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Research into the Biology of Aging
Richard L. Sprott, Ph.D
Executive Director
The Ellison Medical Foundation

First the bad news: each of us will die and there is nothing we can do about it. You can safely ignore all of the hype from the anti-aging medicine and neutriceutical industries. One hundred and fifty or two hundred year old human beings are not likely any time soon.

The maximum lifespan of organisms is clearly genetically controlled. It is no accident that mice live a maximum of 4 years, dogs 20 years, and humans 120 years (121 to be exact, the age at which Mme. Calment died). It is possible to modify these maximum life spans somewhat with interventions. The most successful so far is through calorie restriction. For example, feeding mice a diet with reduced calories (65% of what they eat ad libitum) produces an increase of 15% to 30 % in lifespan. Similar results are obtained with many other species. It is important to note that this is calorie reduction with adequate nutrition, not starvation. The period of increased longevity does not produce a period of longer disability, but rather a longer health span. The animals die of the same diseases, they just do so later. This sort of result, if applied to humans, would not increase the cost of terminal disability. However, very few humans are likely to apply such a draconian regimen, and there is no proof that it would work anyway. On the other hand, understanding how controlled calorie restriction increases lifespan might lead to treatments that do have utility for humans. Achieving a better understanding of the mechanisms that control human appetite and metabolism could also help address the "obesity epidemic" in the U.S. Even so, this modification is tinkering around the margins. Species differences in lifespan show how much more powerful Mother Nature has been shaping life spans than have we with our current science. Does that mean we should abandon longevity research? Absolutely not. But it does mean we should have a clear idea of the objectives of that research and a realistic appreciation of what is really possible.

The increases in human longevity touted by the anti-aging medicine and neutriceutical industries are something quite different from the increases resulting from calorie restriction. The proponents of very dramatic lifespan extension (to 150, 500, or even 1000 years) believe, or purport to believe, that aging is a disease that can be "cured," or that it will be possible to replace or modify the genes which control longevity. If it really were possible to cure aging or "fix" longevity genes and thereby produce 150 to 200 year life spans, the societal consequences would be enormous. Fortunately, from a societal point of view at least, this is simply not going to happen.

What is likely, though, is that modern molecular science will continue to provide advances that allow more individuals to approach the species maximum lifespan. Average life spans in the developed world have increased from under 50 years of age in

1900 to nearly 80 years in 2000. The change is largely the result of improved sanitation in the early part of the last century, and the impact of antibiotics on infectious diseases in mid-century. The most likely impact of gene therapies and other molecular medicines in this century will be to continue this trend. The ideal result would be survival to the average species maximum, between 85 and 100 years, in good health, followed by a quick demise. Some real progress in this direction is quite likely by 2050. We are genuinely likely to see genetic approaches to drug development and use that will "tailor" drugs to the genetic makeup of the recipients. We will surely see great improvements and innovations in organ and joint replacement. This sort of development will make the lives of older people far more complete as the prospects of better functionality in late life increase.

Savings in health care costs from elimination or postponement of some costly degenerative diseases will almost certainly be offset by the larger numbers of individuals who will live longer more productive lives, yet in the end suffer the same end of life diseases. Even without any of these possible medical breakthroughs, life expectancy at birth in developed countries is likely to increase by 4 to 5 years by 2050. Developed country age related health expenditures are likely to rise, on average, by 6 to 7% over the same period.

So, the question then becomes how do we maximize the benefits of modern biology and behavioral science and find ways to afford potential miracles? It seems to me that the best hope is to invest a much greater proportion of our aging and health related budget in solid basic science. Only basic research can lead to the prevention or elimination of the costly chronic and debilitating diseases of later life. Investment in better health care will certainly lead to improved health and wellbeing, and that is surely important, but it won't change the underlying biological processes that lead inevitably to decline. Basic research, that reveals the underlying processes, can do that, and the investment would be repaid handsomely.

Similarly, the most effective interventions available today are behavioral. Mom was right. The most effective ways for an individual to improve late life health involve behaviors like giving up smoking, losing weight, and fastening seatbelts. Research that provides more effective approaches to behavioral modification as well as better understanding of the interactions between biology and behavior would surely provide significant payoffs far exceeding their costs.

We are in the midst of the most exciting and important scientific era in the history of the world. I finished graduate school 40 years ago, and virtually everything I do scientifically today is the result of discoveries made since then. Many of the important discoveries for aging are the product of research undertaken in the last decade. The pace of discovery is increasing at dizzying speed. While this is sometimes disconcerting, the opportunities for improving the human condition are mind boggling without having to imagine 150 year old or 500 year old humans.

The completion of the human genome project has given us the tools to truly understand how our genes interact with our environment (including lifestyle) to affect how long and how well we live. While I don't think we are going to see 150 year old humans any time soon, I do believe that we will find new, effective therapies for age related diseases.

Drugs will be designed to match our genetic makeup so that they are both more effective and less likely to have adverse side effects. For some diseases we will be able to provide replacement genes or gene products to compensate for our own "defective" genes.
The very basic research that underlies these possibilities is providing understanding of the myriad ways our bodily systems interact. For example, research on how telomeres (DNA at the ends of chromosomes), might determine the lifespan of cells, connects with research on the involvement of telomeres in cancer and may explain the strong link between aging and cancer.

Let me expand briefly on the telomere example as it nicely illustrates the potential of modern genetic research. Telomeres are DNA sequences at the ends of chromosomes. The description I am about to give is an over simplification of the relationship of telomeres to aging, but it does suggest how telomeres, aging and cancer might be inter-related. In 1965 Leonard Hayflick discovered that cells growing in culture had a limited lifespan and at the end they entered a state called cell senescence. There was at the time great hope that if we could understand this cell senescence, we would unlock the secrets of aging. More than 20 years later we seemed to have made no progress answering those questions. Then Elizabeth Blackburn showed that when cells divide, telomeres shorten. This shortening is often compared to removing beads from a string of beads as pieces of DNA drop off at each division. Whether telomere shortening actually leads to senescence or not has been the subject of nearly endless controversy. Providing an enzyme called telomerase to the cells prevents telomere shortening and senescence. Many tumors are composed of immortal cells. In fact, immortality at the cell level results in death of the host organism. These cells appear to become immortal when DNA damage results in the loss of senescence capability. While normal differentiated cells do not have active telomerase, most tumor cells do. The possibilities that arise from these observations are quite staggering. Manipulation of telomerase levels could conceivably be used to produce longer cell life by adding telomerase to some cells, thus perhaps keeping organs functioning longer, or to provide a silver bullet for cancer by selectively removing telomerase from tumor cells. This is just one of many examples of potential applications of our new knowledge and tools to the improvement of the human condition.

One outcome of increases in our knowledge will be better "health span." Another will surely be increases in hype, charlatanism, media confusion, and policy controversy. We can view our aging population as a collection of "greedy geezers," as a resource of wisdom, or something in between. It is in the best interests of all us that we begin now to discuss what is realistically possible and how we will deal with the inevitable effects on our society. What we do now surely will have impact on what happens and how it impacts our lives. The changes are coming. We can either meet them prepared or let them overwhelm us. The best way to prepare for those challenges is through research and increased knowledge. The White House Conference on Aging is ideally situated to stimulate the processes of discovery and discussion that can mean the difference between real progress and hype.