Journal of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci
2010 Vol. 65A, No. 4, 382–385
doi:10.1093/gerona/glp164

Advance Access published on November 2, 2009

Review Article

Disuse and Aging, 2009

Walter Bortz

Stanford University School of Medicine, Bolivar Lane, Portola Valley, California.

Address correspondence to Walter Bortz, MD, Stanford University School of Medicine, 167 Bolivar Lane, Portola Valley, CA 94028.
Email: drwbortz@aol.com

Background. Knowledge of the basic processes determinative of the life courses of older persons has progressed dramatically in the past few years. This article is an update of a similar survey performed 27 years ago.

Methods. A literature review of recent contributions gathered from a variety of disciplines seeks a more sturdy and consistent heuristic from which derivative work may proceed.

Results. Publications from basic and clinical sciences as well as related nonmedical fields reveal a new conceptual framework for the understanding of human aging, which suggests a broader framework of contributing agencies and their policy implications.

Conclusions. Aging is not a disease and therefore demands a different lens for analysis. This article provides a deeper focus and insists on the inclusion of a heightened sense of the participation of time. Incorporation of the imperatives applied by the Second Law of Thermodynamics is the foundation of the new definitions.

Key Words: Disuse—Plasticity—Aging.

Received April 28, 2009; Accepted September 23, 2009

Decision Editor: Luigi Ferrucci, MD, PhD

Change what you can
Accept what you must,
AND, know the difference

Niebuhr (adap)

Twenty-seven years ago, I published a paper with this same title (1). It sought an explanation for why my casted right leg, as the result of a ski accident, had within 6 weeks become so withered and weakened. Its condition happened neither because of age as the other leg was just as old and it was fine nor was it the result of the surgeon's repair of the ruptured tendon because if he had placed a cast on the other leg, the same thing would have happened. My leg, any leg, appeared old because it was in a cast.

There was nothing in the biomedical archives that provided a reasonable framework for this apparent homology of disuse and aging. The traditional Disease Model of Medicine, which principally invokes an extrinsic agency as the cause of illness, was inappropriate as an explanation for my compromised leg. Initially, a literature search was performed that ranged widely across different species and different levels of cellular organization and confirmed the congruence of the changes commonly associated with aging and those found with immobility. In this search, the emerging science of space medicine was a valuable resource because weightlessness provides a model of accelerated disuse as gravitational demands are abruptly denied. Space travel, like aging, induces a wide variety of catabolic changes (2). The NASA and Russian literature taught important data that were later to be augmented by the Dallas bed rest study of Levine which concluded that 2 weeks in bed initiated changes that resembled those of 30 years of aging (3).

Disuse Syndrome

Reflecting on the multisystem nature of these changes revealed a similarity with patterns of common clinical conditions. These were subsequently aggregated into the Disuse Syndrome the components of which are (a) cardiovascular vulnerability, (b) musculoskeletal fragility, (c) metabolic instability, (d) immunologic susceptibility, (e) CNS compromise, and (f) precocious aging, frailty (4). As such, the Disuse Syndrome is similar to the previous formulation of Hypokinetic Disease (5) and sedentary death syndrome (6). The recent popularly recognized metabolic, cardiometabolic syndromes are felt to represent Formes-fruste of the Disuse Syndrome (7,8).

Such empirical correlation, although interesting, fails to suggest a specific linking pathogenic mechanism. The central dogma of molecular biology and its reductionistic tenets invoked the genome as the ultimate level for understanding. Several decades of intensive inquiry abetted by

expansive technological effort, however, have yielded little insight into a genetic base for aging and disuse and the other components of the Disuse Syndrome. Failure of the single gene hypothesis to explain very much reflects the poverty of the reductionistic perspective. Genes are far from simple switches, but represent rheostats analog cued to differential energetic shifting signals. They become regularly adaptive, expressed, to the environment. System and process dominate component and event. Biology is delocalized in both time and space. Health is a thermodynamic synergy and stability embedded in constant flux.

No "aging" gene has been identified. Martin and colleagues (9) estimate that 6,000 separate genes may play a role in aging. Strohman (10) suggests that less than 2% of human illness is attributable to single gene deficiencies. Virtually all pathologies are now labeled "polygenic" in their description. The simplistic view of the naked gene operating autonomously has been transformed to the notion of epigenetics, the gene in its environment, as the appropriate focal depth for study. Laughlin (11) recently declared the end of the age of reductionism and its Holy Grail search for a theory of everything. Physicist Philip Anderson famously observed in *Science*, "More is Different," not only different quantitatively but qualitatively (12). The system achieves primacy of import over its components, just as process achieves primacy over events. Systems biology emerges as the master curriculum for medicine.

