Ian Wilmut, the cloner of Dolly the sheep, questions whether "the interpretation of the data offered" by the subsequent cloners of calves is "justified on the basis of the evidence presented." And several letter writers discuss whether "human longevity" can be "predicted by the simple extrapolation of mortality trends."

Quiescence in Nuclear Transfer

When sheep donor cells derived from embryo, fetal, and adult tissues were induced to exit the growth cycle and become quiescent, live lambs were produced after nuclear transfer from such treated cultured cells (*1*). The cells were cultured in reduced serum concentration for several days until there was no evidence of DNA replication as detected by immunofluorescence staining for the S-phase–specific form of proliferating cell nuclear antigen (PCNA) (*2*). However, the majority of cells resumed DNA synthesis when the serum concentration was returned to normal levels for culture. This, together with fluroescence-activated cell sorting (FACS) data, led to the conclusion that the donor cells had diploid DNA content, but were not actively growing.

Cloned calves ACT3, ACT4, and ACT5 at 3 weeks of age.

In a recent report that described the birth of calves after nuclear transfer from fetal fibroblasts (22 May, p. 1256), the authors stated that the donor cells used were not quiescent. The cell-cycle stage of the cells was assessed by FACS analysis and by immunofluorescence for PCNA. FACS analysis measures DNA content, but does not distinguish between actively growing diploid cells (G_1) or nonactively growing diploid cells that have arrested the cell cycle after mitosis and cell division but before DNA replication (G_0). This measurement established that 56% of the cells were diploid, but did not determine how many were in G_0 or G_1.

Because the protocol for PCNA staining used by the authors fixes the soluble complex that is present at all stages of the cell cycle (*3*), the observation provides no information about cell-cycle stage; but because only 82% of the cells were positive for PCNA, it may indicate that some of the cells were dead (*4*).

In short, no evidence is provided either in this or in a previously reported study (*5*) that the small proportion of donor cells whose use resulted in development to viable calves or fetuses was not quiescent. In fact, there is every reason to expect that quiescent cells were present in the cultures, as they had reached 70 to 80% confluence before use as donors, in which condition contact inhibition causes cells to become quiescent (*6*). Additionally, the passage number of the cultures at the time of nuclear transfer is not specified (with time during the culture of primary cell populations an increasing number of cells cease division). Such nongrowing cells, described as senescing, have been reported to enter a presenescent G_0 phase (*7*). In these circumstances, the interpretation of the data offered by the authors is not justified on the basis of the evidence presented.

Ian Wilmut
Roslin Institute, Roslin, Midlothian, EH25 9PS, United Kingdom

Keith H. S. Campbell
PPLTherapeutics, Roslin, Midlothian, EH25 9PP, United Kingdom

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Response

We consider it highly unlikely that the cloned calves in our study were actually derived from a small population of G_0 cells. First, the cells used to produce the calves had been cultured for approximately 8 to 10 population doublings, far from senescence, which occurs at about 35 population doublings. Second, our cell-cycle analysis indicates that a confluency level of 70 to 80%, as defined in our laboratory, is in the middle of the log phase of growth. Third, contact inhibition of cells does not occur at 70 to 80% confluency and, in fact, does not occur at 100% confluency. Contact inhibition only occurs after physical crowding of cells in the dish. Finally, even if a small population of cells was induced to arrest cell division by the culture conditions, they would be overgrown, very rapidly, by the actively dividing population of cells. Although we believe this indirect evidence is sufficient to warrant the conclusions in our paper, we are now also in the process of testing the question directly.

James M. Robl
D. Joseph Jerry
Department of Veterinary and Animal Sciences, University of Massachusetts, Amherst, MA 01003, USA. E-mail: robl@vasci.umass.edu

Steven Stice
Jose Cibelli
Advanced Cell Technology, Inc., One Innovation Drive, Worcester, MA 01605, USA

The Future of Long Life

In his Research commentary "The future of human longevity: A demographer's perspective" (*Science*'s Compass, 17 Apr., p. 395), John R. Wilmoth states that human longevity could be predicted by the simple extrapolation of mortality trends: "[t]he appeal of extrapolation lies in long-term stability of the historical mortality decline." This decline is supported by his fascinating graph depicting remarkably regular decreases in U.S. mortality rates over the last 97 years.

