Glycemic Modulation of Tumor Tolerance

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Introduction

Among the most striking effects in medicine are glycemic modulation of tumor tolerance and the associated improvements in health of cancer patients that can occur within months in the well nourished but semi-fasting state. We cite evidence that strongly supports the old view[1] that neoplastic initiations are always occurring but, in the cancer-free population, are found and reversed by immune surveillance performed by leukocytes, as part of cell mediated immunity (CMI). Part of that evidence shows the 30, 100 and 10,000 fold increases in cancer incidence that result when immune surveillance is diminished by hyperglycemia or lost (as by thymectomy, etc). In essence, although not as drastic as thymectomy, hyperglycemia suppresses and hypoglycemia enhances immune surveillance (in the conditioned patient whose hypothalamic-pituitary-adrenal axis does not produce a lympholytic state by excessive elevation of cortisol). Our use of leukocytes includes three major nucleated cells of the blood: granulocytes (or neutrophils), lymphocytes, and monocytes. The last two are effectors of CMI.

Mechanisms

This paper progresses from a general to a more detailed treatment of some of the evidence on glycemic modulation of tumor tolerance. The evidence is strong that a number of mechanisms exist, and these are simply explained. Some, but not all, of the mechanisms involve glycemic modulation of normal functions of ascorbate. Of these functions, possibly the most important is stimulation of the hexose monophosphate shunt (HMP) by high intracellular ascorbic acid level (IAA). The HMP is necessary for normal function of all leukocytes and runs at a rate that rises monotonically with IAA. Phagocytic cells such as the neutrophil and the monocyte depend upon the HMP for regeneration of reduced Nicotinamide Adenine Dinucleotide Phosphate (NADPH), a coenzyme needed to produce superoxide anion and the more microbicidal hydrogen peroxide). Lymphocytes depend upon the HMP for production of ribose, necessary to copy DNA for cell division and clonal proliferation. Possibly the most important mechanism is glycemic modulation of IAA, HMP and CMI in turn, as detailed in later sections.

At the present time, in spite of the seeming adequacy of the "known" mechanisms, we cannot rule out additional possibilities. In particular, because insulin resistance so frequently accompanies neoplastic disease, it seems reasonable to ask several questions. Since high dose coenzyme Q10 (approx. 400 mg/day in adult humans) has been reported to produce dramatic remissions in terminal malignancy[2], could it be that the known fragile biosynthesis of this quinone is enhanced in hypoglycemia? Similarly, does hypoglycemia also enhance synthesis of small peptide antineoplastons?[3] This seems to suggest ways to effect immune surveillance naturally. Might these small peptides, for example, remove the embryonic features of the neoplasm by facilitating repair of the DNA error that allowed expression of the three fetal characteristics (rapid mitosis, loss of contact inhibition, and metastasis)? If time and space permitted, it would be of interest to consider the evidence that hypoglycemia helps (and hyperglycemia worsens) many conditions of medical interest. Some material related to other disorders is mentioned herein, incidental to our discussion of glycemic effects in cancer.

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Information Overload

The literature of medical science has become essentially inaccessible because of its size. Here, at the University of Washington, our Health Sciences Library receives over 4 million new pages per year from the journals to which it subscribes. Most of this material is both excellent and relevant to clinical medicine. However, no clinician (or even researcher) could possibly find the time to read 1 percent (40,000 pages/year) of the flood. Thus, we are all ignorant of the greatest findings. It might be stated that there is no area of human endeavor where ignorance (of what is known) is growing as rapidly as in clinical medicine. Hence, our ignorance is unavoidable but the arrogance and pretense of omniscience (or even of knowing enough) that we see so often in medicine today are philosophically inexcusable. Of course, the unrealistic and unfair expectations of patients that arise from the public's ignorance of biology place the clinician in a relentless dilemma, one that that researchers never have to face. Clearly, the National Library of Medicine and NIH must accelerate computer aided diagnosis. Unfortunately, most clinicians, due to their time pressures, seem unaware of this need and therefore the issue is not forcefully expressed.

