



Environmental discontinuity hypothesis: Buffer dysfunctions as a source of human disease

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Summary Adaptive physiologic buffers enable organisms to respond to environmental variation with appropriate plasticity. Modern humans have substantially remodeled their environment such that many interactions with the environment have become relatively discontinuous functions compared to the past. Examples include sunlight, temperature, and altitude. We propose that environmental discontinuity represents a Darwinian maladaptation and may promote disease by inducing buffer dysfunctions. Skin pigmentation is an adaptive, dynamic buffer that normalizes sunlight exposure to balance the potential harm of damaging rays with the importance of sunlight in driving systemic biologic functions such as melatonin and vitamin D. Due to lifestyle characteristics such as indoor–outdoor living, well-intended sun-avoidance campaigns, and inhomogeneous use of apparel and sunblock techniques, modern humans increasingly experience sunlight variation as a discontinuous function. The resulting skin pigmentation buffer dysfunction may promote diseases associated with over- or under-exposure to sunlight, the most striking example being melanoma. In addition to promoting discontinuity of sunlight exposure, sun-avoidance campaigns may undermine sun-dependent biologic pathways such as melatonin and vitamin D that appear to protect against cancer. These issues may partly explain the rise in melanoma rates despite the implementation of sun-avoidance campaigns. Also discussed is the potential role that discontinuous temperature variation associated with modern lifestyles plays in diseases such as viral infection, heart failure, and acute coronary syndromes. Acute discontinuous changes in pressure and oxygen levels related to air travel may contribute to autonomic dysfunction, venous thromboembolism, and viral infections. Therapeutic implications are discussed.

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Hypothesis

Adaptive physiologic buffers enable organisms to respond to environmental variation with appropriate plasticity. Modern humans have substantially

remodeled their environment such that many interactions with the environment have become relatively discontinuous functions compared to the past. Examples include sunlight, temperature, and altitude. We propose that environmental discontinuity represents a Darwinian maladaptation and may promote disease by inducing buffer dysfunctions.

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Evidence

Discontinuous variation of sunlight exposure

Exposure to sunlight is generally considered to be a causative agent in the development of cutaneous malignancies [1]. This view has resulted in public health campaigns promoting sun avoidance and sunscreen use [2,3]. Despite implementation of these campaigns, mortality from melanoma has tripled in the last three decades [4,5], and cases of pediatric melanoma have continued to rise [6]. Excessive sun exposure despite the public health campaigns may play some role in this increase, but the magnitude of the rise of skin cancer rates has led scientists to seek additional perspectives. Various hypotheses such as ozone depletion, earlier detection, and carcinogenicity of sunscreen have been promulgated to explain the apparent incongruity between the behavioral change produced by the public health campaigns and the increasing incidence of skin cancers, but the topics remain controversial [2–14]. Is it possible that declining sun exposure levels and greater irregularity in the patterns of sun exposure related to recent behavioral modifications may contribute to the development of skin cancer?

Skin pigmentation can be understood as an adaptive, dynamic buffer that normalizes sunlight exposure experienced by the body to balance the potential harm of damaging rays with the importance of sunlight in driving certain systemic pathways such as melatonin and vitamin D. The buffering phenomenon is apparent to anyone who has experienced tanning after a recent increase in sunlight exposure or paling after a recent decline in sunlight exposure. It is well known that extreme circumstances can render this pigmentation buffer dysfunctional: darker-skin populations who migrated to less sun-exposed geographies have increased incidence of rickets [15] while lighter-skin populations who migrated to more sun-exposed areas exhibit higher rates of skin cancer [16]. These extreme evolutionary dislocations notwithstanding, skin pigmentation demonstrates tremendous plasticity in response to changing light patterns. However, successful skin pigmentation buffering presumes variation in light exposure that represents a relatively continuous function; most species and pre-modern humans experienced sunlight in this fashion during formative evolutionary epochs. For modern humans, the light experience has been altered and rendered far more episodic by indoor–outdoor living, sun-avoidance campaigns, and inhomogeneous use of apparel and sun-

