Statement to the Senate Special Committee on Aging from David Morgan, PhD.

Dear Committee Members

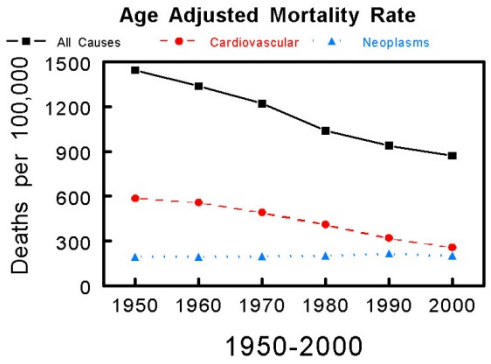
I am David Morgan, PhD, Director of the Byrd Alzheimer's Institute at the University of South Florida and Distinguished Professor of Molecular Pharmacology and Physiology. The Byrd Alzheimer's Institute is an Interdisciplinary Translational Research Center based in Tampa Florida. The Institute activities include Basic Science research, clinical research, clinical patient services, and educational services to caregivers and health professionals. I have a long history or research in aging and neuroscience starting at the Andrus Gerontology Center at the University of Southern California in the 1980s and continuing to this day at the University of South Florida. I am also the Lead Representative of an organization called ResearchersAgainstAlzheimers, an advocacy organization of active scientists with over 400 current US members. Below I respond to the Suggested Panel Questions

1. How have sequestration and financial uncertainty impacted aging research? It has clearly diminished the capabilities of many centers engaged in such research. Both across the board cuts to existing grants and reduced funding rates for new grants have a discouraging impact, particularly on the next generation of researchers. A number of laboratories have increased their activity in contracts with industry and grants from private foundations, but these cannot fill the void left by reduced support from the NIH. Some investigators have either closed their laboratories or, in some cases, returned to their home countries due to a better funding environment than in the US.

2. Expectations for the summit. First I believe it will highlight the benefits of engaging in basic and clinical research into the aging process. The arguments were made in the 1980s that for the purposes of the greatest extensions of life span and health span (aging without morbidity), slowing aging would have greater benefits than eliminating major diseases. Second, I believe we will see there have been considerable enhancements in both lifespan and healthspan over the last half century. This may now be slowing, as less healthy generations enter the retirement period.

3. Views on balancing research in the underlying process of aging with the need for funding disease specific research. If we can gain insight into the basic mechanisms of aging, it would have more impact on lifespan that disease-specific approaches. However, this occurs largely in the realm of preventing the onset of diseases associated with aging. Slowing aging will likely have minimal impact on those who already have contracted such diseases. For people with dementia, who have lost any sense of self-identity, it would probably be ethically inappropriate to extend their lives by slowing their rate of aging.

It is important to recognize the considerable benefits that have come from disease-specific research. The figure to the right shows the age-adjusted mortality rate (that is, takes into consideration the overall increase in longevity) for All Causes (solid black line) cardiovascular disease (dashed line with circles) and cancer (dashed line with triangles). Data are from the National Center for Health Statistics. This shows that our investment in cardiovascular disease research has cut by 50% the risk of dying from heart disease at a specific age. People are still dying from heart disease, but from congestive heart failure in their 70s and 80s instead of heart attacks in their 50s



and 60s. I fact most of the overall reduction in mortality can be accounted for by changes in heart disease deaths. Only after 2000 has cancer research started to show reduced mortality, 30 years after launching the War on Cancer.

I believe that aging has a major impact on the development of chronic degenerative diseases that have antecedent pathologies over decades before the damage reaches the stage of producing symptoms. These include disorders such as diabetes, cardiovascular disease, chronic obstructive pulmonary disease, Alzheimer's disease and cancer (among many). Fascinatingly, the major lifestyle risk factors for most of these diseases (beyond your number of birthdays) are all the same lifestyle choices. Obesity, blood lipid profiles, blood sugar levels, smoking, exercise are known to increase the risk of all of these diseases. I suspect this is because these activities are modulating the rate of aging, rather than directly impacting specific disease risk factors. Unfortunately, it is very challenging to randomly assign folks to these lifestyle choice groups randomly and at known dosages. Thus we will never be able to prove their aggregate benefits directly, or determine if the impact might be on aging *per se.*

