Chapter 13
Concepts and Theories of Longevity

Concepts of Longevity

This chapter is concerned with the concepts, statistics, theories, and future levels of human longevity, particularly extreme longevity. The term, extreme longevity or superlongevity, is used here to refer to centenarians, that is, persons with a verified age of 100 years or more. Among these we identify for special attention a subgroup known as supercentenarians, that is, persons with a verified age of 110 years or more. In both popular and scientific reporting, people aged 85 years and over have often been considered as extreme aged, but the rapid increase in the number of people in these older age groups suggests a redefinition of the notion of extreme aged. Persons in the broad age group 85 years and over are also referred to as persons of advanced age and the oldest-old. The former description now seems appropriate but the latter one does not. Preferences vary among demographers and gerontologists as to the choice of designations for these groups.

Until recently, the age of 100 has been used by demographers, epidemiologists, and others to define the life span of humans. This was considered to be the age to which a substantial number of humans as a species could survive under optimum health and living conditions, but beyond which only a negligible number of persons could be expected to live. The number defining the life span of humans was not based on any empirical investigation but on general observation, the indications of current life tables, and more importantly, conventional wisdom. Although human life span is a theoretical concept and measure for which no precise value can be given, it has been useful to have such a concept for tracking the gap between the longevity achieved by the average person in a given population and a hypothetical maximum longevity achievable by humans under the most favorable conditions. It also serves a useful purpose in comparative analysis of longevity with other species, to which similar measures have been assigned. In the later discussion, I elaborate on the concept of human life span, seeking to give it a more precise meaning.

Individual Measures

Age 120 has often been cited as the maximum life span for humans. This number does not originate in science, but rather in a passage that appears in the Old Testament, "My spirit will not contend in man forever, for he is mortal; his days will be a hundred and twenty years" (*Genesis* 6:3). The record for the maximum recorded human life span, or the highest verified age of a member of the human species, living or deceased, is held by Jeanne Calment of France, who died in 1997 at the age of 122 years, 164 days (Exhibit 13.1). There is no validated record of anyone ever surviving to this age or beyond except Mme. Calment. Discounting the case of S. Izumi (who is reputed to have lived 120 years, 237 days) as a case of incorrect documentation, Sarah Knauss appears next in rank for having lived to the age of 119 years, 97 days. Disregarding K. Hongo also (who had an alleged final age of 116 years, 45 days, but whose records were inconsistent), C. Mortenson (115 years, 252 days) is the oldest male ever to have lived. Survival of many persons even to age 100 is conjectural inasmuch as only about one percent of any large population survives to this age.

I assign the term maximum observed life span to the highest verified age for a living person. The identity of this person changes from year to year because of the high risk of death for people who have reached such advanced ages. As of July 1, 2008, the position is held by Edna Parker of USA at age 115 years, 1 month. The oldest living male is T. Tanabe of Japan, who is 112 years, 7 months, old.
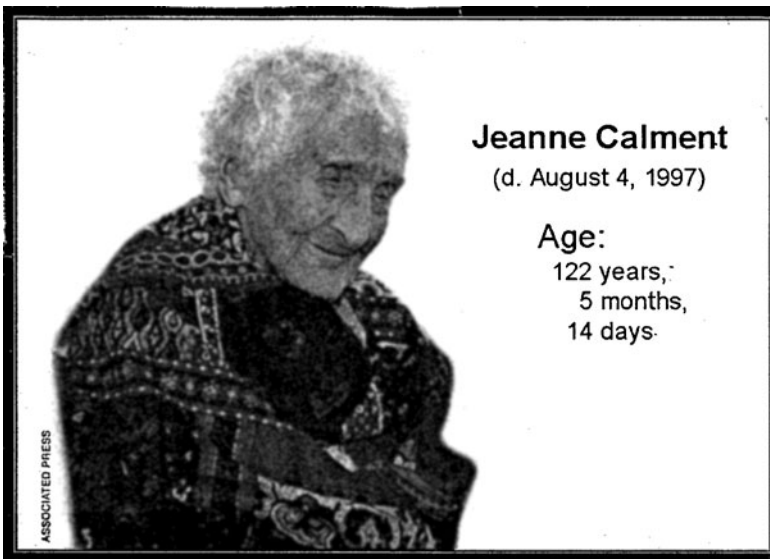

Exhibit 13.1   Portrait of Jeanne Calment, oldest person who ever lived, shown at age 122 years, 5 months, 14 days, just before her death in August 1997

The maximum age at death in a population in a given year is the age of the oldest decedent in that year. For 2007 the oldest authenticated decedent was E. del Toro of Puerto Rico, who died at age 115 years, 156 days. According to the Gerontology Research Group, as of spring 2008 there were an authenticated 77 living supercentenarians (66 females, 11 males). It is quite possible that there are many supercentenarians in the parts of the world other than in the Western countries, especially in the most populous countries such as India and China, but the records in these countries are inadequate for evaluating and authenticating any claims of superlongevity.

Population Measures

The measures of longevity given above relate to individuals. Several measures of longevity refer to population groups. Most simply, there are the absolute numbers of aged persons and the percent changes in these numbers. Table 13.1 shows the number of persons 85 years and over in the United States, distributed by age groups for three recent censuses and 2050 and percent changes in the intervening periods. Next, there is a group of measures showing different percentages of broader totals for the oldest populations. Table 13.2 shows, for example, the percent of the total population that is 85, 95, or 100 and over, the percent 100 and over of those 85 and over, and the percent 85 and over of those 65 and over. The table gives historical and projected series of such measures for 1900–2050, for the United States.

Several other measures focus on the population 100 or more and are based on either the actual population or life tables. One is the average or mean age of all persons 100 years or more. I designate this measure the average maximum life span – survivors; it represents the average age of persons over the age of 100 who are alive on a designated date. Depending on the interest of the analyst, either the data for the actual population or the data in the current life table may be employed to compute it. The corresponding measure for decedents 100 or more in a year is

Table 13.1 U.S. population 85 years and over, by age: 1980–2050

Age	Population (000)				Percent increase		
	1980	1990	2000	2050[a]	1980–1990	1990–2000	2000–2050[b]
Total, 85 and over	2240	3049	4240	20,861	36.1	39.1	392.0
85–89	1532	2047	2790	10,253	33.6	36.3	267.5
90–94	562	760	1113	6,473	35.2	46.4	481.6
95–99	132	205	287	2,984	55.3	40.0	939.7
100 and over	14[c]	37[d]	50[d]	1,150	164.3	35.1	2200.0

Source: U.S. Census Bureau: Internet, www.census.gov;decennial census data
[a]U.S. Census Bureau middle series projections, based on 2000 census
[b]Average decennial increases are 32 percent for ages 85 years and over, and 26, 35, 47, and 63 percent for the component age groups
[c]Records of the Social Security Administration; the census count, 32,000, was reestimated
[d]Reestimated as 22,000 for 1990 and 33,000 for 2000 by Kestenbaum and Ferguson (2005)

Table 13.2 Various measures of extreme population aging based on population data, 1900–2005, and projections, 2010–2050, by decades

Year	Percent 85+ of total pop.	Percent 85+ of 65+	Percent 100+ of total pop.	Percent 100+ of 85+
1900	0.2	4.0	NA	NA
1910	0.2	4.2		
1920	0.2	4.3	|	|
1930	0.2	4.1		
1940	0.3	4.0	|	|
1950	0.4	4.7	|	|
1960	0.5	5.6		
1970	0.7	7.5	|	|
1980	1.0	8.8	0.01	1.0
1990	1.2	9.9	0.01	1.2
2000	1.5	12.1	0.02	1.2
2005	1.7	13.8	0.02	1.3
Projections[a]				
2010	2.0	15.2	0.04	1.9
2020	2.2	13.3	0.07	3.3
2030	2.6	13.4	0.11	4.2
2040	3.9	19.2	0.15	3.8
2050	5.0	24.1	0.27	5.5

Source: U.S. Census Bureau: Internet, www.census.gov; various Census Bureau reports
NA reliable figures not available for years from 1900 to 1970
[a]U.S. Census Bureau middle series projections, based on 2000 census

called the average maximum life span – decedents; it represents the average age at death of those who die at age 100 or beyond in a year. These concepts of life span and their changing values clearly suggest that (maximum) life span is not a fixed number, as has so often been assumed in the past, but may change. Increases in average maximum life span can provide evidence as to whether the members of a given population are tending to live longer or not. Another group measure of extreme longevity, called life endurancy, is a life-table measure only. Life endurancy refers to the age to which 0.005%, 0.001%, or some other specified percent of the initial birth cohort in a life table survives. The shifts in this age for a given level of survivorship from birth may provide evidence that members of a population are living to increasingly advanced ages. Data for these and other measures of extreme longevity are shown in Table 13.3; they are based on the life tables for 1950, 1980, and 2000 prepared by the Office of the Chief Actuary of the Social Security Administration.