Unfortunately, the data on age-specific mortality rates published by the Social Security Administration (*1*) are complex and are not consistent with the declared long-term stability of the historical mortality decline. For example, the U.S. death rates for ages 30 to 34 and 35 to 39 have been *increasing* since 1985 both for males and females (*1*). The impression of long-term stability of mortality decline comes from the use of the aggregated death rate calculated by Wilmoth for the mixture of people of different ages (standardized to the U.S. population in mid-1990). The virtual stability of the historical decline of this highly aggregated mortality index is not very informative and might even be misleading (as is the fallacy of one stable mean body temperature for all patients in hospitals).

The future of human longevity is a complex and as yet unresolved multidisciplinary scientific problem. More research is needed on the driving forces of the age-specific mortality rates and their possible biological limits (*2*), not just extrapolation.

Leonid A. Gavrilov
Natalia S. Gavrilova
Center on Aging, National Opinion Resource Center, University of Chicago, Chicago, IL 60637, USA. E-mail: lagavril@midway.uchicago.edu

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Wilmoth asserts that, in low mortality populations, death rates have fallen steadily during the past 100 years. Actually, death rates have fluctuated throughout most of the 20th century (*1*), and occasionally in low-mortality populations mortality has increased and life expectancy has declined. There is no dispute that the mortality trend has been favorable over the last century, but it is incorrect to state that the decline in mortality has been steady. Further, mortality rates from several important causes of death, such as all forms of cancer combined and, more recently, from infectious and parasitic diseases (*2*), have actually risen throughout most of the 20th century. If the method proposed by Wilmoth were used to extrapolate mortality trends from these diseases, it would predict an eventual rise in total mortality and a decline in life expectancy. It is not clear why Wilmoth uses a method of extrapolation that seems to take into account only trends in death rates that are declining, but not those that are increasing.

Wilmoth correctly notes that extrapolation methods yield more optimistic estimates of life expectancy than those made by the U.S. Social Security Administration. Paradoxically, he characterizes our estimate of 85 years for a practical limit to life expectancy as pessimistic, but we based this number on a 50% reduction in mortality at all ages from all causes of death combined (*3*), which does not seem pessimistic. Wilmoth also acknowledges that, even though declines in death rates have accelerated in some parts of the world, increases in life expectancy have simultaneously slowed down. This entropy in the life table has been demonstrated repeatedly in the scientific literature (*3*, *4*) and is one of the primary reasons why it is inappropriate to perform mathematical extrapolations of historical trends in life expectancy into the future.

There are several biological reasons why extrapolation methods are inappropriate for forecasting death rates and life expectancy. The suggestion that evolutionary theory predicts a sharp rise in deaths in the postreproductive years is, however, not among them. Medawar (*5*) and Williams (*6*) provided evolutionary explanations for why an age-related increase in the harmful effects associated with gene expression could be expected to occur beyond the age of sexual maturity. These evolutionary theories of senescence (aging) were not applied to, and are not consistent with, the arguments made by some demographers that evolutionary theory predicts that a "black hole" of mortality associated with genetic diseases should exist at or near the end of the reproductive period (*7*). Evolutionary theories of senescence also do not predict, as stated by Wilmoth, Gompertzian-type increases in postreproductive mortality rates or catastrophic increases in mortality when reproduction ceases (*8*). Evolutionary theory does predict that the physiological degradation and mortality associated with senescence are an inadvertent byproduct of organisms not designed for postreproductive survival, a rare phenomenon in nature that has become common among humans.

Consider this analogy: The shortest time for a man to run 1 mile, recorded since the middle of the 19th century (*9*), has declined steadily from over 5 minutes in 1850 to 3 minutes and 44 seconds cur-

rently. A linear extrapolation of this historical trend shows that, by the year 2420, someone would be running 1 mile in 1 minute, and by 2580, the race would be instantaneous. This conclusion is absurd, but the same premise is behind the use of extrapolation to project future trends in death rates and life expectancy.

The extrapolation method is valid only if used for short time windows. With regard to trends and patterns in mortality, the time has come to infuse a heavy dose of biological reality into this empirical tool.

S. Jay Olshansky
Department of Medicine, University of Chicago, Chicago, IL 60637, USA. E-mail: sjayo@uchicago.edu

Bruce A. Carnes
Center for Mechanistic Biology and Biotechnology, Argonne National Laboratory, Argonne, IL 60439, USA. E-mail: bcarnes@anl.gov

Christine Cassel
Department of Geriatrics, Mount Sinai Medical Center, New York 10029, USA. E-mail: c_cassel@smtplink.mssm.edu

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Wilmoth argues persuasively that estimates of future death rate and life expectancy should be extrapolated from historical trends, rather than be based on particular sources of pessimism or optimism such as technological breakthroughs. These trends illustrate that the death rate has been steadily declining since 1900, and that the decline has even accelerated for women in the last several decades.

