Telocyte Newsletter
Q3 2020

TELOCYTE™
A future beyond Alzheimer's

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For those interested, here is my video discussion on curing the dementias.

"Those who cannot remember the past are condemned to repeat it."
George Santayana

It is disturbing when otherwise intelligent and even well-educated people routinely make the same errors that have echoed throughout scientific and medical history. We repeat the mistakes of the past blithely and with an arrogant ignorance.

In respect to age-related disease generally and Alzheimer's disease specifically, we routinely confuse the disease with the symptoms. We persist in focusing on measurements, definitions, descriptions, symptoms, signs, components, hallmarks, and biomarkers, while ignoring the underlying disease itself. Dr. Leonard Hayflick (the discover of cell aging) and I were talking a few months ago when he pointed out that "The cause of aging is ignored by the same people who argue that aging is the greatest risk factor for their favorite disease." He is correct: physicians and researchers universally and correctly cite aging as the single most predictive risk factor for age-related diseases – it is far-and-away the best predictive risk factor for Alzheimer's disease – yet then immediately go on to focus on other aspects and entirely ignore the aging process itself. They pay lip service to aging, but then address more superficial and less difficult aspects of dementia. In getting caught up in details, they confuse details with understanding. Having a firm grasp of thousands of details, no matter how important those details may be, is not the same as understanding disease or understanding aging. Knowing details is not the same as understanding how those details work.

Symptoms are not a disease, but are merely the outcomes of a disease.

Two thousand years ago, Galen – one of the greatest of the classical physicians – gave a perfect description of the Antonine plague, yet he had no concept of microbes, viral illness, and infectious disease, nor could he prevent or cure the plague. *Descriptions are not the same as understanding.*

It's axiomatic that "if you can't measure it, then it's not science", but we need to go beyond mere measurement. You can measure precisely and extensively, but if you don't understand what the measurements mean, then it's still not science. Five hundred years ago, Vatican astronomers had superb measurements of planetary

motion but, convinced that the earth was the center of the universe, they had no understanding of celestial mechanics. *Measurements are not the same as understanding*.

In 1895, Lord Kelvin –great physicist though he was – stated that "Heavier-than-air flying machines are impossible", some eight years before the Wright brothers proved him wrong at Kitty Hawk. Lord Kelvin had excellent definitions of weight and air pressure, but no understanding of aerodynamics. *Definitions are not the same as understanding*.

Less than a decade ago, when Ebola virus was a west-African epidemic, we could accurately list the dozens of symptoms of the disease, but Ebola virus is not merely symptoms, but a complex pathological interaction between a virus and a human host. The disease is the process, not the symptoms. *Knowing the symptoms is not the same as understanding*.

Currently, most institutions that purport to fund cures for Alzheimer's and other dementias make the same mistake: they focus on components, hallmarks, biomarkers, measurements, and definitions, but they fail to examine their assumptions about the processes underlying the dementias. Until now, we have seen an institutional bias against innovation or effective therapeutic trials. Ironically, despite the claims of those purportedly interested in innovation, ground-breaking approaches, and tomorrow's medical breakthroughs, the most strident claims are made by precisely the same firms that continue to invest in and to perfect yesterday's technology. Were it now 1903, they would be investing in the "latest" technological advances in gas-filled balloons, yet would not recognize the importance of what the Wright brothers were doing at Kitty Hawk. They don't invest in innovation, they perfect technologies that are about to be superseded by the unexpected and revolutionary.

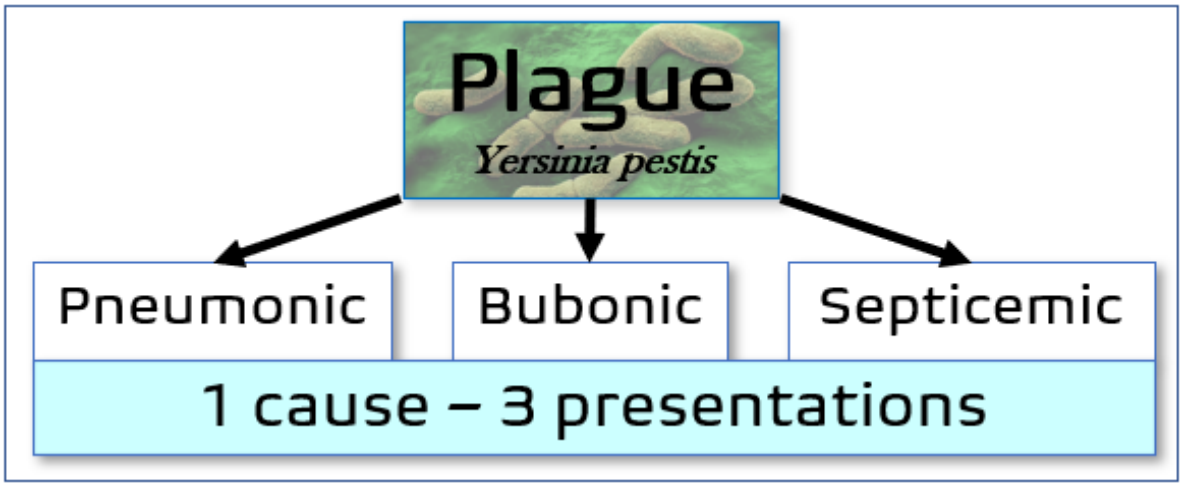
The major global pharmaceutical firms invest in trials that not only fail, but that lack any scientific support for their approach. Their models are based on biomarkers (such as amyloid plaques), not on fundamental mechanisms of disease (such as cell senescence). By mid-2019, Biogen Eisai spent more than $750 million on its failed trials, more than 20 times the amount for which we could easily demonstrate an effective cure for Alzheimer's disease if were to target fundamental mechanisms rather than superficial biomarkers.