Hyperglycemia and Disease

For anyone unaware of the literature dilemma, it would seem truly strange that "modern medicine" in the affluent nations can be oblivious to the long known and striking beneficial effects of the natural (primitive) hypoglycemic state in many areas of human health in contrast with the numerous afflictions of hyperglycemia. For example, as our theory explains and predicts, maternal hyperglycemia depresses fetal HMP so that birth defects are greatly increased in incidence and severity by slowed mitosis, yielding ontogenous defects (including gross malformations) in early pregnancy, but primarily neurological deficits in late. [4,5,6] Another example is vascular disease, which is accelerated by hyperglycemic depression of phagocytic clearance of microscopic thrombi and atheromata.[7] Atherosclerosis is believed to be our leading cause of debility and death, accounting for one third of North American mortality.[8] Yet another example is aging itself where the two best known mechanisms are explained by Harman's free radical theory and glycation as elucidated by Cerami et al. Thus, if we habitually ingest more calories at constant weight: (1) our specific metabolic rate must rise and we will age more rapidly due to the larger number of free radicals (i.e., reactive oxygen intermediates) we must handle; and (2) our blood sugar will rise, increasing the glycation rate of all our proteins including lymphoid tissue, thus accelerating immune senescence and tumor tolerance. The principal outward sign of this process, however, may be only in facial wrinkles (n.b., ascorbate antagonizes glycation[9]).

Some Background

Some history of the glycemia/cancer association. Since the time of Galen, it has been observed that tumors grow poorly or not at all in underfed animals. In the last century, glucose intolerance was reported in 62 of 70 tumor patients in one practice. [10] Similar findings of the next 70 years were summarized by reviewers[11] who reported 35 percent of 557 consecutive cancer patients exceeded 200 mg% (mg/dL) on GTTs (glucose tolerance tests)! They also found an eight fold higher incidence of this hyperglycemic response in breast cancer patients. However, they concluded that the "diabetes" seen in malignancy was a mild easily controllable form (even one day of fasting significantly normalizes many GTTs in such cases). It is vital to appreciate the difference between those with blood glucose (BG) peaks greater than 200 on GTTs and those with an average BG level greater than 200. In "The Framingham Effect" section below, we emphasize that failure to recognize this distinction is one major cause of confusion on the glycemic factor; a second is the lack of mechanisms

and theory to explain the association.

Modern epidemiological studies summarized late in this paper show a very strong world wide correlation of cancer incidence with sugar consumption. It has been estimated that, in the U.S.A. alone, 60 million people alive today will present with clinical cancer in their lifetimes. The "glycemic modulation theory" predicts this one fourth of the population may be identifiable, to a first approximation, as the older half of the upper half by sugar consumption. The basis for this prediction can be sensed in two U.S.A. statistics: we have 30 times more cancer above age 55 than below 35;[12] and the 2-hour value on GTT's rises 10 percent per decade of age.[13] In a later section, we cite another source that lists cancer mortality as 100 times greater above age 55; we presume this may be consistent with the 30 times higher incidence given above due to a three times higher mortality above 55.

Of course, age related thymic involution would be expected to affect immune surveillance (i.e., at age 60, the parenchymal mass of the human thymus is about 1 percent of the pre-pubertal value[14] and, presumably, the secretion of the thymic hormones that mediate the synchrony of CMI (cell mediated immunity) are proportionately reduced). However, in later sections, we argue that even these may be strongly influenced by hyperglycemia and its alteration of the oxidation state of ascorbate.

In the Beginning: Research Serendipity and the First Mechanism

In the 1970's, because of an interest in the mutagenic burden of the penetrating background radiation (secondary cosmic rays at the earth's surface) and its possible role in human aging, life span and neoplastic initiations, we looked for and found what appeared to be a statistically significant latitude dependence in cancer mortality. As is well known, the background radiation decreases at low latitudes. Cancer deaths appeared to exhibit the same trend, except for some low latitude countries whose high mortalities violated this expectation. We found (from WHO data) that they had very high annual per capita sugar consumption, similar to North America and Europe (approx.PP 150 pounds) compared to India and many other low latitude countries (approx. 12 pounds).

