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The Importance of Mass (Core) Temperature in the Development of Cancer: Have We Forgotten the Obvious?

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Abstract

Despite the long history of anecdotal and epidemiological evidence that local and systemic hyperthermia is associated with oncostatic or cancer-diminishing effects, this variable has not been systematically applied. An elevation by only 1°C in incubation temperature markedly facilitated the effects of brief daily exposures of mouse melanoma cells in culture to weak, temporally patterned magnetic fields. Conditions that could mildly elevate core body temperature in mice injected with melanoma cells were associated with reduced tumor masses. The strong negative correlation between diminished core-temperature with aging and increased tumor incidence in human populations in conjunction with the lower prevalence of all cancers in very warm countries compared to temperate regions is consistent with our hypothesis that small shifts in temperature within tissue can modulate cancer growth. Calculations indicate that shifts of only 1°C for protracted periods can supply substantial energies to ion channels and proton pathways with oncostatic potential. Mild hyperthermia may act synergistically with treatments to reduce or eliminate malignant tissue within the human body and reduce their adverse side-effects.

Keywords: *Hyperthermia; Cancer; Patterned magnetic fields; Synergisms; Aging and body temperature; Geographical temperature*

Introduction

One of the fundamental properties of the universe and one of the basic units of physics is temperature. It may not be coincidence that the median wavelength of the 310°K (37°C) of the core mass temperature of the typical terrestrial mammal according to Wien's law is ~10 μm [1,2]. This is the average width of most mammalian cells. Within biological systems cellular vitalities are primarily determined by the liquid crystal properties of the plasma cell membrane that require a narrow range of values for the proportion of water, pH, and temperature. The critical temperatures for this life condition exist within a range of about ± 3°C. Exceeding this narrow band can result in structural alterations that modify the selective permeability of the smectic mesophase of the phospholipid properties and result in cell death. We develop the argument based upon experimental and correlational data that the incidence and prevalence of different conditions that contribute to carcinogenesis and malignancy as well as their inhibition could be related to small changes in core mass temperature of the animal. We also present arguments that the interactions between mild hyperthermia and the most effective treatments for slowing the growth or promoting the demise of cancer cells or tumors produce a powerful synergism that has not been fully implemented for contemporary treatments.

According to Kleef., *et al*. [3] an anecdotal observation by WB Coley of the spontaneous remission of a lymphosarcoma within the cephalic region of a patient following the fever induced by a serious *streptococcal*-induced erysipelas infection reiterated what had been known for centuries. There has been a long history of reports of spontaneous regression of tumors in patients displaying the symptoms of

malaria, tuberculosis, influenza and small pox when accompanied by fever. In fact the "missing fever" during ontogeny was considered by many physicians living in the late 19th century and early 20th century to be an important factor for predicting the development of cancer. Individuals who never experienced fever induced by infections were between 3 and 46 times more likely to develop cancer. Although a recent study by Cooper., *et al.* [4] did not support this link with adult leukemia one must remember that the prevalence of protracted fevers became less frequent in 20th century civilization because of the wide spread use of antipyretic analgesic compounds such as acetyl salicylic acid.

Van der Zee [5] reviewed the employment of heating of patients who had been diagnosed with cancer. He reported that randomized trials showed that patients treated with irradiation and hyperthermia exhibited twice the improvement (68%) compared to irradiation only (34%). The typical tumor-debilitating whole-body temperatures are between 39°C and ~40°C. Regional heating resulting in temperatures of ~43°C for two hours could also be tolerated and effective. Hildebrandt., *et al*. [6] indicated that core temperatures of between 41.8°C and 42.2°C maintained through radiant heat for 1 hr can be effective. The interaction between chemotherapeutic drugs such as cyclophosphamide and ifosfamide and platinum compounds are related linearly to their enhanced cytotoxic effects when temperatures were increased from 37°C to 40.5°C. However there is a limit in terms of both physiological tolerance and the induction of the family of heat shock proteins (HSPs) such as HSP 27 and HSP 70 which can inhibit hyperthermic cell death under certain conditions. The optimal treatment would involve a combination of treatment and mild hyperthermia where such protective features ("thermotolerance") as well as the reduced blood flow in tumors that can occur at temperatures above 42°C [6] would not be elicited.

Cell Line Research

The standard experimental model for exploring the intricate processes involved with the development of aberrant proliferative capacities and the molecular mechanisms that mediate these potentially deadly effects upon the host organism involves the isolated cell line. In modern biomolecular and cell biology laboratories an elaborate technology of incubators has been developed to maintain ambient temperature within a very narrow range around 37°C. Such constancy may facilitate control of chemical reactions but it does not reflect the realistic variability of living systems. Even within the homeothermic mammal local temperatures can range over at least 10°C. The fibroblast-rich boundary, the skin, is one relatively tonic hypothermic example.

