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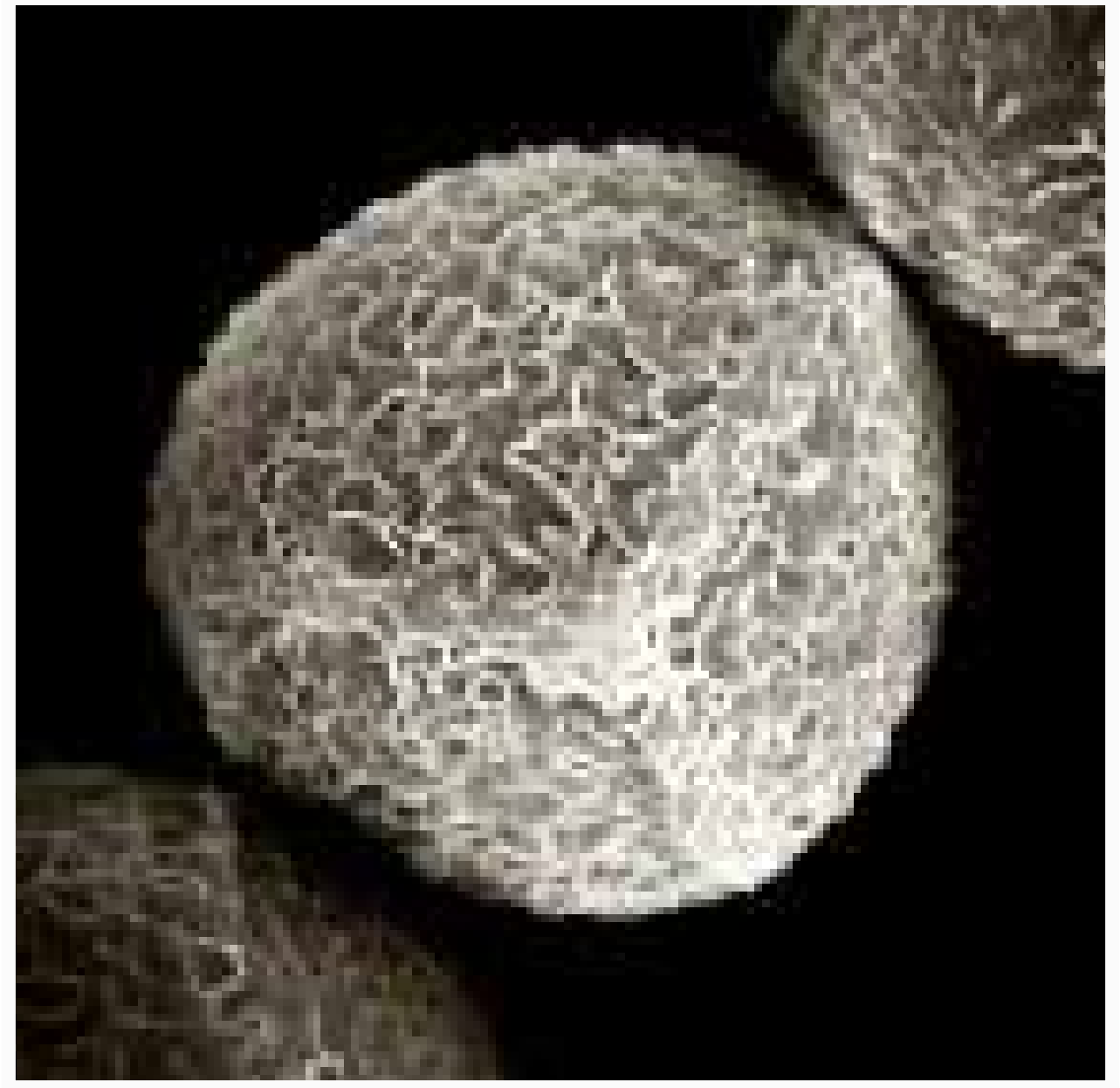

Future of Human Evolution
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Programmed Death

Is senescence (biologic death) a programmed trait? Perhaps no topic in evolutionary biology evokes more controversy.

Senescence was once assumed to be the result of so-called "wear and tear"; namely, an organism ages and eventually fails as it accumulates defects that are insufficiently corrected. However, the existence of senescence is not a thermodynamic necessity. Although entropy must increase within a closed system, organisms are not closed systems unto themselves. Since it can extract free energy from the environment and reduce its own entropy, an organism typically grows more resilient from seed stage to reproductive maturity. Indeed, life tables for humans suggest that the lowest likelihood of death in females occurs around the age of 14, which coincides with the prehistoric age of reproductive maturity. Organisms appear to be capable of self-repair when beneficial; indeed, certain organisms such as Hydra do not exhibit signs of senescence.

