ activation induces the heat loss mechanisms - 119) and of angiotensin II (81), assuming

that the process involves the sweat glands and their calcium dependent secretion mechanism (this function seems to be a balancing response to the hyperthermic effects of PGE -- 82). At a later stage, the raised calcium may become the "last straw that breaks the back of the bone marrow and the immune system," since dysregulated raised cytosolic calcium can deplete the ATP reserves and bring about cell death (78) (Ca²⁺ induction of transglutaminase seems to be implicated) *Fig. 9*. Consistently raised PGE₂ can promote the increased production of transglutaminase (95) that, in the presence of Ca²⁺, is efficiently induced and, since the bone marrow macrophages contain TGE (96), an additional mechanism of inhibition of lymphocyte proliferation or blastogenesis can be established (TGE activity is discussed below). Macrophages seem also to take up cystine, manufacture and secrete cysteine that is essential for T cell proliferation and activity (87). When, in AIDS cases with clinical manifestations, the cystine level in the serum is decreased (72, 86), the lower cystine content of the serum in AIDS seems to be a more logical reason for T cell depletion or its ineffective function, particularly with the associated insulin receptor damage (quite apart from the damaging effect of high glutamine content of the serum seen in AIDS). A similar argument in the case of macrophages' "inefficiency" in AIDS may be valid.

If the central histamine-CRF-ACTH-Adrenal axis regulation of metabolism is the primary line of defense to abnormal stresses inflicted on the body, ACTH can directly and strongly inhibit antibody production (54). *In vitro*, ACTH also inhibits interferon production (54); it is interferon-alpha and not AZT that suppresses HIV expression in chronically infected cell lines (117). The same action of histamine in PGE production will render B cells unresponsive and thus antibody production will be under strong PGE regulated negative signalling (115). Bone marrow suppression and decreased macrophage production can also

AIDS: STRESS-INDUCED

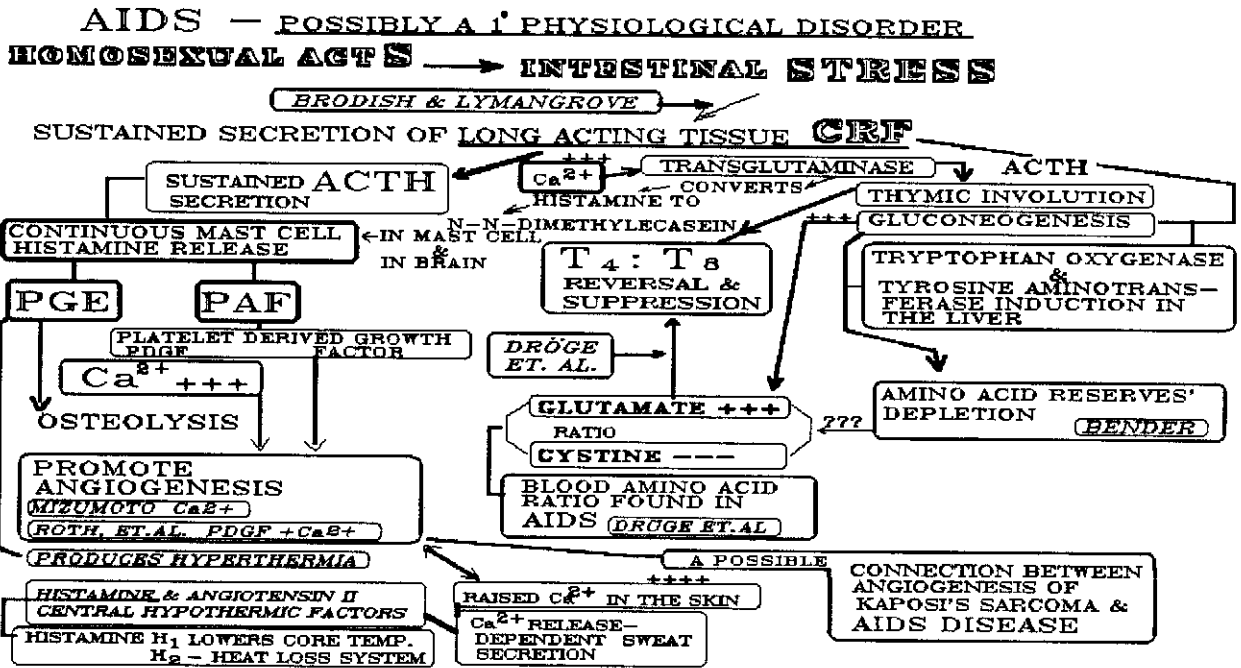


Fig. 9: A proposed schematic model of biochemical events precipitated by intestinal manipulation-induced stress in homosexual behavior and life style, leading to immune system devastations in AIDS.

be the result of the combined action of bradykinin and PGE in the environment of stem cells (128).

