Pain: A Need for Paradigm Change

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(Guest Lecture)

Abstract. From November 1979 to May 1982, I had the "honor" of serving time at Evin political prison, Teheran Iran. Evin is the historical prison which has set the pace of revolution in the country. At Evin it was discovered that increased regular intake of water improved the clinical picture of peptic ulcer disease. One of the main components of this picture was pain of varying severity, sometimes very severe indeed. Theoretical research to find the physiological reasons for the observed effect of water, in a condition currently classified as disease, has revealed a neurotransmitter, an osmoregulator, a water intake promoter status and a role for histamine. The action of histamine seems to be coupled to the efficient function of the cation pumps. Histamine and serotonin are involved in the regulation of the body's water balance. Cellular "free water" insufficiency produces a disturbance of tryptophan metabolism; it is this disturbance and induced functional deficiency altering the homeostatic balance that produces pain and eventually tissue transformation and/or damage. This pain is being introduced as a signal system denoting free water deficiency of the cell and, therefore, it should be classified as thirst pain. Histamine and the renin-angiotensin system also coordinate the water intake and sodium balance of the body. With the induction of renin-angiotensin system for increase in water intake, threshold rates for water intake and the threshold rates for raising blood pressure seem close.

Treatment of clinically diagnosed peptic ulcer disease with increased regular intake of water at Evin prison has been reported (1,2). The prison diet consisted mainly of starch and pulses (such as beans, peas, lentils, a great amount of broad beans), low in animal protein or fat. In this report, observations on water induced relief of abdominal pain, which could not have been clearly associated with peptic ulcer disease, were also recorded. Accordingly, there was the indication that, as well as the symptoms and signs of the clinically diagnosed peptic ulcer disease under the existing, yet constant environmental factors, being transformed with increased water intake, other types of pain also responded to "water test". A number of patients with hematemesis, apart from blood transfusion, were for the first 36-48 hours given a regular drink of a strong sugar solution, followed by regular water intake (1,2,25).

In the older age group, in the same environment, the main clinical manifestation of stress was hypertension of varying severity. On a few occasions, individuals without a history of hypertension registered a systolic pressure of well over 200 mm. mercury. One patient's systolic pressure reached 300 mm. mercury. These patients were also advised to increase their water intake in addition to the medication they were receiving.

The clinical observations made at Evin required scientific explanation. In the laboratory we record our observations on laboratory animals; here, observations were made on human beings. If water was producing the recorded responses in conditions that are normally classified as disease, then either the classifications are wrong or the physiological effect of the substance we recognize as water has not received due attention. A very extensive theoretical search has produced the following concepts. It now seems that the scope of the regulatory physiological effect of water has not received sufficient attention when evaluating disease processes, and that the body's response and reaction to simple water deficiency...
has led to confused trends in medicine. In the hope of generating interest, the following thoughts on the involvement and possible role of disturbances in water metabolism responsible for disease production are presented. This course has become necessary, since there are no means of comparing water with any other substance in order to discover its effect. One can only rely on the body's response to regulated water supplementation, and this means simple clinical evaluation of the patient and his complaint before, during and after adequate hydration: this is exactly what took place at Evin.

THE BASIC PARAMETERS

Assuming that man is one type of space satellite of the initial "replicators" from the "primeval soup" and that he has brought his salt water dependence with him, in the same way as man takes his capsule into space with him; again assuming that subdisciplines of the science of biology are to be viewed according to the Darwinian concept of evolution, the law of the "survival of the stable" (3) would continue to apply to the descendants of the first cellular creation of the earlier creative replicators. On the basis of this paradigm, man, the ultimate "survival machine" of the first replicator cell(3), would also have to cope with the osmotic forces of the solutes in its cell environment. We see that it has retained the power to equilibrate effectively the osmotic balance of the cells by sending sodium ions out of the cell and returning potassium ions inside the cells. This mechanism has developed into a very complex pump system called the cation pump or sodium potassium adenosine triphosphatase pump. Coupled to this pump action is the activation of the energy transforming enzyme phosphatase. For the transport of three mol. of sodium and two mol. potassium, one mol. of ATP is hydrolyzed (4). The same pump mechanism is developed around the hydrogen ion, calcium ion and possibly the magnesium ion, to activate the ATPase (4,5,6,7). Even the shift of the dominant cellular polyvalent ions, such as magnesium and phosphorus, seem to be coupled together with the shift of potassium into the cell. According to Cronin, there is a close relationship between the movement of magnesium, and potassium in the cells of the body. In general, a change in the serum level of one ion causes the other to deviate in the same direction. Calcium ion movement, absorption and its bone tissue metabolism seems also, in turn, to be coupled to magnesium turnover (7). According to Hesketh (99), evidence has accumulated indicating that cations play important roles within the cell in controlling metabolism. In particular, it is now established that changes in the intracellular concentration of calcium regulate not only contraction in the muscle, but conduction in nerve, coupling of secretion to stimulus in cells such as platelets and mast cells, the initiation of development in fertilized eggs and, possibly, the activation of growth in normal cells. A second Ca++ transport across the cell membrane, other than Mg ion dependent movement, seems to be coupled to Na+ movement; this Na+/Ca++ exchange action is dependent on the transmembrane Na+ gradient maintained by Na+-K+ activated ATPase. Current evidence suggests a stoichiometry of 3Na+:1Ca++ and that the exchange protein functions independently of ATP, although, in the presence of ATP, the ionic affinity of the system increases. Again, according to Hesketh, the electrogenic Na+/K+ exchange catalysed by the Na+K+ ATPase, may in turn be coupled to an electrically silent Na+/H+ protein. In some cells this latter protein appears to regulate intracellular pH, whereas in others Cl-/HCO3- is the predominant mechanism. The mast cell secretion activation depends on free calcium ion in the cell. It seems that, of the total calcium content of the cells, 0.01% exists in the free ionised form and, of the rest, 40-60% is sequestered in the mitochondria, either ionised, bound or precipitated as the carbonate or phosphate salt, 20% occurs in the endoplasmic reticulum and the remainder is either accumulated in secretory granule or the nucleus, or bound to macromolecules. It should be borne in mind that the activity of the plasma membrane cation pumps, in conjunction with the leakage across the membrane determines the steady-state concentration of free ions within the cytosol (99,100). According to Edelman and Hiatt, biosynthesis and regulation of Na+/K+ pump protein is thyroid dependent; this augmentation of the transport system accounts for 50-75% of the thermogenic action of the thyroid hormone. An equally important function of the Na+/K+ pump is the regulation and maintenance of the cell volume (100). The existence of linked passive transport of Na+/Ca++, K+/Ca++ and Na+/H+ exchange that are coupled to the action of the Na+K+ pump is also noted. There are other cotransport systems for glucose and amino acids that are coupled to Na+ exchange because, active transport of organic solutes by animal cells is sodium dependent, without exception (141). Also, pH gradient across membranes appear to be determined by the action of the H+/Na+ transport (100). According to Kaufmann and Silman (101), it seems that the appearance of ion channels is pH regulated. In reconstituted membranes, significant opening and closing of ion channels takes place at pH range 2.5-3 and
no appearance of channels is observed at below pH 2 (101).

Today, medical research has forced the conclusion that many disease conditions need to be controlled through purposeful limitation of sodium intake, or its encouraged expulsion from the body. The drugs most used are synthetically modified carbonic anhydrase inhibitors (8).