However, most organisms undergo a failure of repair mechanisms, an increase in entropy, and an emergence of senescence after reproductive age—despite having free energy available around them. This observation has led some to wonder if senescence occurs because the selection pressure against it is insufficient. In his lecture An unsolved problem of biology (published 1952), Peter Medawar suggested that what happens to an organism after reproductive age is only weakly reflected in natural selection through its effects on

younger relatives. Medawar's view suggests that traits that affect an organism's viability after reproductive age have little effect on its ultimate fitness. Thus, some have also concluded that senescence could not be adaptive, since there would be little selection pressure for or against senescence as a programmed trait that emerges only after reproductive age.

On the other hand, the idea of senescence as an adaptive trait has been considered since the early days of evolutionary theory. This notion was first widely promulgated by August Weismann, building upon the evolutionary theory of his intellectual predecessor, Charles Darwin. Weismann suggested that senescence might be a programmed trait because the old needed to remove themselves to make room for the next generation, sustaining the turnover that is necessary for evolution.

According to Wikipedia, Weismann's hypothesis suffered for the following reasons: (1) it fails to explain how individuals would acquire the genes that make them get old and die; (2) it does not explain why individuals that had aging genes would be more successful than other individuals lacking those genes; and (3) it offers a teleological explanation but does not provide a mechanism.Weismann himself apparently disavowed his own theory later in life.

However, Weismann's hypothesis has more recently regained momentum. The word "phenoptosis" has entered the lexicon to describe the phenomenon of programmed death of organisms. The scientific community has recently treated as heresy the idea of phenoptosis, much as it treated the idea of cells undergoing programmed death when this concept was raised several decades ago. Now, the programmed death of cells, or apoptosis, has become a generally accepted concept. The programmed death of organisms may soon approach that level of scientific acceptance.

Wikipedia catalogues some of the circumstantial evidence that

supports the theory of programmed senescence: (1) progeria and Werner syndrome are both single-gene diseases that can cause accelerated senescence, suggesting a common mechanism to the disparate manifestations of aging; (2) lifespan varies greatly among very similar species, suggesting relatively minor changes to genotype could cause major differences in lifespan; (3) mammalian lifespan varies tremendously, but the symptomatic manifestations of aging remain similar across species, suggesting a common mechanism; (4) genes that control aging and possess no other function have been discovered; (5) caloric restriction increases the lifespan of many organisms under experimental conditions, once again suggesting a common mechanism; (6) apparent acutely programmed death has been observed in certain animals such as the octopus, salmon, and Australian marsupial mice.

In Wikipedia, the cited evolutionary argument against programmed senescence is that individuals who possess the genes for programmed senescence would be displaced by those who did not possess those genes. That is, the latter would produce more offspring during their longer lifespan, and they could promote the survival of their offspring by providing more extended parental support.

Although we agree with the notion that longer survivorship can potentially allow individuals to engage in more reproductive events and provide more support for descendants, we counter that individuals engaging in reproductive events during dotage may compete with the efforts of their own offspring in seeking opportunities to mate. For example, fathers may be competing with their sons and displacing the available fecundity of females. We also counter that aging individuals can compete for other scarce resources with their own offspring in a way that more than offsets their support of descendants.

As for the contention that Weismann's hypothesis is invalid because it does not offer a plausible mechanism, a number of theories on

the mechanism of aging (mutation accumulation, antagonistic pleiotropy, disposable soma, etc.) have been advanced and debated elsewhere, although none have been widely accepted to date. On the other hand, we have heretofore proposed that autonomic dysfunction is the Occam's razor of senescence—the unifying theory of the mechanism of diseases of aging. Specifically, the autonomic neuroendocrine system that augments survivorship during early life becomes dysfunctional and biases towards sympathetic predominance in later life, producing a myriad of conditions referred to as the diseases of aging.