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 (88,89). 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 (89), although this may not be the

case in the infected cell culture (121). 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 total pathogenic concentration on HIV seems to be the vogue, the above logic for the possession of a mechanism of virion production for the maintenance of the memory-banks of the immune systems of the body could also apply to other viral disease recurrences seen in AIDS - some select viral antigens augment the growth of HIV-1, whereas, some other viruses are not able to produce the right monokines for the expression of HIV-1 in culture conditions (121), indicating that there is a means of "batching" the antigenic reaction for the immune system memory bank recognition.

The above physiologic approach to the two associated conditions, AIDS and KS, can possibly become an explanation for the views of Levy and Ziegler, who consider AIDS to be an opportunistic infection and KS a result of secondary immune stimulation (66); Amadori et al. (116) also show an immune stimulatory initial response to HIV-1 by the body; Fahey et al. (114) also demonstrate markers of the initial immune stimulation by HIV-1. Similarly, Edelman and Zolla-Pazner (79) in their review

on AIDS, acknowledge an autoimmune disease stage to the condition, even before AIDS clinical manifestations, and they also propose that T4 loss is not the only explanation of the disease and its HIV infection. They consider the disease to be associated with an immune regulatory breakdown that possibly begins with an active immune suppression. They also propose a shift from the present total commitment to HIV research to an additional research of the immune system dysfunction as the initial precipitating factor, also proposed by Batmanghelidj (1). The obvious starting point should be the study of the physiological effects of persistent intestinal stress, and the proposed cortisone release factor induced physiology associated with repeated homosexual acts (1).

TRANSGLUTAMINASE AND IMMUNE SUPPRESSION

If a persistent natural drive for the water metabolism regulation (rationing) and intake of the body also involves the production of prostaglandins, particularly PGE, and PGE₂ as a result of osteolysis alters the Ca²⁺ metabolism of the body, then, the increased production (96) and activity (101,92,97) of the enzyme transglutaminase (TGE), of which a "tissue" type and some cytosolic variety are now recognized, must be anticipated. TGE is strongly anti-inflammatory and immune suppressive (100); it is involved in altering the property of antigenic factors and rendering them non-antigenic. An example: the allograft sperm that becomes non-antigenic to the uterus of the female, a proposed TGE effect (90, 91). Macrophages contain both "tissue" and the cytosolic TGEs. TGE is also present in fibroblasts and **mast cells**; factor XIII is a non-"tissue" TGE that requires cleavage by thrombin to form factor XIIIa; bone marrow-derived macrophages contain both cytosolic and "tissue" TGE, the "tissue" TGE only requires Ca²⁺ for its activation (97). TGE is involved in the cross-linking of glutamine residue of one protein (receptor) to lysine

residue of another protein (receptor). This is a proposed mechanism for plug formation in vascular hemostasis (clot formation) or binding of an "antigen" to a receptor (91). It seems that the resting peripheral blood lymphocytes (PBL) secrete TGE, whereas, the mitogen stimulated lymphocytes do not (98). *In Vitro* experiments show that extracellular TGE modulates TGE release from PBL (feedback augments further secretion ??) and, by altering and modifying the plasma membrane protein of the peripheral blood lymphocytes, is a potent suppressor of mitogen-induced lymphocyte blastogenesis. There is an inverse relationship between the TGE activity and cell proliferation (98). Indeed, it has been proposed that TGE is directly involved in bringing about senescence and the programmed cell death (apoptosis) of different tissues (92,99,102), particularly in the thymus gland induced by glucocorticoids (92) and in the liver (102). It seems that the process involves a drastic change of the protein structure of the cell membrane, rendering it rigid, altering its diffusion and permeation rate (92); this must be the reason for the shrinkage and insolubility of the apoptotic cells seen in the liver (102). The apoptotic cell will undergo phagocytosis (92) and, presumably, until its structure is solubilized, the "host" cell must seem to be multinucleated. This process of TGE-induced apoptosis of T cells (probably from a macrophage source) seems to offer a physiological explanation for syncytia formation seen in AIDS, a phenomenon considered to be the reason for T cell depletion in AIDS (89). However, one of the more logical reasons for the T cells undergoing a "programmed cell death" may be the disturbance and malfunction of the cysteine-dependent cytosolic physiology that involves the insulin receptors as well, rather than the direct action of the HIV.