According to Wiggins, it seems that the mechanism that controls, or brings about the effective function of the said cation pumps, utilizes an energy transforming property of water, the solvent of its environment. The source of energy for cation transport or for ATP synthesis lies in increases in chemical potential with increasing hydration of small cations and polyphosphate anions in the highly structured interfacial aqueous phase of the two phosphorylated intermediates (6). Efficient operation of the (Na⁺-K⁺)-ATPase seems to require that the chemical potential of K⁺ decreases in the highly ordered phase. The properties of the water must then be such that lightly hydrated solutes (large univalent cations and anions and small non-electrolytes) decrease in chemical potential when the phase change occurs (6)." 

Water in the cells of the body, according to Hempling, is considered to be utilized for two different functions: water which is osmotically active and, by difference, that volume of cell water which is not active osmotically. "The key points were that the percentage of water in the cells remained constant, but the fraction which was osmotically active decreased as the cell progressed through the cell cycle" (9).

In light of the above, the efficiency of the function of the cation pumps and energy transformation would then be contingent upon the proportionate or quantitative presence of "free water" in the area of "demand"; be this demand within the brain and the spinal cord, renal tissue, the gastrointestinal tract, or for that matter any other tissue or organ of the body.

In the aquatic or amphibian species, except for the marine mammals such as the whale or the seal that cannot easily utilize the sea water (10), the fluid environment would present a uniform consistency, enabling the species concerned to adapt and maintain a uniform fluid intake. In terrestrial animals that have to adapt to a non-uniform and changing environment, what would happen if water intake is not sufficiently regular to maintain a uniform, let alone an upgraded demand on the cation pumps?

Histamine is now being recognized to be a neurotransmitter (11,12). By the presence of L-amino acid decarboxylase and the specific L-histidine decarboxylase, found in very high activity in catecholaminergic and serotonergic neurones, histamine is being considered to be a neurotransmitter, with also a specific neuronal system of its own, particularly in the proximal part of the duodenum (11,102,103). The basophil, the mast cell, the enterochromaffin-like cells, as well as the neuronal tissue that contain histamine (13), particularly the neuronal tissue and the mast cell, demonstrate differing mechanisms for the release of their amine granules (11). A highly significant characteristic is the effect of potassium ion induced depolarization; histamine of the neurones and the synaptosomes is released when depolarization takes place, whereas histamine granules of the mast cell are not released (11). Mast cell degranulator, compound 48/80, whilst it effectively and proportionately degranulates the mast cell, has no effect on the release of neuronal or the synaptosomal histamine (11). ACTH also invokes a proportionate release of histamine and serotonin from mast cells; the release process is very rapid and up to 90% of HA. and 5-HT of rat mast cells is released by ACTH, and the response to ACTH being enhanced in the presence of Ca²⁺ (104). Another significant phenomenon is the mode of recovery of the amine; the synaptosomes need to be hypoosmotically treated before the granules can be recovered intact in the synaptic vesicles (11,12,14).

The histaminergic receptors are stated to belong to either H₁, H₂ or H₃ sub-class. H₁-receptor mediated responses include glycogenolysis, stimulation of cyclic GMP formation, potentiation of cyclic AMP formation, possibly linked to phosphatidylinositol breakdown and mobilization of Ca²⁺ from its endoplasmic reticulum stores involving Ca²⁺-calmodulin complex. H₂-receptors seem to be directly linked to an adenylate cyclase, and their stimulation results in enhanced electrophysiologically recorded response to excitatory agents. H₁ and H₂-receptors jointly seem to stimulate activation of protein kinase C, resulting in phosphorylation of a protein regulating the H₂-receptor-linked adenylate cyclase (105). H₃ receptors are autoreceptors mediating inhibition of histamine release from and biosynthesis in histaminergic nerve terminals in the CNS. In vitro experiments have shown the inhibitory action of H₃-receptors to be concentration dependent with a maximal inhibition of up to 60% (105). H₃-receptors are presynaptic and modulate production and release of histamine as a result of feedback from
stimulus coupled H1 or H2 receptors' response (106). When histamine is introduced into the lateral hypothalamus of rats it induces drinking even in satiated animals. Gerald and Maickel have shown that 80 micrograms of histamine, when injected in the hypothalamus, produced a three-fold increase in water intake even in rats that were satiated. They suggest that central histaminergic functions may be involved in thirst-induced consumption of fluids (15). Leibowitz has shown that when small dosages of about 50ng. are injected into the different parts of the hypothalamus, histamine can elicit water consumption in water-satiated rats; with the statement that this action of histamine is a centrally and not a peripherally mediated phenomenon (16). According to Kraly, histamine is also involved in the induction of drinking by a gastric vagotomy (17). In another paper, Kraly and associates demonstrate a histaminergic mechanism for drinking elicited by insulin in the rat (18). Kraly further demonstrates a preabsorptive pre gastric vagally mediated histaminergic component of drinking by eating in the rat (19,20); selective gastric vagotomy abolishes drinking response to low doses of histamine in the rat, while the combination of vagotomy with angiotensin-converting enzyme inhibitor (captopril) abolishes drinking elicited by higher doses of subcutaneous histamine (107). According to Goldstein and Halperin, histamine is the mast cell amine involved in the triggering of the drinking response induced by a hypertonic load through the activation of an H2 receptor. They propose that the mast cell has certain characteristics one would expect to see in an osmotic receptor (21). Goldstein and associates, in another paper, further demonstrate a firm association of histamine and water metabolism of the terrestrial vertebrates, the mast cell of the fish and the amphibians differ from those of higher vertebrates by being devoid of histamine; on the other hand, in the reptilians, the first truly terrestrial vertebrates, tissue histamine is mainly stored in mast cell (reported from Reite). They further report, also in the reptilians, as stressed by Kaufman and Fitzsimmons, that a new dimension of water balance appears, namely the ability to drink water when the need arises. With water deprivation and food intake, they demonstrate an increase in the mast cell number in the rat mesentery (22).

Hiroshi Izumi and associates have demonstrated that compound 48/80 and histamine stimulate water intake by different mechanisms, peripherally through stimulation of the renin-angiotensin system and centrally mediated by its direct action on the brain. They also report a change in plasma Na+ and K+ levels after administration of compound 48/80, histamine and isoproterenol (23).

Humes also expands on the different aspects of the thirst mechanism involving the renin-angiotensin system, first demonstrated by Fitzsimmons (108), indicating that the subfornical organ is the only site for the dipsogenic receptors for angiotensin II in the entire brain. Beta-adrenergic agents stimulate drinking, but their action appear to be mediated via the renin-angiotensin system. Hume also states that, "since extracellular fluid volume is determined by Na+ balance, the major determinants of intracellular fluid and extracellular fluid volume homeostasis are clearly separate: sodium balance regulates extracellular fluid volume; water balance regulates intracellular fluid volume, (24)." It seems that, in any water loss, approximately 66% comes from intracellular fluid volume, 26% from interstitial fluid volume and only 8% from intravascular fluid volume (24). Thus, hypovolemic shock is rare in pure or "free water" loss or deficiency (24).

