



Editorial

The hegemony of empiricism: The opportunity for theoretical science in medicine

Summary Partly spurred by the rapid emergence of discovery tools, empirical science founded on experimental validation now dominates academic funding, publishing, and recognition while forums for theoretical science have been marginalized. Although this hegemony of empiricism instills useful discipline to the scientific process, it also limits the pace of science to sensor innovation and renders the ontogeny of scientific knowledge path-dependent, concealing potential discontinuities in intellectual trajectories. Theoretical science, founded on intuition, inspiration, and abstraction, can complement empirical science by creating disruptive paradigms that facilitate detection of spurious results and frame new hypotheses. For example, framing the compendium of human diseases as varying manifestations of buffer dysfunctions – insufficient or maladaptive responses to stress – portends new insights into disease mechanisms and treatments. As a specific incarnation of this theory, the “trauma hypothesis” suggests that the coordinated regulation of inflammation, coagulation, vasoconstriction, and fluid retention that evolved as a prehistoric adaptation to predatory stress and environmental injury conspires in modern times to produce acute coronary syndromes, heart failure, renal dysfunction, stroke, and pulmonary embolism. The theory also exposes the paradigmatic flaw behind the half-century detour perfecting balloon-deployed endovascular interventions. As the basis of buffer acquisition shifts from genetic to cognitive, phenoptosis – the theory that adaptive programmed death of organisms yields opportunity to successors – is rendered maladaptive, as an extended lifespan permits more efficient trait acquisition compared with life-death recycling. While forestalling death is a largely unfruitful medical game of “whack-a-mole” today, the recognition that aging and death may be programmed adaptations suggests they may also be amenable to systemic reprogramming. Epitomizing this opportunity are tumor cells, which reprogram themselves to escape their apoptotic fate and assume indefinite persistence. The prevalence and resilience of these cancer cells, and their ability to withstand the protean assaults of toxins, poisons, radiation, and host defenses, presage the potential robustness of life when appropriately programmed. Paradoxical medicine and dynamic range management may represent initial strategies to reprogram the neuroendocrine stress axes to modulate lifespan at the organism level, and many other strategies are anticipated. The key to theoretical science is original insight, but the prevailing pressure to conform to medicine’s educational and practice standards dis-incentivizes independent thinking. A scientific future is envisioned when the commoditization of experimental science will enable its outsourcing, liberating health scientists from the tyranny of empiricism to engage in a more balanced process of discovery infused with theoretical considerations.

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Empirical science represents the cornerstone of modern medical research, its foundation arising from the iterative algorithm of hypothesis and measurable experimental result. By contrast, theoretical science explores fundamental truths through an inductive process that relies on intuition, imagination, and logic to build intellectual frameworks. Since at least the classical era, the relative merits of theory versus empiricism have been debated. Partly due to the rapid emergence

of tools for discovery, empirical science now dominates academic funding, publishing, recognition, and governmental regulation in the modern era, while forums for theoretical science have become scarce. While the systematic, algorithmic approach to empirical science generally produces incremental advances within prevailing paradigms, it also tends to be shackled by those same processes. First, experimental validation can produce specious conclusions. Many studies fare poorly in

terms of reproducibility [1], and a reporting bias favors studies that achieve statistical objectives. Second, empiricism constrains the pace of scientific advancement to the rates at which experimental tools develop, particularly those which involve sensors that enable observations. Most importantly, the hegemony of empiricism renders the ontogeny of scientific knowledge path-dependent. It not only conceals potentially valuable discontinuities in intellectual trajectories, but also promotes wasteful efforts spent toiling in blind alleys. Indeed, the history of science can be traced as stretches of relative paradigmatic stability reinforced by empirical science, occasionally transformed by disruptive paradigms promulgated by non-conforming theorists such as Darwin, Freud, and Mandelbrot. As theoretical science relies less on the existing canon as a point of intellectual departure, it can complement empirical science where the latter falters.

When properly balanced with empirical execution, theoretical science can accelerate the advancement of medicine by yielding paradigms [2] that can frame hypotheses, facilitate the detection of spurious results, and reduce path dependency in the ontogeny of knowledge. One can view the progress of life in thermodynamic terms as an emergent property of energy, namely, the accumulation of buffers as adaptations to stress [3,4]. Framing illnesses as buffer dysfunctions – insufficient or maladaptive responses to stress – can yield new insights into diseases [5]. For example, the “trauma hypothesis” suggests that the counterproductive upregulation of inflammation, coagulation, and vasomotor dysfunction evident in acute coronary syndromes represents a maladaptation of a prehistoric response to trauma forged when predation and environmental injury were stronger forces of selection than they are today [6,7]. Empiricists – with staunch allegiance to evidence-based medicine and molecular science – have espoused for decades a set of well-intended balloon-deployed interventions such as angioplasty and stents that can inadvertently exacerbate the underlying vascular trauma and worsen adventitial autonomic dysfunction [8]. The “trauma hypothesis” exposes a potential Faustian bargain of these interventions, a fundamental paradigmatic flaw that portends long-term clinical failure of these therapies despite apparent short-term angiographic and symptomatic success. Many other conditions including congestive heart failure, renal failure, gout, stroke, and pulmonary embolism may also represent modern maladaptations of the prehistoric trauma response – an archetypal example of “Darwinian dysfunction” [9–11].