The various measures of life span discussed so far are to be distinguished from life expectancy at birth, which, as we have seen, represents the average years of life remaining for a child born in a given year for a particular population, as indicated by a life table. There is currently a gap of roughly 25 years between life expectancy at birth in the United States and average maximum life span (77 years vs. about 102 in the year 2000). This difference suggests how much progress in mortality reduction must be made at this time for the average person in the United States to reach the

Table 13.3 Selected measures of superlongevity of males and females based on period life tables for the United States Social Security Area: 1950, 1980, and 2000

Measure	Males		
	1950	1980	2000
Average maximum life span–survivors[a]	101.7	101.9	101.8
Average maximum life span–decedents[a]	101.9	102.2	101.5
Percent survivors 100 years and over	0.14	0.38	0.46
Percent survivors 100 and over of survivors 85 and over	0.5	0.9	0.7
Life expectation at age 100	1.92	2.20	1.98
Total life expectation at age 100[b]	101.9	102.2	102.0
Life endurancy (Pr $= 0.01$)[c]	95.1	97.4	98.2
Life endurancy (Pr $= 0.001$)[c]	100.7	103.0	103.0
Measure	Females		
	1950	1980	2000
Average maximum life span–survivors[a]	102.1	102.1	102.0
Average maximum life span–decedents[a]	101.6	102.5	102.2
Percent survivors 100 years and over	0.33	1.72	1.74
Percent survivors 100 and over of survivors 85 and over	0.6	1.8	1.5
Life expectation at age 100	1.92	2.42	2.26
Total life expectation at age 100[b]	101.9	102.4	102.3
Life endurancy (Pr $= 0.01$)[c]	97.5	101.5	101.4
Life endurancy (Pr $= 0.001$)[c]	102.4	106.4	105.9

Source: Based on U.S. Social Security Administration (2005, August)
[a]Mean age of life table survivors or decedents 100 years of age and over
[b]Life expectation at age 100 plus 100
[c]Age to which the proportion shown of the original birth cohort survives

average age of very long-lived persons. Assuming uniform reductions in death rates at every age, age-specific death rates for the United States in the year 2000 would have to decline by over 99% to achieve a life expectancy at birth of 100 for the population of the United States.

Sources of and Quality of Data

Data on the numbers, age distribution, and survival probabilities of the extreme aged may be obtained from censuses and various administrative records (e.g., the files of Social Security beneficiaries and Medicare enrollments). They may also be obtained from baptismal and genealogical records, and estimated from vital statistics or a combination of vital statistics and population data. For studying the issues of extended longevity, use can be made of aggregate data as well as microdata (i.e., individual-level data) drawn from the general sources just cited. Particularly valuable are historical data compiled in mortality and population

databases. Among the databases that are especially useful for studies of longevity are the Human Mortality Database (Univ. of Calif., Berkeley), the Utah Population Database (University of Utah), the Umeå Demographic Database (Umeå University, Sweden), the Iceland Demographic Database (deCODE genetics), the International Database on Longevity (Montpelier University and Max Planck Institute), and the Kannisto-Thatcher database on Old-Age Mortality (Odense University). For example, the Iceland database links genealogical data to medical information for the country's entire population (Amundadottir et al. 2004) and the Utah database provides genealogical, genetic, epidemiological, and demographic information for over 6.5 million individuals in the United States.

In general, the U.S. data on the extreme aged, both population and death statistics, have tended to be of too uncertain quality for researchers to be able to determine definitively what the true numbers at the advanced ages are. Often the people at these ages are unable to respond to census takers, so others, such as family members, neighbors, or nursing-home staff, report on their behalf with regard to their residence, age, and other demographic characteristics. Population coverage at particular ages in the census may be grossly misstated and ages are often misreported. In one classic example of age misstatement, analysts at the Social Security Administration determined that a significant number of people who were listed as centenarians in the 1990 Census were, in fact, under the age of 10 (Kestenbaum 1992). The reason for the error was that the wrong century was recorded as the year of birth. Census Bureau analysts discovered a similar problem in the 1970 census.

The data on deaths at the oldest ages from the vital registration system may also suffer from serious errors of age reporting. For example, the tabulations of deaths over age 100 for the United States have typically included some deaths at ages over 120. No validation of these ages has been conducted and it may be assumed that the persons have been assigned erroneous ages.

Because of these errors in population and death statistics, death rates at the highest ages, based on official collection systems and published in official publications, are often inaccurate and should be disregarded when the numbers of persons or deaths, and the resulting death rates, appear too erratic. Accordingly, the official death rates at advanced ages have at times been adjusted before use in life tables, such as by mathematical extrapolation of the rates recorded at the earlier ages or by borrowing rates from alternative sources.

Numerous devices have been employed to improve the quality of census population data. First, it is important to edit the microdata for obvious errors of reporting or processing. This procedure may eliminate only some of the erroneous entries but it is used largely to adjust the data only for gross errors. Sometimes more drastic adjustments or modifications are required. In one unusual case, the census of Taiwan in 2000, the elderly were reenumerated in face-to-face interviews after the initial general census had been conducted by mail-back methods (Yue 2005). Alternatively, the census data may be replaced by estimates when the original data are thought to be unreliable. One method of doing this is to extend census data from younger ages forward to the next census date by methods of demographic analysis.

For example, the population 80 years and over may be "survived" 10 years with the use of current survival rates in order to reestimate the population 90 years and over:

$$_{as}P_{90+} = {}_{as}P_{80+} * {}_{as}S_{a,a+5}{}^{a+10,a+15} \tag{13.1}$$

where *as* refers to age/sex detail and $S_{a,a+5}{}^{a+10,a+15}$ is a survival rate for a 5-year age group for a 10-year time period. This is a simple application of what is known as the cohort-survival method, involving the application of survival rates to the initial population distributed by age groups. Substitutes for census data may be employed for the base population, as by "projecting" Medicare enrollments for the population 90 years and over at one date forward for 10 years by survival rates to derive the population 100 years and over 10 years later (Kestenbaum and Ferguson 2005).

Another device that can provide alternative estimates of population at the extreme ages is "la méthode de générations extinctes," the method of population reconstruction by reverse cumulation of cohort deaths (Vincent 1951). In this method, for example, the population 90 years and over at a given past date is estimated by combining the deaths that have occurred or will occur to this cohort from the date of estimate forward until its complete extinction by death, that is, by adding, approximately, deaths 90 and over in year 1, deaths 91 and over in year 2, and so on.[1]

$$^{y}P_{90+} = \sum ({}^{y}D_{90+} + {}^{y+1}D_{91+} + {}^{y+2}D_{92+} + \cdots\cdots + {}^{y+15}D_{105+} + \cdots.) \tag{13.2}$$

The method assumes that ages of deaths are more accurately registered than the ages of the population are recorded and that reasonably good "guesses" can be made of the number of future deaths for the most extreme ages. A time lag is required for enough deaths to be registered after the reference date to complete the population estimate. This method is not useful for preparing a reliable current estimate of the population 95 or 100 years and over.

The age distribution of the older population for some countries, if considered to be reliably enumerated, may serve as model distributions for other countries whose data are not as accurate (Coale and Kisker 1990). For example, data on the age distribution of people at the most advanced ages for the countries of northern and western Europe are generally recognized as of superior quality. These data may serve as models of the distribution of the population at the extreme ages for other countries of Europe and the United States.