On the basis of the above information, namely that hypovolemic treatment stabilized the histamine granules within its vesicles, and that the effect of the K+ by itself, enhanced by the presence of Ca++ which degranulate the sympathetic amine histamine; the indication that histamine and the sympathomimetic amine isoproterenol affect plasma Na+ and K+ levels and that H2 receptor stimulation enhances electrophysiologically recorded responses to excitatory agents: the indication that the cation pumps are "driven" by water - it is proposed (25) that: histamine is a neurotransmitter amine that demonstrates a mechanism of production and release that is extremely sensitive to the inefficient function of the cation pump; that histamine is reproduced and released when there is a K+ build up around the site of action or increased activity forced on the tissue. The tissue most susceptible to such fluctuation would, of necessity, be the nervous system and its transmission mechanism.

It has also been proposed that certain neurotransmitters, histamine in particular, demonstrate certain properties that would make them candidates to be classified as responsible for the efficient operation of the cation pumps; whilst promoting water intake by the body, in the interim, they act as an emergency substitute for water with respect to bringing about the cation pump drive (25), as well as promoting post receptor energy release (26,105) for this function.

In light of this and other information on
the apparent involvement of histamine in the water intake of the body and its functional role as a neurotransmitter and an osmoregulator, in order for cation pumps to revert to their natural mode of function, histamine, it seems, has become a messenger in the loop that promotes water intake by the "animal". It seems that the prominent serotonergic neuromodulating neuronal system is another major water intake promoting part of the loop. According to Holstein, the dipsogenic effect seen in the absence of intestinal perfusion indicates that 5-HT may be involved also in the regulation of drinking (27). Serotonin seems to be involved in regulation of the gastrointestinal tract function: it promotes water intake, inhibits acid production; inhibits acid production by histamine at 33% salt water perfusion of cod intestine; while, with 67% salt water perfusion of the intestine, the action of histamine is not inhibited by serotonin (27). Serotonin also promotes mucus production making the gastric effluence more viscous. Despite inhibition of acid secretion, volume outflow increases during i.m. water support, not during intestinal perfusion (27). Accordingly, 5-HT is dipsogenic in the cod and, as with all, the dipsogenic response is suppressed by an intestinal satiety mechanism, the latter probably activated by intestinal distension (27). Serotonin inhibits acid production in the rat stomach. As shown, 5-HT on the serosal side caused significant inhibition of the acid secretory response to histamine (Canfield and Spencer 28). According to Kraly, histamine and serotonin independently elicit drinking in the rat, possibly through the peripheral action of renin-angiotensin stimulation when they are released from the mast cells (109). Laczi and associates demonstrate presence of a strong stimulatory effect on the release of arginine-8-vasopressin by histamine in man (115). Panula and associates (116) report that the distribution of histamine resembles the distribution of serotonin; that histamine participates in the physiological regulation of pituitary hormones, for example, ACTH, perhaps by releasing vasopressin, which has corticotropin releasing hormone activity. Shenker and associates (119) postulate the presence of a direct central stimulatory effect of serotonin on secretion of aldosterone.

When a satiety mechanism is being anticipated, it is interesting to note that, according to Christofides and associates, water intake promotes a volume dependent sustained secretion of hormone motilin (29). Yet hormone motilin itself has been isolated in the EC cells (30); and its serotonin-like characteristics are being postulated; it is likely that the serotonin and motilin granules of density 1.20 in this study are identical and thus represent EC2 granules" (Bryant and associates,30).

According to Fernstrom, growth hormone secretion, blood pressure, pain, sleep and appetite seem to be strongly affected by the serotonergic neuronal system of the brain (31). Blood pressure is reduced, the pain threshold is raised, and appetite for carbohydrates is reduced, whilst protein intake is not affected. According to Costa and associates, the more confirmed hypothesis is that the decrease of serotonergic function in the brain or spinal cord causes an increase of sensitivity and reactivity to noxious stimuli, whereas an increase of serotonergic neurotransmission is correlated to analgesia (32). Seltzer and associates, on the subject of chronic maxillofacial pain tolerance, state that manipulation of diet to favor tryptophan and therefore a rise in brain serotonin, results in a significant reduction in pain intensity (33). Pollack and associates also state, a high tryptophan diet can alter chronic pain sensitivity (34). It seems that even morphia induced analgesia is produced through the serotonergic neuronal system in the raphe nuclei of the brain, particularly raphe magnus. The activation of this nucleus can even produce depolarization of cutaneous afferent terminals of mechanoreceptors as well as noicceptors (35).

According to Katchalski-Katzir(36), three to ten amino acid residues are highly flexible in solutions of low viscosity; as the viscosity of the medium increases, conformational changes slow down. In solutions of high viscosity, the peptide chains become completely frozen in their conformation. Their data reveals that, conformational flexibility of peptides or nucleotide oligomers enables them not only to recognize the biological receptors but also to fold into the specific three- dimensional receptor structure. It is further stated that this requirement applies to endorphins, enkephalins, ACTH and growth hormone. In the same vein, it is stated that globular proteins "breathe", allowing oxygen consumption and opening of channels to release their formed products. This same efficiency of function, as a result of conformational change acceleration, also applies to immunoglobulins and side chains to proteins. The implications of this aspect of hydration are vast. It seems that the aromatic amino acids within proteins also continue to breathe or force their inherent characteristics on the constituted protein(36). Munro and associates have calculated the conformational change for tryptophan. At 5°C it has practically no rotational freedom, whereas at 43°C it rotates with a correlation time of 0.14 nano-seconds, indicating
that it arises from rotation of tryptophan with the whole protein or a large domain of it. At 43°C, this tryptophan residue acquires rotational freedom independent of the whole protein (37). This rotational property of tryptophan must also apply to its loose binding to albumin.

Tryptophan has to be carried through the blood brain barrier (as well as through cell membrane in the gastrointestinal tract or the cells dependent on its metabolism) competing with the other large neutral amino acids - leucine, isoleucine, valine, tyrosine and phenylalanine - that share the same carrier mechanism. Insulin, secreted as a response to carbohydrates in the diet, alters the odds in favor of tryptophan against the competing large neutral amino acids for its transport across the blood brain barrier, by stimulating the entry of the branched-chain amino acids into muscle tissue (38,39).

This increase in tryptophan conformational change, with increased enthalpy, will favor its easier release from albumin binding site and make a faster lock into the transporter protein possible; it will give it still one more advantage at the antiluminal side of the brain capillaries, where the mitochondria of the capillaries and the cation pumps are situated (40). This heat excitability of tryptophan must be involved in the “shaving” mechanism attributed to the brain capillaries for their uptake of tryptophan from albumin. The heat produced by the cation pump has been calculated by George and associates (6), and Hempling also talks of “high heats of activation” (9). There seems to be substantial evidence that “free water”, as the driving force of the cation pump and also essential in the initial phase of fat and protein breakdown in gluconeogenesis, is actually bringing about energy transformation and enthalpy of activation and, therefore, is indirectly upgrading the rotational properties of proteins and polypeptides as well as the amino acids, tryptophan in particular. Accordingly, it effectively becomes responsible for the efficiency of conformational change of tryptophan and carrier or transporter proteins enabling them to keep up with the demand for their very diverse functions in the body (42,43,44). In the case of axonal transport, kinesin class of transporter proteins have been identified (41, 112), the assumption is that a similar mechanism and type of protein transporter systems involving microtubule activated ATPase exist within other cells (113, 114, 110).

Theoretically, the need for free water in gluconeogenesis, if continued, can bring about “free water loss” and, is thus responsible for inefficient protein and enzyme function, as a result of increased microviscosity of the cytosol, further embarrassing the transport systems within the cell, be it the axonal transport or blood brain barrier transport systems. Particularly, a novel hypothesis forwarded by Weiss and Gross, predicts (a) the force for cell transport to be non-specific in character, (b) the transport to be micro stream born, i.e., a hydrodynamic phenomenon (111).