In the pursuit of developing novel treatments that affect only malignant cells but not normal cells we found that exposures for only 1 hour per day for 5 days to 1 to 5 microTesla physiologically-patterned magnetic fields reduced cell growth of human and mouse cancer lines from a variety of sources by about 25% to 35% [7,8]. Normal cells were not affected. One effective pattern, known as the "Thomas pulse" or "decelerating frequency-modulated pattern" is known to produce marked analgesia in rodents [9], invertebrates [10], and human volunteers [11]. While investigating the effects of this class of weak, physiologically-patterned magnetic fields upon cell growth of malignant and non-malignant cells we noted that the mouse melanoma (B16) cells maintained at 38.5°C compared to the usual 37.5°C incubator environment displayed much greater cellular dropout when this weak, patterned magnetic field was presented compared to when it was not. This difference of only 1°C did not affect the growth rate of melanoma cells exposed to sham field conditions.

The surprising and very promising effect is shown in Figure 1. Each of the eight points in Figure 1 refers to the results of triplicates of experiments. This shows the decrease in growth of cells exposed for either 1 hr, 6.5 hr, 12 hr or 24 hr per day within the incubator to the frequency-modulated (Thomas) pattern with 3.25 point durations. The 3.25 ms refers to the duration each of the numbers between 0 and 257 (-5 to + 5V) that compose the pattern was presented to the three sets of solenoids oriented in the three spatial planes that generated the magnetic fields to which the plates (stacks of six) of B16-BL6 mouse melanoma cells were exposed. The technique is the same as the one we have been using hundreds of times over the last four years. However we had always adhered to the standard protocol of incubator temperatures set at 37°C with 5% CO_2. All cells were harvested at traditional times and counted by our standard Trypan blue hemocytometer counting protocol [7].

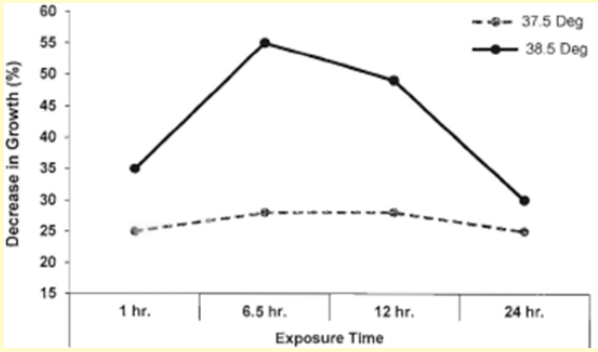

Figure 1: *Decrease in growth rate of melanoma cells (relative to sham field-exposed cells) maintained within either typical (37.5°C) incubator temperatures or 38.5°C temperatures while being exposed daily for either 1 hr, 6.5 hr, 12 hr or continually (24 hr) to a weak, temporally patterned magnetic field.*

When the cells were incubated at 37.5°C over the 5 days the dropout of about 25% compared to sham field-exposed cells was evident by the fifth day. This was typical of previous experiments. As noted by Buckner [8] the effect was largest with 1 hr daily exposures and did not increase with greater durations per day. However by increasing the temperature to 38.5°C (ΔT = 1°C) and exposure duration to 6.5 hr an additional 25% drop out (~50% total) occurred. The drop out almost doubled for the one-hour exposures and was more than doubled for the 6.5 hr of daily magnetic field pattern exposures.

Application to Mouse Tumor Research

The usual procedure for contemporary oncology research is to apply an effective treatment for cells lines to mice to discern if it has potential utility for human treatment. Our research group [12] had found that C57 mice injected subcutaneously with B16-BL6 melanoma cells and exposed for 3 hr per night for about three weeks to the same patterned magnetic field that reduced the proliferation within the cell lines maintained in incubators also showed a marked reduction in the terminal tumor masses. The reduction has ranged from 50% to 95%.

However there is usually at least one mouse within a cage of 4 mice that had a much smaller tumor than the other three mice regardless if the group had been exposed to the experimental treatment or to sham field conditions. Behaviorally the mouse with the smallest tumor was the most dominant one in the cage as well as the most active member of the group. In six different experiments involving 80, C57 mice we measured dominance behaviourally. The mouse that emerged first from the group of 4 mice to investigate (and usually to initiate agonistic behaviours with) a novel mouse has been shown to be reliably dominant. In some experiments the effect accommodated more than 50% of the variance. The mean and standard deviation for tumor weights before the endpoint (determined by the first mouse of a group that showed ambulatory dysfunction due to the size of the tumor) was reached for the non-dominant mice was 2.47g and 1.28g while these values for the dominant mice were 0.87g and 0.49g. The difference was very robust [$F(1,78) = 29.36$, $p < .001$].