Histamine is a most important neurotransmitter that is directly involved in the regulation of stress-induced physiology, as well as being a promoter of growth in the body

(1,55,56,57,58,59,60). Transglutaminase enzyme systems are also important regulators of many intricate functions, from immune system suppression to the regulation of some hormone receptor coupling activity by the production of newly formed biopolymers (122) and receptor mediated endocytosis (123). A most important phenomenon that has been presented in a by-the-way manner is the fact that TGE, in an assayable manner, cross-links histamine into N-N-dimethylcasein (124). If histamine is a neurotransmitter that, through its down-stream sub-systems, involve PGE, regulates water metabolism, as well as its being a cellular growth promoting factor - and PGE induces the Ca⁺-dependent TGE activity - the brain tissue also possesses the same transglutaminase activity, capable of (*in vitro*) the crosslinking of human neurofilament protein into insoluble polymers (125). If, under these stress-induced (dehydration and cellular water loss -1) physiological states, the toxicity of aluminium is added to the "inflammatory" process, production of a dementia of the Alzheimer type will not be out of the question (1).

If the brain neurotransmitter histamine is also affected by the brain TGE and constantly converted to N-N-dimethylcasein, then the normal stress response of the body physiology, at some point in time, will not be effective enough to cope. If, at the initial stages the CRF, ACTH and the subordinate systems are actively integrated through the gradual loss of the histaminergic activity of the brain, the centrally stimulated CRF production will possibly be inadequate for the extreme stresses (emotional, intestinal injury, infection and possibly recreational chemicals- in AIDS or drug abuse) that the life-style of the homosexual behavior will exact on the body, although the body has other normally and possibly non-stress regulated but selective mechanisms for CRF production (126). What possible effects the high tissue TGE content of the ACTH producing cells in the human pituitary gland (127) and the mast cells may exert under the ex-

aggerated PGE and Ca^{2+} production seen in AIDS also need clarification. Lower steroid production at the final stages of clinical AIDS must be a primary factor in the terminal pathology of the disease - a form of programmed death associated with the life-style - written into the natural design of the human body.

The disorders that are classified under AIDS can be better explained from the angle of a physiologic understanding of the inter-related events than the stretching of the imagination with any perceived role of the retrovirus (only one of the four class of operative stressors to the body in AIDS) in the immune system suppression. As examples: Disturbed glutamate metabolism and its neurotoxicity is implicated in serious neurological disorders (103, 104), including Alzheimer's disease (129). Therefore, is it not logical to blame the many fold, high glutamate levels present in the serum of AIDS and AIDS associated conditions than to try and establish an imaginative role for the virus in the neurological disorders seen in AIDS (89)? Hemophiliacs who receive factor VIII concentrate also receive factor XIII, a transglutaminase. Is it not more logical to look for the immune suppression of TGE than the effect of the retrovirus in the hemophiliacs (105-108)? Liver damage is more prevalent in these cases (109); would it not be difficult to reason a role for the virus and to ignore the actual apoptotic effect of TGE on the liver (102), when TGE is being administered to these patients on a regular basis? It seems the virus must be allocated a position of secondary importance in precipitation of AIDS in hemophiliacs, who must have a disturbed immune system to start with. Hemophiliacs are persistently thrombocytopenic (109) and, since KS cell growth seems to depend on platelet derived growth factor (93), development of KS also seems not to be a mode of disease presentation in hemophiliacs with AIDS.

In the immune compromised expectant mothers with AIDS, further immune sup-

pressive mechanisms allow the allograft sperm to establish the intrauterine life of the fetus for the duration of the pregnancy. In the third trimester of even normal and non HIV infected pregnancies the T4/T8 percentage composition is altered, a seemingly H_1 - H_2 receptor ratio-dependent phenomenon (147). In the infant that is immune naive and can rely only on the mother's immune system for protection when the same amino acid pool is available to the fetus as to the mother, just because of its presence and infection of some white cells, the HIV virus should not be considered as the primary and only virus can cause immune system suppression in infants with AIDS; inoculation with other slowly replicating viruses can possibly produce the same immune system imbalance. Prior to any other consideration, the investigation of the associated disturbed amino acid metabolism of the patients (86,87,72), the mother and the child, is indicated. In a family with AIDS, the socio-economic elements that could produce additional imbalance to the already established stress physiology are innumerable (110).