Another source of information on the identity of long-lived individuals in the United States is computerized online genealogies (Gavrilova and Gavrilov 2005). The names of the persons can be checked against early census data and the Social Security Administration's (SSA) Death Master File. Such match studies by the Gavrilovs demonstrated the value of computerized genealogies as a basis for developing a family-linked database on extreme human longevity.

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[1] In the actual computations, care must be taken to combine deaths that fall in the precise cohort for which the population is being estimated.

To derive mortality rates at the extreme ages, mathematical models may be fit to the mortality rates for the younger ages of the same cohort and then extended, but this procedure incurs the risk of failing to allow for any inflections in the series. Data on deaths from the SSA Death Master File may be substituted for the vital statistics from the registration system because of the presumed superior quality of the former. The mortality data for the extreme ages may also be taken from administrative records such as Medicare records, which contain both the numerator and denominator for computing such rates and are more thoroughly evaluated and edited than census data or vital registration data. Alternatively, the year-to-year changes in the death rates from the Medicare enrollments at the advanced ages (e.g., 85 years and over) may be linked to the death rates from the vital registration system at a younger age (e.g., 84 years). (See U.S. NCHS 2002a.)

The considerable uncertainty surrounding the reported figures on the number and ages of alleged supercentenarians and the timing of their deaths is changing, at least for some countries. Increasingly, methods of verification are being applied to the reports of supercentenarians and deaths at the very extreme ages, and a validated file of the extreme aged is being developed for several countries of northern and western Europe, Japan, the United States, and Canada. In recent decades two international collaborative efforts have been undertaken to assemble international databases on supercentenarians. One source of data on this special group is the International Database on Longevity, maintained by Montpelier University and the Max Planck Institute (Robine and Vaupel 2002), and the other is the Gerontology Research Group, which is located at the University of California at Los Angeles. Records in more than 10 countries of alleged supercentenarians are being collected from national statistical offices, health departments, other government agencies, and private sources, and validated by teams of researchers. They apply a variety of rigorous tests of assessing age, and maintain a running tally of all verified supercentenarians currently alive and of all previously authenticated supercentenarians. At the end of 2007 more than 500 validated records of supercentenarians have been assembled by these groups. We can now identify with some confidence the supercentenarians in these countries over the last several decades.

Because of the valuable information that living centenarians may provide on the factors contributing to longevity, several studies are being conducted that involve subject populations consisting wholly of centenarians. They are being interviewed periodically and, in some cases, physically examined. Among these centenarian studies are the Boston study (Perls et al. 1999), the Sardinian study (Poulain et al. 2004), the Okinawan study (Willcox et al. 2008), and the Georgia study (Poon 2008). Two of these are taking place in areas where there are known concentrations of centenarians – Sardinia and Okinawa. The latter are so-called founder populations; these are geographically isolated and hence are characterized by considerable endogamy and no immigration. The reader will note that I have not included the once-celebrated, but now notorious and debunked, centers of mythical superlongevity in Ecuador (Vilcabambans), Pakistan (Hunzas), and Georgia (Abkhazians), where the reports of superlongevity were grossly exaggerated (Leaf 1982).

Analysis of Changes at Very Advanced Ages

The number of persons reaching age 100 in any year may be viewed as the survivors of the births occurring 100 years earlier, augmented by immigrants and reduced by emigrants over this period with ages corresponding to the same cohort as the births.

$$^{y}l_{100} = (^{y-100}B * S_0^{100}) + (I_x - E_x) * S_x^{100} \tag{13.3}$$

where S represents a generation survival rate either from birth to age 100 (S_0^{100}) or from the median age of net arrival of immigrants to age 100 (S_x^{100}). For simplicity in this theoretical model, we are assuming that the level of mortality of the births and the migrants are the same, differing only for the length of the survival period and the ages of exposure, and that "net immigrants" are exposed to the risk of dying for the average period of their residence in the country. For countries not affected by immigration or, for the case disregarding immigration, the number of persons surviving to 100 is simply the product of the number of births 100 years earlier and a cumulative survival rate from birth to age 100:

$$^{y}l_{100} = {}^{y-100}B * S_0^{100} \tag{13.4}$$

The number of births and survival rates change continuously because of changing population size, age-sex composition, fertility and mortality levels, and migration. The annual changes in the current numbers of 100-year-olds reflect past changes in numbers of births, survival rates, and net migration. The numbers of current and future centenarians tend to rise if either past births or survival rates rose, if both rose, or if net migration led to an increase in population numbers. Similarly, the numbers of centenarians tend to fall if either the number of births or survival rates fell, if both fell, or if net migration was negative. For a heavily immigrant country with improving mortality, such as the United States was over the last century, the numbers of births would tend to rise from year to year a century earlier and the current numbers of centenarians would tend to increase from year to year. Concomitantly, the maximum age at death would tend to rise from year to year because, with each passing year, a greater number of survivors will reach any particular extreme age and will be available to survive to a higher age. The maximum age of survivors and of deaths will also tend to rise if the number of births remains unchanged and survival rates rise.[2] On the other hand, if either the number of births or survival rates fall, the number of centenarians, the maximum age at death, and maximum life span would tend to fall in later years. In sum, there is a long-term relation between the change in birth-cohort size and mortality trends, on the one hand, and maximum age at death and maximum life span, on the other.[3]

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[2]Consider a standard life table with a radix of 100,000 births and one remaining survivor at age 113. If the radix were 200,000, there would be two survivors at age 113 and one would likely survive to age 114.

[3]The average maximum life span, that is, the average age of persons 100 and over, would not necessarily rise if the number of births was increasing a century earlier or if survival rates over

Since the maximum age at death can be "driven up" in the way described, some analysts have concluded that maximum life span has no natural limit (Wilmoth 1998). Others have suggested that, even if population size rises and survival prospects for successive birth cohorts are improved, there are biological and biomechanical constraints on maximum life span that can only be overcome with developments in biogerontology that slow the aging process (Olshansky et al. 1990).

On the basis of population size alone, we would expect to find the greatest number of centenarians and supercentenarians in China and India, where the numbers of births have historically been huge in comparison to the numbers in the more industrial countries. These countries should also show an increasing maximum age of decedents because of presumed increases in the numbers of births a century earlier. We cannot be sure that these propositions are true, however, because historical survival rates in these countries have been so much lower than those of the more developed countries that the likelihood of survival of the larger numbers of births to the very advanced ages may have been sharply reduced. The census data and other source data on persons of extreme age for these countries have not been evaluated sufficiently to incorporate their records into a supercentenarian databank.

On the other hand, data that have been thoroughly evaluated for some countries of northern and western Europe provide the demographic evidence needed to demonstrate that the numbers of persons of extreme age and the maximum ages at death have been rising in these countries. However, the numbers of births have been falling in these same countries in recent decades. Many of the newborn children will survive beyond their 100th birthday, but the numbers of persons reaching such extreme ages as well as the maximum ages of deaths in these countries may tend to fall a century from now, unless sharply declining mortality at the advanced ages helps to maintain their numbers.

Historical and Theoretical Evidence for Increased Longevity

How long can humans live? Are there limits to life expectancy and life span? These questions have long intrigued not only scholars but the "average" person. The evidence, arguments, and theories relating to these questions are being debated by biodemographers, epidemiologists, molecular biologists, and other scientists. I consider these questions here under five headings, labeled (1) demographic perspective, (2) epidemiological perspective, (3) biological and biodemographic perspectives, (4) evolutionary perspective, and (5) engineering reliability theory. The dividing lines between these various areas of analysis are not clear-cut as all of them have interdisciplinary aspects, and hence the arguments overlap.

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the century have been rising. Such changes could make the extreme aged population "younger" as larger numbers of survivors reached the younger ages in the centenarian age range.