Histamine produces a capillary dilation of the blood brain barrier, an H2 receptor phenomenon (45,46). On the other hand, K+ turnover seems to regulate capillary dilation or local circulation in the brain (47,48) and presumably in capillaries elsewhere. The two-way transport system through the blood brain barrier places a great demand on the efficiency of the local or general circulation of the brain tissue, particularly as some transport systems have rate limitations per unit surface area of the capillary. Therefore, the efficient operation of the cation pump has to be in place to cope with the demand by increasing the microcirculation of the brain tissue in particular.

The hormone receptor coupling depends on the three dimensional fit of the hormone into the receptor site. Rimon and associates state, that when the hormone or the neurotransmitter bind to the receptor, the catalytic unit of the cyclase is activated and produces cyclic AMP at the inner surface of the membrane. Membrane fluidity affects the catalytic unit directly, as the maximal activity of the enzyme increases as a function of membrane fluidity. It is apparent that the adenosine dependent activity, the adrenaline dependent activity and the Na+-stimulated activity increases as a function of membrane fluidity. Ca++-ATPase, Na+-K+ ATPase and the Beta-galactoside transport system were also found to depend on the membrane fluidity. They postulate, “Either the receptor and the enzyme are mobile and float in the membrane, or the receptor and the enzyme are permanently coupled to each other” (49). It seems that the adenylate cyclase activation is a diffusion-controlled process. Increase in membrane fluidity also causes a maximal threefold increase in the adenylate cyclase activity, based on the assumption that the bet-adrenergic receptor and the cyclase are separate units and diffuse freely in the membrane (50). Ross and Gilman, also quoting Livitzki and co-workers, state that increase in the rate constant for activation of GPP(NH)p plus epinephrine is inversely related to the “microviscosity” of the bilayer. They are of the opinion that the floating receptor model for regulation of the adenylate cyclase is essentially accurate (51).
It seems that the rate of lateral diffusion of the enzyme unit of the bound receptor within the bilayer membrane of the cell determines the effectiveness of the hormone receptor function; and this lateral diffusion in the bilayer membrane is inversely proportional to the microviscosity within the bilayer.

We have all, at one time or another, seen the lipid-globular protein mosaic model of a cell membrane depicting a bilayer structure, with "tuning fork" like projections into the bilayer from both sides. We have been told that the external surfaces are hydrophilic and the projections into the bilayer are hydrophobic. Some may wrongly assume that the "hydrophobic" property means that water does not get into the bilayer membrane. Rand and Parsegian have shown that water separates the bilayer structure of lipids to either a fixed distance of 20-30 Å in the case of a charged membrane, or to indefinitely large separation in the case of an electrically neutral bilayer or to indefinitely large separation of up to 100 Å in the case of a charged bilayer(52).

A lateral diffusion pressure is also developed with the introduction of water in the bilayer. The above information permits the thought that these hydrophobic "tuning-fork-like" projections may act as mixers or stirrers in the bilayer membrane, by being responsible for a build-up of the lateral diffusion pressure between the fork-like projections; they may bring about a more efficient "hormone-receptor-enzyme" action within the bilayer membrane (for the receptor types that stimulate function within the bilayer), the microviscosity of the space having also been adjusted, when free water diffuses through the phospholipid membrane. Because the inherent property of the cell membrane is to be a barrier for ions and most polar molecules, whilst permitting water through the lipid membrane by the process of diffusion. The permeability coefficient (cm/sec) for water is 10^-3 and for sodium and potassium it is 10^-12 (53). The diffusion rate through the membrane is ultimately dependent on the composition of the membrane, cholesterol contents of the membrane being the determining factor in the rigidity, and thus in the comparative impermeability of the membrane (53,54,55). These concepts indicate the importance of water in fine regulation of the interlocking hormones, neurotransmitters and neuromodulators' action in the body. This concept may seem important to the function of neuromodulators or neuroendocrine systems that regulate themselves on the basis of a feedback mechanism. This could also include the short loop negative feedback that seems to exist between renin production and angiotensin II inhibition of renin production (56), and also the fast and delayed feedback mechanisms that regulate corticosteroid inhibition of adrenocorticotropin release from anterior pituitary gland (117).

Kinins are involved in renin release from the glomeruli (57). It should be noted that sodium deprivation promotes kinin production and release into the circulation through production of kallikreins in the glands (salivary, sweat, pancreatic, kidney and digestive tract), particularly submandibular gland (58); kinins regulate renin production, when all the time the renin-angiotensin mechanism is involved in thirst production and water regulation; sodium seems to be involved in cell pH regulation through the action of Na^+-H^+ pump (59,60,99), when pH changes can convert prekallikrein to kallikrein, with the resultant formation of bradykinin or kallidin from kininogens, kinins, capable of causing pain (61), as well as the other functions they perform.

The serotoninergic system in the brain and the periphery is another such complex network of a neuronal system that seems to be affected when there is a deficiency of hydration. The serotoninergic system in the brain has three types of receptors: S1, S2 and S3. The receptor classified as S2 is an autoreceptor; it is presynaptic and mediates collateral inhibition, or it may have a direct inhibitory action. The S3 receptor is found in many parts of the brain: it too has an inhibitory function. S1 receptor is found in postsynaptic locations, its function is neuromodulatory (62). Subtypes D and M are reported in the muscle and the skin, with type M being further divided into three subtypes, one of which is involved with pain registration (63). Skin serotoninergic receptors are also involved in the thermoregulation of the body. Histamine receptors will similarly be influenced by the efficiency of the feedback mechanism, particularly since H3 receptors have a major role in H1-H2 inhibition.

In the discipline of gastroenterology, the epigastric pain not associated with the presence of an ulcer crater or with a definable pathology, such as cholecystitis or pancreatitis is not considered important, in most cases, it also shows equal response to antacids, cimetidine or placebo” (64). When, with a similar pain, a macroscopic ulcer crater is seen, the treatment of choice then becomes H2 receptor blocking agents. Between that initial nondescript pain and the final visual stage, the "same characteristic pain", with some local mucosal change, is classified as gastritis, duodenitis, esophagitis and so on. At times, an autoimmune state is postulated. Is separation of these stages as different conditions accurate? If the ultimate stage is to be treated with an H2 blocking agent, then we are interfering with a neurotransmis-
sion mechanism that is involved in the water intake of the body, and possibly substituting for the function of water for the cation pump drive, until the deficiency is replenished. It seems reasonable to assume that in such circumstances the interlocking control mechanism may possibly not be operative until full hydration takes place. The parietal cell uses up vast quantities of water; full function of the parietal cell requires transport of large volumes of water from the circulation (13). It requires water in order to operate the H\(^+-\)K\(^+\) ATPase pump (6). When this normal physiology is not efficient, histamine takes over, since the capillary circulation of the stomach has H\(_2\) receptors (65). Histamine will continue to maintain the integrity of the local circulation, at the same time producing a central pain alarm; low pH conversion of kinogens to kinins may be the pain inducing mechanism (61).