block techniques. As a result, modern humans increasingly experience sunlight variation as a discontinuous function. The resulting skin pigmentation buffer dysfunction may promote diseases associated with over- or under-exposure to sunlight. That vitamin D deficiency still occurs in many populations [17] and hypovitaminosis has been identified in many groups seemingly not at risk [18,19] may exemplify the former. That melanoma rates are still rising may exemplify the latter. While sunlight avoidance may protect against cancer during its practice, it renders the skin more vulnerable to cancer during breakthrough periods of sunlight exposure. Clothes and inhomogeneous sun block application can add irregularity to sun exposure and contribute to skin pigmentation buffer dysfunction.

In addition to promoting discontinuity of sunlight exposure, sun-avoidance campaigns may undermine sun-dependent biologic pathways that appear to protect against cancer. Indeed, sunlight exposure appears to correlate with increased survival in various cancers [20–22] and ultraviolet radiation appears to protect against the development of certain cancers [23]. These counterintuitive observations have been attributed to the sun-dependent synthesis of vitamin D [21–23], which exhibits numerous immunologic properties that protect against cancer [24–27]. Another sun-dependent pathway that influences immunologic functions related to cancer is melatonin. Exposure of the eye and skin to sunlight regulates the conversion of serotonin to melatonin [28], a hormone which appears to protect against growth of melanomas [29–33]. Melatonin has not been actively pursued as a treatment for melanoma [34], perhaps out of concern regarding the potentially biphasic nature of melatonin's effects [35]. The association of levodopa with melanoma in Parkinson's disease has been a subject of debate for many years [36]. Levodopa remains contraindicated in patients with a history of melanoma. Levodopa has long been known to reduce serotonin [37], and more recent studies have shown that it decreases melatonin production by the pineal gland [38].

Discontinuous variation of temperature exposure

Ambient temperature in nature can vary considerably over circadian, seasonal, and multi-year cycles in both predictable and unpredictable ways. Some organisms including humans that rely on temperature normalization to optimize biologic functions have evolved thermal buffering mechanisms

that enable them to survive under changing thermal conditions. A circumstance perhaps unforeseen during the Darwinian selection of these buffers, however, is the acute changes in temperature experienced by modern humans. Mechanical thermal control systems and apparel designed to normalize the human thermal experience also create discontinuous temperature changes as individuals move in and out of temperature-controlled environments.

As robust as the biologic thermal buffers may be, they may behave dysfunctionally in contexts associated with discontinuous temperature change such as stepping out of a heated house into the cold outdoors. The acute response to a drop in ambient temperature is brown fat thermogenesis and shivering mediated by the sympathetic system [39]. The well-known association of acute coronary syndromes in patients entering cold weather or cold water may be partly mediated by an acute sympathetic response, particularly if patients exhibit underlying autonomic dysfunction [40]. The same mechanism may underlie increased rates of acute exacerbation of heart failure [40] during winter months. Sympathetic bias also shifts T helper (Th) immune bias to Th2, a state more favorable for viral infection [40]. The phrase “catching a cold” suggests an association of viral infection with a drop in temperature, and it is possible that the acute sympathetic bias promoting Th2 immunity can increase the vulnerability to viral proliferation. While local cooling can stem inflammation, systemic cooling may counterintuitively worsen the inflammatory component of conditions often associated with Th2 bias such as urticaria and asthma [41–43], though the bronchial response to cold-induced sympathetic bias may also provide symptomatic relief in the latter case.