Increasing scientific specialization has led to the atomization of human ailments into an ever-lengthening laundry list of newly-named diseases, but we believe it is highly unlikely that as we age, so many different things could go wrong through so many disparate mechanisms. Furthermore, the vast array of human ailments manifests through a small set of symptoms such as nausea, rash, dizziness, etc. that are partially driven by the autonomic nervous system. In Cellular Automata, Stephen Wolfram argued that apparent complexity may be the result of simple rules, recursively applied. Or as Sir Isaac Newton pronounced, "We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances. Therefore, to the same natural effects we must, so far as possible, assign the same causes." Autonomic dysfunction may be the simple rule that manifests as the panoply of diseases associated with senescence.

In some ways, the autonomic nervous system is an obvious suspect in the mechanism of programmed death. After all, one effective way to kill a system is to disrupt a key regulatory network, and the autonomic nervous system can be seen as the fundamental regulatory network in the body.

A more upstream look at the ontogeny of autonomic dysfunction

warrants further investigation. The potential causes of programmed post-reproductive autonomic dysfunction may include end-organ autonomic dysregulation (end-organs, without central hegemony, exhibit intrinsic sympathetic bias), efferent nerve dysfunction, feed-forward neuroendocrine dysregulation, afferent nerve dysfunction, central hypothalamic dysfunction, patchy apoptosis of the suprachi-asmatic nucleus (SCN), and pineal involution at puberty, leading to downstream hypothalamic-pituitary axis dysfunction.

Mandelbrot's fractal theory, which predicts self-similarity of phenomenon at different scales in nature, may have bearing on our analysis. Perhaps the programmed cell death of a key system hub precipitates the programmed death of a multi-cellular organism. Patchy apoptosis of cells in the SCN of the hypothalamus has been observed during senescence. The hypothalamus can be seen as the central command center that integrates afferent information and activates efferent outputs of the autonomic system, and the SCN is the specific locus where the inputs and outputs are processed. The programmed death of the SCN may disrupt the autonomic network and, in fractal fashion, drive the programmed death of the organism.

But what catalyzes the apoptosis of the SCN and the hypothalamus? The pineal gland may be an interesting place to look. The pineal gland's primary functions include serving as the central clock of the body and regulating the hypothalamic-pituitary-adrenal axis. The pineal gland is notably the first major organ to involute in the human body, generally beginning to fade at the onset of puberty and calcifying in early adulthood. What if the timed apoptosis of the pineal gland sets off a cascade of events that enables organism senescence and death over time?

There are a number of plausible mechanisms by which this could happen. Pineal involution may precipitate hypothalamic dysfunction and apoptosis, leading to global autonomic dysfunction. Pineal gland

involution may disrupt other neuroendocrine pathways such as growth hormone, sex hormones, and stress hormones–each of which has been associated with maintaining youth. Pineal gland involution may also disrupt melatonin-mediated wound healing pathways such that injuries that would heal during pre-puberty would instead respond with fibrosis by post-puberty. Pineal gland involution may induce systemic chronobiological dysfunction throughout the body, leading to a generalized dysregulation of multicellularity. Pineal gland transplant has been shown to increase lifespan in animal models. Ironically, the phrase "to give a clock" (Chinese: 送鐘, Chinese: 送钟) is pronounced "sòng zhong" in Mandarin, which is a homophone of a phrase for "to send to death" (both can be written as 送終or 送终).

History of Life and Death

Early in the history of life, unicellular organisms were essentially biologically immortal. That is, a cell would undergo necrosis if an insult upon the cell was sufficient, but otherwise the cell could live indefinitely and would persist through the process of division. It appears that the capacity for indefinite persistence was an inherent characteristic during the origins of life.

Programmed cell death (PCD) may have emerged as a later innovation in the history of life. Apoptosis-like phenomena have been described in multiple taxa of unicellular protists, sharing many features with the programmed death of human cells. Eukaryotic apoptosis is thought to have evolved from the PCD of bacteria. The development of apoptosis has been considered a necessity for any complex multicellularity to emerge. Apoptosis is present in biofilms, which can be thought of in some ways as the transition state from unicellular

organisms to highly organized multicellularity. Perhaps PCD promotes fitness when cells of shared lineage live in close relationship to another (whether as clusters of prokaryotes, biofilms, or multicellular organisms).

If death is also a programmed feature of human life, the tantalizing possibility exists that it could be reprogrammed out of human life. Although seemingly a remote possibility at first glance, cancerous transformation of cells supports the opposite view—that reprogramming may be readily achievable. A cancerous cell can be viewed as an apoptotic cell (i.e. programmed to die) that modifies a few elements—such as inactivating tumor suppressor genes—and returns to an immortal state. Tumor-infiltrating lymphocytes and other cells in the immune system essentially police cells that try to escape programmed death to the detriment of the greater system of the body. Think of these cells as the Sandmen in William Nolan's prescient fictional novel Logan's Run that hunt down fellow humans trying to elude programmed death at age of 21.