According to my clinical observations and the exposed theoretical reasons, the abdominal pain, when other local pathology such as cholecystitis or other definable conditions are not suspected, should be considered to be a "thirst pain"; in fact, a glass of water can serve as a diagnostic tool (1,2,25). This initial pain is the important signal representing the malfunction of a water regulated system, because, when insufficient hydration that has caused pain continues, a physiological state inductive to tissue transformation and/or tissue damage is then created. Depending on the duration of the body protein and enzymes' lower rate of production and functional down-regulation, which could include the class of body proteins known as 'receptors' - be they interferon receptors, cholesterol receptors, insulin receptors, sex steroid receptors, or any other class of receptors - the different stages of disease conditions will be seen. This question about the rationale of separation of pain and the different stages of tissue damage in peptic ulcer disease has been voiced by Spiro (66).

Unfortunately, in "stress", assumed to be induced by cellular free water depletion, the amino acid tryptophan - which determines the level of activity of the serotoninergic neuronal system and possibly other indoleaminergic activity, that among other functions raise or shift the pain threshold (31,35), as well as regulating all aspects of the pituitary-adrenal functions (67,68,69) - will be one of the more important elements that will become quantitatively depleted as a result of its over metabolism by the liver, and the tryptophan that remains is rendered less effective by the decrease in its rotational properties. One of the events, that seems to take place is a change in the ratio of free to bound tryptophan in circulation (70). If the level for free tryptophan reaches to more than twenty percent, the liver will metabolize the excess (71) by induction of the enzyme tryptophan oxygenase; also as a result of increased free tryptophan in circulation, the enterochromaffin cells increase serotonin production which will be taken up by the platelets (133) and mast cells (22), whereas in tissues other than the liver, tryptophan metabolism occurs through induction of the enzyme indolamine dioxygenase and production of superoxides (72,73). It seems that, through induction by cortisol, the liver enzymes, tyrosine aminotransferase as well as tryptophan oxygenase are activated, with the possibility of eventual depletion of the body's pool of tyrosine and tryptophan (Bender 72). Depending on the ratio of the intake (animal protein, meat, has very low tryptophan content compared to its transport competitors, 31), to the over metabolism by the liver (71,72), causing an induced tryptophan insufficiency (74), and altered route of metabolism, signs as well as symptoms will then be produced. It is important to note that when a combination of protein and fat is exposed to oxygen, oxidation of fatty acids and the release of free radicals results in some essential amino acid's deterioration, among them tryptophan, lysine and methionine; lysine loss can be high and methionine loss can be total (74). This information is particularly important since lysine, in conjunction with tryptophan, acts as an enzyme system for recognition and repair of damaged DNA (75). Meat, when exposed for marketing, could be a candidate for this deterioration.

Under such circumstances, tissue damage or its transformation will involve more than just the gastrointestinal tract and its gastric or duodenal disorders.

Tryptophan, is possibly involved in the antiviral tissue defense mechanisms by production of superoxide of anion and hydrogen peroxide. It seems that interferon stimulates the synthesis of prostaglandins in the cells, which in turn bring about induction of indoleamine dioxygenase (73). It is important to consider this link in the chain when conditions of apparent deterioration in the body's immune system are being investigated, even if we are searching for a viral depressant of the immune system because, in certain circumstances, a plasma borne tissue-CRF, with extreme potency and prolonged course of action, "intestinal stress" induced, can be transferable through blood or plasma (124,128,142).

Tryptophan is involved in protein synthesis and in tissue repair, especially in high turnover tissues.
such as the stomach and the intestines, when protein synthesis and the regeneration of cells need tryptophan in particular. According to Majumdar, force feeding of L-tryptophan stimulates amino acid incorporation into albumin, fibrinogen, transferrin and ferritin; by its effect on protein synthesis in the gastric mucosa, there is indication that dietary tryptophan plays a significant role in maintaining the structural and functional properties of the gastric mucosa (76) and, undoubtedly, other tissues of the body.

Even at the level of damaged DNA, it is postulated that tryptophan, in conjunction with lysine (and glycine), acts as an enzyme system for the recognition of a damaged site and for its repair (75). Also, according to Seymour Zigman, among the sub-groups PPI and PT2 demonstrate cell division antagonism, and also act as enzyme and protein inhibitors, since they mimic the action of organic peroxides. PT2 appears to be a better macromolecule synthesis inhibitor than other tryptophan oxidation products (77). Whether photooxidised or indoleamine dioxygenase induced, it appears that by-products of tryptophan metabolism have marked influence on the defense and regulation of cell function when the function of the cation pump is adequately maintained.

It is worthy of note that, even when H2 blocking agents are used to "repair the ulcer", the repair time depends on a natural healing rate; according to Gregory, even with the "tissue" covering the ulcer crater, morphologically the site of damage is not considered normal or fully repaired (78). It seems that the H2 blocking agents, among them the tricyclic antidepressant drugs being very potent H2 blocking agents (79), influence the serotonergic neuronal system (80). In view of the fact that the cerebral capillary system has H3 receptors for dilation and increased circulation, the question arises: when these drugs are used, is the brain tissue being forced into a functional hypoxic down-regulation to heal the ulcer, or to treat depression?

Having discovered that the renin-angiotensin system is histamine induced (23), and being armed also with the knowledge that the renin-angiotensin system is the operative peripheral drive for water intake by the body (23, 24), it becomes equally very important to know that the threshold rates for water intake and the threshold rates for raising the blood pressure seem to be very close (81). In the dog and rat these rates are antidiuretic and antinatriuretic (81), possibly because angiotensin III, a septapeptide metabolite of angiotensin II, has a direct aldosterone secreting property (118). It is understandable, since the blood circulation operates within a closed system, that any volume change has to be compensated for immediately, otherwise a "gas lock" could develop, causing a malfunction of the system. This compensation seems to be secured primarily by "borrowing" water from the other two compartments to the extent of 92% (24), while the other 8% is made up by closing the system proportionately. If through inadequate intake of water, the body continues to run on a deficit (82, 83, 84), then, by manipulation of the osmotic forces through salt retention (or glucose threshold manipulation and possibly retention of uric acid), it will continue to borrow water from the other compartments in order to maintain a comparative integrity of its blood circulation and, therefore, brain cell volume. It is interesting to note that, with salt deprivation, there is a higher turnover of glandular kallikrein in the glands of the body, apparently as an agent for induction of vasodilation to maintain circulation (58). This sodium retention could have a much more important functional role than merely being needed for maintaining the extracellular fluid volumes. Since membranes are functionally asymmetric, particularly with respect to the ionic pumps (53), and the primer of these pumps is a build up of the particular ion on the "intake side" of the pump, and since the function of all cells has an inherent property of continuously buffering its energy charge as well as its pH change (53), this sodium retention may be a very delicate balancing component of the cell pH buffering system in some cells (99). Selvaggio and associates, expanding on the work of Rindler and associates, have demonstrated the existence of a Na+/H+ pump (59). Livne and associates also propose Na+ to be involved in the pH buffering system of the body (60). It is assumed that this pump also operates in a similar way to the other cation pumps, namely that "free water" is responsible for driving it. According to Cooke, sodium uptake by the enterocytes may be affected by the level of tryptophan made available to the tissue (rabbit jejunum); "tryptophan increases electrogenic sodium absorption, followed by inhibition of the active sodium absorption." This regulation between inhibition and stimulation of absorption depends on the quantity of the amino acid made available to the tissue (85), when serotonergic neuronal system directly and indirectly, through aldosterone secretion, also promotes sodium retention (119). In light of the above, malregulation of the cell pH may be the cause of pain in tissues other than those of the gastrointestinal tract, in the same way as was proposed for the abdominal pain, particularly as, according to Goldstein and associates,
generation of endogenous kininogen splitting enzyme(s) responsible for bradykinin production is inaccessible to exogenous or circulating substrates (121).