In 1973, we had already deduced and related to Linus Pauling a theory called the "Glucose Ascorbate Antagonism". It argued that the clinical trials of ascorbic acid (AA) against colds and cancer may have failed because of the high blood sugar levels in the affluent nations. Essentially, this theory can be stated in three parts. (1) Certain cell types normally have intracellular ascorbic acid (AA) levels that are "pumped up", largely by insulin and another process, resulting in vastly higher AA levels than plasma in the surrounding blood (approximately 50 times higher in leukocytes and 300 or so in fetal cells). This is especially true if the BG level is in the low range that was normal until the 1900s and is still seen today where the primitive diet prevails. (2) The high AA levels in such cells are necessary to drive the HMP shunt (or pentose pathway) needed for some normal functions, including mitosis, phagocytosis, etc. (3) "Modest" BG elevations (≈ 50%, common after western diet meals) competitively inhibit insulin-mediated active transport of AA into these cells, resulting in low intracellular AA levels, low HMP shunt, and cell dysfunction. Leukocytes, therefore, do not respond to mitogen, attack tumors or pathogens, etc. (in CMI), or remove thrombi in vascular disease, and fetal cells divide too slowly.

The theory was inspired by two findings on leukocytes published by others: the HMP shunt runs at a rate that rises monotonically with increasing intracellular AA;[15] and, the leukocyte phagocytic rate is strongly depressed by modest hyperglycemia in the 90 to 130 mg % range.[7] We obtained experimental support for the

theory by studies on humans and animals from 1978 to 1987. One simple test of the theory showed that leukocyte AA fell approximately 50 percent in ten minutes after an iv GTT using 25 grams of glucose in normal human adults.[16] The theory has relevance to atherosclerosis, birth defects, cancer, infectious diseases, etc.

Aggressive Glycemic Control in Humans and Animals

This simple glucose ascorbate antagonism theory gives rise naturally to "Aggressive Glycemic Control" (AGC) as a modality that, properly used, appears to have much value against the disorders named above. The three main features are: a planned "primitive diet" with reduction of caloric intake and minimizing refined carbohydrate; ascorbic acid (40 milligrams/kg or more, tid); and a planned increase in exercise to bring blood glucose into the 75 mg% range (or as low as possible without stress). In 1978 and 1979, two stage-4 breast cancer patients with large tumor burdens, worsening rapidly ("one month" prognoses) although already on chemotherapy, elected to use AGC and both became tumor free in six months (reaching normal weight by losing 40 and 60 pounds respectively) and were still alive in 1992. At least three other humans have been observed to experience rapid tumor-free recoveries from advanced cancer while undergoing insulin-coma therapy, originally planned for their psychoses.[17] An American Cancer Society Institutional Research Committee (at Fred Hutchinson Cancer Research Center and the University of Washington) approved AGC as a research topic in 1983. We were able to reproduce the human result strikingly in an animal model, thus showing strong glycemic modulation of tumor tolerance.[18] The very significantly different ($p<.005$) mortalities in three groups of mice, 70 days after injection with an aggressive mammary tumor, were: (1) 16 of 24 (slightly) hyperglycemic mice (GHb 5.36); 8 of 24 normoglycemic (GHb 4.67); and (3) only 2 of 20 hypoglycemic (GHb 3.69).