Demographic Perspective

To evaluate the possibilities for a rise in maximum human life span as well as a continuing increase in life expectancy, demographers have analyzed data mainly for the countries of northern and western Europe, Japan, and North America. As suggested earlier, the records for these countries, particularly those of northern Europe, are believed to be sufficiently accurate to serve as probative material for these questions. As evidence, demographers point to (1) the long, essentially uninterrupted historical rise in life expectancy, (2) the acceleration in the rise of the numbers of older aged persons (85 years and over), (3) the increase in the numbers and percents of centenarians and supercentenarians, (4) the steady rise in the maximum recorded life span and the maximum age at death, (5) the deceleration in the course of death rates at the advanced ages of the life cycle, (6) the lack of a strong positive correlation between levels of mortality and rates of improvement in mortality, and (7) the momentum of cohort succession.

Historical Trends in Longevity

In the United States life expectancy at birth grew at a rapid but diminishing pace over the century from 1900 to 2005. As the reader may recall, in 1900–1902 it was only 49; it reached 68 by 1949–1951; and in 2005 it stood at 78 (Table 6.3).

By fitting a straight line to the logarithms of the highest recorded annual life expectancy for any country for the 1900–2000 period (in effect, fitting an exponential curve to the original data for these countries), Oeppen and Vaupel (2002) observed that the national world record for life expectancy at birth has increased at a steady rate for more than a century. They then predicted that life expectancy would continue to rise in the United States at the same average historical pace as during the twentieth century, and reach 100 years by the year 2065. The past trend is a matter of record, but its use to "determine" the future in this way is a matter of debate. Lee and Carter (1992) applied time series analysis to age-sex-specific death rates from 1933 to 1987, with very different results from the prediction of Oeppen and Vaupel. Their projection of life expectancy for 2065 is well below 100 years – about 86 years – but substantially higher than the projection of the Social Security Administration's Office of the Actuary for that year – about 83 years.

As discussed in Chap. 6, several dozen countries around the world have the same or. greater life expectancies at birth than the United States. The U.S figures in 2005 were 75.2 years for males and 80.4 years for females. Japanese women are setting the international record for females with a life expectancy at birth of 85 years, and Icelandic men and Japanese men are setting the international record for males, with life expectancies of 79 and 78 years, respectively (Population Reference Bureau 2005). The rise in life expectancy at birth shows no signs of stopping at this date. The United States ranked higher among the countries with respect to life expectation at age 65 and even higher at age 85, particularly for females, in spite

Table 13.4 Life expectancy at age 85 and age 65 for males and females, for selected countries: 2003–2005

Country (year)	e$_{85}$ Male	Female	e$_{65}$ Male	Female	Ratio Male	Female
Australia (2003–2005)	5.9	7.1	18.1	21.4	.33	.33
Austria (2005)	5.3	6.1	17.0	20.3	.31	.30
Canada (2004)	5.9	7.2	17.7	21.0	.30	.31
Denmark (2004–05)	5.0	6.3	16.0	19.0	.33	.34
France (2004)	5.8	7.2	17.7	22.1	.31	.33
Germany (2003–2005)	5.3	6.1	16.5	19.9	.33	.33
Israel (2005)	6.5	6.7	18.0	20.2	.32	.31
Japan (2005)	5.9	8.0	18.1	23.2	.36	.33
Mexico (2005)	6.4	6.8	16.4	18.4	.33	.34
Netherlands (2005)	4.9	6.2	16.4	20.0	.39	.37
Spain (2003–2004)	5.4	6.2	17.0	20.9	.30	.31
Sweden (2005)	5.2	6.5	17.4	20.6	.30	.32
Switzerland (2004–2005)	6.7	6.8	18.1	21.5	.37	.32
United States (2005)	6.1	7.2	17.2	20.0	.36	.36
Uruguay (2004)	4.7	6.0	14.5	19.2	.32	.31

Source: UN *Demographic Yearbook*, *2005*, Table 22; U.S. NCHS/Kung, H.-C., et al. (2008). *National Vital Statistics Reports*, 56(10)

of its relatively poor record for life expectancy at birth (Table 13.4). As a result, the ratio of life expectancy at age 85 to life expectancy at age 65 is near the highest among the industrialized countries at 36.

As a result in large part of the increased survival to age 65 and the reduction of death rates above age 65, in the United States in recent decades, the numbers of persons 85 years and over and 100 years and over in this period have increased sharply (Table 13.1). In fact, there appears to have been an acceleration in the rise in the numbers of persons 85 and over and 100 and over. The number of centenarians appears to have increased 22-fold between 1950 and 2000, from 2,300 to 50,000, although even now centenarians are still relatively rare.

A definitive study of the relative contribution of fertility, mortality, and immigration to the recent rise in the number of centenarians in the United States has not been conducted. It is likely that all three factors contributed to the rise since the numbers of births were increasing during the last decades of the nineteenth century and the first decade of the twentieth century, mortality rates were falling steadily through the twentieth century, and the flow of migrants was strong at least until the First World War. However, I am postulating that most of the rise in the number of centenarians today can be attributed to the increased survival of the birth cohorts of a century earlier.

Whether we consider census data, vital statistics, Medicare data, or Social Security records, we cannot accurately assess the numbers and trends of supercentenarians in the United States because the U.S. figures are too unreliable for that purpose. Data from western Europe tell us that the number of supercentenarians is increasing rapidly in these countries (Robine and Vaupel 2002). The first

confirmed supercentenarians go back to the 1960s but their numbers have increased exponentially since then. It is uncertain how many supercentenarians might have [lived] prior to the twentieth century.

All of the measures of advanced longevity for the United States show net increases in the half century after 1950, but closer examination reveals that those measures reflecting change within the 100-and-over age group hardly increased between 1950 and 2000. According to the U.S. life table for 1950 the mean maximum life span of survivors aged 100 or more was 101.9 (for both sexes combined), and according to the 2000 life table, the corresponding figure was 102.0 years. In 1950 total life expectation at age 100 (life expectation at age 100 plus 100) was 101.9, and in 2000 it was 102.2. In 1950 the age corresponding to a life endurancy with a probability of 0.01 was 96.3 years, and based on death rates at that time, 0.24% of the initial birth cohort would survive to age 100.0. The corresponding figures in 2000 were age 100 and 1.22% of the initial cohort. From these figures and the others in Tables 13.2 and 13.3, we can reasonably conclude that survival to the century mark has been increasing, but that the measures of progress within the centenarian population do not show this trend. We cannot say with confidence, therefore, that the centenarian population in the United States in 2000 is older than it was a half century earlier.

Maximum Age at Death

The evidence from Europe gives a different impression. The maximum age at death or the maximum recorded life span has been steadily increasing at least for 140 years in Sweden (Wilmoth and Robine 2003). The "rate" of increase has also been rising. It was 0.4 year per decade before 1969 and 1.1 years per decade thereafter. Maximum age of death in several countries of Western Europe has risen even more rapidly. It rose linearly since mid- nineteenth century at an average "rate" of three months per year (2.5 years per decade) for females and at an average "rate" of 2 1/2 months per year (2.0 years per decade) for males (Oeppen and Vaupel 2002). For every year since 1977 the oldest validated age at death was 110 years or higher. For the 7 countries with the most thoroughly validated data, maximum age at death rose 1.4 year per decade from 1977 to 2000 (Wilmoth and Robine 2003). Wilmoth and Robine attribute the rise in the maximum age at death in Sweden largely to declines in mortality over age 70 and secondarily to increased numbers of survivors to old age (reflecting both larger birth cohorts and increased survivorship from birth to age 70).

Age-Pattern of Mortality Rates

In Chap. 3, I described various efforts to model the age-specific curve of mortality mathematically. Recall that the rate of increase in death rates according to the Gompertz model approximates constancy at most adult ages but then tends to

slacken off at the very advanced ages. At the more extreme ages the rate of increase may possibly become zero or even negative, although one cannot be certain of the pattern because of the sparseness of the data above age 105. As stated in Chap. 4, the phenomenon of decelerating old-age mortality was actually observed and reported by Gompertz using English data (Gompertz 1825). It has been known for more than 175 years, therefore. Other analysts have noted it in the years since 1825 and several of them have described it recently: Robine and Vaupel (2002); Horiuchi and Wilmoth (1998); Wilmoth (1998); Olshansky et al. 1998; and Robine and Saito (2003). The phenomenon has been observed to occur in several countries, and it has also been observed in a number of subhuman species. Robine and Vaupel (2002) reported, on the basis of the experience of a list of validated supercentenarians constructed from the International Database on Longevity (IDL; n = 159), a probability of dying at age 110 of 0.52 and then virtual stability of the rate just below this level until age 114. However, the sparse numbers used to generate these probabilities make it difficult to assess their reliability.