From a fractal perspective, self-similarity is observable at different scales, so the conversion of an apoptotic cell to a cancer cell portends that such a transition may be possible at the organism level. Cancer as a phenomenon is so robust it occurs independently millions of times a year in different individuals, through many different mutations. Perhaps the path of human evolution towards immortality will be similarly robust and manifold.

Has Death Outlived Its Usefulness?

Key features of Charles Darwin's theory are variation, natural selection, and reproduction of traits. Natural selection operates through preferential elimination of less fit traits, known as "survival of the fittest", or the preferential replication of more fit traits. Without

resource constraints, the latter process makes sense. However, as populations approach limits of resource capacity, the former process may predominate. Thus, one can view the life-death cycling as nature's way of recycling components continuously to allow for potentially more fit genes to emerge over time. For genetic evolution, death may be seen as a useful adaptation that allows decomposition of an organism into building blocks, permitting future reassembly into potentially more fit genotypes.

Human cognitive evolution, however, has increased the role of memes (idea, style, or behavior) in trait acquisition. Memes have a number of advantages as a medium of trait acquisition when compared to genes.

Let's say there are two colors of otherwise similar berries, blue being poisonous and red not. Gene-based evolution of the higher-fitness preference for red berries would entail a distribution of mutations with variation of preferences, and negative selection of members with less fit preferences through poisoning. While the trait has been selected, the process has been very "expensive" from the perspective of biology. Many members died during the process of trait evolution. By contrast, memes can be learned by an individual during his lifespan, without the need for biologic variation and selection of individual behaviors. Indeed, memes are highly communicable. Genes, with some exceptions, are passed vertically down through the generations through reproduction. In contrast, memes can be passed vertically in either direction (grandparents can learn from kids), horizontally, over long distances, and through non-living media. No doubt this applies more to behavioral traits than physiological traits.

The vast superiority of memes over genes as the means for behavioral trait acquisition has put humans in an interesting spot in evolutionary history. Life-death recycling of the body may have been the right mode to evolve useful genetic traits in the past, but dying gets in the way of accruing memes. Indeed, mortality has forced humans to

restart meme acquisition with each generation, necessitating inventions such as books, art, language, and schools to render memes heritable. Longer life spans would make meme acquisition by each generation less pressured by time. Indefinite life spans would e liminate the need for inter-generational meme transfer. Whereas dying may have been a way to innovate during gene evolution, living may be the way to innovate during evolution dominated by memes.

So where does that leave us? Humanity today may be stuck in an awkward transitional period of evolutionary history. Humans may have inherited death as an adaptation to drive gene-dominated evolution, but now death may be maladaptive in the setting of meme-dominated evolution. Indeed, many of the high-value memes being passed on by dying members are precisely the kinds of scientific knowledge that may one day lead to medical inventions that eliminate phenoptosis and provide indefinite biologic lifespan to humans.

Would biological immortality accelerate the path of humanity to collapse (as many have predicted) by causing overpopulation? Human civilization, in some ways resembles a cancer that has transformed from being an ordinary member of the planetary ecosystem to one that has metastasized from Mesopotamia into distant continents, growing exponentially in size, taxing resources, and inducing environmental stress along the way for the past thousands of years.

Yet strangely, the lengthening life span (thanks to medical innovation) is creating a curious demographic phenomenon. Probably due to a number of factors, humans who forecast long lifespans are delaying childbearing and having kids at below replacement levels. As of 2012, every First World country that is enjoying longer life spans is also exhibiting a replacement fertility rate below 2.1 children per couple. It is as if nature has baked in a self-correcting mechanism such that as lifespan elongates, fertility decreases, mitigating the possibility of population explosion. If so, both selection (elimination of weak

members) and reproduction, the hallmark features of Darwinian evolution, would decline, simultaneously favoring the ascension of meme-dominated evolution.

As John Donne said in his immortal meme, "death, thou shalt die". Let post-Darwinian evolution begin!

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Status Update

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Status—the position within a pecking order—can affect access to resources, mating opportunities, and many other elements of evolutionary success. Just as our reptilian brains are drawn to cues for sex and violence, we are also hard-wired to focus on cues for status. Those who are not attuned to status likely faced adverse selection pressure during prehistoric human evolution. This paper explores how prehistoric factory-setting behaviors towards status affect modern consumer behavior.