Thus, AIDS and its associated conditions seem to fit a stress-induced physiological/metabolic disorder more easily than a primary virus induced immune system suppression.

In animals, it has been shown that CRF itself is involved in mood and behavior transformation, a possible response to environmental stress, producing alertness, increased sensitivity, increased hesitancy, but lowered adventure and exploration activity (73); all of these central actions of CRF have been demonstrated in rats. In the rhesus monkey, the central action of CRF injected directly into the brain, apart from the disruptive behavior pattern, suppresses the normal sexual behavior (73). Is it remotely possible that during the growth periods in childhood, environmental, social, economical and emotional factors could cause the establishment of a stress physiology in the body; and with the persistence of the stressors' influence, in

those unable to adjust and surmount the stress, possibly bring about the central influence of high CRF production, and in some, step by step, lead the "child" to the physiological ending of immune deficiency syndrome in early adult life and sexual aberrations, be steps in the process?

DISCUSSION

If the immune system activation is experimentally demonstrated to be initiated and dependent on interleukin-1 (IL-1) - among the many other functions of IL-1 (135) - IL-1 seems to be a recognized neuroactive substance synthesized in the hypothalamic, the arcuate, the periventricular, the preoptic and the ventromedial nuclei of the brain; IL-1 fibers are also recognized, establishing a neurotransmitter system status for IL-1 (136). IL-1 receptors are sub-divided into alpha and beta subgroups that may have different functional activities in the regulation of the immune system, including the hypothalamic-pituitary-adrenal axis stimulation (136).

While the central action of histamine regulates the water intake of the body, even peripherally, histamine release factor(s) (HRF) is/are produced by the mononuclear cells (130,131,132,133,134 - recognized more in B cells), even the two cell human embryo in culture produces HRF (130). The production of this factor may be a signal system for the "fluid" flow and energy regulation during normal physiological functions of the particular tissue that produces the HRF. By the fact that basophils seem to have an intracellular transport system for the gradual release of their granules which they resynthesize, these roving cells must be fulfilling a more important function in the maintenance of homeostatic balance within the range of their flow than the views of their being responsible for allergic or anaphylactic reactions. The same ar-

gument applies to the mucosal mast cells that have almost 1/10 the histamine content of the tissue mast cells and their histamine release mechanisms differ. However, since histamine also has a major role and responsibility for crisis management, to observe a priority and rationing procedure for the immune system, a distinguishing mechanism and system seems to have been naturally devised. Histamine induced histamine release inhibitory factor (HRIF) is produced by the mononuclear cells that, at very low physiological levels inhibits the action of HRF (130); the action of HRIF is exclusive to inhibition of histamine release by HRF, it does not prevent the release of histamine by other secretagogues (130,131,132, 133,134).

If the central activity of IL-1 regulates the immune system and the central activity of the neurotransmitter histamine is directly and indirectly involved in the energy, water intake and blood flow regulation, although not yet exposed, there must be a central integration of function between the histaminergic and the IL-1 neuronal systems. Under normal circumstances, this integration of activity should be "silently" regulated, until and unless the stress-induced, or age dependent dehydration of the body places a greater burden on the central and peripheral histaminergic neuronal system. With increased demands on the water regulatory role of histamine, there seems to be an equally integrated rise in the rate of histamine production. If we appreciate that the main function of vasopressin is water preservation and this activity is induced by the central action of histamine on vasopressin release then, among the primary histamine regulated activities seems to be the inhibition of water elimination. The two main sites of water loss are the urinary system and the evaporative processes in the lung and the skin surfaces. If the core temperature of the body is reduced by the central H₁ receptor action, surely the bronchial constrictive mechanism attributed to histamine reaction (137,138) should also be read as a naturally

designed mechanism for reduction of water loss through the respiratory tract. If the histamine granules are water soluble and ultimately and gradually release (or undergo intracellular metabolization) from the basophil and the mast cells by the direct action of only water (120), and increased water intake regulates the intracellular fluid volume (1) - that must initially regulate the fluid volume of the mucosal mast cells and the basophils in circulation - surely one way of dealing with excess histamine release in hypersensitivity reactions would be by the conscious regulation of water intake of the body as a more natural treatment method (1).

If AIDS has a primary stress-induced metabolic component, and this stress response of the body involves the continued activity of vasopressin, it is important to note that one of the HIV envelope proteins shares antigenic epitope with T-cell leukemia viruses; a similar antigenic epitope is found in human and rat brain hormone vasopressin-neurophysin (142). Is this relationship an insignificant happenstance, or is there more to this phenomenon than is apparent at the moment?

