TESTIMONY OF

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I. Context

The research outlined below stems from two sources. One is the Senate hearing on the fiscal stability of the Social Security Trust Fund relative to forecasts of mortality held in 1983 (Manton, 1983). This arose out of the fact that Social Security actuaries had not anticipated increases in male life expectancy after a period of stagnation 1954 to 1968. The anticipation of future increases in life expectancy might have been based simply on the observation of female life expectancy, which continued to improve unabated over the same period. Apparently, one reason for the failure to anticipate mortality changes was due to the SSA actuaries' reluctance to anticipate the growing role of women in the U.S. economy.

The connection here to Medicare is that the SSA life expectancy and population forecasts are directly used in Medicare cost projections. Thus, SSA forecasts are the demographic basis for Medicare projections. What would be strange to an economist is why the investment in health does not affect the SSA forecasts; i.e., why is population and health change exogenous to Medicare expenditures (and health forecasting).

We believe this is the fundamental error in the system. The rest of the discussion provides evidence of the problems this has engendered for a very long time, as well as our approach to fixing the problem; i.e., using biological and health data to construct the feedback between population and health – and a myriad of good and bad things that flow from this linkage.

Ultimately we believe that by constructing a realistic bridge between a population and health model much of the pessimism about Medicare expenditures can be dispelled and many new options identified that are not simply policy driven, i.e., tax increase/decrease or increases and decreases in Medicare benefits. We wish to project the true product of Medicare expenditure (and NIH investment) on the health and functioning of the U.S. elderly population into the future.

Moreover, it is not sufficient to predict mortality and life expectancy changes but, as recognized by WHO, quality of life – which is strongly associated with the available human capital in an aging population and economic growth and productivity (discussions with Greenspan, December 20, 2000, at Washington D.C. Federal Reserve Bank). It is in this context that the National Long Term Care Survey (NLTCS) was planned during the end years of the Carter administration (1980) and implemented during the Reagan administration (the NLTCS was made longitudinal in 1984 and conducted again in 1989). The NLTCS addresses the major reasons that more aggressive steps for altering the Social Security normal retirement age and for modifying the Medicare Program were not taken in 1982; i.e., lack of data in 1982 on how functionally capable and healthy were survivors to later ages (Feldman, 1983). Indeed, in 1982 it was unclear even how to conceptualize the linkage of survival and health (Fries, 1980; Manton, 1982).

Now that we have 18 years' worth of NLTCS data, 1982 to 1999 (and soon 23 years with the 2004 NLTCS) – linked to Medicare records, with clinical diagnoses and bills – we can begin to systematically address that question; i.e., how rapidly does life expectancy increase relative to the portion of life expectancy in a wholly functionally independent state without severe medical problems? Furthermore, we are making projections under our current NIA funded research that include that information and, in others of our projections, information from the most comprehensive and recent longitudinal epidemiological data sources; e.g., the 46 year follow-up from the Framingham Heart study and data on genetic and protein biomarkers to be drawn from biological specimens collected in 1999 and in an enhanced 2004 (and planned 2009) NLTCS.

The biomarker data could assess future treatments that could drive future Medicare re-imbursement systems to improve human capital in the U.S. to stimulate future GDP expansion.

II. The 1982 to 2004 National Long Term Care Survey and Biomedically Motivated Forecasting Models – the Tools.

At the Center for Demographic Studies at Duke University I have been the P.I. on cooperative agreements with HCFA/CMS to study the 1982 and 1984 NLTCS and then P.I. on NIA grants to conduct the 1984, 1994 and 1999 NLTCS and to analyze changes in the human capital present at later ages in the U.S. population aged 65+. In the course of these projects we have developed both an evolving (but with a stable core) data collection strategy plus a number of analytic tools to model, and forecast, health changes and health costs of the elderly U.S. population.

The fundamental finding of the NLTCS is that chronic disability above age 65 has consistently declined in the U.S. population from 1982 to 1999. Indeed, the rate of change has accelerated. It was 1.7% from 1982 to 1999. But it was 2.6% from 1994 to 1999, i.e., the fastest decline is in the most recent survey cycle. Evidence of any decline was controversial in 1982-1984 because it was then assumed that, as life expectancy increased, so did the period of time the individual spent in decline and decay, i.e., "pandemics" of chronic disability and disease (e.g. Kramer, 1980) which were assumed to be associated with the social and ecological stress of modern industrial states (Omran, 1971). I did not believe in this (Manton, 1982, 1989).

This pessimism prevented the Greenspan commission from recommending significant action to deal with Medicare and Social Security issues with a two-year increase in retirement age delayed to 2000 and then only phased in over about a 22 year period. It was felt that there was insufficient national data to justify any more of an increase; i.e., it was not known how health and function had changed as a process as life expectancy increased (Feldman, 1983). Consequently, when we published about a decline in the 1982 to 1989 NLTCS a *National Academy of Science* panel was convened to study its validity. The report (Freedman and Soldo, 1994) suggested that the evidence was interesting but that one should wait until the 1994 NLTCS before concluding a positive trend existed.

When the trend towards a decline in disability was strengthened with the results of the 1994 NLTCS, it became difficult to ignore the evidence – and serious consideration of the fact of a disability decline started. Indeed, the decline was so rapid 1982 to 1989 that, in order to have sufficient respondents to our detailed community interview in 1994, we had to:

a) oversample 1200 elderly who were not disabled,

b) add in variables to assess higher degrees of physical and mental function.

We also included important measures such as nutrition, exercise, and risk factors to begin to determine how to intervene in the aging process and promote the decline in disability.

The value of the time series on disability greatly expanded in 1999 because we had two time points (1994 and 1999) with detailed clinical diagnoses (ICD-9) and because we added biomarkers (blood and buccal cell samples) for approximately 2700 persons. This means we could look at clinical and biomarker correlates of the trends in functional disability, and we had the necessary data to determine how medical management, and even molecular medicine, could influence future disability trends. With Medicare records, we had the tools to determine how to revamp the Medicare Reimbursement System to promote adoption of new effective therapies and treatments. Further, we now had evidence of a 1.7% decline in disability over 18 years in a

follow-up of 42,000 individuals – enough to begin to convince actuaries that there was something to pay attention to (Stallard, 2004).

Recognition of this success evidenced by long-term declines in disability was shown by the interest of OECD, the G-8 and U.S. policy makers in the declines in the Denver, Colorado meetings. A crucial observation in the 1999 NLTCS was to confirm:

a) declines in the use of institutional care in the U.S.;
b) declines in serious disability (ADL) in the elderly population;
c) identification of sources of large declines in severe cognitive impairment at late ages, and, most important;
d) that for the growing non-disabled elderly population there were declines, inflation adjusted, in per capita expenditures in Medicare 1982-1999 (especially for males 65 to 84).

Many of these results will be examined in the 2004 NLTCS that is now in process.

The following sections will cover these topics in greater detail starting with the provision of evidence of the undue pessimism of SSA and Medicare (because they are driven by SSA projections and don't reflect a feedback of health status) forecasts about the current and future health state of the U.S. population. In each argument we will bring in supporting data to examine why the basic demographic trends on mortality have been misinterpreted and not well anticipated.

III. SSA Modeling of U.S. Mortality Trends; an Evaluation of Underlying Health Dynamics

The initial failure to accurately project increases in U.S. life expectancy by SSA and Medicare actuaries was due to increases in male cardiovascular disease risks (increases paralleled in Britain with male life expectancy increases there occurring to about 1964 (Kaplan and Keil, 1993; Manton, 1999). This view was so extreme as to posit (Table 5: Bayo and McKay, 1974), in the 1974 SSA projections, an ultimate biological limit to human longevity of 69.0 years for males and 76.9 years for females, to be reached in the year 2000 (Myers, 1981).

The facts are quite different. SSA life tables indicate a life expectancy of 74.0 years for males and 79.4 years for females for 2001. The values for 2001 from NCHS were 74.4 years for males and 79.8 years for females. Life expectancy increased a further 0.2 years to 2002. Thus the 1974 SSA "ultimate" life expectancy values projected to occur in 2000 were 5.0 years too low for males and 2.9 years too low for females – over a period of 26 years. These are huge projection errors for the Social Security and Medicare programs for mid-range projections.

In Figure 1, adapted from NVS Reports, Vol. 52, No. 14 (p. 4), we see very rapid increases in life expectancy that show no signs of abating (especially for white males). If the mortality trends are so consistent, why did the 1974 SSA life expectancy projections differ so much from the facts in 2000? This is because the SSA actuarial procedures essentially ignore empirical data trends after 25 years, using instead "ultimate rates" based on "expert opinion". This is basically a philosophy of "good things eventually fail".