The price consumers are willing to pay for different goods and services evidences the economic value of status. Since industrial progress has allowed many of our base needs for food, clothing, shelter, and comfort to be met, consumer goods and services have increasingly become signaling devices for status. Want to convey status? Where you shop, what restaurant you eat at, what clothes you wear, what kind of cell phone you have, what bags you carry, where you vacation, what street you live on, what class of airline seats you travel in, and what kind of beer or wine you drink—these things all signal your status.

Virtually all consumer goods and services can contain a status quotient. Especially as functionality gets commoditized, the status value of a consumer good or service may vastly exceed its utilitarian value. Although a Toyota Camry can take you around town about as well as a Ferrari, the latter fetches ten times the price. In some cases, as with diamond jewelry, utilitarian value is virtually absent compared to status value. The luxury and glamour markets figured this out long ago.

The status quotient of consumer goods or services impacts not only how others perceive consumers, but also how consumers perceive themselves. When we stay at Ritz Carlton, the subservient behavior of the service staff makes us feel like a high status person. When we shower in a luxurious shower or cook in our remodeled kitchen, it makes us "feel better" or "enjoy more", but what we are experiencing is in no small part a status elevation.

It has been reported that when a sports team wins, not only do the players experience a testosterone boost, but so too do the team's fans.[1] Since testosterone is one of the dominant modulators of pecking order (status rank) in social species, brands we choose can modulate not only our perceptions of our own status, but affect our biological status.It is intuitively appealing to speculate that all consumer choices we make could modify our status hormones (testosterone being the key one among them) and affect our rank in the social pecking order.

In figuring out that we pay for consumer goods and services that raise our status, marketers are not alone. The entertainment industry has long recognized that humans preferentially pay attention and pay dollars to higher status performers. Sylvester Stallone is one of many actors who control camera angles in order to appear taller. Elevated stages raise the perceived status of the performers. A big screen television grabs your attention more than a smaller one because all the people portrayed on it are that much larger.

Humans appear wired to attune themselves not only to status, but also to status changes. If a status change is occurring within a social group, it has potential fitness import for the witnessing party. People can participate in contrived activities for the sake of amusement whereby they experience status changes themselves or witness status changes in others. Such activities are called games or sports, and participants may describe their experience as “fun” or “exciting”, particularly when it involves status elevation, also known as “winning”.

Our natural attentiveness to status changes has been exploited by the modern multi-billion dollar entertainment industry. A sport where the score is kept and a winner is declared is operating through status changes among participants. A football game might be called "great" if there are many lead changes (status changes) and "dramatic" if a status change occurs against all odds late in the game. A game where the underdog defeats the favored team might be perceived as "exciting" because of the unexpected status change. Indeed, we as consumers often demand that rank order be clarified for our own satisfaction, and are willing to pay for that satisfaction. The annual call for a college football playoff system is an example.

No doubt the entertainment industry panders to our hard-wired tendency to rubberneck sex, violence, and useful information, but our obsession with entertainment is also partly reflective of our obsession with status changes. A typical American male constantly checks score updates of their favorite teams and wakes up on Mondays to see how the Top 25 rankings of college football have changed since the previous week. Casey Kasem had a long-running popular weekly radio show where the rankings of the top 40 songs were updated. The most titillating moment of the hit television show American Idol occurs when a singer, whom the audience has been led to believe is of lower status, undergoes status transformation during the span of a single song. Downward movement of status (such as when a celebrity hits a rough patch) sells newspapers to a hungry public. The top 100 colleges and universities issue of the U.S. News and World Report attracts readers who are fascinated by the movement of institutions up and down the ranking ladder.

The human mind seems voyeuristically drawn to undulating story lines of status changes in books, plays, and movies. The mood changes in the scene sequences of Shakespeare's Romeo and Juliet can be described as alternating between low and high status: street

brawl, intervention by the Prince, Romeo mopes, meets Juliet, learns she's a Capulet, marries Juliet, kills in-law, consummates marriage, etc. Renegotiation of status change is considered one of the tools not only for drama or tragedy, but for comedy, too.[2]

Facebook is many things to many people, but in many ways a Facebook page is a signaling device for status. How many friends we have, who our friends are, and what cool thing we did over the weekend are all status attributes. Every posting on the Facebook page changes our status, unto our own profile and relative to others'. Indeed, the most powerful place in all of social media today is a box near the top of the Facebook page simply labeled, "status update".

