Biological Basis of Determinants of Health

Clinical medicine and health policy planning find common cause as they seek to define the determinants of health. There is substantial recent interest in the social ecology in which health is embedded. However, biology is where these contributing environmental factors are translated.

I provide a new conceptual framework for the biological determinants of health. The old public health rubric of host, agent, and environment as the features that define the root elements of health is an impoverished scheme, because it does not represent our new appreciation of genetic and aging contributions to phenotypic health. I propose genes, external agency, internal agency, and aging as more operationally helpful determinants that effectively describe the biological experience of the organism.

This scheme has the advantage of differentiating those agencies that are practically approachable, and therefore deserving of increased attention and investment, and those that are currently intractable. (*Am J Public Health.* 2005;95:389–392. doi:10.2105/AJPH.2003.033324)

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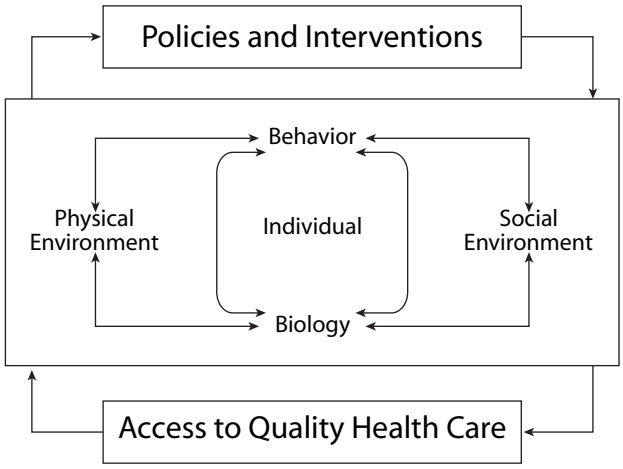
ZIMMERMAN'S LAW STATES

"No one notices when things go right." This simple homily underlies the fact that 95% of the US healthcare economy is allocated for direct medical care, and only 5% is allocated to health improvement.[1]

Aligned with this economic reality is the fact that medical science has devoted almost the entirety of its intellectual and financial capital to the elucidation of disease mechanisms and their relief. The pathogenesis of most illness is now known in great detail, yet the causative features that underlie health remain largely unexplored.

It is commonly acknowledged that the root causes of both disease and health involve multiple agencies. The hierarchical nature of multiple causes, "causes of causes," recognizes that some causes are more proximate or immediate than others.[2] The death certificate form in California requests the following information: (1) immediate cause of death, (2) secondary cause of death, and (3) other contributing conditions. McGinnis and Foege examined this "cause of cause" idea in their article "Actual Causes of Death in the United States."[3] McGinnis and Foege contrasted the traditional list of causes of death with actual causes, most of which were behavioral and lifestyle in origin.

The summary figure of the determinants of health provided in *Healthy People 2010* displays multiple contributing agencies within an interactive matrix formulation (Figure 1).[4(p18, Figure 7)] However, within the formulation, it is evident that the biological factors are more proximate determinants than the socioeconomic contributors, which are upstream and ultimate in their role. Nearly the entirety of the March–April 2002 issue of *Health Affairs* was devoted to the determinants of health and emphasized the social ecology in which health is enmeshed. Deaton lamented the ignorance of the biological determinants that are not revealed by clinical measurements and that are obscured by the long time interval between cause and outcome.[2] However, it is from biological factors that the functional well-being of the organism basically derives as the final common pathway to health. I explore these biological determinants of health and provide a new simple conceptual framework for their consideration. I hope that such a proposition assists in strategic planning that differentiates those determinants that are tractable and those that currently lie outside clinical approach.[4]



Source. Adapted from *Healthy People 2010: Understanding and Improving Health.*[4]

FIGURE 1—Determinants of health.

DETERMINANTS OF HEALTH

To establish a conceptual framework for the biological determinants of health, I propose 4 discrete agencies. The metaphor of car health may help establish this scheme. The life of a car depends on 4 elements: design, accidents, maintenance, and aging. If the car is a "lemon," is involved in many accidents, or is poorly maintained, it will not have the chance to grow old. These same 4 categories apply to the human organism but are more appropriately designated as (1) genes, (2) external agency, (3) internal agency, and (4) aging.