IV. Some Epidemiological Evidence about Cancer Mortality Trends and Forces Shaping Them

Of interest is the timing of the reversal of mortality increases (life expectancy declines) relative to the Framingham Heart Study (NHLBI) which was started in 1948, with several other

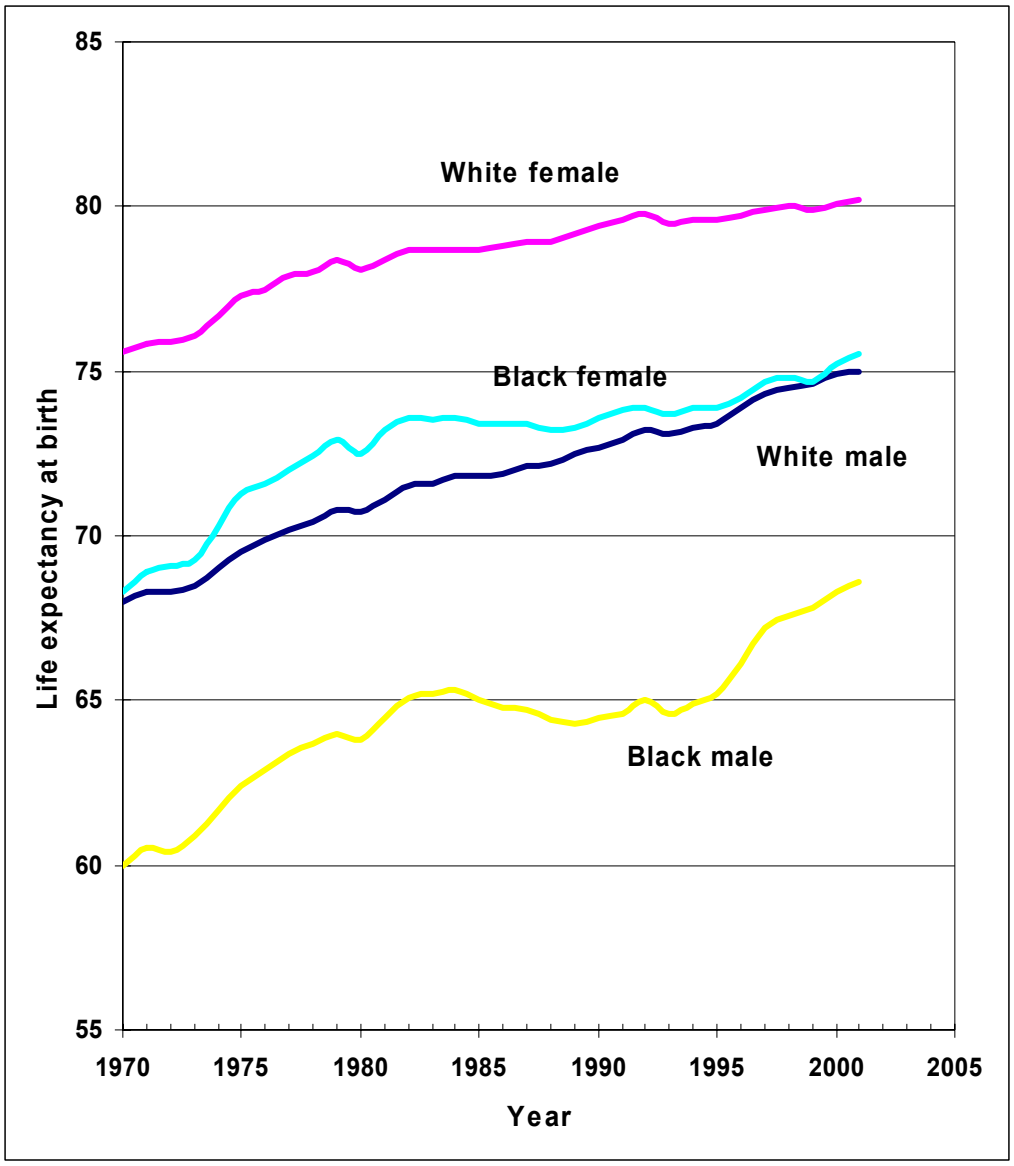


Fig 1. Life expectancy at birth by race and sex: 1970-2001

longitudinal cardiovascular disease risk factor studies starting later (e.g., Charleston Heart study about 1960; Kaplan and Keil, 1993). The first significant findings about circulatory disease risk factors were probably available in the Framingham 10-year follow up (i.e., 1960) which was followed by the above-noted reversals of male cardiovascular disease mortality increases about eight years later (1968-1969). This major mortality turning point was not only not anticipated by SSA actuaries, but they did not accept the evidence on the turning point until 1978-1979. This acknowledgement of the change is roughly concurrent with the convening of Senate Finance Committee hearings (see Manton, 1983) and the Greenspan Commission.

Twenty-two years after the Framingham Heart study was started, the NCI "war on cancer" was initiated by President Nixon (1972). The war on cancer was heavily criticized as not being effective in changing adult solid tumor mortality, both 14 years after the war started (Bailar and Smith, 1986), and even after major cancer mortality declines started in 1990 (Bailar and Gornik, 1997).

This could be partly attributed to a defect in the procedures by which cancer drug therapies were developed; i.e., candidate drugs were tested on one set of rapidly growing cell lines such as childhood leukemia. Thus, it was no surprise that the first therapies were most effective against childhood leukemia and adult lymphomas. In about 1978, the screening panel was modified to contain breast cancer and other solid tumor cell lines (Weisenthal, 2004). After this occurred, progress started to be made against rapidly growing hormonally dependent tumors (e.g., breast and testicular cancer), and even later, colorectal cancer.

One fundamental reason that some tumors remained resistant to chemotherapy was that the theory of pharmacogenesis (Gonzalez and Nebert, 1990) suggests there was co-evolution of plants and animals, i.e., plants developed toxins so as not to be eaten and animals developed physiological mechanisms so as not to be poisoned. The protective mechanism in animals involved a gene coding for a glycoprotein that pumped water-soluble toxins out of cells (Gottesman, 1989). Thus, digestive organs like the stomach, liver and kidneys were resistant to water soluble compounds. As a consequence, lipid soluble agents had to be developed (e.g., liposomal delivery of doxorubicin) and alternate cell structures attacked; i.e., taxol and taxotere attacking the proteins forming the cytoskeleton. This made therapy far more effective.

In 1983, an article in the *New England Journal of Medicine* questioned the use of cell sensitivity panels, so this type of test became unpopular. The most appropriate, and effective, use, however, seems to be testing of drugs against a patient's own tumor cells from biopsy, which may increase therapy efficacy by up to 20 fold (Weisenthal, 2004). By doing so, a postulated 20-fold increase in the therapeutic efficacy of current chemotherapy regimens could lead to further major breakthroughs in cancer patient survival.

The technology exists today to do this very cost effectively (e.g., use of micro array genetic screening procedures; automated testing of sets of tumor cells from a biopsy to multiple chemotherapy agents). What was needed was to pair the technology for the biopsy assessment with new candidate (for the person) drugs and basic biomedical research, and theory, on cell metabolism and proteomics and intracellular molecular dynamics (Manton et al., 2004; Hai and Manton, 2004; Hai et al., 2004). The issue is to merge this research and theory on the cellular (and intracellular stochastic molecular) micro level with epidemiological and demographic data on the meso (individual) and macro (population) level. This is the thrust of our current intra-disciplinary research program at my Center for Demographic Studies, e.g., Manton et al., 2004, which involves a mix of M.D./Ph.D.s, physicists, mathematicians, computer scientists, and economists totaling 35 to 40 persons. I believe this is a unique combination of talent and data resources directed to a well thought through research strategy.

V. Social Correlates of Trends

Associated with these "macro" mortality trends and biomedical innovations were social changes. Stomach cancer in the 1930's was the most prevalent tumor type of death, partly due to the presence of *H. pylori* in water in rural farm communities (e.g., Minnesota). As water quality improved, stomach cancer dropped from the number 1 cause of cancer death in 1930 to number 6 in the 1990's. Concomitant with this were rises in lung cancer mortality due, in part, to the provision of cigarettes to soldiers in W.W. II. The 1962 Surgeon General's report altered U.S. cigarette consumption, so that the peak lung cancer mortality for males occurred in 1995 – with attendant cost consequences for Medicare.

The point is that the use of biological, epidemiological and demographic data, in models that use those data in a biologically consistent fashion, can predict mortality turning points for the Social Security and Medicare trust funds. This is not now done, nor is it planned, though I recommended it in my testimony at another Congressional hearing (Manton, 1999).

In 1999, I was present at hearings held by Representative Nick Smith of Michigan in a closed door session with Dr. Haseltine (a biophysicist, formerly of Harvard University and now CEO of Human Genome Sciences) and the Social Security actuaries (Manton, 1999). The topic was the inability to predict major changes in mortality and how much life expectancy could increase and over what time. In that hearing I repeated much of what I said in 1983 – and now I am repeating much of what I said in 1999.

What I presented at that hearing was the use of Framingham data, and longitudinal data from the 1982 to 1989 NLTCS, to develop scenarios by which U.S. life expectancy could increase to 90 to 95 years (Manton et al., 1992, 1994) with a larger proportion of life span spent in active states. Our models have increased greatly in scientific sophistication and information content since then.

The 1982 to 2004 NLTCS survey records linked to Medicare records, and to biomarker data, may be more information rich than the simple time-to-death distributions exploited in actuarial forecasts (Manton et al., 1992, 1994). Since then we have made great strides in both the linkage of multi-faceted longitudinal data sets and in modeling (e.g., addition of biomarker data to the 1999 NLTCS).