CONCLUSION

During the last few decades the systematic research of the different disciplines of human and animal applied sciences has produced and clarified a vast quantity of information; when these discoveries are viewed in the isolation of the arbitrary divisions of the different disciplines, the understanding of disease emergence in humans becomes more complicated every day. But, when viewed from the grass roots approach to water metabolism disturbances of the body, most of these isolated research findings establish a logic and a theme, demonstrating an integrated order around the functions of water in the total body physiology (1). The milieu interieur and the microenvironment of the cell is still fun-

damentally important to the normal defense mechanisms of the body. The histaminergic neurotransmission system, the serotonergic neurotransmission system and the renin-angiotensin system are interdependent and, in an integrated way, regulate the microenvironment, the regional and the total body's homeostatic balance.

Because of the body's total dependence on its metabolism, the principal element it seeks for its regulatory action is water; accordingly, its intake and regulation mechanisms in the body will also become the prime objective of each and all of these involved neurotransmission systems. Since all of these are determined systems, their direct or downstream manipulation will only mask the signals associated with the prime purpose of these systems or their subordinate down-stream effectors, but will not alter the determination and the responsibility of these systems to maintain the dependent functions. To overcome the obstructive effects of various chemical manipulations, the systems will go into over production. In effect, when prostaglandin inhibitors are used, the fine-tune regulatory functions involving the facilitation of flow in the microenvironment and cell growth, inhibition - as well as the promotion of cell maturation and final differentiation - is being down-regulated. This could possibly result in an increased suppressor cell activity in the bone marrow; because the histaminergic drive and H₂ activation of the dominant suppressor cell population of the bone marrow and HSF production could increase, since the feedback inhibitory effect of PGE₂ on histamine production will also be blocked when PGE production is inhibited. If there is a remote possibility that T₈ is a less mature form of T₄, then PGE's role in maturation of growing cells will also be less effective.

If H₁ receptor blockers are used, the outcome can (possibly) be almost the same, except that it will become operative at a much higher level of interaction, and will also involve the cat-

ion exchange regulation. H₂ blockers are probably less damaging because the same adenylate cyclase pool is probably being activated by other receptors, releasing energy for the cell function; however, in the absence of adequate free water, capillary circulation to the brain is also an H₂ regulated action (1). It should be remembered that the brain cell consists of 85% water (80) and is very sensitive to water loss. It should also be recognized that water is not the structureless bulk material it has been viewed up to now. Water seems to have as yet unaccounted for properties; it is an active component of the macromolecular structure of the cell building-block in its own independent right (80). Its loss or displacement would cause the disintegration of the framework of the cell structure (80).

Over-produced and circulating histamine, unless physiologically inhibited, can release extra energy within the cell, locking it into an amplification of stimuli and a forced drive of the dependent functions (the effect of Slow Reacting Substance may be a part of this phenomenon). These functions may be cell division or excess acid production, although the primary physiological responsibility is to maintain neurotransmission and neuromodulation and all the energy dependent functions of cation exchange at the inner membranes of the cell or the outer cell membrane.

One very important fact seems to emerge from research of the neurotransmitter histamine. While the immune system regulatory role of histamine has been recognized for a long time, the more important water regulatory functions of this neurotransmitter is only now gradually being recognized. When the body becomes gradually and chronically dehydrated (1), placing a much greater demand on the regulatory role of histamine, unless the immune system regulatory role of histamine is naturally suppressed, dehydration would generate a constant lymphatic inflam-

matory response. If the prostaglandin activation by histamine simultaneously brings about the activation of transglutaminase, with all its lymphocyte and bone marrow inhibitory effects, then, histamine itself seems to demonstrate the induction of an indirect mechanism for immune system inhibition at times of continued dehydration. The glucocorticoid hormones (histamine and stress induced) also inhibit the immunoregulatory actions of interleukin-1 (148), when histamine can inhibit interleukin-2 and interferon-gamma production (149).

Having argued against a primary role for the HIV in AIDS, it seems, the fear of impending slow but sure death, that the media treatment of this condition has drummed in the mind of the heterosexuals, can become a contributing stress factor and, in those who have accidentally been infected with the virus, may do more damage than the virus itself.