The deceleration in age-specific death rates appears to occur after about age 85 in the United States data. This pattern appears in the official life tables for the United States in 1979–1981 and 2000. These official U.S. life tables show rising rates of mortality between adjacent 5-year age groups until about age 85, after which the increase in the rates begins to drop off until about age 105. Table 4.2 shows rates of mortality change for single ages from age 84 to age 98 for 1997 based largely on Medicare data. There is a steady and substantial decline in the rate of increase in death rates over the whole range of these ages.

Some demographers maintain that the historical trends described and the pattern of decelerating rises in death rates at the later phases of the life cycle are inconsistent with the assumption of limits to life expectation and life span. They contend that, based on such evidence, life expectancy and life span can continue to increase without any specifiable limit and that there are no biological or demographic constraints on the trajectory of death rates preventing their rate of increase from declining to zero (Wilmoth 1998). According to this view, the maximum life span is indeterminate (Oeppen and Vaupel 2002; Vaupel 2003; Wilmoth (1997); Wilmoth et al. (2000).

On the other hand, maximum recorded life spans or maximum ages at death may be viewed as outliers not likely to characterize any general population. The upward trend in maximum recorded life span may come to a halt and reverse itself at any time. Past increases in the size of the population at advanced ages cannot assure us that the maximum age at death will continue to rise, because the sizes of birth cohorts a century earlier or survival rates at some higher ages may fall. The slowing of the rise of mortality rates in later life may be due in large part to the heterogeneity in the health composition of the members of a cohort. The concept of heterogeneity here implies that any cohort includes subgroups with different risk levels and, as a result, the subgroups with the higher hazard rates die off in greater numbers earlier in life while those with lower hazard rates survive to later ages. This process transforms the population in the advanced age groups into one with

more uniformly lower mortality levels than the "same" population at the younger ages, which included the less healthy subgroup that was eliminated. This process may also result in populations at the advanced ages that are healthier than the population in the same advanced ages at an earlier date. It can be demonstrated that the rate of increase in death rates with rising age of a population group can fall even though the death rates for the two segments of this group with different hazard rates are rising. However, some analysts argue that the relative declines in age-specific death rates at the advanced ages have been too great to be accounted for wholly by heterogeneity with regard to health (Vaupel 1997; Wachter 2003). They maintain that the deceleration of death rates is due in large part to declines in the hazard rate for individuals.

Temporal Shifts in Age/Cause Pattern of Mortality Rates

In Chap. 6, I described the epidemiological transition as a shift from diseases that are externally caused, acute, and relatively easy to treat (i.e., exogenous causes) to diseases that are internally caused, chronic and progressive, and difficult to treat (i.e., endogenous causes). In the industrialized countries deaths from the former causes typically occur in childhood, youth, and young adulthood. Death rates for these ages have fallen so low in these countries that there is little room for further improvement. Any further major improvement in mortality rates must come from reductions in the death rates at the older ages, where the deaths from endogenous causes are concentrated.

   The significance of this shift in the age-cause pattern of mortality is that further reductions in mortality could be increasingly more difficult to achieve because endogenous causes of death are influenced strongly by the biological processes of aging and knowledge of these processes is quite limited. Recall that, while death rates from the major cardiovascular diseases fell sharply in the 1970s and 1980s, the rate of decline since 1990 has been well below that for the earlier decades and the mortality from cancer, diabetes, and several other endogenous diseases had either increased or remained nearly stable from 1970 to 1990 or beyond. It is reasonable to contend, therefore, that the death rates from endogenous diseases are unlikely to decline during the next several decades at the same rate as they declined during the last several decades, and that overall age-specific death rates will not decline in this century at the same rate as they declined during the last century. The rates may not only show far smaller declines but they may even shift direction, as discussed further below.

Relative Changes in Mortality and Longevity

In Chap. 4, I indicated that relatively large declines in age-specific death rates have been associated with relatively small increases in life expectancy at low levels of

mortality. Refer again to Table 4.13 for a comparison of percentage reductions in age-adjusted death rates and percentage increases in life expectancy at birth during the decades from 1900 to 2000 for the United States. The historical relation between these series is not very close, however, so that we cannot say that, when U.S. life tables are analyzed over a range of mortality levels, declining increases in life expectation at birth are strongly associated with increasing reductions in age-specific death rates. That is, these data do not provide evidence of a strong negative correlation between changes in levels of mortality and changes in levels of life expectancy.

Although substantial reductions in death rates and substantial increases in life expectancy at the older ages occurred in the last half of the twentieth century, it appears that at current high levels of life expectancy sizeable percentage reductions in death rates must occur to achieve relatively small increases in life expectancy. For example, an increase in life expectancy from 77 years, the figure for the United States in 2000, to 85 years, or by 8 years, would require the equivalent of a uniform 50-percent reduction in age-specific death rates. Achieving a life expectancy of 100 would require a uniform reduction in present age-specific death rates of about 95% (See also Olshansky et al. 1990). Figure 13.1 illustrates the relation between a (uniform) percent reduction in death rates and the percent increase in life expectancy at birth, based on calculations with the U.S. life table for 2000 (e_0 = 76.9 years).[4] It shows a moderately curvilinear relationship between these measures. These calculated increases in life expectations associated with the assumed percent reductions in mortality rates are probably somewhat understated because they were based on a life table for year 2000 that terminated at ages 85 years and over rather than 100 years and over.

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[4]Keyfitz' H and Δe formulas, discussed in Chap. 4,

$$H = -\int_0^\infty l(x) \ln\{l(x) \div l_0\} dx \div T_0$$

$$\Delta e = -(-k)\, e_0 * H$$

can also be applied to derive a theoretical series of estimates of gains in life expectancy at birth corresponding to uniform percentage reductions in age-specific death rates for the United States in 2000 (H = .1590 and k = assumed percent reduction in death rates):

% reductions in death rates	Gains in life expectancy	Life expectancy
0	—	76.9
.10	1.22	78.1
.50	6.11	83.0
.80	9.78	86.7
.90	11.00	87.9
1.00	12.23	89.1

Again, we observe the curvilinear pattern of the changes in life expectancy. The series terminates with the unrealistic result that, with 100% reductions in death rates, e_0 increases by only 12.2 years.
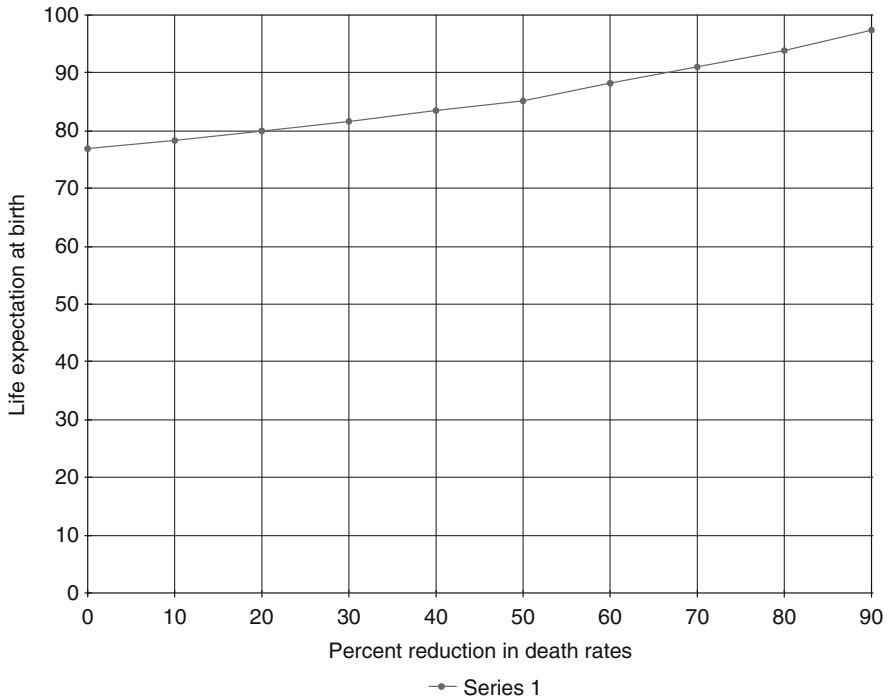
Fig. 13.1 Life expectancy achieved by reductions in life table mortality rates: United States, 2000 (Note: The estimates are biased upward to a small extent because the base life table for 2000 terminates at ages 85 years and over)