VI. The Combined Effect of Biomedical and Social Forces on Recent Cancer Trends

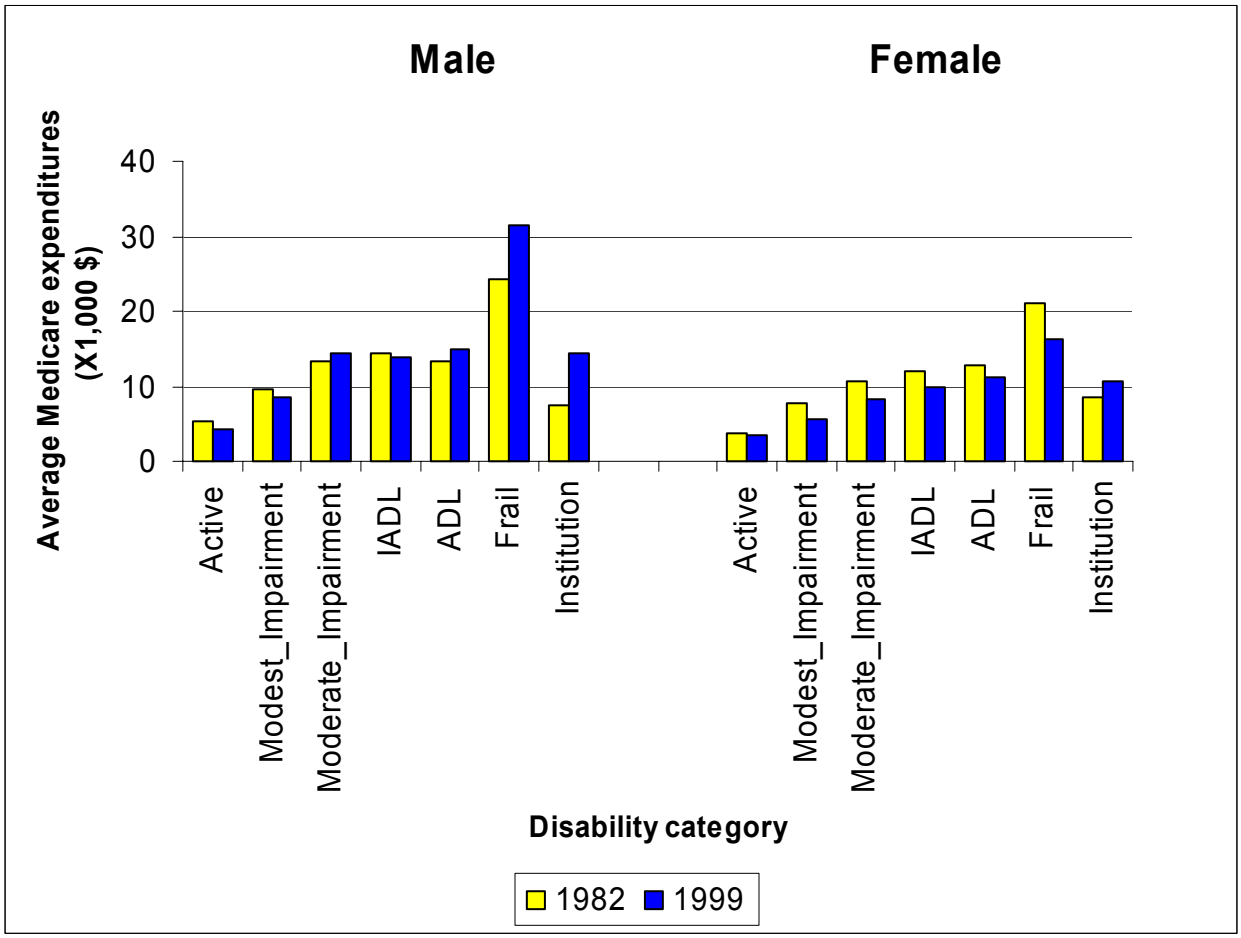
As a consequence of public health (stomach), social (lung, smoking trends) and medical (breast, age at first birth) factors, total cancer mortality started to decline in 1990 (even before the peak in lung cancer mortality and long before Bailar and Gornick, 1997). Certain types of cancer declined much earlier. The declines continued to at least 2002. CDC indicated that cancer incidence dropped 0.5% 1991-2001 – possibly an underestimate due to improved screening procedures. From 1993 to 2001, cancer mortality rates dropped 1.1% per year. Thus, about half of the decline appears due to public health measures and cancer prevention and half due to improvements in treatments – NCI funds both types of efforts. However, much more could be done in treatment if best available technologies were used in general practice (e.g., Weisenthal, 2004). Cancer is thus another example of a major mortality turning point that was missed by the SSA actuaries, but which was predictable from a multi-faceted biologically and medically informed analysis. Obviously, if one relies on mortality data alone, one can never anticipate such crucial turning points; i.e., they will only be recognized after 10 to 15 years because there is no information on health changes prior to death.

VII. Active Life Expectancy – A Crucial Innovation

Our research suggests vital statistics and Census data may have produced a serious underestimate of the benefits of investment in biomedical research at NIH, as well as in the health care delivery system of the U.S., including Medicare. As a further consequence, it misses identifying a very reasonable, positive way to significantly reduce Medicare and Social Security funding problems. Indeed, financial and demographic factors may demand it. For one, the decreasing age of retirement in the U.S. has reversed (Burkhauser and Quinn, 1997) and is

apparently continuing to increase. There may be significant underreporting of employment of low income elderly who work in service occupations to supplement Social Security payments. An economic incentive to the more affluent to continue work is that the debt burden of the U.S. elderly population has apparently started to increase – a powerful incentive to continue employment.

Actually, the global effect involves four factors: a) declining disability (e.g., Singer and Manton, 1998; Manton and Gu, 2001); b) decreasing inflation-adjusted Medicare costs for non-disabled persons and increased Medicare costs for severely-disabled persons (see adaptation in figure 2 of Figures from the Harvard University Conference, Boston, Massachusetts, April 28, 2004); c) increasing employment over age 65 (Burkhauser and others); and d) improving scientific productivity of NIH (e.g., Tolley et al., 2004 and other papers) in new econometric and demographic models using NLTCS and Medicare data.



1982 data was adjusted by Consumer Price Index (CPI) for medical care services for the U.S. city average; data from DOL (5.9% per year).

Fig 2. Average Medicare expenditures and the distribution of person by seven pure types (after mortality adjusted): Age 65-84.

In Figure 2, the bars to examine are the left-most pairs labeled "active" which, in the 1982 to 1999 NLTCS, are increasing at a high rate (1982 to 1999 by 1.7%; 1994 to 1999 by 2.6%); a

rate accelerating to at least 1994 to 1999. Medicare costs are declining within the growing non-disabled population, with the largest (inflation-adjusted) declines for males aged 65 to 84. Overall, we estimate this saved 26 billion dollars in Medicare expenditures in 1999 alone.

Medicaid is also strongly affected by declines in severe disability and nursing home use. This may have reduced LTC costs of the elderly by another 4 to 5 billion dollars in 1999. Thus, the combination could have reduced combined Medicare/Medicaid costs 30 or more billion dollars in 1999 – more than enough to pay for the entire NIH budget – without considering the $60 to $90 billion dollars' increase in federal tax revenue due to increased participation of persons over age 65 in the work force under the current projected changes of the normal retirement age to 67 (Tolley et al., 2004). Further increases in this age could have tremendous additional benefits.

Our econometric models show that at an interest rate of 7%, the "optimal" investment in NIH research is about $60 billion. Our results indicate that, at an interest rate of 4%, the "optimal" (to stimulate economic growth) investment is several hundred billion dollars. At 1% the optimal rate of investment is higher. This is simply common sense. Rather than let money stagnate at 1%, investment in any enterprise that reasonably advances economic productivity would be welcome (Tolley et al., 2004).

Our studies of the 1994 and 1999 NLTCS indicate that the institutional population is an area of remarkable improvement. Not only did the number of persons in nursing home beds decline from 1.74 million in 1994 to 1.42 to 1.46 million in 1999 but the number in traditional nursing homes declined to 1.2 million persons, with about 250,000 nursing home beds in graded care, assisted living facilities (not present in 1994 – a new residential option emerging because of the effects of the 1988 Catastrophic Care Act on Medicare Home Health Agency use and the re-focus of nursing home care on post-acute care – not residential). Geriatricians I have discussed this with (e.g., Dr. Bruce Kinosian of the University of Pennsylvania) suggest that, of the remaining 1.2 nursing home beds, good quality care could reduce long term care nursing home patients by 65 to 75%, paralleling the proportions found in the 800,000 assisted living residents in 1999. This is an interaction of economic growth, social change, and geriatric medicine (much of which was funded by NIA and the V.A.).

VIII. Some Possible Strategies to Innovate, and the Potential Leverage of NIH Research, on Economic Growth

a.) Research on Aging

Both basic science studies of aging and epidemiological studies of aging have yielded tremendous insights into how to modify and slow, or even reverse (Regenerative Medicine), the effects of time on human physiology.

Epidemiologically, it has been found that, at advanced ages, the incidence of cancers, osteoporosis, and Alzheimer's disease slows. This could be due to an advanced age "selection of the fittest" (e.g., centenarians are generally relatively healthy as a group relative to the population at age 80 – 89; see NIA centenarian studies). Or it could be due to the aging process in average persons changing at very advanced ages. For example, cancers are rapidly growing cells. They are most lethal in children, where the entire body is rapidly growing. In young adults, germ cells (e.g., testicular cancers) are selectively rapidly growing. At late ages, many types of cells are in "replicative senescence;" i.e. fully functional but only slowly dividing.

Thus, this phenomenon may not be due to selection, but rather to adaptational consequences of senescence for metabolism that is genetically programmed.