Energy Flow in Medicine

The lack of an established explanatory framework within genomics for this inquiry prompts return to first principles. What are the generic properties of life, which establish its essence? What is aging? Whatever the answer, it must transcend biology as everything in the universe ages, galaxies, canyons, Chevrolets, redwoods, and turtles. Aging involves the three aspects of time, matter, and energy. Surveying these aspects, one finds the components codified within the Second Law of Thermodynamics. A terse, but universal, explanation for aging is that it is the effect of an energy flow on matter over time. Possibly within it may be found the source of the aging and disuse relationship. Albert St. Gyorgy observed "biologic phenomena possibly are to a great extent expressions of subtle changes which take place in dimensions unknown which belong to the realm of quantum mechanics and can be described within its language."

In 1944, at Trinity College Dublin, eminent quantum physicist Erwin Schrodinger's lecture "What is life?" is now credited as providing the first explicit linkage of nonlinear thermodynamics and living process (13). Pauling traced molecular biology to this formulation, the first which attempted to reconcile physical theory with biological observations. The creative and ordering effects of a flow of energy on matter define life. Such flow generates the creative, adaptive, and stabilizing characteristics of living creatures. Harold Morowitz in "Energy Flow in Biology" wrote "on the dry bones of the nature of atoms and the distribution of energy in the universe are assembled the flesh and blood of life" (14).

Clinical medicine has been virtually oblivious to the fundamental relationship, which assumes increasing urgency with the epidemic of chronic illness now apparent.

Defining Aging

A 1991 book chapter entitled "why things grow old" suggested that the process of aging may, in effect, be a reflection of the imperatives inherent in the Second Law, aging as entropy (15). This perspective initially failed to achieve traction. In 1995, Hayflick wrote, "We don't know the explanation for aging" (16), but in 2007, he wrote "biologic aging is no longer an unsolved problem," and invokes the Second Law in its solution (17). Aging is describable as entropy, a gradual degradation of order, intrinsic to both cosmic and human realms. Furthermore, formulation of aging in thermodynamic terms provides access to the basic mechanisms that characterize the most common pathology of aging, frailty, which similarly lacked an explanatory framework until recently. The physics of frailty explains how the process of aging gradually erodes the integrated physiology and anatomy of the organism (18).

Use it or Lose it

Inherent to the understanding is the display of the remarkable adaptation of the organism to its environment (niche construction). The organism shapes and in turn is shaped by its surroundings. The classic work of D'Arcy Thompson in 1928, "On Growth and Form" in Nature gave physical explanations for the shape of a nautilus, zebra stripes, and the biological scaling rules operating in Nature (19). The term homeostasis was coined by Walter Cannon in 1929 to emphasize the amazing stability of living organisms when perturbed by the enormous environmental challenges they encounter (20). Yet, this stability obscures the fact that the body is incredibly dynamic. The tricarboxylic acid cycle turns over 2.66×10^{21} times per minute. Ninety-eight percent of a body's atoms are replaced every year. Protein metabolism similarly reflects the turnover of 7.7% per day. This nonstatic functionality is described by the important new term homeodynamics (Yates) (21), which in effect places energetic flow at the heart of living process. The slow pace of the structural reflection of the dynamics often hinders recognition and thereby emphasis. The anatomical and physiological resultants of the "use and disuse" relationship demonstrate "lag."

The mechanism for such energetic interchange is enabled by the understanding of the newly elaborated field of receptor sites. These protein molecules studding every cellular surface serve to transduce the various forms of energy with which a cell interfaces, mechanical, chemical, osmotic, electrical to a usable message, which in turn directly affects

the structural machinery of the cell. The structural anatomy thereby reflects functional demands. The mRNA content of cells reacts acutely and specifically to its contingent energetic field, providing a plastic reactivity rampant throughout nature. The cell becomes what it does.

The entire field of phenotypic plasticity remains unexplored by clinical medicine (22). The remodeling of the vascular system, the plasticity of the CNS, the robusticity of the skeleton (Wolff's Law) are tacitly acknowledged, but undervalued (23). Medicine's reductionistic habit emphasizes components and episodes, which disserves the reality that most clinical events do not occur de novo but merely represent the moment of recognition in which an attenuated distributed process has become apparent. A hip fracture, a tumor, a vessel occlusion are more aptly understood as the end product of a time-dependent decremental distributed process The implications of this linkage of "use" and function are highlighted by VO2 Max, the central biomarker that is strictly coded to fitness. VO2 Max represents a critical biomarker of how the organism extracts oxygen from the atmosphere and transmits it via a sequence of channels to the mitochondria where it is used to combust energy sources.

The important article by Blair and colleagues (24) in *JAMA* "Physical Fitness and all Cause Mortality" is a notable contribution in which all cause mortality scales to individual VO2 Max. A fit 70-year-old person has the same oxygen delivery capacity as an unfit 40-year old, a 30-year offset.