I find Wilmoth's arguments and data convincing, but he does not to point out a conclusion that would naturally follow. Extrapolating from the data in the graph, it appears that the death rate among women will reach zero around 2005, and for men around 2050. Although we must expect that a "floor effect" will force the death rate curve to level out before actually reaching zero, the commentary seems to imply that, within a few decades, we will be essentially immortal. Although this conclusion is quite remarkable, it is clearly predicted by past trends, and in Wilmoth's words, "the burden of proof lies with those who predict sharp deviations from past trends."

Joseph J. Strout
Department of Neuroscience, University of California, San Diego, La Jolla, CA 92093–0608, USA. E-mail: jstrout@ucsd.edu

Response

These three letters make important points and contribute to the discussion about the future of human longevity. A key argument, made by the Gavrilovs and by Olshansky *et al.*, is that the decline of death rates in industrialized countries during the past century has not been "steady," as I stated in my essay. Semantics aside, it is important to emphasize that the putative stability of historical mortality trends is valid only over the long term and as a description of a general pattern. Certainly, there have been periods of faster and slower decline, and there have even been mortality increases in some time periods for some age groups and causes of death. For example, death rates from automobile accidents rose from around 1950 to around 1970 in a number of industrialized countries, but then headed downward thanks to safer cars, seat-belt laws, reduced speed limits, and improved emergency medical care (*1*). Epidemics (of automobile accidents, AIDS, and so forth) do happen, but humans in technologically advanced societies typically see what is happening and respond, even though such responses are not always immediate or successful.

Regarding the statement by Olshansky *et al.* that cancer mortality has been rising during the 20th century, it is important to note that many experts attribute the observed rise in death rates for some cancers to changes in diagnostic practice and not to real increases in the age-specific risk of death by those forms of cancer (*2*). In any event, most of the observed rise in cancer mortality is due to lung cancer, which can and probably will be reduced in the future thanks to active anti-smoking campaigns. Furthermore, there is now solid evidence that cancer mortality has declined during the 1990s in the United States, Canada, and Western Europe, and that this improvement is due only in part to changes in smoking behavior (*3*). On the other hand, as noted by the Gavrilovs, the rise in death rates among young adults in the United States is a disturbing phenomenon, caused mostly by AIDS and an increase in violent deaths (*4*). AIDS research and prevention and new therapies are an ongoing effort, and they are having a measurable effect, at least in rich countries like the United States (*5*). Future trends in violent deaths are less clear, but they point to the

social uncertainties affecting mortality rates, not the ill-defined "biological realities" that Olshansky *et al.* mention.

Overall, the presence of exceptions in some particular cases does not invalidate the observation that the dominant historical trend is characterized by lower and lower death rates in industrialized countries. At the same time, the existence of a dominant, favorable trend does not suggest that we should be complacent about the health and social problems facing such societies.

A second point, made by Olshansky *et al.* and by Joseph J. Strout, is that some extrapolations yield absurd results. Clearly, my essay was not the proper venue for a detailed discussion of demographic forecasting methodology, but I should have mentioned one crucial point. Demographers and actuaries routinely extrapolate mortality trends in a logarithmic scale, not in the raw form depicted in my graph of the aggregate death rate (from the original essay). One consequence of this methodological convention is that extrapolated death rates never attain zero or negative values. Aside from these obvious practical advantages, logarithmic extrapolation is also well justified by empirical analyses of past mortality trends (*6*).

An empirical extrapolation always includes selection of a model, and equations whose mathematical characteristics logically contradict the phenomenon of interest should be eliminated from consideration. Thus, extrapolating a linear decline for measures that are necessarily non-negative, such as death rates or racing times, is an elementary mistake in empirical forecasting. The forecast of record times for running a mile proposed by Olshansky *et al.* violates this most basic methodological principle. Their example is not a valid indictment of forecasting methodology. It is simply a bad forecast.

In typical practice, logarithmic extrapolation is applied to mortality trends at individual ages. Thus, logarithmic extrapolation is equivalent to a model of exponential decay, which can be expressed in terms of half lives and rates of decay for age-specific death rates. This model also illustrates why a halving of current death rates should not be put forth, by mere assertion, as a "practical" lower bound that cannot be surpassed (*7*). In the United States during 1900–1995, the average half lives of mortality rates at ages 0, 20, 40, 60, and 80, were 22, 36, 46, 73, and 85 years, respectively (*8*). Thus, across the age range (except perhaps at very high ages), death rates for the U.S. population have been cut in half at least once during this century, and in some cases two, three, or even four times.