As noted, Oeppen and Vaupel (2002) predicted that life expectation in the United States would reach 100 years in 2060. According to the U.S. life table for 2000, only about 1.8% of a birth cohort reaches age 100 (U.S. NCHS 2002a) and the complete expectation of life at age 100 is 102.6. For a life expectation of 100 in 2065, about 56% of the birth cohort would have to reach age 100, age-specific death rates would have to be reduced by about 95%, and the complete expectation of life at age 100 would have to be about 106 years. This would be an amazing achievement! Olshansky et al. (1990) consider that attaining an expectancy figure of 100 is implausible, if not impossible, because it would require the elimination of all deaths from endogenous causes. My empirical calculations (Fig. 13.1) and theoretical calculations based on Keyfitz' H and Δe_0 also suggest that it is highly improbable that this goal can be achieved.

Cause-Elimination and Limits to Life Expectancy

If we track the life expectancy that would have been achieved in the United States between 1960 and 1990 on the assumptions that each of the causes of death

(including the "all other causes" class) was eliminated and that the causes are independent, we would have a nearly horizontal trend line at about 90 or 91 years:

Years	Life expectancy without "gains"	"Gains" in life expectancy	Life expectancy including "gains"
1989–1991	75.4	14.3	89.7
1979–1981	73.9	18.6	92.5
1969–1971	70.8	20.1	90.9
1959–1961	69.9	18.9	88.8

Source: Based on U.S. NCHS decennial life tables for the indicated years

For example, in 1990, the sum of the years gained by eliminating each of about 20 classes of causes of death, 14.3 years, and the current figure for life expectancy, 75.4 years, yields a total of 90 years. The corresponding figures for 1960 sum to 89 years (=69.9 + 18.9). Given the ongoing marked reduction of death rates at the older ages after 1970, and the associated rise in life expectancy, the total number of years gained by the independent elimination of the various causes of death would tend to decline after that year. The addition of the declining number of "years gained" to the rising life expectancy yields a series of hypothetical life expectancies of 89–92 years for the United States in these 30 years, with a mean of 90.5 and no discernible trend.

Inasmuch as this series displays a fluctuating trend rather than a monotonic one and is not fully comparable, it is not possible to extrapolate it with confidence. I would expect the series to be nearly constant if the data were accurate and the figures consistent and comparable. As life expectancy rises and cause-age-specific death rates fall during any period, the increase in life expectation and the reduction in the total gains from eliminating the various diseases should approximately balance.

Competing risks and comorbidity. The independent elimination of causes of death suffers from at least two interrelated paradoxes. The first is the so-called Taeuber paradox, which posits that the elimination of a cause of death in later life would result in increases in other associated causes since the population saved from one disease is exposed to the risk of dying from another. The assumed elimination would result in increases in the size of the population exposed to risk as well as in the rates for other causes that affect various ages in the same general vicinity as the cause eliminated. This is a reflection of the principle of competing risks.

The independence of mortality risks is not a realistic assumption for the relation of cause-specific death rates, as the Taeuber paradox suggests. Because of (1) the competing risks of death, (2) the multiplicity of causes that contribute to or are associated with each death, that is, the comorbidities characteristic of older persons, and (3) the impossibility of human immortality, in the event of the elimination of any cause of death, or even its sharp reduction, the death rates from other causes – particularly those usually associated with the cause eliminated and with average ages of death close to that of the cause eliminated – will tend to rise. Stallard's (2002) study of underlying and multiple-cause mortality showed

conclusively that "death is due not to just one single disease but to a complex set of interacting pathological processes. In these cases the designation of any single disease as the underlying cause of death provides a distorted description of the causal pathways." It is even conceivable that the sharp decline recorded for death rates from cardiovascular diseases between 1970 and 1990 "contributed" to some extent to the lack of substantial progress in reducing cancer during this period, even though cancer is not usually reported as a contributing cause of death from cardiovascular diseases. Accordingly, the net gain from eliminating some major diseases could be quite small, even over the short term.

The second paradox, which we may dub the cause-elimination limit, is closely related to the first. If we eliminate the causes of death as if they were independent of each other, as is assumed in constructing the cause-eliminated life tables of the National Center of Vital Statistics, the total number of years added to life expectancy at birth would amount to about 18 (ranging from 14 to 20), not the infinite number of years implied by the eradication of mortality. This interpretation of the cause-elimination tables suggests limits to the possibilities for extending life expectancy. The total of the gains from cause-elimination can be considered as a current maximum estimate of the possible additions to human life expectancy by eliminating various causes of death.

On the other hand, it could be argued that, if certain causes of death were eliminated, the death rates from some other causes would be lower than recorded because the specified eliminated cause could not have contributed to earlier deaths from these other causes. Furthermore, one might argue that, whatever factors contribute to declines in the risk of death from any single intrinsic cause are likely to have a similar dampening effect on other intrinsic causes of death. I believe, however, that this argument is less cogent than the one presented earlier.

It is unrealistic to assume that the major causes of death will be eliminated in the foreseeable future, but we may reasonably assume that some reduction in them can be achieved. The net effect on total life expectancy from the hypothetical elimination of any particular cause of death in an environment of competing risks can be only roughly estimated because the extent of the linkages of the various causes is not well known. With present knowledge, it is not possible to state how many years, if any, would be added to life expectation under the circumstances of the elimination of any single cause. It may not add any years to life expectancy in the real-life scenario. Hence, it may be hypothesized that the figure of 91 years could be viewed as a rough maximum for total life expectation for either males or females under the grand assumption of the reduction of death rates from a wide range of causes and the principle of competing risks.

Other Demographic Considerations

No chronic degenerative disease has been eliminated, or even nearly eliminated, in spite of all the efforts in this direction. There is no evidence that the age of onset of any major endogenous disease has been raised, although establishing the

age of onset of a disease is rather difficult. We have been able only to manage some of these conditions better so that their disabling effects are postponed and the quality of life for persons having the conditions is improved (e.g., hypertension, diabetes, atherosclerosis). Clearly some additions to life expectancy may result from medical interventions but these interventions can extend life expectancy only within narrow limits. Some classes of diseases may prove to be intractable. For example, the death rates from various forms of violence were reduced by only one-third between 1970 and 2000, so that these causes may be expected to continue contributing substantially to future mortality. As mentioned, the death rate for several leading endogenous diseases (e.g., cancer, nephritis, chronic obstructive pulmonary diseases, Alzheimer's disease) and septicemia, rose in this period and they may be expected to "ride high" for a long time. The obesity epidemic among children and the continuing widespread practice of smoking will contribute to the future difficulties of reducing the death rates of a range of endogenous diseases.

Epidemiological Perspective

The epidemiological view shares the demographic perspective in recognizing the role of the epidemiological transition (i.e., the shift from predominantly exogenous causes of death to the current dominance of the endogenous causes of death) and in having a moderately favorable view with respect to the prospects of reducing the endogenous causes of death. The "overweightness" and obesity "epidemic," especially among children, and persistence of smoking among a substantial share of the population, however, are expected to figure prominently in exacerbating the task of reducing the endogenous causes of death. Another major concern is the changing role of infectious diseases – a reflection of the new epidemiological transition. The resurgence of some old infectious diseases and the emergence of new ones may also make future progress in reducing mortality difficult, both at the younger and at the older ages.