The Framingham Effect

There is an interesting paradox that may explain one of the reasons mentioned above for modern medicine's failure to recognize the glycemic modulation of tumor tolerance that occurs strongly in the 80 to 130 mg% range. In essence, if tumor incidence is increased somewhat near 120 mg %, one expects it to be much greater above 200, but it is not. First, to show the BG values in a country with 1/10 our rCHO intake and 1/3 our cancer incidence, we should mention that, in the Calcutta Diabetes Study, the postprandial BG range reported for nondiabetic male controls aged 40 to 70 was from 50 mg% to 90![19] Now, the paradox is the observation with good statistical weight from the Framingham study of over 20,000 diabetics that those with average BG > 200 mg% have no more cancer mortality than normoglycemics![20]

To explain this, our theory offers the following plausibility arguments that were well received in the immunology section of a large annual meeting.[21] A first plausibility argument is that leukocytes, because of their very high intracellular AA levels (approx. 50 times higher than plasma), require strong AA transport and hence are very susceptible to the impairment of this transport by small increases in glycemic level. Most tumors, however, are expected to have much lower AA levels[22] and hence a lower requirement for AA transport with less susceptibility to disruption by BG elevations until quite high. A second plausibility argument is that the insulin resistance (reversible internalization of insulin receptors) that, at very high BG, afflicts all cells (including the tumor) makes it difficult to provide the large amounts of glucose required by the tumor's inefficient glycolysis. However, the fact that the Framingham Study also showed 15 percent lower tumor mortality for males

(believed to have lower AA levels than females) seems consistent with the first plausibility argument. Perhaps both or other mechanisms operate. Regardless of the correct explanation, the very existence of the Framingham effect must have discouraged acceptance of the glycemic modulation concept. We have never had opportunity (in animals, or human tissue culture) to test the concept of stopping intractable tumors with very high BG.

The Chromium Question

For glycemic control, the importance of tri-valent chromium had seemed clear for many years. Supplementation of various concentrated preparations (approx. 150 mcg/d to complement the reported 40 mcg/d of our diet) has become widespread and has generally been regarded as both efficacious and safe. It is also thought to be necessary in North America and other countries that share our low soil chromium and/or our high refined-carbohydrate diet.[23,24] Recently, work has appeared that questions the safety of long term ingestion of chromium supplements.[25,26] This work is very complex and is based on computer modelling, chemistry and cell culture genotoxicity. It may be that, even at the supposed MDR level (200 mcg/d), chromium can accumulate in humans in only a few years to levels at which DNA damage has been observed in animals and in vitro. It appears that even the ligand, picolinate, may be genotoxic. These questions pose a quandry for clinicians especially. Clarification will be sought via a retrospective study by the USDA Human Nutrition Lab comparing long term supplementers with controls.

DHA: no renal threshold (the mandate for AA in chemotherapy)

In 1980, a theory was advanced that predicted there should be no renal threshold for dehydroascorbic acid (DHA) (Ely 1980, unpub.). This theory predicts that significant depletion of AA body stores and suppression of CMI should occur in patients on chemotherapy unless ascorbate is supplemented (titrating to urine AA levels). Recently a study has been made (on urine from 300 patients not on chemotherapy) that appears to support this hypothesis. A manuscript is in process. (Warner et al., unpub.).

DHA Elevation and Impaired Leukocyte Function

DHA is elevated in many conditions, including hyperglycemia (as discussed herein), infectious disease, intoxication, puberty, scurvy and stress, real or perceived.[22,27–29] It is accepted as an unfortunate fact of the AA-DHA redox pair that elevation of the DHA/AA ratio shifts the redox potential in the oxidative direction, opposing the reduction of DHA to AA, and slowing or preventing recovery of leukocyte function.[22,28,30] If DHA elevation is prolonged or extreme, tissue injury including thymic involution will result. Neutrophils have very high reducing power, protecting them from DHA elevation, but still perish in a few days because of their intense respiratory burst and the oxidants they produce. However, although more sensitive to DHA, the lymphocytes, important to CMI, are long lived. Note that, in addition to insulin-mediated active transport of AA and DHA into cells, only DHA can diffuse from plasma into cells because: (1) the DHA level is lower there (due to reduction to AA by glutathione); and (2) the less polar DHA is more lipid soluble. Because glucose outcompetes the ascorbates for insulin, hyperglycemia is expected to depress the active but not the diffusive transport. This asymmetry and the differing reducing power of leukocyte types makes their differing susceptibilities to hyperglycemia complex.