4. Is NIH funding initiatives for the delayed aging model? Yes. I presently serve on a review committee for the Interventional Testing Program to identify agents that can be administered which might extend the lifespan of mice. This is a very rigorous program that has identified one agent, rapamycin that can extend longevity. On this basis it is argued that this slows the aging process. Over 20 other agents have completed testing or are in process. This is a highly objective means to try and identify chemoprevention for aging. However, expanding to other species that may have causes of death different than those of mice would seem a good use of funds. Research on caloric restriction and caloric restriction mimetics continues to receive such funding. Unfortunately, the studies in nonhuman primates had inconsistent outcomes, and these were long and expensive research studies. This leaves open the question regarding caloric restriction and longevity in humans.

5. How would NIH consider partnership with industry? Most certainly it would. A fine example of the government, industry and private philanthropic partnership is the Alzheimer's Disease Neuroimaging Initiative (ADNI). Almost 1000 publications have come from the data collected in this very large multicenter study. This is an example of the "precompetitive " research space, where the pharmaceutical industry sees that all can gain benefit before competing with specific proprietary drugs. These are ideal relationships.

6. How has the delayed aging model been received by the medical and academic research communities? I have been aware of the argument since the 1980s. Extending overall longevity has considerable advantages in improving individual productivity and quality of life. A key unanswered question is the purported compression of morbidity. Will this happen or simply be extended to the same degree as the overall extension of the lifespan? There is little current evidence.

7. What are some of the major concerns in researching the delayed aging model? Perhaps one of the most vexing is how to measure "aging". One means often used is longevity, but this is often biased due to species specific causes of death in different test models. There are a large variety of potential biomarkers of aging that shift throughout the lifespan. A collection of these might be used to more rapidly assess success or failure (without requiring death of subjects). But, these may be difficult to agree upon. With the possible exception of caloric restriction, we do not have any agreed upon means of slowing the aging process. These models would have to be developed and validated. Another concern is that whatever might be used as a chemopreventive of aging, it would have to be extremely safe. We would propose giving this to perfectly healthy young individuals. In the early days of caloric restriction studies, it was not uncommon for 5-10% of the cohort to succumb when the restriction paradigm was imposed. This has improved, but what fraction of the population having side effects would be tolerated for an anti-aging chemopreventive approach (we have some data

regarding aspirin and the risk of heart attack, with a recent study arguing the benefits in women do not outweigh the liabilities).

8. What are the ways technology could be used to advance the delayed aging model? Not an area of specialization for me. I think the use of very large datasets, and aggregation of well characterized clinical data (in easily queried databases) would be very useful.

9. Could delayed aging health cost savings be enhanced using technology? I would have to see specific technologies proposed to have an opinion here.

10. Do you envision public private partnerships to develop technology to develop drugs to slow aging? Absolutely. Industry is decreasing its funding of internal basic research in part because of costs and in part because of the success of the public sector in this area. Universities are investing in drug development centers to move prospective agents into early stage development, leading to biotechnology spin-offs and, if fortunate, licensing for clinical trials by major pharmaceutical companies.

11. How important is prioritizing efforts to find interventions to extend healthspan right now? This is very challenging question. I believe we have made important advances in benefiting the lives of people who have contracted age-associated degenerative diseases. This has come from specific and targeted investments. There are millions of American suffering from chronic degenerative disorders today. Ignoring them would be very challenging and a little heartless. The benefits of delayed aging are, at least for the present, theoretical. We do not know that morbidity will be compressed, which might just extend suffering. The beneficiaries will be those future generations, not the ones presently paying into the research pool. Even the tools to measure aging *per se* are not fully agreed upon. In the 1980s when I worked in Tuck Finch's laboratory, we never did a survival study, because he did not believe that death was aging. I will admit as one who studies an age-associated disease, I have a personal investment in this regard that may influence my opinion. However, I did study fundamental processed of aging while at the Andrus Gerontology Center. While the field has advanced considerably, there is no clear Roadmap to seek these purported means of slowing the aging process. I believe the present balance is probably about right.