I propose that these 4 factors account, occurring in innumerable combinations and chronologies, for the totality of the human

health experience, both individual and collective. Hypothetically, if the first 3 of these 4 factors could be eliminated through a perfect design or gene set, no accidents or external disruptions, and ideal maintenance or balanced internal dynamics, then the car or body would have the opportunity to die of "natural causes"—aging, which rarely if ever occurs with either.

Genes

The 30 000-gene human genome was widely touted as the ultimate determinant of well-being and illness. This conjecture has now largely been displaced by the recognition that genes actually represent only restricted arbiters of health whose repertoire depends on differential cueing.[5]

Quantitatively, Strohman estimated that less than 2% of human illness is attributable to a faulty single gene locus.[6] Virtually all diseases exhibit mosaic patterns with genetic complexity. An approach widely used to quantify genetic contribution is to investigate the health history of identical twins. If genes were ultimately determinative, and the other 3 agencies were only negligible factors, identical twins would die simultaneously of the same disease. This situation is far from the case. Common neurological diseases of older persons have been shown to have low concordance among twins.[7,8] Further, studies of monozygotic and dizygotic twins indicate that heredity accounts for 15% to 20% of the differences in human longevity.[9] Genes matter; however, their real significance lies not in their essence, but in their interrelations with the other components of health.[10]

External Agency as a Health Determinant

Throughout recent history, the major threat to human health has been the byproduct of an adverse encounter with a hostile threat. Pasteur demonstrated that the previously held attribution of sickness to metaphysical punishment motifs was wrong and that a microbe was more properly labeled as the devil.[11] The appropriate recourse to this new reality was to construct a therapeutic armor to shield the unsuspecting host from his or her dangerous environment. The varieties of health threat that the external world presents are immense in scope and timing. Injury, infection, and malignancy each are huge demerits. These threats may diminish the health reserve catastrophically or may conspire through the accumulation of trivial or sequential insults. For the most part, they are acute in their representation and are usually confined to a defect in one of the body's component parts.

In my opinion, the conditions involved in external agency are responsible for the development of the majority of the current medical enterprise of hospitals, surgery, technology, and pharmacy. Medical science has gaudy credentials gained by confronting the conditions secondary to faulty external agency. Technical advance has allowed address and redress of countless illness states that were unapproachable just a few decades ago. In addition, the issue of prevention is presented when considering external agency as a health determinant. Most infection, injury, and malignancy is preventable—and preventing them is a strategy far preferable to curing them (cheaper, too). To paraphrase Oliver Wendell Holmes, "The shield is nobler than the spear."[12]

Internal Agency as a Health Determinant

The era of the dominance of external agents as prime determinants of health has been replaced by the reality of disordered internal function as the principal causes of the chronic illness patterns prevalent today. Conditions caused by faulty internal agency do not feature a dominant external perturbation. These conditions tend to involve the entire system rather than components as in external agency problems. Instead of the environment being a threat to well-being, internal agency connotes an appropriate and constant interplay of the host and environment. The environment becomes the source of organic order, stability, and, therefore, health. This new conceptualization is captured by the term homeodynamics, as specified by Yates.[13]

Homeodynamics is a substantially more effective term than homeostasis, helpfully supplied by Cannon more than 80 years ago.[14] Homeostasis addresses the reality of our internally stabilizing processes, but the connotation of stasis is alien to living processes. Yates's proposition defines how environmental energetic stimuli are inscribed onto the organism through myriad transduction processes. The extraordinary plasticity of all parts of our body is a vivid demonstration of how form follows function and how the body is constantly remodeling in response to the energetic field in which it is immersed. We become what we do through homeodynamic reshaping at every level.