Some Background and Details on Glycemic Modulation in Oncology

It is well known that an inordinate increase in malignancy occurs in those with CMI incompetence. There are many ways

to suppress CMI. The evidence we review here indicates that blood glucose elevation and subclinical scurvy may be the two commonest The aged and populations with therapy-depressed CMI (to prevent rejection) exhibit a 100 fold neoplasm incidence above average. The transformations that clone to clinical size, presumably due to inadequate immune surveillance in these groups, may arise from chemical carcinogens or spontaneous mutations. However, the strong temperature dependence of spontaneous mutations suggests their source is the tail of the Maxwell-Boltzmann distribution law governing the kinetics of all molecular components and structures. Because of the factor exp(-E/kT) in this law, where kT is approximately .01 electron volt (ev) at 37°C, energies available for interaction become extremely improbable much above 1 ev and multiple hits are required, contributing to the slowness (many years) of most such transformations. In contrast, the tumor incidence in children neonatally athymic is even 100 fold greater than that of the geriatric and organ transplant populations (i.e., 10,000 times that of normal children[1,30]) in spite of the facts that the very young neither smoke nor ingest highly mutagenic diets nor suffer industrial exposures nor have time for the slower multiple hit mutations to accumulate. This suggests that a significant fraction of prompt transformations may result from the high energy cosmic rays that deposit a minimum of 200 ev in traversing a nucleus, penetrate one half of our cells each year, and produce DNA hits in 1/60th of our cells per year (10^{12} in a 70 kg human); other products of the cosmic ray flux including neutrons and carbon-14 add to the prompt mutations[32]. This inescapable, penetrating radiation: (1) consists of secondary particles primarily relativistic muons and electrons, created in collisions between galactic cosmic rays (primarily high energy protons) and atomic nuclei in the upper atmosphere; (2) constitutes a mutagenic burden; (3) provides both a life long test of immune surveillance and a potentially prompt penalty for its failure at any age; and (4) may contribute to the basis for the often stated concept that histologically scattered random neoplastic initiations may be a daily occurrence in each of us.[31,33,34] In conclusion, regardless of mutation source, a high incidence of primary tumors follows CMI suppression even in total avoidance of chemical carcinogens.

Since CMI is of paramount importance in host defense against viral and neoplastic disease,[35,36,37] variations in its intensity would be expected to produce pronounced effects. For example, patients with atopy or anergy differ markedly in tumor frequency. In one study, a sampling of non-cancerous patients showed allergy in 13 percent while only 3 percent of 1300 cancer patients had such history.[38] The well known CMI suppression due to scurvy is similar to that observed in steroid therapies which are not only lympholytic (i.e., inducing cellular anergy via thymic involution) but also destructive of AA stores (i.e., directly suppressing the HMP shunt in all effector cells). The thymic involution that starts in adolescence and reaches 90 percent by age 50[39] may be due to steroid elevation and may be ameliorable by AA elevation (observations are needed on animal pre-pubertal castrates and on humans practicing lifelong AA supplementation for effect on thymus mass and function). With regard to this aplasia, we might estimate from the mouse model and scant human data, barring severe stress or malnutrition, a geriatric T-cell function less than 10 percent of maximum.[40] However, it was found that Stage I, II, and III tumor patients with median age 50 did exhibit delayed hypersensitivity (DH) to a neo-antigen (DNCB) of 85, 63, and 37 percent respectively prior to treatment. Moreover, after conventional removal of tumor burden (and its associated CMI suppression), 11 of 17 initially negative to DNCB changed to positive, and, 6 months later, 80 percent of all showing an increasingly positive reaction remained free of

disease. Of those still anergic or failing to increase reactivity, 88 percent suffered recurrence in 6 months.[41] This correlation of prognosis with DH suggests that even the elderly are able to maturate prothymocytes and direct them against new tumor antigens if conditions are favorable. From this and much other work, it seems clear that the tumor patients' long range prognosis is delicately hinged on CMI competence, especially the numbers and effectiveness of T-lymphocytes. It then seems also clear from the present and the previous paragraph that the hyperglycemia-induced significant immune suppression described in following sections is not tolerable in the cancer patient nor the general population.

