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Review Article

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Disuse and Aging, 2018

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Abstract

Two previous articles, published in 1982 and 2007, drew attention to homology between disuse and changes commonly found in aging. The scientific framework for this continues to expand. This current paper inserts the new experimental evidence that validates this connection.

Introduction

The Serenity Prayer insists on knowing the difference between what is changeable and what is not. [1] The changeability quotient is critical. Despite the near-universal evidence of plasticity throughout natural processes the entire sphere of phenotypic plasticity is under recognized by clinical medicine.

The remarks of Strohman are appropriate. [2] He wrote, "The laws of thermodynamics are intimately related to the phenotype of the organism through the agency of dynamical systems. Sadly this central point has been all but ignored in the rush to find agent-based genomic-proteomic explanations. Looking back that substitution of agents for agencies must be recognized as an epistemological error of great moment." Earlier I lamented the failure of Medicine to appreciate the central role of plasticity in determining lifelong health. [3] Underappreciated is the role played by process rather than by agent in life.

In my view the fixation on the gene as the prime determinant of our well-being is tragic. Decades of scientific pursuit and billions of research dollars have been short-circuited by our concentration on the gene as our primary focus. The theme of genetic determinism is largely discredited, but its remnants persist in agent-centric science.

A major domain of recent history goes by the term genome wide association studies, or GWAS for short. Thousands of research papers and many millions of research dollars have been spent looking for the gene responsible for XYZ. Such a simplistic strategy has not succeeded, and has effectively dug a black hole consuming far too much societal resource. GWAS neglects the vast spatial and temporal complexity inherent in the organismic/environmental interface. This dereliction is now rescued by the elaboration of a new term, environment wide association studies or EWAS for short. [4] EWAS recognizes that within the Metabolic Field it is the interface of the organism and its environment that defines the essence of life, hence of aging as well. [5]

Harold Morowitz has championed the cause of energy flow in biology. In his book the title of which is Energy Flow in Biology he sought a relationship between biology and physics and emphasizes that biologic phenomena are ultimately consequences of the laws of physics. [6] The 1917 book of D'Arcy Wentworth Thompson on Growth and Form argued that our bodies are shaped not by chance

but are the necessary results of physical force and geometric constraints. [7] The structure of living organisms is the necessary result of mathematics and physics. Morowitz points out the coincidence of the introduction of the theory of evolution in biology and the Second Law of Thermodynamics in physics. The First Principles of each appear to conflict. The Second Law predicates increasing disorder, entropy, whereas biology presumes a hierarchy of increasing order. The new field of Physical Biology explores this frontier.

We become what we do by way of the intricate mechanisms that define phenotypic plasticity. These mechanisms are just now coming into clearer focus. In this context differentiation between those conditions commonly encountered in older people that are sternly coded in thermodynamic decay, entropy, and those that are subject to intervention, frailty, (the Disuse Syndrome) are critical. [8]

Source of New Understanding

Freeman Dyson observes that major understanding results from 1) new knowledge and 2) new tools. [9] The new knowledge of aging's losses are directly attributable to the epochal lectures delivered at Trinity College Dublin in 1944 by Erwin Schrodinger. Schrodinger, a quantum physicist, based his lectures, "What is Life? The Physical Aspects of Living Cells" upon the Second Law of Thermodynamics. [10] These lectures were the breakthrough, the Rosetta stone for understanding life. They provided the template that links physical processes to the living world. Subsequently, Prigogine termed the forms that resulted from the interplay to be "dissipative structures," temporary islands of matter interposed between different flows of energy. [11] Schrodinger's lectures were the first to define bioenergetics, the metabolism that differentiates the animate world from the inanimate. Further, he predicted the DNA structure for replication by the term "aperiodic crystal." Pauling credited Schrodinger for birthing molecular biology. [12] This breakthrough suggested that biology can be understood by reducing it to its substituent components of physics and chemistry. Life can be explained as a product of existing basic laws. Ernst Mayr, the paterfamilias of American biology, argues the negative insisting on the autonomy of biology. [13] However Ho [14] and others [15] acknowledge the inadequacy of present physics and chemistry to address the huge domain of biology, but predict that new expanded versions of the physical sciences will emerge and thereby generate a reconciliation. In seeking this new interdisciplinary biology, Geoffrey West advocates for "a quantitative predictive multilevel theoretical framework that both complements the present approaches and stimulates a more integrated research agenda that will lead to novel questions and experimental programs," an integrative biology. [16]

A comprehensive and fundamental understanding of the process of aging is lacking. In 2013 Rando and Chang called the underlying cause of aging to be, "One of the central mysteries of biology". [17] Despite explosive increase in data relating to aging most are proximate results but not the ultimate cause.

The First Principles of Aging

In his bold article in 2007 Hayflick pronounces that, "Aging is no longer an unknown", and invokes the principles of thermodynamics in its exposition. [18] He feels that the First Principles involved with the process of aging are the result of the inevitable decay in molecular function and fidelity. This focuses attention on metabolism that is the gearwheel of life. Metabolism is concerned with the transduction of energy that exists between the organism and its environment, between nature and nurture.