Recent decades have seen the resurgence in the United States of several infectious diseases that had largely been obliterated, specifically measles, tuberculosis, whooping cough, and diphtheria, and the appearance of new infectious diseases, primarily HIV/AIDS, but also SARS, monkeypox, and West Nile virus. In addition, the death rate from influenza has increased considerably in the last decades of the last century. This trend is due to the diminishing effectiveness of many established antibiotics – the result of the mutation of viruses – the transfer of new viruses from animals to humans, hospital-acquired infections, the entry of masses of unskilled and uneducated immigrants, and the increasing numbers of poor persons, especially children, living or working under unhealthful conditions.

As suggested, an ominous threat is the recent sharp increase in "overweightness" and obesity – 37% between 1977 and 1999 – with their numerous negative health implications, such as an increased risk for diabetes, heart disease, hypertension, stroke, osteoarthritis, and various types of cancer (U.S. NCHS/Hoyert et al. (2004).

Olshansky et al. (2005) have estimated that the current negative impact of obesity on life expectancy in the United States will be a minimum of one-third to three-fourths of year, but that it is likely to rapidly approach and could exceed 3.5 years – approximately the negative effect of cancer on life expectancy.

Biological and Biomedical Perspectives

The biological perspective focuses mainly on the considerable age-related somatic deterioration after the peak fertility years in humans and most animal species, the relative contribution of genetic and nongenetic factors in health, disease, and human behavior, the many successes of medical and other human interventions, and the prospects for their continuation and extension.

Senescence

Given the steady accumulation of age-associated diseases with advancing age in the post-reproductive years, one can justifiably maintain that "normal aging" in humans is a roadmap to disaster in later life for most people. Accompanying the passage of chronological time and the accumulation of age-associated diseases is the process of senescence, the molecular and cellular pathogenesis that degrades the functional integrity of the physiological systems of the body. As a result, the longevity of individuals, as well as the life expectancy and average maximum life span of populations, are likely to be limited. Because of the biological processes noted, there is an average 50–80% loss in the functioning of the various physiological systems by one's 80th year relative to their peak capacity in adolescence. These relate to the functioning of the heart (e.g., reduced pumping rate), immune system (e.g., loss of bone marrow, compromised functioning of the system), endocrine system (e.g., declines in testosterone, estrogen, and growth hormone), lungs (e.g., lowered forced expiratory volume), kidneys (e.g., insufficient clearance of waste from blood), and bladder (e.g., reduced capacity) (US National Institute on Aging 2006). There are accompanying declines in muscle mass and strength, bone density, aerobic capacity, and glucose tolerance. The declines in psychological functioning are also enormous by the tenth decade (Baltes 2002).

The Aging Process, Molecular Instability, and Homeostasis

Since the leading causes of death are age-associated, the greatest risk factor contributing to increases in the leading causes of death with advancing age is the aging process itself. With increasing age, molecules, cells, organs, and physiological systems lose their functional capacity. In this way age changes increase the vulnerability to death of humans and other forms of life. Aging in later life may

be regarded largely as a stochastic (i.e., random) process associated with biological changes in the body. Hayflick (1998, 2004) describes the aging process from a biological point of view as the stochastically driven, systemic loss of molecular fidelity that, after reproductive maturation, exceeds repair capacity in animals that reach a fixed size in adulthood. Carey (2002) refers to aging as a shifting pattern of vulnerability to genetic and environmental insults. With advancing age the body finds it more and more difficult to maintain homeostasis (i.e., internal equilibrium of the various physiological systems), in spite of ongoing efforts toward repair, compensation, and accommodation. These efforts become increasingly less effective, and at some point it becomes impossible to achieve the proper functioning of one system without compromising the functioning of another system or systems and life itself is threatened. Biological research suggests, then, that death is the result of a number of probabilistic events, reinforcing one another.

Given these biological forces, Carnes and Olshansky (1993) see age 80 as the limit of the biological warranty period for humans and age 85 as the limit of life expectancy, barring scientific developments that slow the aging process (i.e., modify the biological rate of human aging). In their view survival to an age much beyond these years will be limited until such knowledge is secured. Hayflick (1998, 2000) is equally conservative. He argues that extending human life span can only be achieved by probing into the causes of the aging of cells, i.e., by determining why older cells are more likely to fail than younger cells, and he reminds us that, relatively speaking, not much research effort is being directed at this basic question. He doubts that the human life span can be significantly prolonged by genetic engineering. On the other hand, several other biogerontologists have a far more expansive view of the possibilities of slowing the age process, anticipating a considerable extension of human life span in this century.

Processes Contributing to Molecular Instability

Numerous factors and processes have been identified as contributors to molecular instability (Exhibit 13.2). These factors mainly cause genetic mutations. Among them are oxidative stress resulting from the action of oxygen free radicals and other oxidative processes in the cells – a product of cell metabolism-glycosylation (i.e., attachment of glucose) to proteins, DNA copying errors (including copy number variations), and radiation damage. Other destructive processes that have been identified are loss of heat-shock proteins, which aid in regulating the immune system, and DNA methylation, a process in which methyl groups, a class of air pollutants, attach to genetic material. The myriads of continuous cell divisions add to the risk of copying errors. As a result of these processes, over time genetic mutations accumulate. Some regulatory processes fail (e.g., tumor-suppressor and other disease-suppressor genes become ineffectual), and repair and scavenger operations, a process called autophagy, become weaker and cannot keep up with the destructive processes. In addition, some multifunctional genes that are beneficial early in life become destructive in later life, a process called negative pleiotropy.

A →	B →	C
Maintenance mechanisms	Causes of aging	Signs of aging
Continuous cell division	DNA copying errors Cumulative genetic mutations	Tumor-suppressor genes less effective
Detoxification of harmful chemicals[a] Autophagy[b]		Scavenger and repair operations less effective
Normal metabolic processes Proteostasis[c]	Oxidative stress Misfolding of proteins	Proteins cannot perform normal functions
Familial genetic characteristics[d] Negative pleiotropy[f]	Cell senescence[e] Glycosylation[g]	Loss and decreased effectiveness of heat-shock proteins[h]
Gene expression[i]	Mitochondrial dysfunction Methylation[j]	Genes are silenced; genes needed to suppress certain diseases are shut off
Epigenetic controls and stability[k]	Epigenetic defects	Development of tumors
Immune system		Decline in immune response
Temperature control Wound repair Physiological homeostasis[l]		↓ Cells die ↓ D Biological aging

Note: A factor in column A may lead to change in more than one process in column B and a factor in column B may lead to change in more than one process in column C. Roles of factors and processes overlap. Factors on the same row are not necessarily associated

[a]Including effects of radiation, smoking, and other environmental factors.

[b]Process by which defective and dying cells are cleaned up, often by self-ingestion by their own enzymes.

[c]The proper folding of proteins in cells

[d]For example, combinations of genes in siblings that support longevity

[e]For example, telomere shortening

[f]Multifunctional genes that are beneficial in early life but become destructive in later life

Exhibit 13.2 Principal biological factors in the aging process

[g]Glucose attaching to proteins; also known as cross-linking
[h]Heat-shock proteins (HSPs) are a family of proteins involved in maintaining cell homeostasis and regulating the immune system
[i]For example, genes that "drift away" from their early-life function of controlling development to other functions in later age
[j]Process in which methyl groups (CH_3) attach to DNA
[k]Epigenetics refers to the ways genes are expressed in different cell types and to the processes by which the genetic program is expressed in the development of an organism
[l]Coordinated functioning of all physiological systems, i.e., a healthful equilibrium of these systems

Exhibit 13.2 (continued)

Proteins do much of the work in the body at the molecular level. A protein's functioning depends on proper folding of its sections and alignment with other proteins. If a protein is formed incorrectly or becomes damaged and then misfolds, it cannot perform its normal function(s) or cannot be properly disposed of by cellular machinery. These processes lead to disease.

Another explanation also sees biological aging as primarily a genetic process, but differs from explanations of aging that focus on the accumulation of genetic (DNA) and cellular damage. This view posits that certain genes that control development weaken in time, "drift away" to other functions. Then, when they should respond to disease or injury to the body, they fail to do so and fail to support older cells in regenerating as easily as younger cells. This hypothesis does not assume that the aging process is directed by a few genes that specifically control longevity.