It is interesting to note that procaryotes regulate the fluidity of their membrane by varying the number of double bonds and the length of their fatty acid chain to alter the fluidity of their membrane; as a process of adaptation to environmental change, they take this course in order to survive. This has been shown in E. coli (53). In eucaryotes, cholesterol is the important regulator of membrane fluidity. Thus cholesterol moderates the fluidity of the membrane (53). This phenomenon seems to demonstrate itself in the tracheal epithelial cell apical membrane. According to Worman and associates, increases in fluidity correlate with increases in water permeability of these membranes. At a transition temperature of between 28-26°C, cholesterol significantly decreases water permeability above phase transition temperature of planar lipid bilayer, and increases it below the transition temperature (54). If water permeability through the cell membrane commands such fine regulation as even to dictate a membrane's structural change, and if in chronic water loss the cellular water content becomes depleted, and if each cell in the body, to a lesser or greater extent, has an individual power of adaptation very much like that of E. coli, then should we not expect a "cholesterol" adaptation phenomenon? If these adapting cells are exposed to the osmotic forces of the blood, drawing their water directly, would there not be a logical regional defensive buildup of cholesterol within the cell membrane, to bring about a form of protective adaptation, in order to survive?

**DISCUSSION**

Up to now, we in the medical profession have taken the water consumption of the body for granted. We have considered it to be a self-regulating mechanism that will take care of itself. We have relied on the sensation of thirst as an everlasting quality of the body. It is true that whenever we treat a sick patient in hospital, we fuss about water intake and the electrolytes, but by and large our other patients are not controlled for their fluid intake (not drying agents, such as coffee tea and alcohol, the latter through inhibiting the secretion of antidiuretic hormone 140,24). We must assume that all sensations of the body lose their edge with the passage of time, including the thirst sensation. Stirling Meyer has shown that from the age of twenty onwards, the brain capillaries gradually lose their responsiveness to breathing 100% oxygen, and increased CO₂ tension (86). We must assume that if the receptors involved in evaluation and compensatory adaptation to fluctuations of oxygen and carbon dioxide tension lose their edge, from the age of twenty onwards, then the same probability applies to the ability to evaluate the water content of the body to the point of inducing thirst mechanism as a finely adjusting sensation, in order to keep protein and enzyme function at the optimum for that body (25). Bruce and associates have also demonstrated a definite predisposition to a lasting change in the body water composition with age. The ratio of extracellular water content to intracellular water content change from an approximate 0.8 to almost 1.1 between the ages of 20 to 70 - a very drastic change in composition (87). We are more and more coming to realize that older people are chronically dehydrated, losing the capacity to rehydrate their body, even though obviously dehydrated (82,83,84), with a predisposition to hypothermia, yet we do not make a strong effort to compensate for this problem over a longer period of time before their "ailment" is treated, sometimes very drastically, as for example with vascular surgery for intermittent claudication, or allow anginal pain to proceed to its logical conclusion. We must reevaluate the concept of dry mouth as a sole sign of thirst, first proposed by Haller and ardently supported by Cannon; we must accept and explore Schiff's original evaluation of thirst as a general sensation of the body (108).

It is taken for granted that, coupled with the process of aging, the body gradually loses its reserve capacity; protein and enzyme functions are trimmed to the basic day-to-day requirement, yet, at any age a form of homeostatic balance is established for that body and its norm of activity. To optimize the protein and enzyme functions for this period of life, maximum activity of the cation pumps and the energy transforming enzymes should be assured, through increased hydration. It is also in this group of people that pain, as a signal system of the inefficient operation of the cation pumps, develops significance and importance.

At this point, Medawar's opinion finds significance. Dawkins (3) considers that the body is just a survival machine for the genes we have inherited. He is of the opinion that every function of the body is genetically determined, even predetermined. He expands on Medawar's opinion that there are late acting semi-lethal and lethal genes. It is said that senile decay is the result of the activity of
these genes, when the "good" genes have given way. It is being said that there are certain "cues" which "turn on" the late-acting lethal genes. Let us expand on this subject. Crowther, in his research on the effect of cations on the rheological properties of purified mucus glycoprotein gels, discovered that Na⁺ reduced the gel elasticity, whilst the divalent cations generally increased the elasticity of mucus. He uses the interesting concept of "charge shielding" by the monovalent cations (88). Thomas Record has proposed the existence of a specific control mechanism involving the direct effect of change in ion concentration on the interaction of proteins and nucleic acids and on the stability of nucleoprotein complex (89). We understand that the cytoplasm of the cell is negatively charged. We understand that when the three Na⁺ are exchanged for two K⁺, after the initial electrogeneally silent exchange of the H⁺ for Na⁺, the cation pumps are maintaining a pH and ionic equilibrium in this direction, particularly as the shift of the other polyvalent ions into the cell is in turn coupled to the shift of K⁺. In this way the possibility of the damaging effect of excess hydrogen ion and the effect of "charge shielding" of the monovalent cation on the glycoprotein structure of DNA is decreased. Is it possible that the inefficient operation of the cation pumps could predispose to "jumping genes" and creation of "selfish DNA?" Are "selfish DNAs" the "cues" for the action of the "semi-lethal" or the "lethal" genes? If so, then, by the same token it is possible that the maintained activity of tryptophan (through adequate balance in the cell free water content and a balanced diet with least deterioration of the essential amino acids) could be more effective in the recognition and repair of the damaged DNA (75). According to Levinson, "there is compelling evidence that human cancer develops as a consequence of genetic damage (90). Dawkins ventures an opinion that viruses are genes that have broken loose (p.196,3). Green and Wyke indicate that recent advances in molecular biology have shown that viral oncogenes of rapidly transforming retroviruses were shown to be derived from and represented a subset of host's cellular genes (cellular or proto-oncogenes) present in normal cell DNA. Proto-oncogenes are now believed to play a vital role in cellular proliferation and/or differentiation. Cellular homeostasis exercises a regulatory action on the activity of these proto-oncogenes (138). Bishop proposes that retrovirus oncogenes characterized as of external viral origin are possibly from the host's cellular loci and not of external viral origin; this discovery is considered to be a very fortunate happenstance, indicating that in carcinogenesis the enemy could be from within (135). Marx considers the two steps of immortalization of the tumor cell and its tumor formation are separate steps involving different genetic drivers or possibly removal of the inhibitory phenomena in which the role of interferon is stressed (136). Weinberg is of the opinion that the environment of the cell is of utmost importance in responsiveness to viral oncogenes and its spread (137).