Investors do much the same thing. One large group of investors for alumni of major US universities brags about its funding for age-related diseases, but they fund approaches that have no scientific rationale, that are contradicted by their own published data (e.g., senolytics companies), and that focus on hallmarks, biomarkers, definitions, components, and symptoms, rather than considering the systems process that underlies and causes these tragic diseases. These companies and their investors confuse the components with the process, mistakenly thinking that if we can list hallmarks and biomarkers, then we have understood the process. We have not: hallmarks and biomarkers are not disease processes and are not effective clinical targets. You cannot cure Covid-19 using cough medicine; you cannot cure age-related disease by using small molecular approaches.

Peter Diamandis, a known investor in the longevity market, touts the "key technologies" of what he calls a "trillion-dollar industry", but then gets lost in the components of aging but without any understanding of aging itself. For interventions, he focuses on the latest techniques (stem cells, CRISPR and senolytics, for example) and cites miniscule components of the aging process (the Wnt pathway, for example), but without any fundamental understanding of aging as a fundamental process. The latest fads, the latest techniques, and the latest investments are not the same as understanding the aging process. Aubrey de Grey, touted as an author and would-be scientist, leads panels on "hallmarks of aging", but has no understanding of the fundamental aging process itself. Hallmarks and biomarkers are not aging anymore than symptoms are a disease.

Consider an analogy, that of a common infectious disease in the centuries prior to our understanding that such diseases had microbial etiologies. We now recognize that classic plague is the result of an infection of *Yersinia pestis*, yet in the middle ages it was often described in a multitude of ways and occasionally diagnosed as being entirely different and unrelated forms of plague. Nor was this necessarily an error, as even now for example we recognize several types of *Yersinia pestis* infection which, while sharing precisely the same bacterial etiology, differ in their clinical presentation and course depending upon the initial site of entry and tissue spread of the bacterial invasion. Pneumonic plague, bubonic plague, and septicemic plague all differ in their clinical presentation, in their course, and even in their mortality rates, yet each of these is fundamentally the same disease, caused by the same bacteria. Diagnosing each as a separate clinical syndrome is warranted, despite the shared underlying cause, that of *Yersinia pestis* infection. The fact that 1) pneumonic plague has a pulmonary focus, 2) bubonic plague has a focus in the lymphatics, and 3) septicemic plague occurs

predominantly in the vascular system may confuse the novice physician (let alone the medieval healer with no knowledge of bacteria), yet they still share a fundamental and unified etiology: the *Yersinia pestis* bacillus.



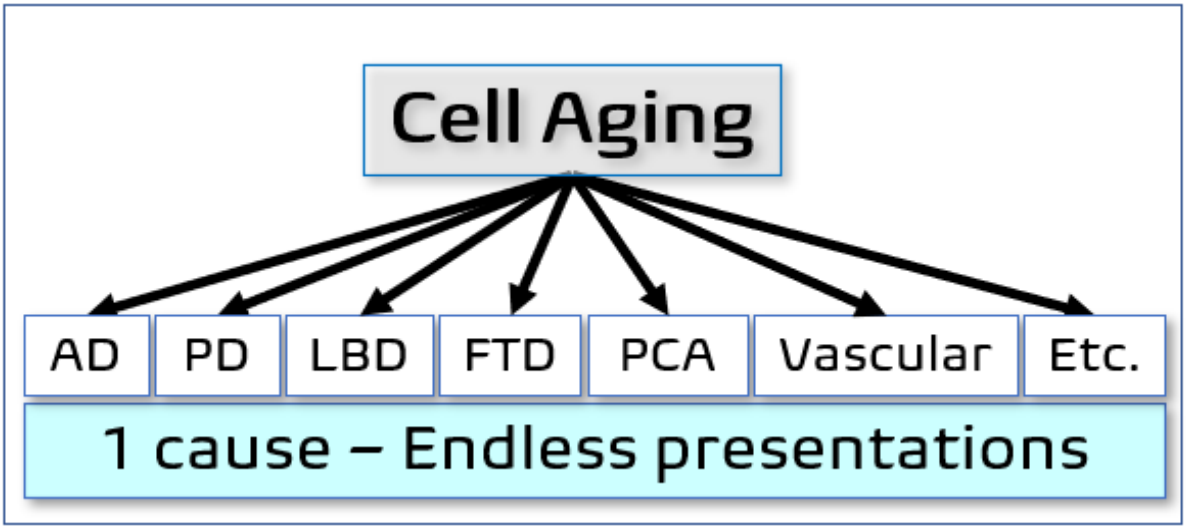
Whether we consider plague to be three diseases or one disease might be a matter of judgement, but to simply assume that the three clinical presentations represent independent etiologies due to completely different causes avoids the fundamental insight as to the commonality of basic cause. They may present differently, but we cannot understand (or treat) plague unless we understand not merely the syndromes, but microbial disease generally, *Yersinia pestis* specifically, and the role it plays in those three different presentations. Moreover, effective intervention requires that we understand not merely the syndromes, but the unified underlying microbial etiology that lies beneath these syndromes. Only when we understand the disease process, can we cure the disease.