Research also tells to reject the classic genetic paradigm of disease. One of the biological scientists at our center (Professor M. Golubovsky) is an expert in stochastic epigenetic changes (Golubovsky and Manton, 2004a,b). An understanding of genetic transmission ($DNA \rightarrow RNA \rightarrow protein$) as modifiable is an area of specialization of the theoretical organic chemist on our staff (Dr. S. Volovyk) whose specialty is free radical theory. He has worked with me on how to modify damage associated with gamma radiation and incorporated radionucleides (Manton et al., 2004) in neurodegeneration. This is of interest in that, in Ukrainian studies of Chernobyl, cancer was not as important as accelerated aging of the circulatory system and the brain. I have postulated that modification of osteoporosis drugs could prevent uptake of the most damaging radionucleides (Sr^{90}). Research at the University of California at Berkely on the use of alpha lipoic acid (a special anti-oxidant) and N-acetyl carnitine could reduce the Chronic Radiation Syndrome effect of radionucleides' exposure and reverse decline of energy produced by age related decay of mitochondrial efficiency (Walter et al, 2001; Liu et al, 2001; Hagen et al, 2001). I have started to examine this at a fundamental level in a thyroid-based model of human senescence (Manton, 2004a). This leads to the next suggestion of how to better leverage NIH research dollars.

b.) Better Use of International Data on Human Population Exposures (e.g., in former Soviet States)

One approach to leveraging NIH research is the production of international collaboration studies. For example, one could use large international investments in major, but tragic, human population exposures to stressors such as the effects of low-dose ionizing radiation on neurodegeneration and circulatory disease in Chernobyl (followed 1986 to 2004 in the Ukraine, Russia, and Belarus). The Soviet/Russian investment in these longitudinal studies is irreplaceable and, if the same exposure conditions existed today (e.g., nuclear terrorism; radioecological pollution due to reactor dismantling or failure of radionucleide storage systems), would cost billions of dollars to replicate. These are large-scale, natural human laboratories to study specific diseases and fundamental biological processes related to aging (and most chronic disease) such as inflammation (e.g., IL-6 and the increase in inflammation with age, Cohen et al., 1997).

c.) Potential Effects

Such studies could lead not only to the preservation of human capital, but also to the regaining of function, as suggested by Dr. Haseltine in the 1999 hearings, by promulgating the notion of using human growth factors (proteins and enzymes) to control disease and regain function. For example:

a) Remicade, a TNF-α inhibitor may "cure" rheumatoid arthritis by "resetting" the immune system. It is of great benefit in ulcerative colitis – and possibly multiple sclerosis.
b) Evidence suggests that supplementation with Vitamins C and E and low dose aspirin may prevent most Alzheimer's disease (Zandi et al, 2004). In't Veld et al. (2001) found that ibuprofen (Advil) use may prevent 80% of Alzheimer's disease if started before disease onset (see Manton et al., 2004 for discussion of possible mechanisms).

c) Exercise and nutritional supplementation (e.g., calories and select amino acids – glutamine, arginine) may modify such factors as endogenous growth hormone release.

d) Even the health effects of chronic exposure to low dose, endogenous radionucleides (e.g., ingestion of ^{90}Sr and ^{137}Cs) can be prevented by a) preventing the operation of bone-building cells during exposure to the radio-nucleides (say by re-engineering osteoporosis drugs) or b) eliminating chronic radiation syndrome effects by ingesting alpha lipoic acid and N-acetyl-carnitine (an anti-oxidant and a fatty acid metabolizer) – effects that could even reverse the signs of aging (Liu et al., 2002; Walter et al., 2002; Hagen et al., 2002, etc.).

d.) Strategies

Our preliminary studies with the NLTCS and economic simulations (Tolley et al., 2004) suggest that health costs will decrease if NIH research sponsors a wide range of new areas of investigation in human populations. With the recent doubling of NIH budget, proposals to diversify research are essential if the economic stimulation of the NIH funding is to be realized. The goals must be to improve diversity of research, benefit the nation's health, increase human capital (not only in the elderly, but also to reduce Medicaid expenditures in younger populations), improve the fiscal status of Medicare and Social Security, and stimulate the U.S. total economy. These factors, of course, will have to be related to tax policy and other initiatives to foster use of growing late-age human capital (including intangibles such as providing long-term care by one spouse to another; e.g., Lakdawalla and Philipson, 1998, 1999, etc.).

IX. A Demographic Analysis and Simulation to Show How Much Current Actuarial Assessments May Underestimate U.S. Health Improvements

It is often argued that U.S. life expectancy is lower than that of Japan, France and Scandinavian countries and that life expectancy in the U.S. has been relatively stagnant. First, the most recent "stagnation" of mortality (1954 to 1968) is no longer true (at least for males) because, in part, of declines in cancer mortality 1990-2001. Comparisons of life expectancy with Scandinavian countries are unfair because of the small size of those countries and the relative homogeneity of their populations. Japan and France are perhaps better comparisons, but Japan is less than half the U.S. population and is ethnically homogeneous. There are many large ethnic and racial groups in the U.S. with extremely different health distributions (Manton and Stallard, 1994). At advanced ages (i.e., ages 80+), it appears the U.S. may be the world's leader in life expectancy (Manton and Vaupel, 1995). To examine the situation look at Table 1:

Table 1. Life Expectancy for selected industrialized countries (2004)

Country		Japan	Andorra*	Germany	France	Sweden	Canada	U.S.
Population (Millions)		127	0.1	82	60	9	33	293
Life expectancy at birth (years)	Total	81	83.5	78.4	79.4	80.3	80	77.4
	Male	77.7	80.6	75.6	75.8	78.1	76.6	74.6
	female	84.5	86.6	81.7	83.3	82.8	83.5	80.4

*highest life expectancy in 2004 C.I.A. Fact book.

One scientific interpretation of these numbers is that, given the continuing rapid rises in life expectancy, the 1974 postulated limit to human life expectancy in 2000 by SSA actuaries (Myers, 1981) of 77 years was wrong (see above). Indeed the postulated limit of 85 years by Fries (1980) and Olshansky et al. (1990) now seems in jeopardy – and is occurring much faster than most scientists believed possible.

Second, it appears that, in terms of life expectancy at birth, the U.S. ranks last in this group. How could it be number 1 at age 80? The answer is twofold: a) problems in data and life expectancy models (which have tremendous effects on Medicare and Social Security trust funds) and b) the size and diversity of the U.S. population. We will address both those issues before addressing qualitative factors (i.e., ALE).

a.) Vital Statistics and Demographic Data

One useful example is to compare the life tables from NCHS and those produced by the Social Security actuaries for the year 2001 in Figure 3. In these life tables we added adjustments described below for Hispanic and other non-documented immigrant farm workers to the 2001 N.C.H.S. estimate (i.e., 1.2 years).

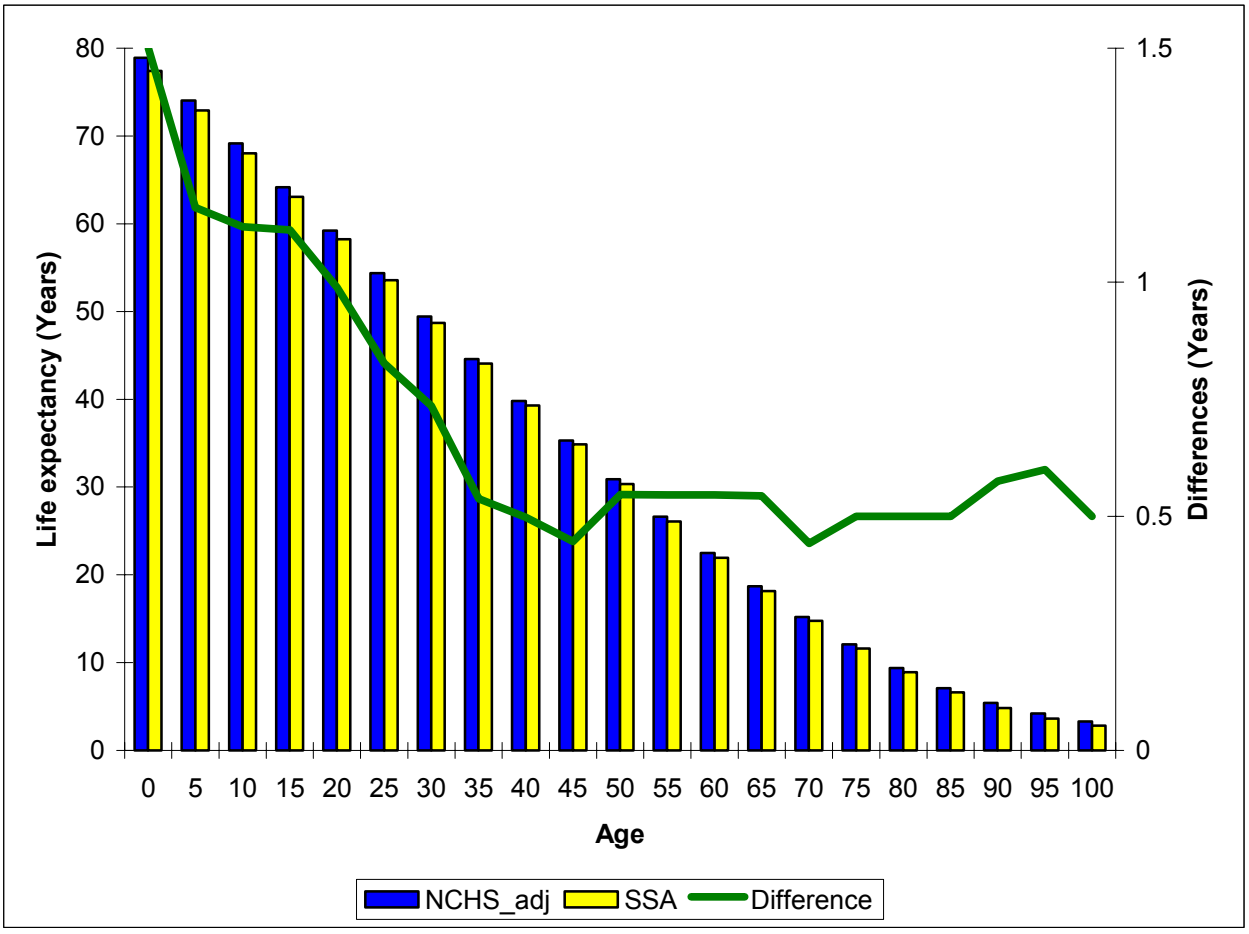


Fig 3. Life Expectancy Differences between data from (adjusted) NCHS and SSA.

In Figure 3, the left axis is absolute life expectancy; the right represents life expectancy (NCHS* – SSA) differences in years. The blue bar is the adjusted NCHS life expectancy, which is – at birth – 1.5 to 1.7 years higher than the unadjusted 2001 SSA estimate. This is from the same vital statistics data for roughly the same date using roughly similar life table calculations. Of interest is the fact that the difference in the SSA tables and the adjusted NCHS tables of about 0.5-0.6 years is relatively constant past age 35 (after the adjustment for non-documented workers ends about age 45), suggesting a simple shift in the life table functions. We would have expected the differences to decline with age (the early decline is dominated by an adjustment for illegal immigrants (especially Hispanic farm workers) health effects). Crucial to SSA and Medicare is that a 0.6-year difference in life expectancy at age 65 (of about 18 years) is about 3.3% – the relative differences at later ages grow. This is a serious problem in trust fund modeling – a fixed model error due apparently to actuarial assumptions for 2001, not the effects of assumptions to 2075.