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Food Allergy, Asthma, Anaphylaxis, and Autonomic Dysfunction

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Food allergies are a rapidly growing medical and public health problem. Recent studies estimate an incidence of 5% in children younger than 5 years old and 4% in adults. In severe cases, subjects can experience anaphylaxis and even death if exposed to a food to which they are sensitive. There is no known cure. Rather, doctors recommend that the sufferer avoid exposure to the allergen. The mechanism of disease is thought to be immunologic.

A number of drugs can be used during an acute food allergy attack, but only one—intramuscular injection of epinephrine—immediately resolves all of the symptoms associated with the episode. Tellingly, epinephrine is a neurotransmitter/hormone of the autonomic nervous system (ANS) that augments sympathetic function. Emerging data in the literature supports a neuro-immune connection, particularly in light of how the ANS innervates and regulates lymphoid tissues and other constituents of the immune system. It is possible that food allergy syndrome (and perhaps all cases of anaphylaxis) may require both an allergic sensitivity and an underlying inability to generate an adequate sympathetic response (or an underlying parasympathetic/vagal dominance).[1]

To test this hypothesis, we performed extensive autonomic testing on a 5-year-old subject with a history of virally-triggered asthma and severe tree nut allergy.

The subject's heart rate was measured during deep breathing. During inhalation, activation of lung stretch receptors normally suppresses

vagal activity, promoting tachycardia. The subject's heart rate during inhalation was 104 beats per minute, which is normal for a 5-year-old. During exhalation, unloading of lung stretch receptors reverses vagal suppression, typically reducing heart rate by 20 to 30 beats per minute (bpm). The subject's heart rate declined to 54 bpm, suggesting sympathetic under-activity. Heart rate response to CO2 retention and release did not alter heart rate variability, suggesting central autonomic dysfunction, possibly at the brain stem level. Large fiber autonomic neuropathy was ruled out through additional testing. Skin sympathetic response (SSR) tests were performed limb-to-limb to localize the autonomic dysfunction. Delayed sympathetic function was observed only between the upper limbs, suggesting a possible defect somewhere along the cervico-thoracic sympathetic arc.

The findings appear consistent with the subject's history of asthma (characterized by expiratory wheeze and bronchospastic cough) and food allergy syndrome (anaphylaxis, angioedema, gastrointestinal cramping, hypotension, and bronchospasm). In the case of asthma, an allergic response to a viral antigen (characterized by degranulation, release of substance P, and activation of other cascading pathways) activates the autonomic afferent fibers, which are biased towards vagal dominance in this subject. During exhalation, insufficient sympathetic counter-response to vagal resurgence (associated with unloading of lung stretch receptors) results in expiratory wheeze (bronchoconstriction) and asthmatic cough (bronchospasm). In the case of food allergy syndrome, an allergic response to tree nut antigen (characterized by degranulation, release of vasoactive intestinal peptide, and activation of other pathways) triggers autonomic afferents.

Given the subject's underlying vagal bias, the subject exhibits symptoms consistent with vagal overload including angioedema, bronchoconstriction, hypotension, and gastro-intestinal cramping. These are all hallmarks of anaphylaxis. The underlying autonomic dysfunction

effectively turns a routine immunologic response to an antigen into a catastrophic, maladaptive response. Historically, epinephrine was the treatment of choice for acute asthma attacks given its elevation of sympathetic response. Today, selective sympathomimetic drugs (beta2 agonists) are used for the treatment of acute asthma. Epinephrine remains the treatment of choice for food allergies, and beta2 agonists can be used to treat the respiratory component of food allergy attacks.

Vagal motor tone exerts parasympathetic innervation to all organs from the cervical region to the transverse colon (with the one exception of the adrenal glands). This varied control includes parasympathetic control of the heart (rate), GI system (peristalsis), vascular (sweating and microvascular permeability such as swelling). Neurotransmitters associated with parasympathetic nerves include acetylcholine, vasoactive intestinal peptide, neuropeptide Y, nitric oxide, enkephalin and somatostatin. However, acetylcholine is the predominant neurotransmitter released from large diameter post-ganglionic cells and acts primarily on the M3 receptors, resulting in increased glandular secretion from the mucous/serous glands of the sinonasal membranes. Overstimulation of these foci triggers many of the cholinergic side effects.