A parallel observation applies to age-related human dementias. Understanding of the shared, common, and fundamental etiology, at the cellular or epigenetic levels, explains the multitude of clinical presentations and offers an effective point of intervention. Until we understand the fundamental, unified etiology, we can never cure the dementias.

To construct such a unified model, we need to distinguish between systems models and mere components. For example, at the macro-level, a number of clinical findings are typical of aging human beings, including grey hair, memory loss, sarcopenia, osteoporosis, osteoarthritis, declining GFR (glomerular filtration rate), arterial disease, skin aging, poor healing, immunosenescence, etc. Although these are typical "components" of aging, they are not aging *per se* and they certainly are not a systems model of aging. Rather, they are simply the component outcomes of a more fundamental process that expresses itself in these macro-level findings. At the micro-level, we also see innumerable component findings that are typical of aging human beings, including inflammation, declining DNA repair rates, increased mutations, lipofuscin deposits, a declining ATP/ROS ratio (adenosine triphosphate/reactive oxygen species), methylation changes, acetylation changes, telomere shortening, and thousand of other arcane alterations in cell function. Nevertheless, important, or even defining as these various changes may be, they are not themselves the aging process,

but are merely the component outcomes of a more fundamental process that expresses itself in these micro-level findings. Aging is the process, not the biomarkers that we observe as we age. We should never confuse biomarkers (or components, hallmarks, signs, symptoms, etc.) with the process that drives such biomarkers: to do so is to make a fundamental conceptual error. Aging is the system process; the clinical findings are the components. This is true throughout clinical medicine: a disease process is not just a list of symptoms.

Much the same confusion occurs when we consider the human dementias. We see large global pharmaceutical firms and individual academic researchers alike conflate specific dementia syndromes with their correlated histology. But just as Alzheimer's disease is not merely beta amyloid plaque, tau tangles, or inflammation, the same is equally true of any of the age-related dementias. Dementias are not merely a list of common findings, such as mitochondrial dysfunction, inflammatory changes, glial activation, alpha synuclein deposits, disruption of the blood-brain-barrier, glymphatic alterations, and so forth. These may serve as clinical guideposts to disease, yet none of these are the disease process itself. They are outcomes, not causes. A process is not its components, a disease is not its symptoms.



We must understand fundamental causation rather than exploring the superficial biomarkers that lie downstream of the basic disease process. Why do beta amyloid plaques form in Alzheimer's disease? Why do alpha synuclein deposits form in Parkinson's disease? Why do hypertension and hyperglycemia appear to trigger vascular dementia? To merely wave one's hands and ascribe the more fundamental process to genes, aging, or ''vascular changes" avoids the fundamental question raised here. Genes (the ApoE4 allele, for example) play a role, but we see patients with double ApoE4 alleles and no disease, and we see patients with Alzheimer's and no apparent genetic risks. Genes are associated with disease, but they are not the disease itself and certainly do not provide a fundamental model nor an explanation. Likewise, age itself is no explanation unless we can explain why some 50-year-old develop dementia, while some centenarians do not.

We offer an effective systems model[i] that accounts everything we know of age-related dementia, successfully predicts the universal failure of prior clinical trials, explains the cognitive decline seen in other species (and why their histology and physiology differ from the human counterparts), and – most importantly – offers an innovative an effective point of intervention. No other model, no other biotech company can do so.

We simply need to take it to human trial.

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[i] Fossel M. A Unified Model of Dementias and Age-Related Neurodegeneration. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. January 2020. https://doi.org/10.1002/alz.12012