General Session III: Discussion

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DISCUSSION

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Bakos et al. ("Genetically Informed Identity") state that "We believe that aging and longevity have genetic origins." And the title of the paper by Yashin et al. states "How Genes Modulate Patterns of Aging-Related Changes on the Way to 100."

However, the belief that genes play a direct role in the cause of biological aging has not been demonstrated. This is because of the failure to distinguish between aging and longevity determinants.

There are only two ways in which age changes can occur. First, as the result of a purposeful program driven by genes or, second, by stochastic or random, accidental events.

Arguments based on increases in longevity by manipulating genes in invertebrates like worms and flies are flawed because the endpoints in those experiments are based on all-cause mortality. Other than aging, a cause for all of these deaths could be disease, pathology or accidents.

For over 100 years we have known how to increase longevity in invertebrates. These methods include manipulations of temperature, light, moisture and population density. Everything in the universe changes or ages in space-time without being driven by a purposeful program. That is the first evidence for the belief that aging is not programmed by genes but is a stochastic process. Second, there is no direct evidence that proves age changes are governed by a genetic program. Finally, there is a huge body of knowledge indicating that aging is a stochastic process rooted in the intrinsic thermodynamic instability of complex biological molecules. The function of all molecules depends on how long their precise three-dimensional folded structures can be accurately maintained. The fact that they are maintained only until reproductive maturity is what results in age changes.

The common denominator that underlies all modern theories of aging is loss of molecular fidelity or structure, which leads to dysfunction. The loss occurs because of the Second Law of Thermodynamics which states that energy tends to disperse or spread out unless it is restrained. The restraint is mostly the relative strength of the chemical bonds that hold molecules together. The prevention of chemical bond breakage is the *sine qua non* for the maintenance of molecular function and therefore life itself—at least until reproductive maturation.

Without this condition, species would not survive.

The tendency for molecules to lose energy is never entirely eliminated because it can be circumvented for varying time periods by the enormous capacity for many biological systems to replace or repair them.

The second law cause of biological aging also governs aging in the material world as well. For example, there are no instructions in the blue prints that designed your car instructing it how to age. Your car is brilliant because it knows how to age all by itself.

The molecules composing the car dissipate energy over time, thus structural and functional capacity is lost. All this occurs spontaneously with no instructions. Analogously, your genome does not contain instructions for aging because, like the car, instructions are unnecessary. Genes are unnecessary to drive a spontaneous process.

The process might be circumvented in cars for some years by parts replacement. Then the philosophical question arises: After how many parts are replaced does the original car no longer exist? The present excitement about regenerative medicine has yet to come to grips with brain regeneration, which, even if possible, would result in loss of self-identity and memory.

The occurrence of dysfunctional molecules and their repair begins at conception. After reproductive maturation, the balance that favored repair and synthesis shifts in favor of the accumulation of dysfunctional molecules that begins to exceed the capacity for repair and synthesis. These events define the aging process and the subsequent increase in vulnerability to pathology or age-associated disease. The repair and synthesis machineries are themselves composed of complex molecules that also suffer the same dysfunctional fate as the molecules they repair or replace.

In its present state, nothing lasts forever. Immortal living things do not exist. The only biological property that approaches immortality is the information coded in information-containing molecules, but even that information is subject to mutation or change.

We spend the first 20 years or so of our lives producing, ordering and replacing our molecules with close to absolute fidelity. Through natural selection, that fidelity must be maintained until reproductive success or our species would vanish. Thus, through evolution, natural selection has favored energy states capable of maintaining molecular fidelity until reproductive success, after which there is no species survival value for those energy states to be maintained.

The apparent exceptions to this rule are the many animal species that do not age at all or whose rate of aging is imperceptible.

Unlike the second law that characterizes aging, longevity determination is not a random process. It is governed by the reserve in physiological capacity reached at the time of sexual maturation that, through natural selection, was achieved to better guarantee survival to that age.

The determination of longevity is incidental to the main goal of the genome, which is to govern events in order to reach reproductive maturity. Thus, the genome only indirectly governs longevity. Genes do not drive the aging process but by governing the levels of physiological capacity, they do govern the determinants of longevity—the energetics of all molecules including those that compose the machinery involved in turnover, replacement and repair.

No genes specifically drive longevity because all do. The variations in excess physiological capacity, repair and turnover account for the differences found in longevity both within and between species.

One might think of longevity determination as the energy state of molecules before they become dysfunctional and irreparable. This energy state addresses the question: "Why do we live as long as we do?" One might think of aging as the state of molecules after they have incurred irreparable damage leading to altered function or inactivity. This condition addresses the question: "Why do things eventually go wrong?"

Aging then is a chance-driven catabolic process. Longevity determination is an anabolic process that, indirectly, is genome driven.