An important corollary regulatory feature is symmorphosis. This term introduced recently by Weibel (25) describes how all the sequential steps inherent in substrate usage scale quantitatively with one another. Stated in another way, it is like all boats in a harbor rising and falling to the same tidal message. As such, symmorphosis is a tautology, but it serves beyond this simplistic understanding to explain why physical activity is so universally effective and physical inactivity so harmful in many situations. The converse of the anabolic potential of symmorphosis is the Disuse Syndrome in which linked catabolism is noted in a variety of settings. Cardiovascular vulnerability, musculoskeletal fragility, metabolic instability, immunologic susceptibility, CNS compromise (sensory deprivation), and premature aging or frailty represent the incorporation of a thermodynamic perspective to clinical expression.

Similarly, the concept of symmorphosis is invoked to propose a basic rate of age change as athletic records over the decades show a near linear decay rate of 0.5% per year (26). Because performance depends on optimal function of all systems, no single organ or function can deteriorate faster than 0.5% per year or it would become rate limiting. This figure coincides too with numerous biomarker data (27).

Biological Determinants of Health

These examples of human biology lead naturally to a revised formulation of the determinants of health. Instead of the traditional triad of host, agent, and environment, which emphasizes the primacy of the external locus for pathogenic process, a remnant of the Infectious Disease era, a new formulation was suggested that notably includes the gene and aging within its construct, but mainly it recognizes the central participation of phenotypic plasticity in clinical events (28).

The energetics inherent in the new paradigm suggests the following reclassification, the components of which are quantifiable and lead logically to altered policy allocation.

Determinants of health:

1. Genes
2. Extrinsic agency infection, carcinogen, allergen, trauma, toxin
3. Intrinsic agency stress, disuse
4. Aging

Critically, two of the determinants, the genes and aging, the alpha of life, derive from cosmic law and are therefore immutable, Nature. Conversely, the accidents and maintenance categories (extrinsic and intrinsic agencies) are largely derived from behavior and therefore are eminently susceptible to change, Nurture not Nature. Whereas most situations caused by extrinsic agency have a short time line, acute presentation, Dx, and Rx those conditions attributable to intrinsic, dysynergistic agency are attenuated in their course, but, importantly, are reversible by redress of the dysynergy.

Prigogine in his magisterial formulation " Order Out of Chaos" restated the role of the environment in health (29). Instead of the old concept in which the environment represents a hostile encounter zone from which the organism needs protection, it, with the appropriate energetic interface, becomes the progenitor of order, that is, structure and function. Nature and Nurture thereby cohere. It is variably estimated that 50%–60% of clinical encounters have a dominant behavioral (maintenance) causation. In this regard, the critical *JAMA* article, "Actual Causes Of Death" in 1992 by McGinnis and Foege is a landmark contribution (30).

An analogy to the energetic premise of the Disuse Syndrome is the General Adaptation Syndrome proposed by Selye 60 years ago (31). His formulation posited that a variety of harmful effects in numerous organ systems resulted when the organism was confronted with too much energetic load, "Stress." His thesis is newly stated by McEwen as "Allostatic load," in which as with Disuse, the body deteriorates not because of the action of an external agent but because of a faulty adaptation to an energetic stimulus (32).

The emergence of a new paradigm of bioenergetic involvement explains most of the identified heterogeneity and disparities in health patterns particularly as we age. We are born equal but made unequal by differential gene expression. Twins genetically identical at birth become progressively more dissimilar (33). Feral man and savants are extraordinary examples of plasticity. Arabidopsis seeds grown at sea level and at the Sierra crest although sharing identical genetic

profiles demonstrate vastly different life histories reflecting cumulative gene environment interaction, representing a graphic example of the interplay of nature and nurture.

We lack the ability to change our Nature, our genes and aging, our alpha and our omega, but we are ultimately responsible for our Nurture, which reflects directly our epigenetic, bioenergetic environment. Medicine must assume a lead role in helping to assure our best external and internal environment to express our ensemble of genes to our biological potential. Health is a choice informed and assisted by our profession.

An international conference similar in emphasis to the important Waddington research conferences of the 1980s, "The Dynamics and Energetics of Health and Aging" www dynamicsenergeticshealthaging was held at the National Institutes of Health in 2002 and submitted recommendations to the Director suggesting a major shift in priority from genes to systems biology and its domains, such as metabolic control analysis (34). Such policy redirection acknowledges the primacy of the whole over the components and process over event. Feinberg's (35) recent statement "Epigenetics at the Epicenter of Modern Medicine" is an explicit plea for an expanded conceptual framework for Medicine.

Clinical medicine should adopt the new paradigm shift from repair to prevention in accord with the emerging thermodynamic imperatives.