There are older studies [13] that indicate that core-body temperatures in rodents are increased by a fraction of a degree in dominant rats that are also more active and consume more food and water. Dominant rodents in a group often show higher levels of circulating corticosterone and ACTH which can contribute to elevated core body temperatures [14]. According to our hypothesis, the reduced tumor size would be coupled to their higher core body temperatures.

Human Populations: Aging and Metabolism

From a very large (millions) population perspective one would expect that the diminished metabolism associated with ontogeny should be conspicuous, particularly in females subsequent to menopause, when metabolism-coupled chemistry is markedly altered. If slight elevations of mass temperature inhibit cancer growth as noted in our cell line experiments, then the age increment where the

inflection occurs for decreased core temperature should be similar to the inflection increment when all cancers increase. Although inclusion of "all" cancers may appear to be simplistic or erroneous, there is strong electrophysiological data that cancer cells, regardless of type, generally share a similar (hypopolarized) range in resting plasma membrane potential compared to non-malignant cells [15].

There is support for this supposition that is replete within the scientific literature but may have been subjected to alternative interpretations. When the age-specific cancer incidences (normalizing to peak) for 16 major types of cancer per decade of age from 30-39 years, 40-49 years, etc. to 80+ years were quantified from the graph of Pompei and Wilson [16] and correlated with the median values for core body temperature (°F) per decade for men and women combined [17], the inverse association was clearly evident. The results are shown in Figure 2. The statistically significant ($p = 0.001$) Pearson correlation between the standardized cancer measures and mean core body temperatures per decade was $r = -0.97$ (males = -0.94, females = -0.94). The Spearman rho value was -0.94.

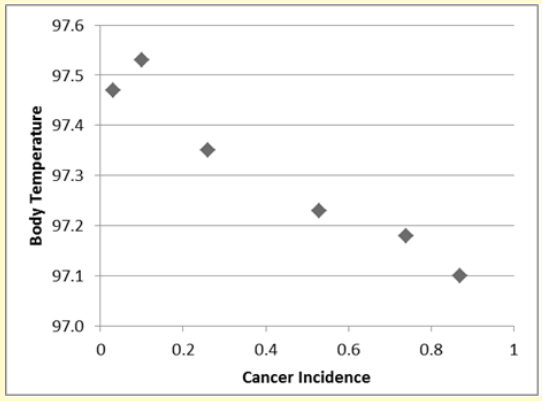

Figure 2: *Scattergram of the association between core body temperature in degree F per decade and standardized cancer incidence per decade.*

Obviously correlation, even one this strong, does not prove causation from the perspective of biological mechanism. However in some disciplines, such as epidemiology, such reliable strong correlations that are not due to confounding variables, that exhibit no obvious source of other variance, and that involve a feasible mechanism can be considered "causal".

Small Temperature Shifts Have Powerful Potential

Although the shift of core temperature over age span might be considered very small (~0.4°F, 0.22°C), it is important to emphasize that temperature within the body is not homogenous. According to Lawson., *et al.* [2] the normal range in oral temperature is 97.7°F to 99.5°F (36.5°C to 37.5°C) which represents the whole body. On the other hand the thyroid's temperature can be typically 104°F (40°C) while the internal mammary artery would more typically approximate 90°F (33.2°C). This "normal range" does not accommodate the anomalous relative hyperthermia that could follow local vascular anomalies and chronic inflammations due to infections or injuries or hypothermia from vascular insufficiency or modified perfusion rates.

A difference of only 1 deg C at 37°C involves remarkable intrinsic energy that is available to molecules within a cell. The difference in energy between 37°C and 38°C (310°K, 311°K) when multiplied by the Boltzmann constant ($1.38 \bullet 10^{-23}$ Joules per molecule) is $1.5 \bullet 10^{-23}$ J. This is equivalent to $0.9 \bullet 10^{-4}$ V (by dividing Joules by the unit charge $1.6 \bullet 10^{-19}$ A•s). Because the opening of a prototypical ion channel involves about $3 \bullet 10^{-7}$ V, this additional energy from an increase of 1°C could involve about 300 channels. Over a period of 6.5 hours (the maximum peak we measured in the cell lines exposed to the Thomas pulse magnetic field, Figure 1) that could involve up to 10^6 to 10^7 channels being affected. The typical numbers of ion channels within the plasma cell membrane of mouse melanoma cells is in the order of 10^6 channels. Recently Buckner., *et al*. [18] showed that the Thomas pattern magnetic field selectively influenced T-type calcium channels. Consequently if a 1°C increase in incubation temperature supplied sufficient channel energy to increase the T-channel effects the

enhanced efficacy for diminishing melanoma growth from the synergism between this specific field and the mild hyperthermia might be explained.