In infants, the process of growth normally involves a much higher rate of histamine production and release. Histamine naturally produces an immune system suppression (149). This suppressive activity of histamine seems to be associated with a high rate of cAMP production. If we assume that cAMP production is a post energy release phenomenon, a (well monitored) high calorie (sugar for its insulin releasing effect) and well balanced protein diet (high pulse containing), plus a substantial increase in water content of the diet (to reduce excessive histamine production), may possibly improve the odds for survival of the HIV infected children. The calcium content of the milk may also have to be reduced, or milk in the diet decreased.

Clinical experience has shown that increase in the daily water intake removes the symptoms of a stress precipitated "disease" condition. At present, H₂ receptor blocking agents are being used for the temporary treatment of the same condition (13,14). The histaminergic neuronal system has H₃ receptors for its feedback inhibitory mechanisms (16,17). Adequate water intake, to promote cell hydra-

tion by a process of free diffusion of water, instead of a predominance of ionic coupled flow, can possibly make this feedback inhibition more efficient (1). The mast cell in amphibians does not contain histamine granules and, with adequate hydration, the mesenteric mast cells in the rat decrease (21,28). Dehydration and stress can produce an imbalance in the amino acid metabolism of the body. Adequate intake of a balanced protein diet as a supplement to increase water intake is essential in the treatment phase of the histamine related immune system disturbance and the associated pathological states, with immune deficiency manifestations, further devastated by stressing the intestinal tract repeatedly (1), or by the chemical interference with the direct or indirect downstream water regulatory functions of neurotransmitter histamine in the body.

The primary concern of histamine, PGE, kinins and PAF in the body, is water intake and flow regulation, as well as osmoregulation, totally or regionally; the associated pain signal is a secondary alarm for the immobilization of the water deficient and compromised region. This is most apparent in the rheumatoid arthritic joint, where the vascularization of the joint capsule may be the only efficient and direct way of bringing increased water to cartilaginous joint surfaces that depend on adequate hydration for their efficient function (instead of the normal diffusion of water through the vascular system in the bone structure, that must give priority to the needs of the bone marrow when there is chronic dehydration). Superoxide and hydrogen peroxide production within the same fluid medium may also have to be viewed as a means of providing supplemental free oxygen for the cells that are involved in the repair systems of the joint surfaces; it is not certain that superoxide production has any other function than a useful integration and a biological modulation of important physiological events (118). Within the projections of this logic, the fluid in the joint is absolutely essen-

tial to the repair systems of the arthritic joint, its protein content acts as a buffer to the H^+ produced; its extraction may delay repair time. In any event, the reactions and pain regulation of the joints seem to be centrally (139) and possibly bilaterally regulated.

Many of the medications used as antidepressant drugs have very strong antihistaminergic action. It should be acknowledged that histamine, directly and indirectly, is responsible for energy release in the cells of the body, particularly the brain cell. cAMP that is produced by the action of histamine and its other sub-systems, involved in water and flow regulation, has a direct suppressive function within the cells that generate it. It seems, if there is any suppressive action associated with histamine metabolism of the neuronal tissue, increased and regulated water intake may prove to be effective in alleviating the symptoms of depression. It is becoming more apparent that although modern humans are N millions of years down the road of transformation from the original species that stepped out of water, the physiological translation of stress and anxiety still reflects the anxiety of being dehydrated; the associated neurotransmitter systems and their sub-systems are all water intake regulators for that particular body and every single cell of it, without exception. Even to the point of allowing a transformation for some of the cells that champion a better regulation of their regional water intake (1), by the fact that some of the tumor cells begin to demonstrate a histamine synthesizing ability (140), the breakdown mechanism for histamine seems to be disturbed in tumor bearing animals (141).

Now that extensive research is exposing the neurotransmitter status and the natural role of histamine in the water regulation of the body, a physiology oriented approach to prevention and treatment of many disease conditions may become more easily achieved. Thus, the need for the recognition of a metabolic component - in particular, water - in disease emer-

gence is strongly indicated.

The alternative understanding of the neurotransmitter histamine was initiated by the first observation that a glass of water relieves the dyspeptic pain associated with a disease condition (13,14) and is strongly supported by research that demonstrated a need for paradigm change in the science of medicine (1). In effect, the paradigm change took place when the first patient suffering from PUD responded to purely water that relieved his pain, a form of treatment he preferred to the customary advice and the medications that are at present at the tip of a physician's pen. How quickly the transformation of medical attitudes to the paradigm change takes place is dependent on the value placed on the relationship between the physician and the patient, and on how committed to the advancement of science the individual or the health system of the society is to begin to evaluate the all-round advantages of the alternative views on the natural functions of the neurotransmitter histamine, and adoption of a paradigm change for the good of the human body.

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