References

1. Bortz WM. Disuse and Aging. *JAMA*. 1982;248:1203–1208.
2. Evans WH. *Astrofit*. New York, NY: Free Press; 2002.
3. McGuire DK, Levine BD, Williamson JW, et al. A 30 year follow up of the Dallas Bed Rest and Training Study: 1. Effect of Age on the Cardiovascular Response to Exercise. *Circulation*. 2001;104:1350–1357.
4. Bortz WM. The disuse syndrome. *West J Med*. 1984;141:691–694.
5. Kraus H, Raab W. *Hypokinetic Disease: Disease Produced by the Lack of Exercise*. Springfield, IL: CC Thomas; 1961.
6. Booth FW. Sedentary death syndrome. *Can J Appl Physiol*. 2004;29:447–460.
7. Hamilton DG, Hamilton MD, Zderic TW. Role of low energy expenditure in obesity, metabolic syndrome, diabetes, and cardiovascular disease. *Diabetes*. 2007;56:2655–2667.
8. Pettman TL, Buckley JD, Coates ML, et al. Prevalence and interrelationships between cardio-metabolic risk factors in clinically obese individuals. *Metab Related Disorders*. 2008.
9. Martin GM, Bergman A, Barzilai N. Genetic determinants of health and life span etc: progress and new opportunities. *PLoS Genet*. 2007; 3(7):E125.
10. Strohman R. Ancient genomes, wise bodies, and unhealthy people. Limits of a genetic paradigm in biology and medicine. *Perspect Biol Med*. 1993;37:112–145.
11. Laughlin WB. *A Different Universe, Reinventing Physics from the Bottom up*. New York, NY: Basic Books; 2007:227.
12. Anderson P. More is different. *Science*. 1972;177:393–396.
13. Schrodinger E. *What is Life? The Physical Aspects of Living Cells*. New York, NY: Cambridge University Press; 1967.
14. Morowitz HJ. *Energy Flow in Biology*. New York, NY: Academic Press; 1968.
15. Bortz WM. *We Live Too Short and Die Too Long*. New York, NY: Bantam Books; 1991:27.
16. Hayflick L. *How and Why We Age*. New York, NY: Ballantine Books; 1995.
17. Hayflick L. Biologic aging is no longer an unsolved problem. *Ann N Y Acad Sci*. 2007;1100:1–13.
18. Bortz WM. The physics of frailty. *J Am Geriatr Soc*. 1999;41: 1004–1008.
19. Thompson D'AW. *On Growth and Form*, 2nd ed. London, UK: Cambridge University Press; 1942.
20. Cannon W. Organization for physiological homeostasis. *Physiol Rev*. 1929;9:399–4325.
21. Yates FE. Order and complexity in dynamical systems: homeodynamics as a generalized mechanics for biology. In D Mikulecky and M Witten (eds). *Dynamics and Thermodynamics of Complex Systems*. New York, NY: Pergamon Press; 1993:49–74.
22. Hollenburg M. Growth factors, their receptors, and development. *Am J Med Genet*. 1989;34:35–42.
23. Wolff J. *Das Gesetz der Transformation der Knochen Kirschwald 1899 [Translated by P.Maquet and R Furlong]*. Berlin, Germany: Springer-Verlag; 1986.
24. Blair SN, Barlow CF, Paffenbarger RS, et al. A prospective study of healthy and unhealthy men. *JAMA*. 1995;273:1094–1098.
25. Weibel ER. *Symmorphosis: on form and function in shaping life*. Cambridge, MA: Harvard University Press; 2000.
26. Bortz WM, IV, Bortz WM, II How fast do we age? Exercise performance over time as a biomarker. *J Geron*. 1996;51A:223–225.
27. Sehl M, Yates FE. Rates of senescence between 30 and 70 years of age in healthy people. *J Gerontol*. 2000;13:198–208.
28. Bortz WM. Biologic basis of determinants of health. *Am J Public Health*. 2005;995:389–392.
29. Prigogine I, Stengers I. *Order Out of Chaos*. New York, NY: Bantam; 1984.
30. McGinnis JM, Foege WH. Actual causes of death in the United States. *JAMA*. 1993;270:2207–2212.
31. Selye H. *The Story of the Adaptation Syndrome*. Montreal, Canada: Acta; 1952.
32. Seeman JE, Singer BH, Rowe JW, et al. Price of adaptation—allostatic load and its health consequences. *Arch Intern Med*. 1997;157: 2259–2268.
33. Fraga MF, Ballestar E, Paz MF, et al. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci U S A*. 2005;102:10604–10609.
34. Bortz W, Yates FE, Veech R. *The Dynamic and Energetic Basis of Health and Aging, NIH*. Bethesda, MD: The Ellison Foundation; 2002. http://www.ellisonfoundation.org/awrds.jsp?program=gid&type=Conference&year=2002.
35. Feinberg AP. Epigenetics at the epicenter of modern medicine. *JAMA*. 2008;299:1345–1350.