Hyperglycemia in the Aging and in the Neoplastic

Since 1885, the diabetic-like hyperglycemic response (HR) on the GTT has been reported to range in incidence from 26 to 90 percent in numerous studies of cancer patients.[10,11] In leukemics, a range of incidence of 71percent has been given.[42] In one comparison of 850 adult cancer patients (to over 80 years old) and of matched benign controls, HR occurred in more than 34% of the former and less than 10 percent of the latter group. The frequency of HR in the two groups was shown to increase fairly steadily after age 20 to approximately 70 and 20 percent respectively at age 80, with rather rapid increases of 35 and 10 percent in the 10 year interval between ages 35 and 45 (known diabetics constituted only 12.4 and 4.4 percent having negligible effect on the age incidence distribution).[11] In at least two investigations, lasting remissions from cancer appeared to coincide with return of glucose tolerance to norma1.[43,44] Most of the papers we have read either ignore the hyperglycemia or consider it symptomatic rather than etiologic (as the evidence presented in this paper suggests strongly). In essence, we argue that the hyperglycemia is a cultural artifact, and that the CMI depression it produces simply increases the probability that mutant clones will escape surveillance (this would predict both higher cancer incidence and more rapid aging in hyperglycemics). The condition itself probably results from the recent (≈100 years) addition of refined carbohydrates in significant quantities to a digestive system that evolved over millions of years without it. The variations in biochemical individuality and personal habit result in a continuum of regulatory dysfunction, with many people in subclinical type 2 diabetes. It has been established experimentally that reduced glucose tolerance is inducible in animals and man on a high sugar diet.[6,45]

Leukocyte Suppression by Glucose (In Vitro).

Most of the studies of sugar suppression have been done on neutrophils which, although similar metabolically, are not the leukocytes of interest in viral and neoplastic disease. Some work has reported an analogous suppression of lymphocytes. This would be expected from the strong correlation of cancer incidence with high sugar consumption in epidemiological studies.[46] The four functions of neutrophils (chemotaxis, adherence, phagocytosis and intracellular killing) have each been shown, in separate studies, to be strongly suppressed in blood drawn from groups of diabetic patients.[47,48,49,50] In virtually every case, the neutrophils exhibited improved performance, approaching that of normal controls after better management had lowered the BG levels in these same patients. Patients with the poorest initial intracellular killing showed the most striking increases (almost 3 times) after 27% reductions in BG (310 to 225 mg%). Granulocyte adherence as a function of BG level fell linearly (best fit for 22 tests) from 100% of controls at 100 mg% to 20% of controls at 400 mg%. Serum from the untreated diabetics uniformly reduced these same processes in poly's from the controls, and serum from the controls improved the performance of the diabetic

patients' leukocytes. Most striking of all were the two results that first, transferable inhibitory effect of hyperglycemic diabetic serum on control poly's was eliminated by dilution, and second, this effect could be produced in normal serum simply by the isosmotic addition of glucose. Apparently the suppression is entirely due to sugar. Lymphocytes from diabetics and leukemics (both hyperglycemic hosts) were shown to have depressed glucose utilization via the HMP shunt and decreased mitogenic response to PHA. The authors suggest these depressions as etiologic of inadequate CMI in the hosts.[51]

Leukocyte Suppression by Sugars (In Vivo).

Although phagocytosis is endoergic, stopping at levels of BG <10 mg%,[52] a number of investigators have consistently demonstrated a hyperglycemic limit as well. We cite two such reports of prompt significant suppression of neutrophil phagocytosis (of staph epidermidis or beads) by transient hyperglycemia induced in humans by ingestion of various sugars, and one of monocyte ascorbic acid depletion demonstrated by iv GTT (also, indirect evidence of cellular anergy induced by refined carbohydrates is given in following sections).