The third aspect of the finitude of life is age-associated disease. The distinction between the aging process and age-associated disease is not only based on the molecular definition of aging described earlier but is also rooted in several practical observations.

First, unlike any disease, age changes occur in every multicellular animal that reaches a fixed size at reproductive maturity.

Second, unlike any disease, age changes cross virtually all species barriers.

Third, unlike any disease, age changes occur in all members of a species only after the age of reproductive maturation.

Fourth, unlike any disease, age changes occur in all animals removed from the wild and thousands or even millions of years.

Fifth unlike any disease, age changes occur in virtually all animate and inanimate matter.

Sixth, unlike any disease, age changes have the same universal molecular etiology, that is, thermodynamic instability.

Unlike aging, there is no disease or pathology that shares these six qualities.

In the presentation by Sebastiani et al. ("Contribution of Familial Longevity to Living to 100"), the important question they pose is what they describe as the "glaring deficiencies in the current assessment of mortality risk" caused by "the lack of information concerning the impact of familial longevity." They ask: "What is the nature of this predisposition?"

An answer to this question must be based, at least in part, on our knowledge, or lack thereof, of the causes of mortality in old people.

That knowledge is seriously limited. One only needs to examine autopsy data for evidence.

The decline in the performance of autopsies in the United States in the past 50 years has been remarkable. It has fallen from 41 percent of hospital deaths in 1961 (Landefeld et al. 1988) to 17

percent in 1980 (Centers for Disease Control and Prevention 1988), 14 percent in 1985 (CDC 1988) and 11.5 percent in 1989 (Pollock et al. 1993). The figures vary from county to county, however. In the mid 1990s, the autopsy rate fell to between 5 and 10 percent (Hasson and Schneiderman 1995; Hoyert 2001).

ProPublica, in collaboration with PBS' *Frontline* and NPR, took an in-depth look at the nation's 2,300 coroner and medical examiner offices and found a deeply dysfunctional system that quite literally buries its mistakes (*Frontline* 2011).[*]

The following data and observations are from that program.

- "The autopsy rates at teaching hospitals, which are usually run on a nonprofit basis and have an educational mission, are around 20 percent today. But the rate at private and community hospitals, which constitute 80 percent of facilities nationwide, rates can be close to zero. This discrepancy explains the rough average for the number of hospital autopsies done today of about 10 percent of all deaths."

- "Hospitals have powerful financial incentives to avoid autopsies. An autopsy costs about $1,275, according to a survey of hospitals in eight states. But Medicare and private insurers don't pay for them directly, typically limiting reimbursement to procedures used to diagnose and treat the living. Medicare bundles payments for autopsies into overall payments to hospitals for quality assurance, increasing the incentive to skip them. The hospital is going to get the money whether they do the autopsy or not, so the autopsy just becomes an expense."

- "Since a 1971 decision by The Joint Commission, which accredits health care facilities, hospitals haven't had to conduct autopsies to remain in good standing. The commission had mandated autopsy rates of 20 percent for community hospitals and 25 percent for teaching facilities but dropped the requirement."

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[*] For a look at the entire investigation, visit http://www.propublica.org/series/post-mortem.Why is this here? It does not appear here in my original text. MUST be deleted.

- "Hospital autopsies are even rarer when patients older than 60 die in hospitals, representing a lost opportunity to learn about age-related diseases. More than 684,000 such patients died in hospitals in 2008—more than one-quarter of the total deaths in the country—and just 2.3 percent were autopsied, CDC data show."

- "There are three reasons why autopsies are not performed. First, since 1971 hospitals no longer are required to maintain a 20 percent autopsy rate to keep their accreditation. Second, insurance companies do not pay for the procedure. Third, autopsy results may cost hospitals and doctors (and their malpractice insurance carriers) much money if the results provide evidence of medical errors."

A 2002 review by the federal Agency for Healthcare Research and Quality found that when patients were autopsied, major errors related to the diagnosis or cause of death were found in one of four cases. In one of 10 cases, the error appeared severe enough to have led to the patient's death (Shojania et al. 2002).

Other than the relatively few autopsies done for forensic purposes, in those rare instances where autopsies have been performed on a large number of old people, the findings have shown that from 40 to 50 percent of the causes of death appearing on their death certificates have been inaccurate (Mac Gee 1993; Kohn 1982; Patterson et al. 1992).

Our faith in the legal causes of death currently written on death certificates is further undermined by the fact that multiple pathologies occur in older people so the true cause of death is rarely known. This fact is substantially ignored by those who slavishly depend on the statistics that rely on what is written on the death certificates of the elderly.

I conclude that because there are few autopsies, and little research on the etiology of death in older people, the cause of most deaths in old age is still hidden in the proverbial black box.

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