Sympathetic input originates in the intermediolateral column of the upper thoracic segments of the spinal cord. The preganglionic fibers travel through the anterior thoracic roots via the stellate ganglion to the superior cervical ganglion where they first synapse. Postsynaptic fibers then travel via the carotid plexus where it bifurcates, innervating various cranial, cervical, and thoracic end-organs. Sympathetic nerve stimulation induces vasoconstriction, but has only a minor effect on mucous secretion. Neurotransmitters associated with sympathetic nerves include mainly norepinephrine or neuropeptide Y, both potent vasoconstrictors.

Sympathetic receptors are classified as alpha or beta. In general,

alpha agonists act on the resistance and capacitance blood vessels to decrease blood flow and airway resistance, while beta2 agonists are vasodilators. Since there is a marked alpha predominance in respiratory pathway blood vessels, vasoconstriction generally prevails. Thus, disruption or diminution of the sympathetic supply to the respiratory system will result in vasodilatation and increased airway resistance, as is seen in severe food allergies and anaphylaxis. Interestingly, there exist case reports of subclinical injury to the cervical spine region sympathetic pathway, resulting in vagally-mediated rhinitis and swelling in humans. These reported cases were also associated with adrenergic hyperactivity.

In the case of our 5-year-old subject, the origin of the subject's sympathetic under-responsiveness remains to be explored. Possible defect locations include end-organs, afferent fibers, brain stem, hypothalamus, spinal cord, and efferent fibers. Since the autonomic dysfunction appears regional, a genetic or cellular defect seems less likely, although secondary systemic consequences to the autonomic nervous system from chronic use of beta-agonists and steroids should be considered. There is a classic allergic reaction characterized by hyperreactivity of the respiratory and GI mucosa with type I hypersensitivity and provocative exposure leading to eosinophilia, plasma cells, and degranulated mast cells. The authors speculate that a vasomotor adjunct with an imbalance in ANS input results in the vasomotor, cardiovascular, and inflammatory anaphylaxis responses. The disease is characterized by the classic mismatch of parasympathetic over sympathetic drive of swelling, flushing, smooth muscle spasms, arterial spasm, and diarrhea.

Further autonomic testing will be performed to better elucidate the nature of the subject's autonomic dysfunction. Magnetic resonance imaging on the brain and spine will be performed to rule out structural causes of autonomic circuit disruption (e.g. sympathetic lag due to

ependymal stretching from syrinx).

The potential role of autonomic dysfunction in food allergy syndrome and allergic anaphylaxis among the broader population remains to be investigated.

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[1] The sympathetic and parasympathetic nervous systems work in opposition. Sympathetic activity promotes alertness, bronchodilation, hypertension, and tachycardia, while suppressing gastrointestinal motility and erectile function. Parasympathetic activity promotes sleep, bronchoconstriction, hypotension, bradycardia, gastrointestinal motility, and erectile function. Bronchospasm, abdominal cramping, and angioedema are examples of manifestations of vagal bias.

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10x

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When we are young, we aim high. Possibilities abound. Somewhere along the way, we learn to lower our aim.

For the sake of discussion, let's say aiming high means trying to improve our lives 10x, and aiming low means trying to improve our lives only 20%.

We can probably achieve a 20% improvement by simply continuing with what we're already doing, but doing everything just a little bit better.

On the other hand, to achieve 10x improvement, we have to try new things. We must dream and take chances.

For 20% improvement, linear thinking is sufficient. Connecting the dots linearly allows people to project what their lives will look like far down the road. Consequently, most people know the rough outlines of the rest of their lives by mid-life.

We can't attain a 10x improvement with the linear thinking that characterizes a 20% improvement. It takes compound thinking. Picture life as an arc curving upward. Since our minds can't see around corners, the ultimate destination remains shrouded, mysterious.

The biggest problem with aiming high is that we fall short. Perhaps we only achieve 3x, not 10x. The biggest problem with aiming low is that we get there: we get to 20%.

If an investor likes an opportunity, but is willing to wait for a 10%

lower entry price, the investor is behaving as if the expected return is low. If the expected return is 20%, a 10% improvement in entry price represents a significant portion of the return. Yet there is no guarantee that the lower entry price will ever materialize.

If the expected return is 10x, a 10% difference in entry price is just a rounding error, so one can invest at the current price without needing to hope for a better entry price.

Although one might assume that people want the highest returns possible, the actions of the vast majority of investors signal that they actually are aiming for low returns. Thus, while there is virtually no competition for high returns, the competition for low returns is stiff. Indeed, seeking low returns is a crowded trade and quite possibly the riskiest place to be. In today's market, growth stocks that have huge potential yield trade at very inexpensive prices, while Treasury bills that are yielding virtually zero have been bid up to expensive levels by the crowd.