In one study of ten subjects (max. age 34), oral 100 gram portions of glucose, fructose, sucrose, and refined carbohydrates from honey and orange juice all decreased the phagocytic index (PI; rate of ingestion of beads, etc) by 39 to 45 percent from fasting level in from 1 to 2 hours. However, 100 grams of starch produced no significant decrease. The average Pl of eight patients with diabetic type responses decreased 57 percent from their fasting value (which was already nearly 30 percent below that of the ten normals). A final point of clinical interest in that paper was the recording of PI over a 60 hour fast by seven normal subjects. During this interval, the group's average BG fell from 90 to 75 mg% and its PI rose by 60 percent.[7] Although neutrophils are not CMI effector cells, fasting results suggest that anorexia might be a host defense mechanism in cancer.

In the second study, five male dental students drank 24 ounces of sucrose sweetened cola (66 grams of refined carbohydrate) on one occasion leading to an average PI decrease of 49.8 percent in 45 minutes as BG rose from 85 mg% (fasting) to 157 mg%, and 24 ounces of sugar free cola on another day resulting in no significant change in PI.[53] Intra-cellular ascorbic acid was found to fall over 50 percent, in monocytes in less than 20 minutes after a 25 gram iv GTT.[16] Thus, in vivo and in vitro results agree.

Immune Suppression by Sugar Elevation of Cortisol.

It is known that prolonged elevation of cortisol, through its lympholytic and other anti-inflammatory effects, results in impairment of both monocyte recruitment and effectiveness, inhibition of interferon production, and atrophy of thymus, spleen, and lymph nodes, etc.[54,55] In their investigations on the effects of high sugar diets,[56,57] researchers have found that glucose tolerance decreased to some significant extent in virtually all people, but that, in about 25 percent of the tested population, two strong effects developed in only two weeks: a "sucrose-induced hyperinsulinism" of about 30 percent, and a cortisol elevation of over 300 percent. In view of the preceding discussions and the epidemiological evidence to follow, one wonders how much overlap exists between the above 25% and the same fraction of our high refined carbohydrate population predicted to present with clinical cancer.

Cancer Incidence: Correlation with Sugar Intake (Epidemiological Evidence)

Yudkin's claim of a correlation of 0.6 between cancer and sugar consumption[56] appears supported by other studies. In a 41 country epidemiological study of breast cancer incidence, Hems found it correlated with sugar consumption at 0.73 independently of the only other three foods that had

high correlations.[46] In an extensive analysis of the variables in colon cancer, high sugar, fat, and low fiber intakes were impugned by Walker and Burkitt as the leading etiological factors.[58] A recent analysis of dietary factors in colon and rectal cancer found a correlation with sugar intake in those cases where the available data permitted assessment of refined carbohydrate ingestion.[59] An empirical approach to the question of the toxicity of refined carbohydrates was taken by Cheraskin and Ringsdorf.[60] Using a 7 day dietary survey, these authors assessed the refined carbohydrate intake of 395 dentists and 320 wives. The clinical state of the same 715 person group was recorded on the Cornell Medical Index Health Questionnaire (CMIHQ) on which 195 questions on signs and symptoms indicate pathology by an affirmative answer, the higher scores indicating more health problems. When the refined carbohydrate intake in grams was plotted against CMIHQ score, the two converged toward zero together, suggesting that zero refined carbohydrate intake is consistent with optimal health. This study, and a large number of similar analyses on AA, vitamin A, etc., conducted by this University of Alabama group quantitatively substantiated the clinical impressions they had reached. This study motivated the group to conduct further research on the adjuntive use of refined carbohydrate and AA control in cancer therapy.[61]

Cancer Response to Therapy with Glycemic Control (Clinical Evidence)

Possibly the first adjunctive use of both AA and glycemic control in a clinical trial was with radiotherapy of cervical carcinoma.[61] There were two striking aspects of this study: the restriction of refined carbohydrates, along with supplementation of AA and other dietary specifications, and the impressive difference in radiation response achieved. The control group (27 patients) on a regular diet had an average radiation response score of 63.5 percent (S.D. = 51.6%). The experimental group (also 27 patients) had a score of 97.0 percent (S.D. = 2.8%). All refined carbohydrates and alcohol were excluded. The AA dose was 1.2 g/d (0.4 g at each of all 3 meals). The experiment was "single-blind" in that the microscopist who read all of the slides (each two times randomly) did not know the identity of the slides or to which group (experimental or control) they belonged. In addition it was observed that post-treatment macrophage infiltration and phagocytic "clean-up" was much more extensive in the experimental group (Ringsdorf, pvt. commun.).