Discontinuous variation of altitude exposure

Altitude change can act as a stressor on numerous physiologic systems, particular those that govern oxygenation and pressure. During prehistoric evolution, changes in altitude likely occurred gradually for non-avian species, enabling long-term physiologic adaptations such as hematopoiesis and carotid body remodeling to compensate [44]. Mountain climbers encamp for periods of time to allow long-term physiologic adaptations to occur. Modern aviation, however, can expose humans to rapid, relatively discontinuous altitude changes. Buffer dysfunctions such as otodynia can ensue as various physiologic responses fail to adequately accommodate. The acute hypobaric hypoxia associated with

high-altitude ascent [45] can activate the carotid chemoreceptor reflex and promote sympathetic bias. The sympathetic activation can be accentuated by the psychological fear associated with flying and compounded by dehydration and cooler temperatures present at higher altitudes [46].

Sympathetic activity promotes coagulation and shifts Th balance to Th2 inflammation, a physiologic convergence that likely served a useful purpose when trauma was a significant driver of natural selection [47]. Thus, acute high-altitude ascent may pose an increased risk of diseases associated with the ‘trauma triad’ of sympathetic bias, Th2 bias, and coagulation [47]. Acute altitude ascent has been linked to headache, pulmonary edema, insomnia, anorexia, and nausea [48,49]. While the pathophysiologic basis of these associations is considered unknown [48], we propose that these consequences of acute altitude sickness are mediated by at least one part of the ‘trauma triad’. Perhaps the increased risk of venous thrombosis associated with aviation is partly related to the inappropriate activation of the ‘trauma triad’, independent of stasis. Also, the anecdotal increased risk of acquiring viral respiratory infection during aviation may be partly related to a Th2 immune shift, which reduces Th1-mediated viral surveillance.

Implications

As modern humans continue to remodel their environment, the perceived dynamic range of many environmental variables such as sunlight, temperature, stress, diet, and visual focal length has considerably narrowed [50]. In this paper, we suggest that even when perceived environmental variation does occur today, it often occurs as a discontinuous stressor that renders the corresponding compensatory buffer inadequate. We explored three exemplary cases, but the framework may extend more generally. For instance, whereas pre-modern species moved along continuous electromagnetic gradients, modern humans are exposed to acute, relatively discontinuous variations in electromagnetic fields associated with long-distance travel, high-altitude ascent, magnetic resonance scans, and exposure to power lines and microelectronic devices. Similarly, modern lifestyles have created a more discontinuous pattern of exposure to humidity. Modern environmental discontinuities represent potential Darwinian dislocations for which there has been little prior selection pressure, and to what extent they contribute to the pathogenesis of diseases is not fully known.

Multiple sclerosis is an example of a condition that appears to be sensitive to more than one of these variables. Geographic latitude, weather, and patterns of light exposure have been associated with multiple sclerosis in various epidemiologic studies [51–54]. Ironically, fundamental platforms for research including animal- and cell-based model systems, which represent critical tools for studying human diseases, may themselves be distorted by exposure to environmental discontinuities such as unnatural light patterns.

The impact of modern environmental discontinuities on biologic systems may extend beyond the induction of buffer dysfunctions. Organisms ranging from prokaryotes to birds interpret environmental flux including tide, day-length variation, sun location, temperature, electromagnetic fields, and chemical gradients to make important life-history decisions such as timing of development, reproduction, migration, offspring sex ratios, feeding patterns, body phenotype, and lifespan [55]. In some cases, the patterns of environmental variation can serve as external clocks to organize molecular, cellular, and systemic functions. Even the predictable temporal pattern of radiation emitted from periodic solar flares can be viewed as a systemic clock governing the pace of mutagenesis, speciation, and evolution. It is possible that introducing discontinuities to natural patterns of environmental information may account for yet-unrecognized changes occurring at all levels of the ecosystem.

It is noteworthy that many modern therapeutic paradigms involve the controlled disruption of environmental variations. Cooling and heating therapies are already applied successfully in a wide variety of clinical scenarios. Radiation is used to preferentially kill fast-dividing cells. Hyperbaric chambers and magnetic stimulation are being tested in various indications. External light therapy is currently used for mood disorders, psoriasis, insomnia, and other circadian clock dysfunctions. The success of light therapy in particular is in keeping with the increasing awareness that cells communicate with each other by producing and sensing light [56] and leave open the possibility that internal cellular processes such as nerve conduction may involve a component of optical communication. Emergence of implantable light-emitting devices, similar to the implantable heating, cooling, and energy technologies that have already been developed, for disease modulation is anticipated. In the future, we also envision a new paradigm for the prevention and treatment of diseases that involve the controlled restoration, rather than disruption, of environmental continuity.