We believe that the NCHS estimates are better than SSA – but still conservative. The differences we believe are both due to decisions made by SSA actuaries and heterogeneity in ethnic and racial groups in the U.S. In addition, as discussed, there are problems with actuarial long-range forecasts. Declines were detected for total cancer mortality in 1990 and have continued to 2001 at the rate of 0.9% per year (NCHS). The rate of decline in cancer mortality 1990 to 1995 was 0.57%. The rate of decline 1995 to 2001 was double; i.e., 1.14%. We can expect continuing increases in 2004 and beyond because of recent declines in female lung cancer mortality (smoking related) and reductions in breast cancer and possibly colorectal cancer mortality.

These declines were not only due to improved therapies (cytotoxic, radiation and surgery) but also due to the fact that the peak lung cancer risk due to smoking was reached for the Medicare male cohort becoming eligible in 1995 (i.e., males aged about 30 when the Surgeon General's report on smoking was first issued in 1962). These cancer mortality declines were superimposed on stroke mortality declines that have been in place since the 1930's, reductions in stomach cancer due to water quality improvement starting in the 1930's, and cardiovascular mortality declines that became evident for U.S. males in 1969.

b.) Reasons Vital Statistics and Public Health Measures Significantly Underestimate Health Improvements

One reason is the impact of illegal immigrants, and health disparities in some ethnic groups, on national health care measures such as life expectancy. Life expectancy is a crude measure because it, in part, is not adjusted for quality of life. Indeed, WHO has recommended that life expectancy be supplemented by measures of Active Life Expectancy – especially in developed countries. There is a long-standing international effort to advance the use of Active Life Expectancy as a public health measure because it reflects the economic potential of individuals (Reves: Réseau Espérance de Vie en Santé; the International Network on Health Expectancy and the Disability Process, website: http://www.prw.le.ac.uk/reves/). Yet neither Medicare nor SSA utilizes this concept in their projections. Apparently, several studies of inclusion of such factors are now being started by the new director of CMS (communication with CMS staff).

To illustrate the differences in life expectancy and active life expectancy, we provide Figures 4 and 5. They show changes in U.S. life expectancy 1982 to 1999 (4) and changes in ALE (5) using the 1982 to 1999 NLTCS data.

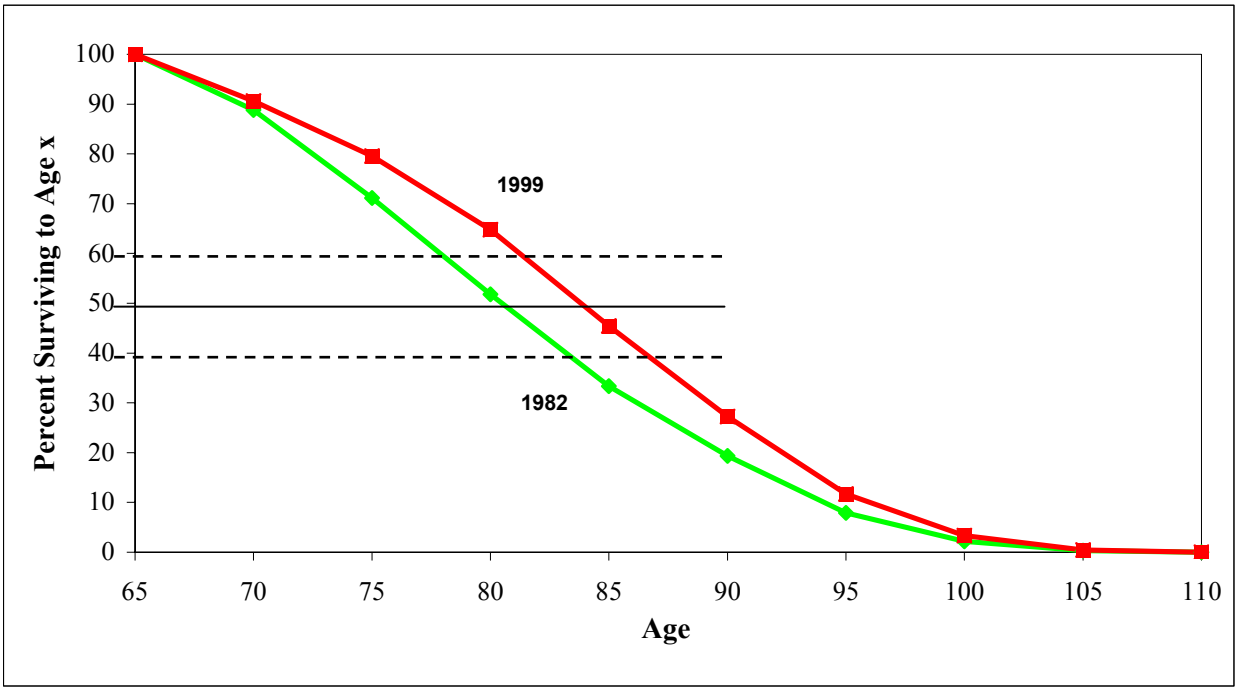


Fig 4. 1982 and 1999 Life Expectancy (and median (50%)) Estimates.

Clearly there are increases in life expectancy above age 65 whose magnitude peak about ages 80 to 85. The corresponding changes in Active Life Expectancy (and the median age at death, solid black line) are seen in Fig. 5.

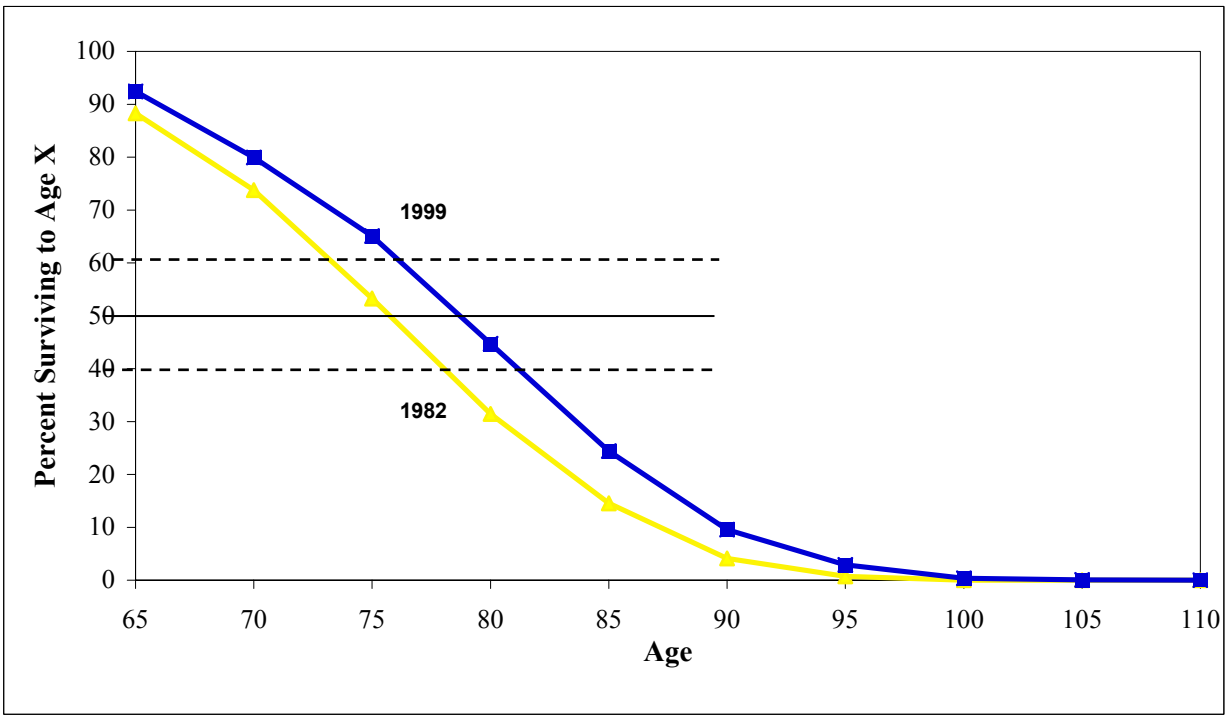


Fig 5. 1982 and 1999 Active Life Expectancy (and median (50%)) Estimates.

U.S. Active Life Expectancy increased 1982 to 1999 – in absolute terms – almost as fast as life expectancy (2.9 years vs. 3.5 years). In relative terms, there was a 4.3% increase in life expectancy 1982 to 1999 while ALE increased 3.8%. Thus the improvement in ALE in the U.S. is quite rapid – possibly the fastest in the world. Britain, for example, has been relatively stagnant in terms of disability declines (Waidmann and Manton, 1998). More important is that, in recent analyses, we found the rate of increase in ALE was much higher at advanced ages (e.g., 85+ and 95+) than at younger ages. We are developing the implications of this in several new papers.

One of the unique design features of the NLTCS to evaluate such trends was to supplement the extreme elderly sample population (i.e., aged 95+) in 1994 (by 540), in 1999 (by 600) and in 2004 (by 1000). This is a unique feature of the NLTCS which is scientifically important because this group is at an age where traditional medicine has relatively few answers and where fundamental research on the biology of physical and neurological degeneration is crucial (Manton et al., 2004).