While his evolutionary theory is reshaping many aspects of medicine, Charles Darwin himself was a classic empiricist, thereby revealing the mutual dependency of the practices of theoretical and empirical science. Theory can frame empirical endeavors, and empiricism can disprove or support – though not absolutely prove – a theory. The limitations of Darwin’s empirical observations become evident with the overlay of a broader “theory of life” upon the theory of natural selection. The progression of life represents the cumulative acquisition of traits that enhance fitness, defined as the accrued sum of buffers against stress, as denominated in thermodynamic terms [12]. Variation, selection, reproduction and death – the hallmarks of the Darwinian theory of natural selection – constitute means by which physical traits are sequentially acquired over generations. As the basis of buffer acquisition shifts from genetic to cognitive, phenoptosis – the adaptive programmed death of organisms to yield opportunity to successors – is rendered maladaptive, as an extended lifespan permits more efficient trait acquisition compared with life-death recycling [13–15]. If death and Darwinian evolution have become obsolete, a new post-Darwinian paradigm for evolution may emerge for humans involving longer if not indefinite lifespan [12].

The recognition that aging and death are programmed adaptations suggests that fundamental, simple mechanisms may underlie the apparent complexity of observed human maladies [9,15]. Although empiricists have atomized medicine into an expanding compendium of named human diseases, the list of symptoms that manifest them remains very short. Moreover, responses to stress at least partially regulate all of these symptoms, suggesting that buffer dysfunctions such as autonomic dysfunction may represent the Occam’s razor for the vast array of human ailments [4,16]. If aging, disease, and phenoptosis are programmed processes, they may also lend themselves to systemic reprogramming. Cells found in tumors may epitomize this opportunity, as they reprogram themselves to escape their apoptotic fate and assume indefinite persistence. The prevalence and resilience of these cancer cells, and their ability to withstand the protean assaults of toxins, poisons, and radiation, not to mention host defenses, foreshadows the potential robustness of life when appropriately programmed. Paradoxical medicine and dynamic range management may represent initial strategies to reprogram the neuroendocrine stress axes to modulate lifespan at the organism level [17,18]. Many other novel methods such as neuromodulation are anticipated. Reduction of the

maladaptive activation of the stress response elicited by illegitimate signaling from sources such as “Darwinian rubbernecking” [19] and dysfunctional xenohormesis may also produce benefits [20,21].

While Gordon Guyatt’s concept of “evidence-based medicine” [22] brought useful focus on empiricism to the science of medicine, theoretical considerations seem to have become marginalized as a result. Yet, parameters that lend themselves to measurement may mislead by detracting attention from less patent but important characteristics. For instance, many illnesses may represent dysfunctions in the relationships among biomolecules, among pathways, among cells, among tissues, among organs, among individuals, and among species in an ecosystem, but such relationships lend themselves poorly to ready quantification [4]. The objectification of patients through diagnostic tests and quantifiable data points may obscure the real cause of disease. For example, physiologic abnormality may serve as the proximate cause of dyslipidemia, but the ultimate source of this malady may stem from dysfunctional social relationships that manifest as psycho–physiologic stresses. The exploration of such dimensions involves more art than science, but even the best attempts at studying medicine at a more abstract level, such as systems biology, remain anchored to reductionism and empiricism at heart.

The conformity demanded by the nature of medical professions may also account for the progressive marginalization of theoretical approaches. Independent thinking is the key to such considerations, but unfortunately, today’s evidence-based practice guidelines and malpractice climate discourage original thinking. Student physicians are winnowed and molded to conform obediently to the prevailing canon rather than to exercise independent thinking, leading some physicians to suggest that we are “turning out cadres of physician employees – homogenized lemmings” [23,24]. Ironically, the erroneous widespread adoption of the lemming metaphor to indicate herd mentality – lemmings are largely solitary rodents whose misbegotten reputation was burnished in a fictional movie – exemplifies herd behavior and the scarcity of original thinking [25].

Whereas empiricism dominated health sciences in the twentieth century, ideas may dominate the impending Healthcare Century. Ideas that improve healthcare will empower human endeavor and prosperity, and prosperous societies consume more healthcare and create more ideas, resulting in a feed-forward virtuous cycle. Currently, many of the brightest minds toil away in survey science – in some cases unimaginatively applying new

tools to old paradigms and generating data for the sake of data. One can envision a scientific future where the commoditization of experimental science will encourage its outsourcing, liberating health scientists from the tyranny of empiricism to engage in a more balanced process of discovery infused with theoretical considerations. The science of medicine has never been more exciting.

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Anthony J. Yun
*Palo Alto Institute,
470 University Avenue,
Palo Alto, CA 94301,
United States*

*Tel.: +1 650 387 6667; fax : +1 650 325 5028
E-mail address: joon@paloaltoinstitute.org*

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