References

- [1] Cleaver JE, Crowley E. UV damage, DNA repair and skin carcinogenesis. *Front Biosci* 2002;7:1024–43.
- [2] Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst* 2003;95(11):806–12.
- [3] Gallagher RP, Rivers JK, Lee TK, Bajdik CD, McLean DI, Coldman AJ. Broad-spectrum sunscreen use and the development of new nevi in white children: a randomized controlled trial. *JAMA* 2000;283(22):2955–60.
- [4] Desmond RA, Soong SJ. Epidemiology of malignant melanoma. *Surg Clin North Am* 2003;83(1):1–29.
- [5] Beddingfield 3rd FC. The melanoma epidemic: res ipsa loquitur. *Oncologist* 2003;8(5):459–65.
- [6] Pappo AS. Melanoma in children and adolescents. *Eur J Cancer* 2003;39(18):2651–61.
- [7] McCarthy WH. The Australian experience in sun protection and screening for melanoma. *J Surg Oncol* 2004;86(4):236–45.
- [8] Oikarinen A, Raitio A. Melanoma and other skin cancers in circumpolar areas. *Int J Circumpolar Health* 2000;59(1):52–6.
- [9] Westerdahl J, Olsson H, Masback A, Ingvar C, Jonsson N. Is the use of sunscreens a risk factor for malignant melanoma? *Melanoma Res* 1995;5(1):59–65.
- [10] Westerdahl J, Ingvar C, Masback A, Olsson H. Sunscreen use and malignant melanoma. *Int J Cancer* 2000;87(1):145–50.
- [11] Autier P, Dore JF, Negrier S, Lienard D, Panizzon R, Lejeune FJ, et al. Sunscreen use and duration of sun exposure: a double-blind, randomized trial. *J Natl Cancer Inst* 1999;91(15):1304–9.
- [12] Bastuji-Garin S, Diepgen TL. Cutaneous malignant melanoma, sun exposure, and sunscreen use: epidemiological evidence. *Br J Dermatol* 2002;146(Suppl. 61):24–30.
- [13] Dennis LK, Beane Freeman LE, VanBeek MJ. Sunscreen use and the risk for melanoma: a quantitative review. *Ann Intern Med* 2003;139(12):966–78.
- [14] Bigby ME. The end of the sunscreen and melanoma controversy? *Arch Dermatol* 2004;140(6):745–6.
- [15] Weisberg P, Scanlon KS, Li R, Cogswell ME. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. *Am J Clin Nutr* 2004;80(6 Suppl.):1697S–705S.
- [16] Armstrong BK, Kricger A. How much melanoma is caused by sun exposure? *Melanoma Res* 1993;3(6):395–401.
- [17] Stokstad E. Nutrition. The vitamin D deficit. *Science* 2003;302(5652):1886–8.
- [18] Isaia G, Giorgino R, Rini GB, Bevilacqua M, Maugeri D, Adami S. Prevalence of hypovitaminosis D in elderly women in Italy: clinical consequences and risk factors. *Osteoporos Int* 2003;14(7):577–82.
- [19] Gessner BD, Plotnik J, Muth PT. 25-Hydroxyvitamin D levels among healthy children in Alaska. *J Pediatr* 2003;143(4):434–7.
- [20] Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricger A, Eberle C, et al. Sun exposure and mortality from melanoma. *J Natl Cancer Inst* 2005;97(3):195–9.
- [21] Egan KM, Sosman JA, Blot WJ. Sunlight and reduced risk of cancer: is the real story vitamin D? *J Natl Cancer Inst* 2005;97(3):161–3.
- [22] Osborne JE, Hutchinson PE. Vitamin D and systemic cancer: is this relevant to malignant melanoma? *Br J Dermatol* 2002;147(2):197–213.

