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The Longevity Dividend: Why Invest in Basic Aging Research?

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Although much of the current research on the biological mechanisms of aging has used death and life span as endpoints, most gerontologists now agree that these are not ideal indicators of healthy aging. They are used because we currently do not have any good biomarkers of aging per se, and ascertaining biological age, as opposed to chronological age, even in laboratory animals where we can conduct more invasive research, remains a difficult task. By *biomarker of aging*, we mean a measurement that gerontologists could make that would be informative about the predictable remaining years of life an individual could anticipate on the basis of that particular measurement or on a panel of comparable measurements. The National Institute on Aging (NIA) in the United States conducted a 10-year program from 1988 to 1998 in an attempt to identify such biomarkers in mice and rats, but although many age-related traits were identified, a specific panel of biomarkers of aging was not achieved (Sprott, 1999; Warner, 2004).

One benefit of having a panel of biomarkers would be so that researchers could identify sensitive targets for assessment of possible interventions in the aging process. Although this implies that one of the goals of aging research is simply to increase human life span, this is not part of the mandate on which the NIA was established by the U.S. Congress in 1974. Rather, that mandate was, and still is, to conduct research on the particular problems that people face as they grow older. The major problems are of course declining health with an increased susceptibility to potentially fatal age-related chronic diseases such as cancer, cardiovascular disease, diabetes, stroke, and some neurodegenerative disorders, as well as age-related disabling conditions such as arthritis, osteoporosis, and sarcopenia. In this article, these will be referred to simply as age-related diseases.

Broadly speaking, the two major concerns of older people are maintaining physical and cognitive functions, and each of the aforementioned diseases contributes to the decline of one or both of these functions. Aging is a risk factor for each of these diseases, so the central challenge is to elucidate how age contributes to their onset. Thus, there is a need to shift our focus from

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research on life span to research on health span as we try to figure out which of the myriad of age-related changes that occur in humans are actually disease risk factors and which are simply benign age-dependent changes, such as graying hair. A corollary to this is why individual humans vary so dramatically in how they age. This will require identifying both the genetic and environmental factors that play a role in the etiology of each disease in an effort to understand why and how age matters.

It has been assumed by many researchers that increasing the average life span of humans will lead to a dramatic increase in the incidence of disease and disability (Gruenberg, 1977). If modern medicine does succeed in increasing life span without a concomitant increase in health span, the result would indeed be a society of sick and frail individuals with poor quality of life. This combination – longer life coupled with poor health – would exert enormous pressure on the economy by increasing the investment required for pensions, medical care, and other retirement benefits. A situation of this nature did occur during the last century: the median life span in the U.S. increased from 47 to 78 years, and there was a dramatic increase in the incidence of chronic diseases and disabilities that had rarely been seen before. For example, Alzheimer's disease was not even described in the medical literature until 1907, but currently there are more than 4 million people just in the U.S. that have been diagnosed with the disease. So the prevalent assumption has been that increasing human life span further would actually lead to an ever more frail society. However, this is not a foregone conclusion for everybody in a population: Hitt, Young-Xu, Silver, and Perls (1999), for instance, found that centenarians were actually healthy for most of their lives followed by a relatively rapid rate of decline.

Most of the efforts of modern medicine are focused on addressing, and ultimately defeating, each of the major diseases burdening our population. The typical elderly person suffers from multiple diseases in parallel, so curing any one of them could still leave them exposed to the ravages of the others. Although much progress has been made in understanding and treating many age-related diseases, it has been estimated that curing any of the major fatal diseases will have only a marginal impact on median life span, usually on the order of three to six years (Olshansky, Carnes, & Cassel, 1990). Even if all of the major fatal diseases are conquered, Miller (2002) has estimated that the combined effect would be less than that predicted by extrapolating the results from rodents on a caloric-restriction regimen to humans. Thus, if cardiovascular diseases could be conquered so that human beings seldom died from them, many people would go on to live useful lives for several extra years, but these extra years might be spent in a general state of diminished health with co-morbidities as other age-related diseases such as diabetes take hold. For example, when the previous major killers, infectious diseases, were overcome by better medical care, improved sanitation, and the development of powerful antibiotics, an unintended consequence was an increased incidence of previously less common age-related diseases.

