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HEAD-TO-HEAD DEBATE ON THE UTILITY OF SHORT LIVED ANIMAL MODELS FOR AGING: PROS AND CONS

Rebuttal to Hasty and Vijg: 'Accelerating aging by mouse reverse genetics: a rational approach to understanding longevity'

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I am grateful to the Editors for the opportunity to comment on the essay by Hasty and Vijg. I find many of its assertions unconvincing, including the authors' confidence in the 'almost universal consensus' (!) that aging is due to DNA damage secondary to free radical effects, and that mutations that extend lifespan in mice do so principally by 'improved DNA metabolism'. I am a good deal less certain than Hasty and Vijg that 'the single most important molecular endpoint responsible for a major category of aging-related phenotypes is mutation accumulation in the somatic cells of an organism during the course of the aging process'; outside the realm of neoplasia, the evidence that somatic mutations have any effect on age-related illnesses is quite weak. The assertion that 'genetic alterations rarely impact aging' is clearly incorrect: all readers of *Aging Cell* can list dozens of mutations that modulate risks of cataracts, cancer, diabetes, atherosclerosis and other aspects of age-related dysfunction. The idea that: 'Damage to the DNA of the genome would probably be more critical than damage to proteins or lipids because the ensuing loss of genetic information is essentially irreversible' is also questionable: there is already good evidence for alterations in lipid oxidation as a key step in atherosclerosis, and alteration of protein structure in cataracts and cerebral amyloidoses, but there is very little evidence linking somatic cell mutations to any aspect of aging except neoplasia. Mutations are indeed irreversible, but so is the daily sloughing of skin and gut cells, phagocytosis of erythrocytes and apoptosis of immune cells. The key issue is not reversibility, but rather to decide what fraction of mutations are trivial (such as mutated albumin genes in a T cell), what fraction are rendered harmless by cell death and replacement, and what fraction actually contribute to the synchronized abnormalities in multiple tissues that lead to the signs and symptoms of aging.

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The hypotheses championed by Hasty and Vijg are testable. Data showing that mice engineered to have excellent antioxidant defences have lower somatic mutation rates as well as decelerated immune, muscle and skin aging, and extended longevity would be pretty convincing. Conversely, evidence that a mouse engineered to have poor antioxidant defences did indeed have increased DNA damage but retained normal lifespan and normal rates of immune, muscle and skin aging would create additional problems for those reluctant to leave this particular bandwagon.

The controversial question of whether somatic mutations contribute to the pathology of aging would merit its own 'Head-to-Head' debate in some later issue of *Aging Cell*. The topic at hand, however, is a different one: to what extent can engineered or spontaneous mutations allegedly leading to accelerated aging contribute to our understanding of the plain old-fashioned aging that is gradually turning us into our grandparents? I have tried to justify my own opinion (i.e. 'not much, and not without a lot of careful cross-checking') in the essay printed above. In his famous papers introducing the idea of 'segmental' aging syndromes (Martin, 1978, 1990), George Martin compiled a listing of human mutations that produced changes similar to those that appear in many old people, and inferred from their relatively high frequency that many thousands of genetic loci could influence the aging process. This makes good sense to me, but I have argued elsewhere (Miller, 1999) for the importance of distinguishing between the many genes that influence the quality of aging (i.e. why does one individual retain good eyesight whereas another retains good immunity and a third avoids cognitive decline?) and the fewer, more interesting genes that modulate the pace of the overall aging process as a whole. Although it is clear from interspecies comparisons that genetic differences lead dogs to age slower than mice and faster than horses, it is I think still open to debate as to whether common genetic polymorphisms within a species do or do not modulate the fundamental pace of synchronized multisystem decline in middle-aged individuals, in the way that aging is indeed retarded by calorie-restricted diets in rodents and by some endocrine system mutations in mice and dogs.

It is not surprising to note that mutations that interfere with fundamental cellular processes such as DNA repair, oxidation resistance, apoptosis or cellular organization lead to dysfunction in more than one cell type and organ system, including cells and organs whose functions are also impaired by aging. Analysis

of the mechanisms by which these molecular alterations produce their pathological effects deserves careful attention and strong support, and mutations that affect these pathways will teach us much about how animals are constructed and maintained, and how they fail. Such research is of such great importance that it does not need to be hyped. It does not need to be marketed as research on 'accelerated aging'.

I should like to propose a challenge for Hasty, Vijg and other advocates of pepped-up senescence. Let us develop, together, a consensus listing of changes normally seen in aging mice, changes documented in multiple strains and stocks in multiple laboratories. Such a list might include muscle weakness, poor immune responses, collagen and crystallin cross-linking, modulation in several hormone levels, and lower activity and learning, as well as both non-lethal (e.g. arthritis) and lethal illnesses. Let us then agree to reserve the term 'accelerated aging' for mutant mice that exhibit, at unusually early ages, at least 75% of the items on the approved checklist.

One should, I think, be wary of insisting, too early, on a universal consensus about a process that is still as mysterious as aging. Fifty years ago we knew as much about aging as physicians did about infection in the early 1800s, when miasma theory represented the universal consensus of the educated elite. Fortunately, things have improved: we now know as much about aging as scientists knew about infection after John Snow's observations on the epidemiology of cholera, which gave the first, premicroscopic hints that germs could make people sick. We now have some possibly useful hunches about how aging undermines homeostasis, why it produces synchronous dysfunction in so many tissues, and why the speed of the process differs by as much as 30-fold within the mammals and as much as 10-fold within some orders of mammals. I myself think it is too early to have a favourite hypothesis, and I look to comparative biology and analysis of long-lived mutants to help select specific mechanistic ideas worth special attention. Others who have already developed a strong, specific, molecular intuition about how aging works and how aging is timed should follow their own inclinations, devising experiments to test the idea that aging can be slowed (or, though I would bet against it, perhaps even speeded up) by tweaking their favourite molecular pathways. Such evidence will need to be stronger than merely showing that crippling an important defence mechanism causes several kinds of organ failure and an early death.

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