- [23] Moon SJ, Fryer AA, Strange RC. Ultraviolet radiation: effects on risks of prostate cancer and other internal cancers. *Mutat Res* 2005;571(1–2):207–19.
- [24] Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. *Exp Biol Med* 2004;229(11):1136–42.
- [25] Colston K, Colston MJ, Feldman D. 1,25-Dihydroxyvitamin D3 and malignant melanoma: the presence of receptors and inhibition of cell growth in culture. *Endocrinology* 1981;108:1083–6.
- [26] Sauer B, Ruwisch L, Kleuser B. Antiapoptotic action of 1 α ,25-dihydroxyvitamin D3 in primary human melanocytes. *Melanoma Res* 2003;13(4):339–47.
- [27] Hutchinson PE, Osborne JE, Lear JT, Smith AG, Bowers PW, Morris PN, et al. Vitamin D receptor polymorphisms are associated with altered prognosis in patients with malignant melanoma. *Clin Cancer Res* 2000;6(2):498–504.
- [28] Slominski A, Wortsman J, Tobin DJ. The cutaneous serotonergic/melatoninergic system: securing a place under the sun. *FASEB J* 2005;19(2):176–94.
- [29] Kiratli H, Gedik S, Us D, Bilgic S. Serum melatonin levels following enucleation and transpupillary thermotherapy in patients with choroidal melanoma. *Clin Exp Ophthalmol* 2003;31(6):505–8.
- [30] Slominski A, Pruski D. Melatonin inhibits proliferation and melanogenesis in rodent melanoma cells. *Exp Cell Res* 1993;206(2):189–94.
- [31] Cos S, Garcia-Bolado A, Sanchez-Barcelo EJ. Direct antiproliferative effects of melatonin on two metastatic cell sublines of mouse melanoma (B16BL6 and PG19). *Melanoma Res* 2001;11(2):197–201.
- [32] Hu DN, Roberts JE. Melatonin inhibits growth of cultured human uveal melanoma cells. *Melanoma Res* 1997;7(1):27–31.
- [33] Kadekaro AL, Andrade LN, Floeter-Winter LM, Rollag MD, Virador V, Vieira W, et al. MT-1 melatonin receptor expression increases the antiproliferative effect of melatonin on S-91 murine melanoma cells. *J Pineal Res* 2004;36(3):204–11.
- [34] Gonzalez R, Sanchez A, Ferguson JA, Balmer C, Daniel C, Cohn A, et al. Melatonin therapy of advanced human malignant melanoma. *Melanoma Res* 1991;1(4):237–43.
- [35] Yerneni LK, Jayaraman S. Pharmacological action of high doses of melatonin on B16 murine melanoma cells depends on cell number at time of exposure. *Melanoma Res* 2003;13(2):113–7.
- [36] Fiala KH, Whetteckey J, Manyam BV. Malignant melanoma and levodopa in Parkinson's disease: causality or coincidence?. *Parkinsonism Relat Disord* 2003;9(6):321–7.
- [37] Fahn S, Snider S, Prasad AL, Lane E, Makadon H. Normalization of brain serotonin by L-tryptophan in levodopa-treated rats. *Neurology* 1975;25(9):861–5.
- [38] Willis GL. The therapeutic effects of dopamine replacement therapy and its psychiatric side effects are mediated by pineal function. *Behav Brain Res* 2005;160(1):148–60.
- [39] Kanzleiter T, Schneider T, Walter I, Bolze F, Eickhorst C, Heldmaier G, Klaus S, Klingenspor M. Evidence for NR4A1 as a cold-induced effector of brown fat thermogenesis. *Physiol Genomics*; 2005 Oct 11 [Epub ahead of print].
- [40] Yun AJ, Lee PY, Bazar KA. Temporal variation of autonomic balance and diseases during circadian, seasonal, reproductive, and lifespan cycles. *Med Hypotheses* 2004;63(1):155–62.