If we accept that age is a common risk factor for the diseases just discussed, slowing the rate of aging would be expected to result in a delay in the appearance of all or most of these age-related diseases, conditions, and ailments (Olshansky, Perry, Miller, & Butler, 2006). If, instead of addressing one disease at a time as if their etiologies were independent, we recognize that age-related biological changes are the main cause behind most age-related illnesses, then addressing the biological changes that drive the process of aging is much more likely to have beneficial effects for humanity (Miller, 2002). It has been calculated that even a small decrement in the slope of the aging rate could result in a significant increase in the proportion of life spent in a healthy disease-free state; a delay of seven years in the appearance of major age-related illnesses could result in a net increase of 50 per cent, based on the fact that age-related decline rises exponentially with age, with a doubling time of approximately seven years (Butler & Brody, 1995).

At this time, such a goal seems potentially within reach in the near future on the basis of results obtained in animal models. In most animal studies where general health has been evaluated in life extension studies, health span is also extended. Three examples include muscle function in *age-1* mutant nematodes (Herndon, Schmeissner, Dudaroneck et al., 2002), and cancer incidence and memory retention in growth hormone–deficient mice (Ikeno, Bronson, Hubbard et al., 2003; Kinney, Coschigano, Kopchick et al., 2001). However, most longevity studies have not been accompanied by robust health measurements, so we do not know whether life extension occurred in a healthy or diseased state. The major exception has been caloric-restriction studies in rodents, where it has been well documented that a 40 per cent increase in life span is accompanied by a delay in the onset of many age-related diseases (Weindruch & Walford, 1988). A very recent published study (Colman, Anderson, Johnson et al., 2009), shows that this is also the case for calorically restricted rhesus monkeys.

Studies with animal models have by now unequivocally demonstrated that longevity can be manipulated and increased not only by diet but by mutations and pharmaceuticals as well (Harrison, Strong, Sharp et al.,

2009; Warner, 2005). Whether a similar effect can be obtained in humans is far from certain, although a six-month clinical trial has shown that a 25 per cent reduction in caloric intake by overweight individuals does reduce fasting insulin levels, body temperature, and DNA damage (Heilbronn, de Jonge, Frisard et al., 2006). Calorically restricted primates not only exhibit some of the healthy physiological changes observed in calorically restricted rodents (Lane, Ingram, & Roth, 1999), but Colman et al. (2009) have shown that calorie restriction also delays the onset of many age-related pathologies such as cancer, cardiovascular disease, diabetes, and brain atrophy, and it also increases survival. Thus, by extrapolating from animal studies, it seems at least theoretically possible to postpone the entire range of age-related diseases in humans, leading to a similar extension of the period of healthy life as well. This concomitant effect at a variety of levels has been termed "the longevity dividend."

The longevity dividend concept refers to more than just health and well-being. A significant concern of developed societies is the potential economic impact of the impending onslaught of age-related disease and disability among increasingly aged populations that threatens to break our systems of pensions and health care in the not too distant future (Vaupel & Loichinger, 2006). The longevity dividend posits that, by addressing the basic biological causes of aging, humans could live longer productive lives. This would translate into tangible economic benefits, as people stayed in the work force longer, withdrawing less capital from pensions and the health care system. The economic implications of this are part of the dividend, and these have been discussed in detail by Olshansky et al. (2006).

The biggest hurdle to this somewhat optimistic scenario is that in spite of more than 30 years of research in many countries on aging, gerontologists have still not identified the most promising targets for intervention to slow the rate of aging in humans. The current subtle shift from an emphasis on life span to a new focus on health span may provide the paradigm shift that is required to slow the aging rate (Miller, 2009). The best targets are likely to be processes that affect multiple tissues and are central to maintaining both cell function and numbers. Some basic processes that seem most likely to be relevant include processes that can:

- maintain cell number by protecting both cell viability and cell replacement systems,
- maintain stress response systems that reduce or repair macromolecular damage incurred by both endogenous (e.g., oxygen free radicals) and exogenous (e.g., carcinogens) toxic agents,
- control inflammatory processes, and
- maintain proper balance between energy production, reproduction, and biosynthesis (Sierra, 2009).

If we do manage to postpone aging in humans, will new diseases and pathologies appear? This seems like a definite possibility just as it happened after infectious diseases were essentially eliminated as the major cause of death in industrialized countries. In general, while centenarians appear to die of the same array of causes as younger individuals, with perhaps a slightly lower incidence of cancer (Berzlanovich, Keil, Waldhoer et al., 2005), autopsies have shown that supercentenarians die with a high incidence of senile cardiac amyloidosis (Leslie, 2008), a pathology that rarely occurs in younger people. Thus, the prevalence of rare diseases could indeed increase as a result of significantly extending life span. Nevertheless, even if only half of the human population reaches 100 years, and then are afflicted with these same diseases, we will still have achieved the important goal of keeping individuals healthy until their 90s. This would be a remarkable achievement for modern medicine.

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