Environmental interfacing with a healthy body has 2 primary expressions: fuel and energy. The role of adequate nutrition in health maintenance has been voluminously documented. Excesses and deficiencies exact certain tolls. Less well displayed is the health risk posed by inappropriate energetic stimulation. This maladaptation becomes increasingly important as age proceeds. This misapplied energy comes in 2 forms: too much and too little. Too much energetic interfacing is known by the term stress; too little is known as disuse. Both have vast negative consequences on the afflicted organism, and both are inadequately recognized as basic health threats. Part of the reason for their lack of proximal recognition, diagnosis, and treatment is the long timeline from cause to effect.

Selye first elaborated the diverse spectrum of stressors with which organisms are assaulted. He labeled the host response to these challenges the "general adaptation syndrome."[15] McEwen coined the term "allostatic load" to quantitate the cumulative physiological toll exerted on a body over time by efforts to adapt to life experience.[16] A 1997 report by Seeman et al. indicated that allostatic load was a better predictor of cognitive decline and cardiovascular performance in older persons than more standard parameters.[17]

The converse of stress is disuse; disuse means too little energetic interchange, usually manifested through a sedentary lifestyle. I codified the common clinical parameters within the rubric of the "disuse syndrome"[18]: cardiovascular vulnerability, musculoskeletal fragility, immunologic susceptibility, metabolic instability, depression, and precocious aging. Each of these diverse components has discrete, deterministic mechanisms that relate insufficient energetic

throughput to the frequently observed disease byproduct. They are not genetic or externally produced, nor are they secondary to aging per se; instead, they are the byproducts of protracted disuse.

The most vivid demonstration of disuse occurs in muscle. With continued use, muscle strength and power deteriorates at a slow rate, but with disuse, as in space travel or a casted limb, muscle strength can decay at 1% per day.[19] Every organ, tissue, and function is beholden to this appropriate homeodynamic linkage. The energy transduction and gene expression details inherent in this remodeling are now known in great detail.

"VO_2 max" is a congregate, physiological parameter that collectively reflects how an organism extracts oxygen from the atmosphere and conducts it through the respiratory and circulatory systems to every cell, where it is used to provide the spark that fuels metabolism and runs life. A physically fit person exhibits a decline in VO_2 max at the rate of 0.5% per year. An unfit person, conversely, loses this basic competence at the rate of 2% per year—4 times as fast. This is not the result of bad genes or extrinsic agency or aging; it is the result of faulty internal agency.[20] Both muscle strength and VO_2 max have been shown to be powerful, predictive biomarkers for subsequent disability and death.[21,22]

In my opinion, this category—defective internal agency—is the predominant determinant of failing health in older people, particularly because chronic, time-sensitive illnesses are our most common demons. Unfortunately, the competence of the medical enterprise and its curing mission finds only limited success with the conditions attributable to defective internal agency. Heart disease, arthritis, type II diabetes, and strokes are palliated at great cost, but they are not cured. However, they are preventable through redress of energetic imbalance and nutritional excess.

Aging

The participation of the process of aging in the human condition has long been the province of playwrights, theologians, and charlatans. Only recently has aging been held to rigorous analysis. No longer is it considered a disease susceptible to a curing potion, gland, or surgery. Instead, it is seen as a lifelong development and undevelopment process that lends itself to a thermodynamic analysis within Yates' formulation of homeodynamics.[13] Aging is the result of entropic decay inherent in metabolic process, which is partially but incompletely offset by countering mechanisms. Aging is wear and tear minus repair.

In the past 10 years, 2 reports provided a vital, quantitative measure of the basic rate of aging.[23,24] The decline in function in 12 organ systems has an underlying rate of 0.5% per year in all systems, from ages 30 through 70, where most data are available. This figure is thought, therefore, to represent the underlying rate at which health reserves are debited, specifically, because of chronological, entropic age process. The 0.5% per year rate of decline also describes the age rate of decline in several athletic performances.[23] Previously noted were observed rates ranging from 2% per year to 1% per week. Such declines are commonly ascribed to aging. However, these declines are caused not by aging but by more tractable agencies.