- [41] Davis MS, Malayer JR, Vandeventer L, Royer CM, McKenzie EC, Williamson KK. Cold weather exercise and airway cytokine expression. *J Appl Physiol* 2005;98(6):2132–6.
- [42] Wanderer AA, Hoffman HM. The spectrum of acquired and familial cold-induced urticaria/urticaria-like syndromes. *Immunol Allergy Clin North Am* 2004;24(2):259–86.
- [43] Kikuchi K, Kobayashi H, Hirao T, Ito A, Takahashi H, Tagami H. Improvement of mild inflammatory changes of the facial skin induced by winter environment with daily applications of a moisturizing cream. A half-side test of biophysical skin parameters, cytokine expression pattern and the formation of cornified envelope. *Dermatology* 2003;207(3):269–75.
- [44] Prabhakar NR, Fields RD, Baker T, Fletcher EC. Intermittent hypoxia: cell to system. *Am J Physiol Lung Cell Mol Physiol* 2001;281:L524–8.
- [45] Chakrabarty K, Fahim M. Modulation of the contractile responses of guinea pig isolated tracheal rings after chronic intermittent hypobaric hypoxia with and without cold exposure. *J Appl Physiol* 2005;99(3):1006–11.
- [46] Yun AJ, Lee PY, Bazar KA. Can thromboembolism be the result, rather than the inciting cause, of acute vascular events such as stroke, pulmonary embolism, mesenteric ischemia, and venous thrombosis?: a maladaptation of the prehistoric trauma response. *Med Hypotheses* 2004;64(4):706–16.
- [47] Yun AJ, Lee PY, Bazar KA. Acute coronary syndromes and heart failure may reflect maladaptations of trauma physiology that was shaped during pre-modern evolution. *Med Hypotheses* 2004;62(6):861–7.
- [48] West JB. The physiologic basis of high-altitude diseases. *Ann Intern Med* 2004;141:789–800.
- [49] Kinsman TA, Townsend NE, Gore CJ, Hahn AG, Clark SA, Aughey RJ, et al. Sleep disturbance at simulated altitude indicated by stratified respiratory disturbance index but not hypoxic ventilatory response. *Eur J Appl Physiol* 2005;94(5–6):569–75.
- [50] Yun AJ, Bazar KA, Gerber A, Lee PY, Daniel SM. The dynamic range of biologic functions and variation of many environmental cues may be declining in the modern age: implications for diseases and therapeutics. *Med Hypotheses* 2005;65(1):173–8.
- [51] Llorca J, Guerrero P, Prieto-Salceda D, Dierssen-Sotos T. Mortality of multiple sclerosis in Spain: demonstration of a north-south gradient. *Neuroepidemiology* 2005;24(3):135–40.
- [52] Ogawa G, Mochizuki H, Kanzaki M, Kaida K, Motoyoshi K, Kamakura K. Seasonal variation of multiple sclerosis exacerbations in Japan. *Neurol Sci* 2004;24(6):417–9.
- [53] Rosen LN, Livingstone IR, Rosenthal NE. Multiple sclerosis and latitude: a new perspective on an old association. *Med Hypotheses* 1991;36(4):376–8.
- [54] Hutter CD, Laing P. Multiple sclerosis: sunlight, diet, immunology and aetiology. *Med Hypotheses* 1996;46(2):67–74.
- [55] Yun AJ, Lee PY, Bazar KA, Daniel SM, Doux JD. The incorporation of iodine in thyroid hormone may stem from its role as a prehistoric signal of ecologic opportunity: an evolutionary perspective and implications for modern diseases. *Med Hypotheses* 2005;65(4):804–10.
- [56] Albrecht-Buehler G. Changes of cell behavior by near-infrared signals. *Cell Motil Cytoskeleton* 1995;32(4):299–304.