OECD has drawn upon the NLTCS data time series to assess the effects of an aging population and the need for chronic care on the economic competitiveness of European countries – including relative to the U.S. (Jacobzone, 1999). They are continuing this assessment for the 1999 NLTCS in 2004-2005. Related findings were presented at the 1998 G-8 conference in Boulder, Colorado (ASPE). Yet the SSA and Medicare actuaries seem unaware that Europe and other countries (and WHO) are revamping their economic (especially human capital) indicators and data collection systems based on a long-standing and easy-to-understand U.S. model and linked data system (the NLTCS and linked Medicare and biomarker data).

c.) Effects of Census Undercounts and Population Heterogeneity on U.S. Health Assessments

One problem is the failure to assess, and adjust for, the adverse effects of illegal immigrants (especially Mexican farm workers in California and N.C.) on measures of U.S. health progress. There are estimated to be 7 to 14 million illegal immigrants in the U.S. who were not captured by the 2000 Census (estimates vary; about 0.5 million entering per year, U.N. report). Deaths in this group are counted in calculating mortality but are missing from the population counts, with most of those "illegals" likely in the 15-35 year age range (assumptions based on modification of Puerto Rico immigration age patterns). "Illegals" will have births while in the U.S. Thus, with an estimated life expectancy of 49 years in migrant farm workers, only the negative effects of these disproportionate numbers of deaths are reflected (in life expectancy estimates) without adding to the exposed population. In addition, infant mortality rates are extremely high among undocumented Mexican farm workers possibly causing the observed increase of U.S. infant mortality in 2002, while overall life expectancy reached its highest level ever.

Below we adjust for these effects by subtracting out projected deaths using the hypothesized population distribution of illegal immigrants by age and estimates of their elevation of mortality risk (i.e., the 49-year life expectancy). The calculations are meant simply to illustrate the effects – alternate assumptions could produce numbers higher and lower. We are simply attempting to illustrate the size of the effects, controlling for the health heterogeneity of specific U.S. ethnic groups in U.S. life expectancy estimates.

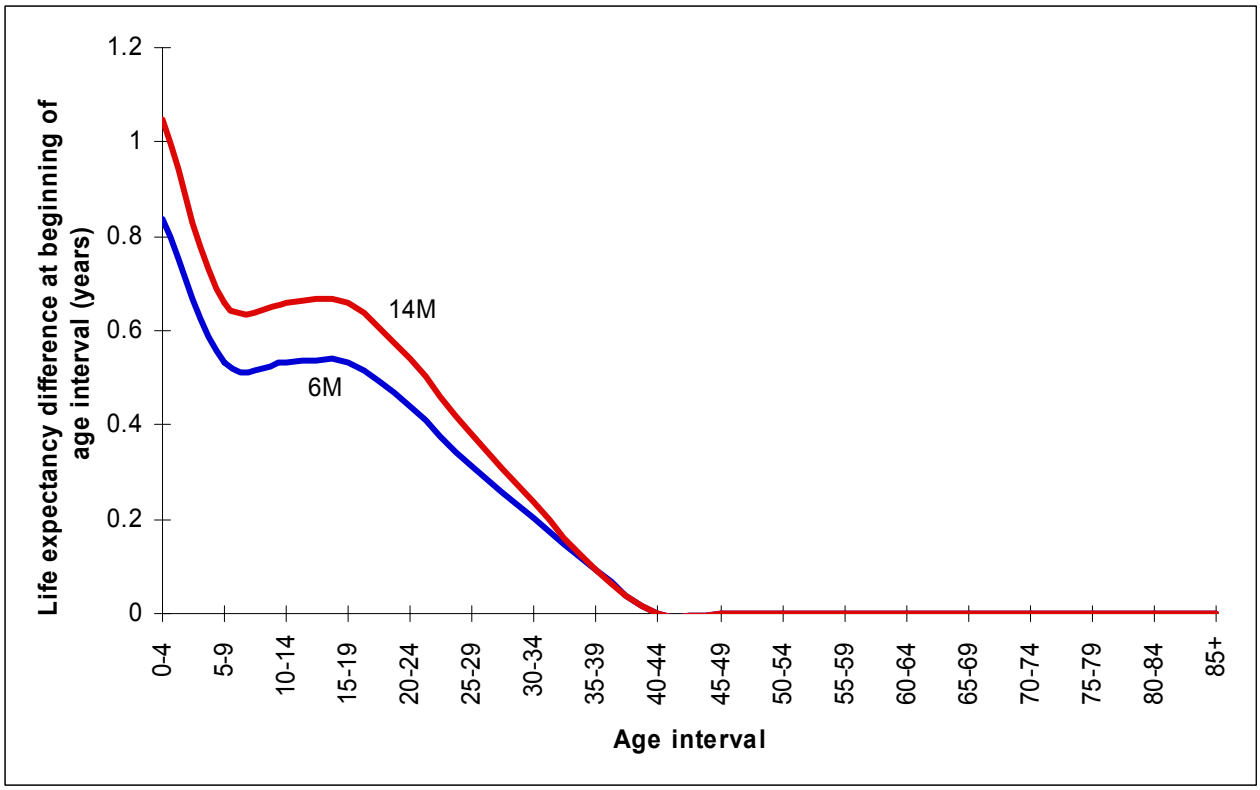


Fig 6. Life Expectancy Differences at Beginning of Age Interval.

We show the effects of Census Bureau undercount estimates on age-specific life expectancy in Figure 6. The low adjustment is over 0.8 years. The high adjustment is about 1.1 years.
In Table 2 we show selected illustrative numbers.

Table 2. U.S. Life Expectancy at Birth with Various Adjustments

2004 SSA (2001 76.7 years adjusted to 2004, + 0.6 years)	77.3
2004 NCHS (2001 77.4 years adjusted to 2004, + 0.6 years)	78.0
2004 NCHS with adjustment for undocumented workers (especially Hispanic) (+ 1.1 years)	79.1
2004 "Adjustment" for all African American health disparities as in NCHS life tables (+ 0.5 years)	79.6
2004 Low "Adjustment" for diabetes, smoking and obesity elevated risk in African Americans (+ 0.5 years)	80.1
2004 High "Adjustment" for Black Health Disparities (+ 0.5 years)	80.6

Table 2 shows that both the NCHS and SSA tables might raise the U.S. life expectancy at birth 0.8 to 1.1 years (depending on assumptions about illegal immigrants). Adding 1.1 years (high estimate), we add 1.8 years to the 2001 SSA life tables. Adjusting for African-American health disparities (e.g., a reduction of life expectancy by 20+ years for obesity and diabetes in African-Americans) raises the estimate 0.5 to 1.0 years, producing the progression in Table 2.

It is important to note that, just as there are large groups at elevated health risks in Hispanic and African-American groups due to behavioral risk factors and problems in health care access, there are also groups in those racial and ethnic categories with health better than that of the

average white American. We are simply attempting to illustrate how much major health problems in a relatively (to U.S. population) small group can bias life expectancy measures. Some of these "small" groups are larger than the entire Swedish population (9 million persons).

The adjusted estimate of life expectancy at birth of 80.6 years is better than Germany, France and Sweden (Table 1), with the U.S. being 0.4 years less than Japan. Now it is quite plausible to believe that U.S. survival at age 80 could be the highest in the world. If we were to further adjust for SES and education, U.S. life expectancy – for middle-income, educated people – could easily surpass that of Japan.

Taking this in the context of health expenditures we present Table 3.

Table 3. Spending (%) on health in the U.S. and other countries (2001)

	% of GDP	% of Govt. Spending
U.S.	13.9	17.6
Germany	10.9	16.6
France	9.6	13.7
Canada	9.5	16.2
Sweden	8.7	13.0
Japan	8.0	16.4

(Source: Economic Opportunity Institute, M.P. Watkins, May 2004)

Given the better performance of U.S. life expectancy (adjusted) than all but Japan, we see that Health Expenditures in the U.S. are proportionally (relative to government spending) not much different than in Germany, Canada or Japan. Thus the biggest difference in the U.S. appears to be in private investment in health in the U.S. – this investment being the likely source of U.S. success. Thus, one may construe the evidence to be that Americans are, out of pocket, more likely to invest in health. This, we believe, is because a) they are more optimistic that modern medicine makes a difference, and b) the general affluence of the U.S. population. We suggest, as a consequence, that the American cultural view of health and its maintenance (positive) is fundamentally different than that of the professional actuary (perhaps more British and negative).

These data might answer important questions about whether our "high" health care investments and increased NIH investments of the right type are worth it; i.e., we have the highest ALE (especially at late ages); we have the most rapidly-improving ALE; and in middle income educated persons with good access to health care we are probably better than Sweden – and perhaps Japan – with their highly homogenous (ethnically and socio-economically) and smaller populations.

X. Analysis of Specific Recent Concerns about the U.S. Health State

a.) Obesity

Questions have been raised about "obesity" as reflecting future declines in health. Again, the groups with the highest diabetes (and stroke and heart disease) risks are likely illegal Hispanic immigrants (and select subgroups of African Americans). In addition, the measure generally used – body mass index – doesn't reflect body composition; i.e., lean body mass. There are other simple measures (e.g., waist to hip ratio) that may reflect this better and might be considered (Willett et al., 1999).

Indeed, the problem in elderly Americans is more likely to be protein malnutrition, cellular dehydration, and avitaminitosis with, as hormone levels decline, increased fat and decreased muscle mass and tone – leading to serious disability, with slowly-declining body weight but increasing proportions of body fat. The physiological dynamics of the phenomena are complex and not fully understood (Manton, 2004b). However, exercise and proper nutritional supplementation may reverse it (Fiatarone et al., 1994). We are developing a mathematical model of aging and mortality, based on the work in Manton and Akushevich (2003), which views the thyroid gland as the master gland in aging processes, since it can influence mitochondrial function and number (Wrutniak-Cabello et al., 2001), and hence basal cellular metabolism.