The relationship of these phenomena in conjunction with changes in the microviscosity of the body and the inefficient function of the cation pumps should be addressed. Because, if histamine is one of the sensor regulators of water balance in the body, it also acts as vasopressin secretion stimulant (115). Vasopressin in turn acts as ACTH secretion stimulant, since it is being proposed that corticotropin releasing factor may be modulated vasopressin (122); therefore, as a potential CRF secretion stimulant, histamine is involved in beta endorphin and ACTH secretion, mediating the integration of body's response to stress (123). ACTH itself also acts as secretion stimulant for mast cell release of serotonin and histamine (104). According to Goldstein and associates, there is also a direct thymus adrenal connection (125), with the result that corticosteroids cause a thymic involution, T lymphocyte mitotic suppression, and inhibition of human leukocyte's phagocytic activity. Lower concentration of glucocorticoids would have the reverse effect: enhanced thymocyte differentiation and increased antibody formation in vitro. Thymus is also being implicated in production and release of tissue-CRF (125,124) with a delayed but prolonged duration of activity which is stress induced (128), Makman and associates have shown, in vitro, an inhibitory effect of cortisol on amino acid transport and nucleoside transport and/or phosphorylation in the thymocyte, through induction of synthesis of proteins with inhibitory influence; they also report on Hechter and associates' observation that there is a marked decrease in K⁺/Na⁺ ratio in thymus of adrenalectomised rats after repeated injection of cortisol (134). Makara also stipulates the role of vasopressin as a CRF in stress induced pituitary-adrenal system stimulation. There is a weaker action of serotonin and angiotensin on ACTH release (124,126), from multiple sites of action (127). The role of serotonergic neuromodulation in the brain has to be separated from serotonin's short term peripheral action when evaluating isolated experimental results.

At this point, reference to some other aspects of tryptophan metabolism becomes important. According to Gerald Huether, serotonin is in-
volved in the regulation of cell division (cleavage, separation of mitotic centres), intracellular flow, cell shape, morphogenetic and pulsatory movements, primary invagination, neurulation; it is also involved in the control of transcription and translation of genetic information. Cell migration and synaptogenesis in the developing brain are controlled by serotonin. As for another tryptophan dependent product, tryptamine is an phylogenetically old modulator of intracellular communication, affecting the metabolic state and the function of developing cell. He is of the opinion that, in nature, an increased availability of tryptophan to individuals of a certain population would never occur, since several substrates and cofactors are involved. He further states that altered nutritional supply of tryptophan during the development of an individual may cause various metabolic alterations. Such responses seem to last and to become continuously modified through several generations - until a new steady state is finally reached (69).

According to Kandel and associates, evaluating the effect of serotonin on modulation of \( \text{Ca}^{++} \) current during behavioral arousal, a depolarizing command pulse produces an inward current due to \( \text{Na}^{+} \) as well as \( \text{Ca}^{++} \) followed by an outward current due to \( \text{K}^{+} \). With repeated commands, the peak inward current becomes less inward. Adding serotonin again now causes the transient current to become more inward, reduces leakage, and shifts the holding current inward. Identical effects are seen in the absence of the \( \text{Na}^{+} \) current (93). This manipulation of the calcium current by serotonin must be considered to be its most important role in the physiology of the body. It must be this effect that inhibits the histamine action in the experiment conducted by Canfield and Spencer, when serotonin from serosal point of contact inhibited the acid secretory effect of histamine, also showing a threshold phenomenon (28).

According to Lippman there is an association between psychosocial factors and the hormonal regulation of tumor growth. He is of the opinion that emotional factors can profoundly regulate hypothalamic-pituitary hormones; neuroendocrine hormones in turn, directly or indirectly, regulate neoplastic cell growth or alter concentration or activation of other hormones that affect cancer cells (131).

If, according to Dawkins, all actions of the body are "genetically" determined, then, philosophically speaking, certain types of pain could be the "genes' cry" in "anticipation" of damage, particularly the recurring dyspeptic pain of peptic ulcer disease (regardless of the presence of a macroscopic ulcer crater); and the tissue damage or its transformation phase is the result of not having recognized the meaning of that pain signal, which now means both water deficiency and inadequacy and disturbance of tryptophan metabolism (25). Depending on the age of the person, the pain signal may well be an indication of a predisposition to the precipitation of a variety of disorders that will be determined by the role of tryptophan in the body. This pain may even herald a continued predisposition to disorders that may affect that person's offspring (69). This all encompassing role of tryptophan and its by-products of metabolism must be the determining factor in the genetic association between a large variety of conditions and peptic ulcer disease that Jerome Rotter lists (91). He is of the opinion that peptic ulcer is not a single disorder, but a host of disorders that share a common clinical finding: a hole in the lining of the gastrointestinal tract; similarly, heterogeneity is being recognised in gastric cancer.

The significance of the role of serotonin and histamine in the regulation of body physiology, through calcium turnover in the cell, is of paramount importance; since histamine through the combination of \( \text{H}_1 \), \( \text{H}_2 \) receptors activates protein kinase \( \text{C} \), which catalyzes calmodulin-dependent phosphorylation of a class of protein that has been identified for sarcoplasmic reticulum of the cardiac muscle as phospholamban, producing a three-fold increase in \( \text{Ca}^{++} \) uptake and \( \text{Ca}^{++} \) ATPase activity, a potential \( \text{Ca}^{++} \) translocator (5), and thus primes the cell growth process that is calcium dependent; and since through the manipulation of \( \text{Na}^{+}/\text{K}^{+} \) pump, which is a voltage inducing pump, generates ionic current and voltage gradient that, according Jaffe (129), is essential for determination of cell growth, histamine may be considered to be a direct primer of growth within the cells. This idea could be further supported by the observation of Bender, who considers histidine one of the essential amino acids for growth in children (72), by the way cimetidine reverses tumor growth enhancement of plasmacytoma tumors in mice (130), and by the fact that mast cells multiply with each degranulation of histamine. The presence of \( \text{L}-\text{histidine decarboxylase} \), an indicator of histamine activity according to Beaven (13), is found in many tumour tissues, including mastocytomas, gastric carcinoid tumours, transplatable hepatomas and mast cell ascites tumour; in the rat tumour tissue, the enzyme is found to reach very high levels (13). The action of serotonin on stabilization of the calcium current, must be the balancing factor in this relationship. This physiological state must be considered a logical adaptation to life on land, when the body is at-
intemally, the body as a whole decides to "sur­
to the needs of the total body, where upon the
environmental factors disrupt integration of adapta-
some parts of the anatomy from environmental
 strains. The same will to survive must be the
natural determining factor in remissions attributed to
the "fighting spirit", a natural component of "fight
or flight", when the body as a whole decides to sur-
It seems that, in stressful sedentary occupations, when
the activity of large muscle mass in the body does
not bring about the dominance of fat metabolism
through activation of the hormone sensitive lipase,
which seems to be time dependent (92), resulting in
a net gain of water for the cells, and protein break-
down continues to be a major component of
 gluconeogenesis; when muscle metabolism does
not adequately utilize the branched-chain amino
acids, leucine isoleucine and valine (72), the blood
brain barrier competitors to tryptophan, the actual
phenomenon of tissue damage and or tissue
transformation associated with stress will develop. A
physiological translation of "fight or flight."