I agree completely with the Gavrilovs' statement that we need more interdisciplinary research on the driving forces behind age-specific mortality rates. Extrapolation has its merits, however, and for the reasons explained in my essay, I still think it offers the best prediction available to policy-makers and serves as a useful corrective for the incredible hype that surrounds the topic of human longevity. It is easy to claim special knowledge of "biological reality," but whose reality are we supposed to believe? As reviewed by Olshansky *et al.*, the specific quantitative predictions of evolutionary biology with regard to human life span are extremely vague. If there were a genuine scientific consensus about the biological basis of the human life span, and in particular about the degree of inherent plasticity in age-specific death rates, then demographers would gladly put aside their crude (but careful) empirical extrapolations. In the meantime, policy-makers need sound guidance about likely future trends. Un-

proven theories and wild speculation may be useful for formulating "What if?" scenarios, but they should not be canonized prematurely.

Finally, Olshansky *et al.* repeat an important point that I made prominently in my essay. Although death rates continue to fall at most ages in industrialized countries, and sometimes at accelerating rates of decline, the rise in life expectancy has slowed down. This phenomenon is well known to demographers and is due to the upward shift in the distribution of ages at death that resulted from an enormous reduction in infant and child mortality. In brief, saving infants and children adds many more years of life expectancy than saving elderly persons, and thus the historical increase in average life span slowed down once younger deaths became relatively rare.

Two important consequences follow from this observation. First, it motivates the standard practice of extrapolating age-specific death rates rather than life expectancy itself. Again, Olshansky *et al.* set up a straw man, consisting of an extrapolatory method that any informed observer would reject without hesitation, as a means of indicting a general practice that, if applied properly, is quite reasonable. Second, the predominant influence of the decline in infant and child mortality supports a widely shared belief that future gains in life expectancy will proceed more slowly than in the past. Nevertheless, this change does not signal a halt or even a slowdown in the historical progress against mortality, because the risk of dying at individual ages continues to fall, with some exceptions, as noted earlier. Furthermore, among the elderly, where most deaths now occur, observed gains against mortality in industrialized countries during the past few decades have been faster than ever before (*7*).

John R. Wilmoth
Department of Demography, University of California, Berkeley, CA 94720–2120, USA. E-mail: jrw@demog.berkeley.edu

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CORRECTIONS AND CLARIFICATIONS

In the issue of 28 August, the following References and Notes should have appeared at the end of the letter "Beetle Juice" (p. 1285).

References and Notes

1. See chapters in R. W. Hemingway and J. J. Karchesy, Eds., *Chemistry and Significance of Condensed Tannins* (Plenum, New York, 1989); for typical terpene compositions, structures, and references, see entry no. 6915, Oil of Lemon, and related entries for constituent compounds, as well as other essential oils, entry nos. 6866–6957, in *The Merck Index* (Merck, Whitehouse Station, NJ, ed. 12, 1996).
2. W. G. Glasser and S. S. Kelley, in *Encyclopedia of Polymer Science and Engineering*, H. F. Mark *et al.*, Eds. (Wiley, New York, 1987), vol. 8, p. 795.

A table that accompanied a News of the Week article by Daniel Clery about the research productivity of European cities ("London, Cambridge lead Europe in output," 21 Aug., p. 1127) incorrectly labeled the second of two columns of numbers ranking the publication output of various cities. The correct heading should have been number of papers "per 1000 residents," not "per capita."

In the Table of Contents (p. 877) of the 14 August issue (under Letters, in *Science's* Compass) separate authors should have been differentiated by semicolons.

The NetWatch item "Primal portraits" (7 Aug., p. 747) contained an incorrect image of a (non-grimacing) madrill. The "grimacing mandrill" can be found at www.selu.com/~bio/PrimateGallery/new/Lofton/mandrill_face01.jpg

In the Random Samples item "Green strategy for water flea?" (3 July, p. 39), "blue-green algae" was referred to as a plant. In most classifications today, "blue-green algae" is called "cyanobacteria" and placed in the kingdom Monera.

In the article "Elephantine gift stirs museum debate" by Eliot Marshall (News & Comment, 22 May, p. 1186), the name of the Smithsonian Institution's first benefactor should have been given as James (not John) Smithson.

In the report "Antagonism of central melanocortin receptors in vitro and in vivo by Agouti-related protein" by M. M. Ollmann *et al.* (3 Oct. 1997, p. 135), in the sequences in figure 1A, mature mAGRP and hAGRP should have begun with Val21 and Ala21, respectively, and mature Agouti protein should have begun with His23.