Problems similar to that for illegal farm workers may affect African Americans. In particular, some ethnic groups have genes that store fat more efficiently – probably due to the need to survive long periods without food in aboriginal settings (e.g., Pima Indians). These groups, which include many Hispanics with an admixture of these "greedy" genes from Indian predecessors, may have a genetic predisposition towards obesity. One of these genes is the APOE gene with the $\varepsilon 4$ allele which, interestingly, is related to Alzheimer's disease risk. This is fundamentally a public health issue, not a failure of biomedical research.

As Professor Willet at Harvard has argued, the famous food pyramid published by the Department of Agriculture had problems because it was based on arguments that proteins and fats and oils might lead to poor health and obesity and should be de-emphasized in diet. The better health associated with the Mediterranean diet and Chinese dietary practices, and the fact that dietary fat and cholesterol have a tenuous connection, suggests a lack of validity of this position. As the basis for a public education program, this food pyramid could have had consequences for U.S. obesity trends – especially in children. Apparently, after interventions from OMB, this pyramid is now being revised to a more balanced form.

These changes are consistent with the research at NHLBI on cholesterol in the Framingham Heart Study in the 1950's and 1960's being modified to show there was "good" cholesterol (HDL) and bad cholesterol (LDL), with perhaps triglycerides (elevated by sugars, certain carbohydrates and stress) being the most dangerous component through its linkage to diabetes and hormonal dysfunction (e.g., insulin release and its relations to stress-induced cortisol elevation). We can expect that, with better diet, recent Congressional initiatives (Senator Frist) and the growing trend towards physical fitness and nutritional awareness, the obesity "epidemic" will subside – leaving the real problem, at later ages, of inadequate nutrition and cellular dehydration (Manton, 2004b).

b.) Alzheimer's Disease Trends

Another often cited population trend used to argue for pessimistic actuarial assumptions is the "epidemic" of Alzheimer's disease argued to emerge as the population ages. First, it is important to realize that not all dementia is of the Alzheimer's type (Manton et al., 2004). Much of it is vascular dementia, or Alzheimer's disease mixed with vascular dementia. The vascular dementia process can be modified much more easily than the Alzheimer's type, since it is driven by diabetes, hypertension and hyper-cholesterolemia and, ultimately, stroke.

Using data from the East Boston study in Figure 7 below, we see that adjusting for education reduces projected relative rates of increase by 40 to 60% past 2020; i.e., by 2050 from the often-quoted 14 million to less than 10 million.

The 3 to 3.5 million cases estimated for 1980 was based on a poorly-educated Italian immigrant population in East Boston and included mild cases of dementia/Alzheimer's disease that were hard to diagnose. A GAO report in 1998 challenged such projections by using meta analysis of 18 different studies – many European. In all of our NLTCS analyses of cognition in the elderly we focus on "severe cognitive impairment" to reduce false negative cases.

It is interesting that while the U.S. elderly population increased from 27 million in 1982 to 35 million in 1999 (about 30%), the actual number of cases of severe cognitive impairment estimated from the NLTCS dropped from about 1.5 million in 1982 to 1.03 million in 1999. If 1982 age-specific rates had not changed, the estimated number of severe cognitive impairment cases in 1999 would have been about 2.1 million – or a reduction of roughly 50% from that observed. This can be compared with the approximately 2.5 million cases of moderate and severe disease in 1980 in East Boston (more than double our estimate of severe cases). Our 1999 NLTCS estimate of 1.02 million cases in 1999 can be compared to the projected over 4 million cases (education adjusted) of mild, moderate, and severe Alzheimer's disease (presumably all cognitive impairment would be even higher) for 2000. The NLTCS estimate of 1.02 million cases in 1999 can be compared to over 4 million projected cases (education adjusted) of mild, moderate, and severe Alzheimer's disease (presumably all cognitive impairment would be even higher) for 2000.

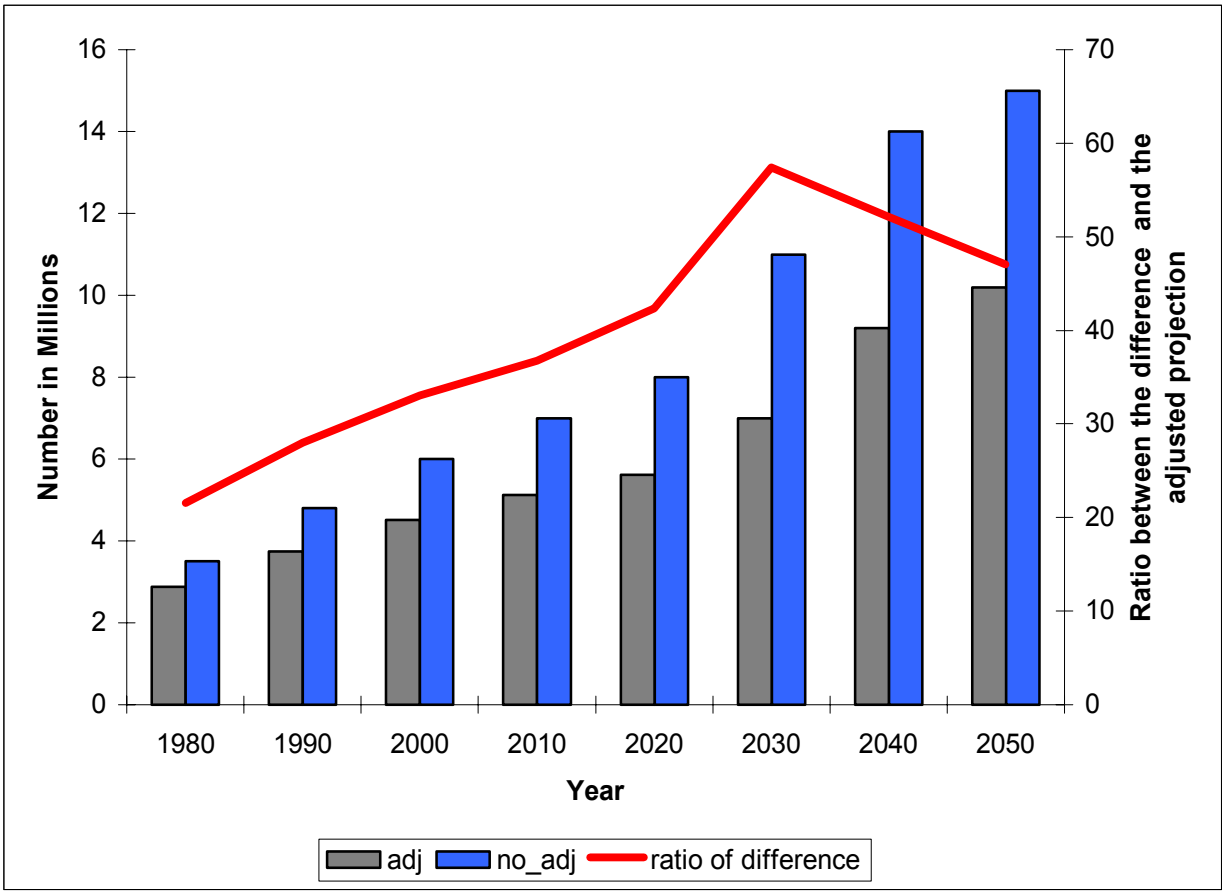


Fig 7. Projected number of persons over age 65 with AD in the US population with middle US Census projections of population growth with or without adjustments for years of education and the proportion change relative to the adjusted population.

In this context it is useful to compare our NLTCS numbers with the 1998 GAO report for moderate and severe cases based on their meta-analysis. Their (GAO, 1998) estimates of 1.1 million cases compare quite favorably with our estimate of about 1.1 million cases in 1994 (and the 1.02 million cases in 1999 reflecting the decline 1994 to 1999). Thus their prevalence estimates using meta-analysis and our analyses of the NLTCS data are very close – with ours likely being conservative (i.e., too high) because we only considered severe dementia (to eliminate false positives), not moderate dementia.

Second, we found large declines 1982 to 1999 in the prevalence of severe cognitive impairment (Manton and Gu, 2004), which in preliminary analyses (Manton et al., 2004) seem attributable to circulatory disease dementia (e.g., dementia as sequelae to stroke). This is in spite of a growing sensitivity by physicians to Alzheimer's disease and related dementia. The Alzheimer's disease rates were relatively stable – though prevention interneuron (i.e., Vitamin C, E and aspirin) could reduce them 93% (Zandi et al., 2004).

XI. Conclusion

We have provided several examples among many to document our assertion that the U.S. health care system is among the world's best – especially for the elderly, with its primary shortcoming being the lack of equitable distribution of health services to specific ethnic groups (e.g., Hispanic farm workers, undocumented workers, and African Americans). The difficulty of having a fully-equitable system is clear because of the size and diversity of the U.S. population.

It is equally clear that U.S. biomedical research is the world's best and has excellent effects on those with full access to it. Social Security and Medicare forecasts fail to recognize this and are overly pessimistic. They are also technically severely limited in that they use only time-to-death data and subjective inputs on health trends. Models could use multiple sources of health data and be based on objective model results with open scientific review of the model structure so it could be made scientifically valid (Manton, 1992; Manton et al., 1994). In this way many important mortality turning points could be predicted and interventions could be made to help promote them.

Overall, it is clear that the use of the NLTCS, and related linked data sets, would help better assess changes in health that could greatly benefit the financial soundness of the Medicare program and the beneficiaries it serves. This is both by more accurately assessing the health of the elderly U.S. population and by developing better strategies to improve health. From this will flow benefits for the Social Security and Medicare systems and, ultimately, the total U.S. economy.

References

Bailar J and Gornik H: Cancer Undefeated. *New England Journal of Medicine* 336:1569-1574, 1997.

Bailar J and Smith E: Progress against cancer? *New England Journal of Medicine* 314:1226-1232, 1986.

Bayo F and McKay S: United States Population Projections for OASDHI Cost Estimates. Actuarial Study. Washington, DC: US Department of Health, Education, and Welfare; Report No.: 72, July 1974.

