Rebuttal to Leonard Hayflick's discussion of the paper "Genetically Informed Longevity," by Bakos et al., presented at the Living to 100 Symposium, January 9, 2014.

REBUTTAL DISCUSSION

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Yes, we do believe aging and longevity have genetic origins and also believe there is ample and obvious demonstration of this. We have, we believe, made the following distinction between "aging" and "longevity": Aging is a biological process that moves biological organisms closer to death while longevity is a process that moves the target, death, further into the future. Aging operates within the confines of the biological design of an organism that is controlled by genes and affected by genetic variation.

As we have pointed out, different biological organisms living on earth—all based on the same genetic design scheme inherited through evolution—age and have lifespans that are different. Clearly, these differences in aging and longevity must be driven primarily by differences within the organisms and not by the common action upon all of them of an external force such as the Second Law of Thermodynamics. There are very significant differences in rates of aging and maximum life spans among species. And within a species, differences, although not as significant, also exist and have been associated with genetic variation. This is powerfully indicative that genetic drivers are associated with the rate of aging and longevity in biological organisms.

The thing that makes some mice (old at 2), some dogs (old at 15) or some humans (old at 80) age at different rates are their genetic differences. And, we believe, there is ample evidence, which we have pointed to in our paper, that differences in aging and longevity within a species, in particular a long-lived species such as humans, is contributed to at least in part by genetic variation among individuals.

Clearly, there are random or stochastic events within the environments in which biological organisms live that can and do contribute to aging and lifespan. In addition, we agree with Professor Hayflick that the laws of science—including the Second Law of Thermodynamics—apply to biological organisms as well as to inanimate objects. And, obviously, a biological species cannot continue to exist if it has not found a way or evolved such that it can effectively reproduce itself since immortality is not yet an evolved characteristic. Therefore, a naturally occurring characteristic of successful species is that they survive, at least, to sexual maturity. We don't necessarily believe that is a goal or genetically designed into organisms as it is well known the evolutionary process has produced organisms or variants unsuccessful at reproducing in sufficient numbers to assure survival or adapt to environmental changes and which, therefore, have gone extinct.

The Second Law of Thermodynamics relates to entropy, a measure of disorder in a system, say a chemical system such as the human body. The second law says essentially that systems move in the direction of disorder which Hayflick attributes as aging and, therefore, is inevitable. Hayflick does not carry his comparison of human aging and longevity to automobiles far enough. Biological organisms, which by definition are living organisms, engage in self-repair or regeneration, which Hayflick notes in his discussion. However, he assumes that self-repair is efficient only up to sexual maturity when things start going downhill. He simply ignores the fact that organisms also die at young ages prior to sexual maturity or that many live a long life after sexual maturity. The Second Law of Thermodynamics is,

obviously, being ameliorated by some outside influence—the genetic and epigenetic control of the regenerative or self-repair processes within living cells.

We might take Hayflick's automobile analogy further and argue some cars are designed and built better than others and will tend to last longer, that is, have a longer useful life. That would be a function of their design, as longer life in humans would be a function of the influences of genetic variation on human design. Hayflick mentions auto maintenance and repair as a contributor to longer usefulness. To that one might add careful use. Similarly, in humans, maintenance, repair and risk avoidance add useful years to a life. One could reasonably argue that human intelligence provided by the human genetic design contributes to that well-being, making genetic variation, at least, an indirect contributor to long life in humans—not however, one might recognize, universally applied.

Hayflick asserts aging is a "stochastic process that is rooted in the intrinsic thermodynamic instability of complex biological molecules." But he also says (emphasis added): "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." He, therefore, seems to believe self-repair operates to delay the degradation of the human body imposed by the second law only through sexual maturity and that an excess or reserve of physiological capacity built up during that growing-up period is then drawn down. How long that takes is the nonrandom determiner of longevity.

In the end, there seems to be not much inconsistency between what our paper says and Professor Hayflick's beliefs as stated in his discussion. We both agree the decay that may be caused by the second law can be "circumvented for varying time periods by the enormous capacity for many biological systems to replace or repair them[selves]." We are merely approaching the concepts of aging and longevity from different points of view and may even be defining the terms aging and longevity slightly differently. While we recognize the laws of science apply, we emphasize differences in rates of aging and the resulting longevity among humans and between humans and other species as being clearly influenced by genetic differences and variation and have provided the support for that belief in our paper. We also believe that human intelligence, which creates an understanding of the biological processes affecting the human body, leads to medical mitigation and treatment of disease and injury, which also positively influence aging and longevity. One cannot deny that human intelligence is an evolved characteristic with genetic origins.

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