Radiation, Thymic and Glycemic Factors: Some Details

In view of the linear "one-hit" nature of penetrating radiation,[32,62] the 10^{12} DNA hits per year per human adult due to sea level cosmic ray particles discussed earlier may be a considerable mutagenic burden, even though very few are carcinogenic. The fact that normalized mortality rates for the five leading cancers are 100 times higher above age 55 (487 per 100,000) than below 35 (5 per 100,000);[12,63] suggests that, in immune competent humans, there is protection against such burden (possibly by classical immune surveillance) until the reproductive age is past. Nothing more could be expected of evolution; we had little selective pressure to optimize for senescence. The 100 times higher incidence in older hypo-thymic individuals does not constitute an argument against the prior existence of normal immune surveillance in them, but for a tumor tolerance that grows progressively with glycemic level. In contrast, the reality of the inescapable ionizing background burden is strongly indicated in both athymic neonates and thymectomized children who, having lost CMI and immune surveillance, exhibit an incidence of neoplasia reported to be as much as 10,000 times higher than normal.[1,31] It is interesting to note again that marked rises in hyperglycemic response and cancer incidence are both reported to occur between ages 35 and 45.[11]

Hyperglycemia and Electrostatic Blocking of CMI.

Since glucose precedes glucosamine, the precursor of sialic acid[64], the observed coating of malignant cells by sialomucin might be favored by hyperglycemia (high levels of cell surface glycoprotein coatings occur in diabetics). Due to the negative surface charges contributed by the sialic acid groups, tumor cells could then electrostatically repel T-cells[65] which are reported to be the most negatively charged cells in the body.[66]

It seems plausible that DHA, an oxidative molecule, can discharge the sialomucin under certain conditions, and eliminate the blocking and this type of tumor tolerance. Thus, the AA-induced regressions of terminal high-tumor-mass patients reported in Scotland[67] might have an additional explanation. This hypothetical removal of tumor blocking would give DHA, usually toxic at high levels, another benign role (in addition to AA's active transport, DHA provides passive diffusive transport into cells where it is reduced to AA).

DHA and Thymic Involution.

A more direct effect of AA level (bearing on the general question of thymic dependent immune competence) has been demonstrated in animal studies and gives additional support for the beneficial effects of AA supplementation. In guinea pigs on decreasing daily AA intakes, the thymus was the only tissue showing a marked change in AA oxidation state with DHA increasing as AA decreased, inverting the AA/DHA ratio.[68] This effect has been observed to be coincident with accelerated thymic involution and suggests that high DHA may be etiologic.[69]

Hyperglycemia, DHA and Thymic Involution.

It is reported that high sugar intake induces (reversibly) a diabetic type GTT in humans,[45,70] and that DHA is elevated in diabetes.[28,71] This, combined with the findings of Dieter[68,69] suggest that hyperglycemia leads to thymic involution and loss of immune surveillance.

Conclusion

Whatever the exact details may be in individual patients, most of the literature seems to support the concept that presentation of clinical cancer represents a tolerance state achieved through escape from immune surveillance.[37] This may occur by one or more of various modes such as low tumor antigenicity; excess suppressor T-cell activity; covering surface antigens with sialomucin or blocking-antibody;[72,73] or by the modes discussed in this paper. Any innocuous low cost modality (such as glycemic control and ascorbate supplementation) that restores homeostasis and heightens several aspects of host defense (especially CMI response which seems to correlate highly with recovery[74]) merits at least large scale empirical clinical evaluation as adjunctive therapy.

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