Burkhauser R and Quinn J: Pro-work policy for older americans in the 21st century. Syracuse: Center for Policy Research, Maxwell School of Citizenship and Public Affairs, Syracuse University Report No.: Policy Brief No. 9, 1997.

Cohen HJ, Pieper CF, Harris T, Rao KM and Currie MS: The association of plasma IL-6 levels with functional disability in community-dwelling elderly. J. Gerontol. A Biol. Sci. Med. Sci 52:M201-M208, 1997.

Feldman J: Work ability of the aged under conditions of improving mortality. *Milbank Memorial Fund Quarterly* 61:430-444, 1983.

Fiatarone M, O'Neill E, Ryan N, Clements K, Solares G, Nelson M, et al: Exercise training and nutritional supplementation for physical frailty in very elderly people. *New England Journal of Medicine* 330(25):1769-1775, 1994.

Freedman V and Soldo B: Trends in disability at older ages. Washington, DC, Committee on National Statistics, 1994.

Fries J: Aging, natural death, and the compression of morbidity. *New England Journal of Medicine* 303:130-135, 1980.

Golubovsky M and Manton K: Genome organization and three kinds of heritable changes: General description and stochastic factors. In Press at *Frontiers in Bioscience Encyclopedia*, 2004a.

Golubovsky M, Manton K: A three-generation approach in biodemography is based on developmental profiles and the epigenetics of female gametes. In press at *Frontier in Bioscience Encyclopedia*, 2004b.

Gonzalez F and Nebert D: Evolution of the P450 gene superfamily: animal-plant 'welfare' molecular drive, and human genetic differences in drug oxidation. *Trends in Genetics* 6:182-186, 1990.

Gottesman S: Genetics of proteolysis in Escherichia coli*. *Annu Rev Genet* 23: 163-98, 1989.

Hagen T, Liu J, Lykkesfeldt J, Wehr C, Ingersoll R, Vinarsky V, et al: Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress. *Proceedings of the National Academy of Science* 99(4):1870-1875, 2002.

Huang H and Manton KG: The role of oxidative damage in mitochondria during aging. A review. *Frontiers in Bioscience* 9, 1100-1117, 2004.

Huang H, Patel DD Manton KG: The immune system in aging: Roles of cytokines, T cells and NK cells. *Biodemographic Effects of Genome-Proteome Interactions* in: the "Encyclopedia of Bioscience," published by Frontiers in Bioscience 2004 (to appear).

in't Veld B, Ruitenberg A, Hofman A, Launer L, van Duijn C, Stijnen T, et al: Nonsteroidal Antiinflammatory Drugs and the risk of Alzheimer's Disease. *The New England Journal of Medicine* 345(21):1515-1521, 2001.

Jacobzone S: An overview of international perspectives in the field of ageing and care for frail elderly persons. Labour Market and Social Policy Occasional Papers. Paris: OECD; Report No. 38, 1999.

Kaplan G and Keil J: Socioeconomic factors and cardiovascular disease: A review of the literature. *Circulation* 88(4):1973-1998, 1993.

Kramer M: The rising pandemic of mental disorders and associated chronic diseases and disabilities." *Acta Psychiatrica Scandinavica* 62(Suppl. 285): 382-397, 1980.

Lakdawalla D and Philipson T: The rise in old age longevity and the market for long-term care. NBER Working Paper Series 6980. Cambridge, MA: National Bureau of Economic Research, 1998.

Lakdawalla D and Philipson T: Aging and the growth of long-term care. Cambridge, MA: National Bureau of Economic Research, 1999.

Liu J, Killilea D, Ames B. Age-associated mitochondrial oxidative decay: Improvement of carnitine acetyltransferase substrate-binding affinity and activity in brain by feeding old rats acetyl-L-carnitine and/or R-a-lipoic acid. *Proceedings of National Academy of Science* 99(4):1876-1881, 2002.

Manton KG: Forecasting life expectancy. Testimony before the Subcommittee on Savings, Pensions, and Investment Policy of the Committee on Finance, U.S. Senate, July 15, 1983. Senate Hearing Document No 98-359, Washington, DC.

Manton KG: Changing concepts of morbidity and mortality in the elderly population. *Milbank Memorial Fund Quarterly* 60:183-244, 1982.

Manton KG: Epidemiological, demographic, and social correlates of disability among the elderly. *Milbank Quarterly* 67 Suppl 2 Pt 1: 13-58, 1989.

Manton KG: How could demographic changes affect the Social Security system: Perspectives on forecasting mortality. Testimony before the House Budget Committee, Task Force for Social Security, April 13, 1999, Washington, DC.

Manton KG: Aging and longevity of human populations. Contributed article in *Encyclopedia of Endocrine Diseases* (Martini L, Ed.). Elsevier: San Diego Volume 1 pp. 116-121, 2004a.

Manton KG: Letter to Editor re: "The Outlook for Hospital Spending: Rapid Growth Is Likely to Persist" by Shactman, Altman, Eilat, Thorpe, and Doonan and "Does the Aging of the Population Really Drive the Demand for Health Care?" by Reinhardt. *Health Affairs*, 23(1) 273-274, 2004b.

Manton KG, Akushevich I: State variable methods for demographic analysis: A mathematical theory of physiological regeneration and aging. *Nonlinear Phenomena in Complex Systems*, 6(3):1-11, 2003.

Manton K, Akushevich I and Kulminski A: Demographic analysis and modeling of human populations exposed to ionizing radiation. *Frontiers of Bioscience* 9:2144-2152, 2004.

Manton KG and Gu X: Changes in the prevalence of chronic disability in the United States black and nonblack population above age 65 from 1982 to 1999. *Proceedings of the National Academy of Sciences, U.S.A*. 98: 6354-6359, 2001.

Manton KG, Gu X: Change in physical and mental function: Prospects. Chapter in *New Dynamics in Old Age: Individual, Environmental, and Societal Perspectives* (Wahl HW, Tesch-Romer C, Hoff A, Eds.), in the Society and Aging Series (Hendricks J, Series Ed). Baywood: Amityville, NY, 2004.

Manton KG and Gu X: Disability Declines and Trends in Individual Medicare Expenditures. In preparation for *Health Affairs*, 2004.

Manton KG, Gu X and Ukraintseva SV: Factors Causing Declines in Chronic Disability 1982 to 1999 in the U.S. Elderly Population. Working Paper, Center for Demographic Studies, 2004.

Manton KG and Stallard E: A cohort analysis of U.S. stomach cancer mortality - 1950 to 1977. *International Journal Epidemiology* 11(1):49-61, 1982.

Manton KG and Stallard E: Ethnic health and disability differences in the U.S. elderly population. Presented at the Workshop on Racial and Ethnic Differences in Health in Late Life, sponsored by the National Institute on Aging and the National Research Council Commission on Behavioral and Social Sciences and Education, Washington, DC, December 12-13, 1994.

Manton KG, Stallard E and Singer BH: Projecting the future size and health status of the U.S. elderly population. *International Journal of Forecasting* 8:433-458, 1992.

Manton KG, Stallard E and Singer BH: Methods for projecting the future size and health status of the U.S. elderly population. Chapter 2 in *Studies of the Economics of Aging* (Wise D, Ed.). National Bureau of Economic Research, University of Chicago Press, pp. 41-77, 1994.

Manton KG and Vaupel JW: Survival after the age of 80 in the United States, Sweden, France, England, and Japan. *New England Journal of Medicine* 333(18):1232-1235, 1995.

Manton KG, Volovyk S, Kulminski A: ROS effects on neurodegeneration in Alzheimer's disease and related disorders: On environmental stresses of ionizing radiation. Accepted by *Current Alzheimer Research* (Lahiri DK, Ed.), 2004.

Myers G: Future age projections and society. In: Gilmore A, editor. *Aging: A Challenge to Science and Social Policy*. Oxford: Oxford University Press, p. 248-260, 1981.

Olshansky S, Carnes B and Cassal C. In search of Methuselah: Estimating the upper limits to human longevity. *Science* 250(4981):634-640, 1990.

Omran A: The Epidemiologic Transition: A theory of the epidemiology of population change. *Milbank Memorial Quarterly* XLIX: 509-38, 1971.

Singer B, Manton KG: The effects of health changes on projections of health service needs for the elderly population of the United States. *Proceedings of the National Academy of Sciences U.S.A.* 95 (26):15618-15622, 1998.

Tolley HD, Palmer H and Manton KG: On government funding of health care research. CDS Working Paper, 2004.

Ukraintseva SV and Yashin AI: Individual aging and cancer risks: How are they related? *Demographic Research* 9(8):163-196, 2003.

United Nations Economic and Social Council. Specific groups and individuals: Commission on Human Rights, Sixtieth session, Item 14 of the provisional agenda; March 3, 2004. Report No.: E/CN.4/2004/NGO/97, GE.04-11451.

United States General Accounting Office. Alzheimer's disease. Estimates of prevalence in the United States. Report to the Secretary of Health and Human Services: United States General Accounting Office; 1998 January 1998. Report No.: GAO/HEHS-98-16.

Waidmann T and Manton KG: International evidence on disability trends among the elderly. Final Report for the Department of Health and Human Services, 1998.

Walter P, Knutson M, Paler-Martinez A, Lee S, Xu Y, Viteri F, et al: Iron deficiency and iron excess damage mitochondria and mitochondrial DNA in rats. *Proceedings of National Academy of Science* 99(4):2264-2269, 2002.

Weisenthal L: Cell culture drug resistance testing (CCDRT). Chemosensitivity Testing http://virtualtrials.com/assay.cfm 2004.

Willett W, Dietz W and Colditz G: Primary Care: Guidelines for Healthy Weight. *The New England Journal of Medicine* 341(6):427-434, 1999.

Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, et al: Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. *Arch Neurol* 61: 82-8, 2004.