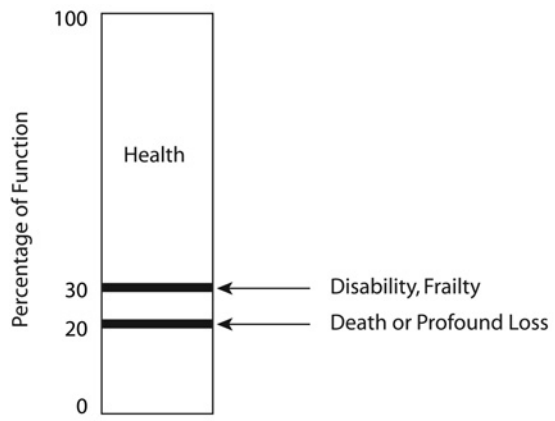
DISCUSSION

Consideration of the healthy state leads directly to an estimate of the functional capacity of the organism. A wide range of function assessment tools exist, ranging from daily activity rating scales to technical physiological measurements. The recognition that there is a maximum, total capacity is intrinsic to an effort to assess the amount of health an organism possesses. Health not only exists at the basal resting state but also exhibits substantial reserve. Such reserve relates clearly to the evolutionary need for organisms to withstand environmental perturbation of substantial variety and extent. Food and fluid availability, temperature extremes, elevation, and energetic loads are the major challenges. For example, a Tour de France cyclist may expend 8000 calories per day for a month, which is several times basal energetic turnover. Physical conditioning implies a full expansion of reserve capacities in which linked, but separate, bodily functions scale together. This systemic, morphological, and physiological reaction to an increased load lies, in my view, at the heart of why physical exercise displays such a wide scope of anabolic benefit.

Diamond surveyed a series of "biological safety factors" in a variety of species from squid to primates and found a range of 1.3 to 10 total functional to basal capacity.[25] In humans, the reserve margin of health is most easily observed in the case of the paired organs in which a total loss of 1 organ leads to little apparent loss in function. Many other capacities—cardiac reserve, oxygen transport, neurotransmitter levels, muscle power, arterial cross-section, creatinine clearance, liver mass, sensory and cognitive capacities—exhibit similar safety margins. A common, but not universal, implication is that not until 70% of maximal capacity is lost does symptomatic impairment of health appear.[26] Verdery termed the zone of 20% to 40% of maximal function "the disability to survival span."[27] The World Health Organization proposed that health represents that state before impaired health becomes apparent.[28] Clearly the lack of awareness of symptomatic loss involves a substantial physiological reserve (Figure 2). This concept suggests that health exists above the symptomatic threshold value of 30% of optimal/maximal function. Below 30% of maximum, there is only a small margin of safety before profound threat to function and survival occurs. I propose that it is in this 20% to 30% range where most medical encounters occur, and most expenses are generated.

A 2001 article about the ecology of medical care confirmed a 1961 report that in 1 month, 80% of adults encounter some life event perceived as ill health.[29,30] Fortunately, most of these people do not eventuate in entry to the medical system and the precipitating conditions are reversible. Only 25% call a physician in that month. Fewer than 1% require hospitalization. The clustering of serious medical encounters and expenses in a small minority of persons is repeatedly noted.[31] Most people spend most of their lives above the symptomatic threshold level of 30% of maximum capacity in the health zone.

The range of 20% to 30% of maximum capacity represents the frailty zone of precariously limited vital reserve. A person can lose 70% of his or her full func-



Source. Adapted with permission from *The Journals of Gerontology, Series A, Biological Sciences and Medical Sciences.*[26]

FIGURE 2—Space of health.

tion catastrophically as a result of external events, or the loss may occur more slowly from accumulated minor decrements caused by internal agency or to aging. In the real world, health is determined by a summation of the effects of 4 listed agencies. What is crucial to observe, however, is that only those determinants caused by faulty external and internal agency are susceptible to clinical intervention. Genetic aberration and the process of aging, which, although theoretically approachable, are still remote in their practicability.

Redress of disordered external and internal agencies, which quantitatively are the major biological determinants of health, is eminently practicable, and attention to the behavioral causes of these causes appears acutely necessary. Such active pursuit is the most likely strategy to succeed in fulfilling the goals of *Healthy People 2010.*[4] ■

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This article was accepted March 12, 2004.

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