Therapeutics as the Next Frontier in the Evolution of Darwinian Medicine

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Evolutionary medicine (also referred to as Darwinian medicine) is the application of evolutionary theory to the understanding of human ailments.[1 2 3] It explores evolutionary mechanisms of disease, offering a complementary framework to the proximate mechanistic explanations that prevail in medicine today. In this paper, we consider the application of evolutionary theory to the *treatment* of ailments.

A major contribution of evolutionary medicine is the framing of human diseases as maladaptations of our prehistoric factory settings. Our physiologic processes were shaped during prehistoric evolution to meet the needs of the era, but those same processes may behave maladaptively in the modern environment and produce disease. We take that notion one step further and propose an overarching therapeutic paradigm for human ailments based on evolutionary theory—the *induction of adaptations* in the body as a way to treat disease. It is the idea of creating somatic traits in the body that evolution might otherwise need to create over many generations through the sheer force of variation and natural selection. In the same way that evolution has endowed us with traits that shield against biotic and abiotic stress to maintain homeostasis, we propose treating patients by endowing the body with buffers against ailments.

Most modern therapies provide relief in the short run, but chronic use can worsen the underlying condition, as the body remodels in the presence of the therapy and decompensates further. Caffeine stimulates acutely, but continued use leads to lowered baseline alertness.

Virtually all drugs exhibit this phenomenon, known as tachyphylaxis, to varying degrees. Modern medicine effectively provides the body with an adaptation, which ultimately de-adapts the body and creates dependence on further therapy. We suggest that providing therapy to induce an adaptation may represent an alternative model for relieving ailments.[4]

In this model, hypertension would be treated by offering patients drugs that elevate rather than lower blood pressure. This is effectively how exercise works. During exercise, we raise our blood pressure and heart rate, such that in the long run our baseline blood pressure and heart rate go down. An appropriate autonomic stimulus, whether physical activity or sympathomimetic drug, would induce vagal strengthening—thereby leveraging preexisting capacities within the body instead of overriding or replacing them.

These types of solutions would reverse the current trend of greater dependence on medicine, which is expensive, inelegant, and ultimately, ineffective. Induced adaptations may offer far superior therapies at a fraction of the cost, exactly the kind of outlier solution needed in this time of crisis in the healthcare system.

In some ways, the idea is hardly new. Vaccination induces a somatic adaptation. Priming the immune response prepares the body for potential future exposure to a dangerous pathogen. Vaccination is arguably one of the greatest inventions in medical history in terms of its efficacy and impact.

While vaccination provides the most sweeping example of induction of adaptation, a number of recent examples suggest the idea can be more broadly applied. Asthma is a pulmonary condition where insufficient sympathetic response in the smooth muscles of the respiratory tract predisposes to spasm and closure of the airways. For a century, symptomatic relief of asthma has featured the use

of sympathomimetic drugs. However, chronic use of beta-agonists induces down-regulation of beta receptors and furthers autonomic dysfunction. On the other hand, Richard Bond has shown that administration of beta-blockers may be a way to treat asthma by inducing an appropriate adaptation.[5]

Similarly, administration of the antigen in small doses has been shown to induce adaptation to cope with both environmental allergies and food allergies.[6] Positive pressure ventilation for respiratory dysfunction can produce not only diaphragmatic weakening, but also a host of other physiologic dysfunctions.[7] On the other hand, diaphragmatic pacing promotes negative pressure ventilation and *strengthening* of the diaphragm, which becomes an adaptation for the patient. Exercise, which has been associated with amelioration of many chronic diseases, is a natural example of adaptation induction.

The progression of life is defined by the accumulation of buffers (traits) against stresses over evolutionary epochs. As advances in technology enable them to live to unprecedented ages, modern humans are now facing many unprecedented stresses, both externally from the environment and internally from within their own bodies. Evolution has not kept pace with these changes; in many ways, diseases can be viewed as maladaptations awaiting the forces of evolution to eventually endow adaptations over the generations. We believe that human innovation can harness knowledge of evolution theory and accelerate the induction of adaptations within generations rather than across them.

In the final analysis, adaptation is the end, and evolution has been nothing more than the means to that end. Over the very long haul, if humans learn to create adaptations to maintain homeostasis, human evolution itself could be at risk for extinction.

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