Pre-Conclusion
In any future drug trials, the curative effect of
water has to be separated from the effect of the
chemical composition under investigation. This
can be done by hydrating the patient well for some
time before and during the time that the trial is carried
out. At the same time the idiosyncrasies of the metabo-
lism of tryptophan should also be taken into account. It
seems that tryptophan loosely binds to albumin and
that free fatty acids compete for that binding site;
not all animal protein has a high tryptophan content,
whilst more than one fifth of the weight of most meat
consists of fat. The presence of unsaturated fatty
acids, when also exposed to oxygen, could potentially
bring about the deterioration of some of the essen-
tial amino acids even before intake of food
(74). It is interesting to note that a high content of
pulses in the diet could provide a reasonably
balanced protein intake, particularly of the amino
acid tryptophan; up to 90% of the "recommended" re-
quirement of the body can be supplied from this
source (74). Attention to the tryptophan content of
food is most important. For, out of the total intake,
only a small portion crosses the blood brain barrier,
getting converted to the indispensable neurotransmitters
as soon as it reaches the serotonergic, tryp-
taminergic or melatonergic neurones. The role of
these neurotransmitters in the maintenance of
homeostasis in the body is complex, and needs
more attention. There seems to be a definite
relationship between the water metabolism of the
body and serotoninergic neuronal function. If the
regulatory role of the brain cells determines the
state of the body physiology, then the role of
serotonin in the maintenance of that regulation is
important. If, according to Hume, in pure water
loss, the brain cells adapt by increasing intracel-
lular osmolality, sugar, salt and "idiogenic solutes" are
involved (24); if according to Fernstrom, SHT syn-
thesis is reduced in the diabetic brain, secondary to
brain tryptophan levels (96); if according to Ikeda
and associate (97) and Hattori (98), xanthurenic acid
can render insulin physiologically less effective,
and we know that xanthurenic acid is a liver metabo-
lite of tryptophan, what could be the role of disturbed
water regulation in production of diabetes? Could
diabetes be a crisis state to brain cell volume reduc-
tion? Could nature be involved in resuscitating the
brain in the same way as we use dextrose saline? Ob-
vviously, there is no "insulin barrier" to entry of
 glucose across the blood brain barrier, whereas, ac-
tive transport of glucose across other cell membranes is
dependent on the Na"-transport protein-glucose ternary
complex formation with a stoichiometry of 1 Na: 1
 glucose (141). Thus, thirst associated with a higher
than normal blood glucose level may be a primary sig-
nal for water deficiency.
We often see double blind randomised trials produce
almost as good a result for placebo response as that
produced by the medication under investigation
(120). Often the placebo response is discarded as too
good to be accurate. It must now be recognised that
water taken with the pill, with all its regulatory
properties, is responsible for the placebo effect
(2,25). Extensive observations need to be made on
the response of raised systemic or so-called essential
hypertension to increased hydration (25), par-
ticularly as water by itself is the best natural diuretic
(8). It seems that we must rethink our approach to the
treatment of hypertensives by administration of chemi-
diuretics and sodium reduced diets. We may have to
allow adequate water intake to adjust the cell
volume, as well as the extracellular fluid volume, as a
preventive measure before tissue damage takes
place; because the natural drive of renin-angiotensin
is directed towards increased water intake (81), and
its hypertensive property is a compensatory
phenomenon. The dietary approach should be
directed towards an adequate supply of the essential
amino acids because histidine turnover may cause a
body depletion of this essential amino acid. Particularly, as Holcslaw and associates have demonstrated a reduced histamine level in the wall of the aorta of the spontaneously hypertensive rats, although possessing an increased histidine uptake capability (132). I have seen very satisfactory results from treatment of essential hypertension with increased water intake (25). It seems to me that what we are seeing in hypertension is the body’s response to extracellular water loss through the early loss of thirst sensation, and we are treating the hypertension threshold and not the basic physiological drive (25), for water, of all things, the most essential component of the body.

When mast cells degranulate and serotonin and histamine are released into the microcirculation, serotonin, as well as histamine and bradykinin, has the property of compromising and breaking the wall and producing gaps in the wall of the capillary (44). This regional effect of histamine and serotonin may be a precipitating cause of local ulceration of the duodenal region that seems to have histaminergic nerve supply (103). When the compromise of the capillary wall occurs in the blood brain barrier region, the resultant local inflammation and plaque formation can be accepted as a logical conclusion. The consequences of this phenomenon could become of catastrophic dimension if a potentially higher aluminium concentration in blood is brought about with increased antacid intake (139) to relieve a thirst pain.

Pain associated with decreased capillary circulation, such as anginal pain and pain of intermittent claudication, needs to be investigated with increased hydration as a form of treatment prior to drug use (25).

In order that actual, or perceived, mental or emotional activity or emotional experiences should not produce adverse symptomatic or physiological response in the body, precaution with increased hydration of the body should be taken, so that the blood brain barrier capillaries are optimally hydrated.

Reassessment of the drug dependence of patients under medication is indicated after increased hydration.

Low back pain need be treated with increased water intake, as the efficiency of function of the discs also depends on their hydraulic property (25,94).

According to Thomas Kuhn, quoted by Crue and associates under the subject of “continuing crisis in pain research” (95), when anomalies in the observations of science proliferate and cannot be reconciled within the rules, or the basic paradigm, then the significance of the crisis produced is the indication that an occasion for retooling has arrived. Crisis loosens the rules of normal puzzle solving. When the anomaly appears to be more than just another puzzle of normal science, the transition to crisis and to extraordinary science has begun. Even former standard solutions of solved problems can be called into question. According to Lakatos and Musgrave, no ordinary sense of the term “interpretation” can fit the flashes of “intuition” or “imaginative posits” through which a new paradigm is often born (95). The accepted paradigm on the metabolism of water is based on the infallibility of the physico-chemical properties of ions within the cells and assumes that it is this property which determines water regulation and the thirst mechanism. This view, whilst sound, does not take into account the “metering system.” If the serotonergic neuronal system is considered to be the regulator of the homeostatic balance in the body - and according to Kandel and others it is even involved in the regulation of the ionic channels within the nerve cells - then what happens to this balance when the tryptophan reserves of the body become depleted and its metabolism disturbed? If thirst sensation is gradually deteriorating, what are the consequences of under hydration and from what age do they begin? The above theoretical discussion, based on human observations, in a constantly stressful “laboratory” condition, where the level of stress and diet of pulse and starch were the constant factors, is intended to expose the important lack of sufficient knowledge of water metabolism in the body; it is also intended to question some of the basic understandings of certain “disease” conditions.

CONCLUSION

When severe abdominal pain, often associated with “peptic ulcer disease,” is relieved with water (and this phenomenon reveals a basic concept of which a very brief form has been presented above), it seems that the time has come to reassess our approach to treatment in medicine. We must now recognize a pain signal to cellular free water deficiency of the body and also recognize the impending consequences of its misinterpretation. We must assume that thirst sensation is no longer a reliable mechanism for the regulation of the delicate balance of cellular hydration. We must encourage people to regulate water intake by establishing the habit of drinking water. It seems that water intake before meals should be encouraged to prevent hemococoncentration, and to bring about a separation of the
sensation of thirst from hunger; confusion of these sensations may be the causative factor in over-eating. It was found that an effective volume and timing for water intake, as a treatment procedure in clinically diagnosed peptic ulcer disease, was one full glass of water half an hour before a meal and another glass two and a half hours after a meal: that is six glasses of water, approximately one and one half liters, per day (1,2,25). It was also found that with regular intake of water, the thirst sensation becomes more pronounced and recognizable by the patients who did not acknowledge their thirst before. As a grass root phenomenon, and in view of presented new perspectives, the role of free water deficiency in cancer transformation warrants investigation (25, unpublished theoretical research); and it certainly deserves application as a preventive measure. The final conclusion seems to be the importance of regular water intake regardless of thirst. The cell, it seems, is just like a city that runs on hydro-electric power, it needs the "water head" over the cation pumps of the membrane barrier for generation of energy and its utilization, just like a "pump storage dam." After all, the initial progenitor cells used the same physical laws when they lived in sea water.

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