Science has generated five physical fields to describe its contextual elements. These are 1) gravitation, 2) electromagnetism, 3) strong nuclear forces, 4) weak nuclear forces, and 5) quantum. Close inspection discloses that none of these have a fundamental time element included therein. Aging is internally consistent with all of the five classical Fields, but by themselves they do not dictate the metrics of aging.

The use of the term "field" to explain physical phenomenon is credited to Faraday. [19] In 1824 he defined electromagnetism as a force with both time and space dimensions, "a field". It implies an action acting at a distance through an intervening medium, a field. Recognizing that the prior classical physical fields lack time in their formulations, I propose a sixth physical field, Metabolic Field (Schrodinger). [20] It constitutes an explanatory platform for biology, and thereby matches the organism to its environment, and includes the entire domain derived from the explosive data generated by molecular biology within the Metabolic Field and thereby provides the essential ingredients for the new ideas about aging and its inevitable decay in molecular fidelity and function. The entire array of commonly observed resultants of this process such as telomere shortening, DNA damage, protein mis-folding, membrane damage, free radical destruction are secondary consequences of

metabolic deterioration. The first consequence of Dyson's new source of understanding that of new ideas is satisfied. [9]

New Tools

The second requirement, that of new tools, is met by an avalanche of new technology currently under development that provides insights into the innermost cosmos of the nano-world. Feynman's epochal pronouncement of, "Lots of room at the bottom" heralded an exploration of the very, very, very small, the basic reduction of matter to its tiniest components, atoms, from which all else derives, structurally as well as functionally. [21]

Several years ago at an Intel Student Science Fair six of the ten assembled Nobel laureates there acknowledged that their breakthrough contributions were the direct results of a new technology that allowed insights that were previously not susceptible with the tools then available.

Robert Hooke, acknowledged as the first developer of the microscope, wrote in 1665, "It has been our principal endeavor to enlarge and strengthen the senses by outward instruments. By this means we find that those effects of bodies which have been commonly attributed to qualities and those confessed to be occult are performed by the small machines of nature which are not to be discerned without these helps. MICROGRAPHIA 1665 [22]

Science's Award for Breakthrough of the Year 2016 went to the development of an optical instrument, called the interferometer. [23] This new tool allows demonstration of gravitational waves a fundamental challenge that goes back to Einstein's era.

Inner Cosmos

In this regard the discovery of a new tool, the atomic force microscope, has been employed to generate pervasive insight into the nano- details of aging. [24] Its resolution is a thousand times more powerful than the best optical microscope and allows the researcher to glimpse particles as small as a single DNA molecule which is 2 nm in diameter.

The AFM reveals that billions of protein molecules are buffeted by water molecules that randomly crash into them 1 trillion times a second, every molecular machine is hit by a fast moving water molecule every 10^-13 seconds which delivers the interior of the cell is unimaginably dynamic. Every molecule in the cell is hit by a fast moving water molecule every 10^-13 seconds, a trillion times per second. In essence these collisions represent a "molecular storm." The scope of this battering indicates that every molecule will encounter every other molecule in the cell in a matter of seconds. The fundamental origin of this molecular storm is held to be a lingering reflection of Brownian movement, that random motion observed by Brown and Einstein and felt to be a remnant of the energy dispersal of the Big Bang. [25] Similarly the jittery motion of dust particles in a beam of light is felt to be a reflection of molecular collisions.

The crowding facilitates interactions between molecules which when conforming to appropriate structural demands yield macromolecules that lead to a multitude of functions that characterize life. The intermolecular collisions generate collections of nano-machines in the form of protein, nucleic acid, lipid, and polysacchride, each with a unique chemical identity. The interactions are, in turn, facilitated by the catalytic action of enzymes. Cells generate power via cell-sized electrochemical batteries that generate gradients that enable ions to cross membranes facilitating the reactions that is eventually transferred to ATP which is the currency of life.

The body contains 250g of ATP yet turns over 70 kg each day. Each of the body's 40 trillion cells contains one quadrillion mitochondria with a combined convoluted surface area of 14,000 m^2 that consume 10 million molecules of ATP every second. This means that every ATP molecule is recharged once or twice per minute. ATP activates the Krebs cycle that turns over 2000 times per second. These dynamics represent the interactome that is estimated to be 650,000. [26] The synthesis of amino acids is similarly dynamic. There are 13 million ribosomes in a single cell. They produce 10 amino acids per second. The ribosomes have a copying error rate of one letter in 10,000. Different amino acids have different affinities and their hydrophobic nature helps create appropriate protein folding. Therefore a large part of the necessary information to form protein is not contained in DNA, but results instead from the physical laws inherent in thermodynamics and statistical mechanics.

The energy that is inherent in the cell's Metabolic Field powers the conformational change in structure. Mitochondria primarily pump protons, 10^21st, every second. Pumping these protons across the membrane generates concentration gradients, and initiates a difference in electrical charge. Such re-dox mechanisms are central to life. Enzymes and allosteric mechanisms abet the developmental process.

Tiny Machines

The resultant flux of energy yields the proximate and ultimate structure of living organisms. The inevitable entropy that results from the molecular storm is the likely fundamental cause of the many catabolic events that characterize the processes of aging.

The molecular processes that underlie the syndrome of frailty are revealed. [27] What remains is the elaboration of the clinical strategies that can retard the many epigenetic pathways that characterize the frailty of old-age. [28]

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