From the perspective of the influence upon the physicochemical properties of water, such as viscosity [19] and the unique properties of interfacial aggregates of water molecules [20,21], this small amount of energy may produce exact effects. The division of $1.5 \bullet 10^{-23}$ J by the mass of a free proton (the bases of pH) is a velocity value of $0.95 \bullet 10^{2}$ m•s^{-1}. The typical distance between two O-H bonds is $1.92 \bullet 10^{-10}$ m. Hence the time required for a unit such as a proton to move this distance would be about $2 \bullet 10^{-12}$ s or 1 ps for a single O-H bond. This is the typical life time of the hydronium ion. These proton movements have been considered one of the major mechanisms by which magnetic fields could affect water and the shifts in pH associated with cancer cells [19,22]. In other words an increase of only 1°C would provide cellular systems with the requirements to shift critical conditions.

Human Populations: Countries and Climate

For environments where the ambient temperature is consistently higher even the homeothermic human should display slightly elevated core temperature for protracted periods. If higher core mass temperature in the absence of fever is the significant contributor to cancer occurrence then people who live in very warm climates should display less incidence and prevalence of cancer. Examination of the per capita cancer rates from the World Health Organization (WHO) supports this contention. The 20 countries (areas) with the lowest per capita prevalence (31 to 57 per 100,000) are all warm countries that include Niger, Angola, Senegal, Mauritania, and Oman. On the other hand the 20 countries within the highest per capital (507 to 646 per 100,000) include Germany, Canada, Sweden, Norway and Denmark.

Human Population Treatments

One of the most popular models in the 19th century for treatment of cancer involved hormesis which presumes that exposure (injection) to a small amount of the "poison" allowed resistance to it. The normal hormetic procedure for treating cancer was to inject small amounts of dead cancer cells. One major consequence of the injection of small amounts of foreign material into the normal body is mild hyperthermia. If our hypothesis is valid a low-level fever (and correlative activation of the immune system) could result in less likelihood of cancer proliferation as noted in our cell line studies and would be consistent with historical observations. The brilliant research by Robert M. Lafrenie has demonstrated the critical role of intercellular cohesive processes and immunological mechanisms for transforming treatment effects elicited at the cell culture level to comparable changes in actual tumor tissues.

During the latter part of the 19th century and early 20th century the proliferation of the use of *acetylsalicylic acid* or aspirin following its isolation and marketing by pharmaceutical companies would have minimized the gross population incidence of maintained fevers. Whereas (except for mixtures or tinctures of white willow bark), the standard treatment for fevers was cold clothes and ice baths these effects would have been transient in comparison to the protracted antipyretic effects of aspirin. According to our assumption this improvement of diminishment of hyperthermias in the population would have contributed to statistical increases in cancer proliferation that should be evident at the level of large populations.

The contemporary treatment for cancer is either chemotherapy or focused but strong dosages of irradiation. The compounds employed for many chemotherapies display "poison"-like properties and dissipate normal cells as well as cancer cells although the latter are more disproportionately affected. Irradiation produces significant cell damage that releases copious cytoplasmic materials into the general circulation. The general response to these conditions would be a mild and protracted hyperthermia. From our perspective a component of the efficacy of these two methods may simply be connected to their propensity to maintain the appropriate, mild, persistent elevation in low level core mass temperature.

Conclusions

Core hyperthermia and its associated changes within local regions of the body may produce the conditions to diminish the growth of malignant cells and minimize the expansions of tumours. The powerful correlation between decreased core body temperature and increased cancer risk with aging is conspicuous. Combinations of contemporary treatments for cancer, such as radiation and chemotherapy, in association with moderate core hyperthermia double efficacy. In experimentally-induced tumors in mice the individuals

within a cage that were most likely to show mild hyperthermia exhibited radically reduced tumor masses. Increasing the incubation temperature by only 1°C doubled the growth inhibition in melanoma cells exposed to weak, patterned magnetic fields. This combination did not affect normal cells and produced no obvious side effects. We recommend that cell culture researchers increase the incubator temperatures by 1 to 2°C when experimenting with novel, non-toxic cancer reducing procedures to discern if this easy and relatively normal condition can enhance the positive effects of the treatment.

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