Identification of these factors and processes has given rise to many biological theories of aging, among them the free radical theory, the glycemic theory, the disposable soma theory, the wear-and-tear theory, the mitochondrial theory, the immunological theory, the neuroendocrine theory, and the autophagocytosis theory (the "junk" theory of aging). There are theories also as to how to extend human longevity, such as caloric restriction supported by optimal nutrition. There is an almost one-to-one correspondence between each maintenance mechanism, or the process by which it is compromised, and each theory of aging. For a long time researchers have devoted themselves to showing how one or another of these theories explains human senescence. More recently, it has been recognized that there are multiple causes of aging and that multiple deteriorative processes such as those described are all at work at once. Biogerontologists are taking a more synthetic view of the aging process (Holliday 2007:32). They are seeking new unifying theories at the same time.

One such general theory is Holliday's trichotomy of the availability of resources to sustain life into, first, normal survival functions such as feeding, metabolism, respiration, and other basic survival processes; second, functions of maturing growth and reproduction; and third, maintenance functions. (The theory resembles the disposable soma theory of aging, which states that the amount of energy available to an organism has three components – growth, reproduction, and maintenance.) The allocation of resources between the second and third functions – reproduction and

maintenance – varies widely among species, leading to the combination of early and high fertility with a short life span, or late and low fertility with a long life span (Holliday 2007:41–42). Aging, says Holliday, is "due to the eventual failure of maintenance. Maintenance is essential for the normal development of the adult and for the several decades of adult life. After that ... we are no longer able to sustain the status quo."

In sum, from the biogerontological point of view, the basis of aging is no longer an unsolved problem. We see that Holliday and Hayflick essentially agree with one another, as do other leading biogerontologists (e.g., Steven Austad, Thomas Kirkwood). As Hayflick (1998) has stated, aging occurs because the complex biological molecules in our bodies become dysfunctional over time as the body's repair systems suffer the same molecular dysfunction and cannot do their job as efficiently. The balance shifts in favor of the accumulation of dysfunctional molecules, and the person manifests the age changes that we associate with aging. The molecular dysfunctional events eventually lead to an increase in vulnerability to age-associated disease.

Genetic Influences on Longevity

We can analyze the problem of aging in terms of the extent to which longevity can be partitioned between genetic and nongenetic influences. Alternatively, we can ask whether humans are programmed for longevity. With the growing knowledge of the human genome, it is thought that it may be possible to identify a gene or combination of genes that are associated with longevity. "Gerontogenes," or "longevity-assurance" genes, are being vigorously searched out by some molecular biologists, such as Guarente and Kenyon (2000). (See also Hall 2003.) So far they claim to have found one or more such genes in some lower-order invertebrates, specifically nematode worms (*C. elegans*) and fruit flies (*Drosophila melanogaster*). Some vertebrates (e.g., tortoises, rockfish, and walruses) live a very long time by human standards, even in the wild, and they may have longevity genes. Molecular biologists have not yet found a longevity gene in humans. Many biologists maintain that there are no longevity genes in humans and question the relevance for humans of the research on aging of nematode worms.

Some studies claim to have evidence that longevity runs in families. Perls and associates found such evidence in data on centenarians from the Boston Centenarian Study. Perls and Terry (2003) examined 444 centenarian pedigrees with at least one member who was 100 years old and over. The centenarians had 2,092 siblings. The researchers found that the relative survival probabilities of brothers of centenarians were 17 times, and of sisters eight times, as great as those of the general population. Figure 13.2 depicts the superior survival of the siblings of these centenarians. The survival curves for male and female siblings of centenarians are compared with the curves for the general male and female populations as represented by the birth cohorts of 1900. The study of Perls and Terry and the studies cited below apply the research approach called demographic selection to centenarians, which analyzes the
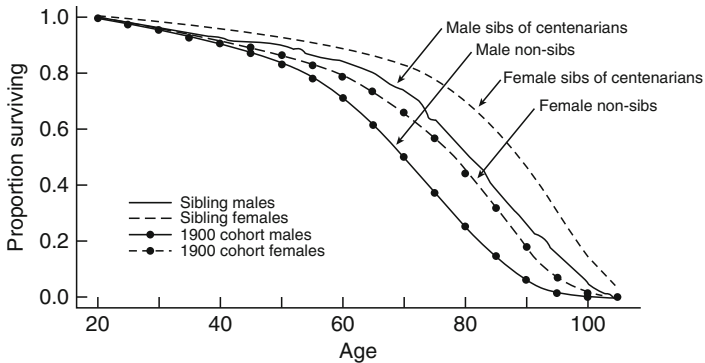
Fig. 13.2 Proportion of siblings of centenarians surviving from age 20 to later ages, compared with the survival of the 1,900 U.S. birth cohort, by sex (Source: Perls et al. (2002); Copyright © 2002 National Academy of Sciences, U.S.A. Reprinted with permission. Primary sources: Boston Centenarian Study; Social Security Administration, Office of the Chief Actuary/Bell and Miller (2002), Table 7)

characteristics and history of persons who are at the upper extreme of longevity to determine the factors that may have contributed to this outcome.

Twin and other family studies have shown a modest genetic effect on longevity (e.g., Ljungqvist et al. 1998; McGue et al. 1993.). A few recent studies suggest that the children of centenarians seem to be unusually healthy (Terry et al. 2004; Barzilai et al. 2001). The children show a markedly reduced prevalence of diseases and conditions associated with aging. Particularly notable are the low risk of cardiovascular diseases and the presence of favorable lipid profiles. According to Perls and Terry (2003), these studies support the hypothesis that phenotypic and probably genotypic characteristics conducive to exceptional longevity are transmitted in long-lived families.

More generally, it appears that a complex set of favorable genetic, environmental, and stochastic determinants of survival need to coexist for survival to age 100 and beyond to occur. Willcox et al. (2008) hypothesize that the high percent of Okinawan centenarians has resulted from just such a coalescence of favorable genetic factors, favorable lifestyle and social psychological factors, including caloric restriction, and a superior public health system.

Biomedical Developments

There are many ongoing and prospective innovative biomedical and sociomedical programs and developments that seek to restore health and reduce mortality. These programs and developments hold out the promise of greatly improving the health status of people of all ages and also increasing human life expectancy. These developments are described in a later section.

Evolutionary Perspective

Some arguments of those who maintain the view that there is a limit for human life expectancy and life span rest on the role of evolutionary biology in aging and senescence. In trying to answer the questions, is there an upper limit to human life, and if so, what is it, evolutionary biology brings to bear the comparative analysis of the longevity of different species, including invertebrates as well as subhuman vertebrates. Comparative analysis of primate life spans conducted by Judge and Carey (2000), correcting for body and brain size, suggests that the evolved life spans of humans probably fell in the range of 72–90 years. These numbers are important because they set a line between the segment of human life span that evolved (e.g., 75 years) and the segment that is very probably an artifact of living in a protected environment (that is, greater than 75 years).

Role of Natural Selection in Prereproductive, Reproductive, and Postreproductive Life

Evolutionary theory informs us that animals have responded to the high levels of extrinsic mortality (i.e., accidents, disease, starvation, and predation) throughout their existence on earth by reproducing early in life – 40 years of age or younger for humans – and then experiencing failure of their bodily structures. This evolutionary mandate dictates an age beyond which the probability of continued survival is extremely low. Only a century ago life expectancy hardly extended past the reproductive years, but today most people survive well beyond the ages of reproduction. Carnes et al. (2003) have called the extended period allowed by evolution for human survival the "biological warranty period." For them, the duration of life needed by humans to achieve maturation and reproduction – the period from about age 13 to about age 40 – helps define the beginning of their biological warranty period.

Evolutionary theory also maintains that somatic degradation is associated with the decline in the force of natural selection in later life. That is to say, after the end of the reproductive period, natural selection does not work to preserve the integrity of body structures and processes with the same level of efficiency as it did before puberty and during the reproductive period. Maturation and reproduction are the key elements in the survival of a species and pressures from extrinsic causes of mortality (i.e., accidents, predation, starvation, infectious diseases) establish a period within which maturation and reproduction must occur. The time scale for reproduction and natural selection vary according to the life span of the species, but the curves of the force of natural selection for sexually reproducing organisms, particularly mammals, look nearly identical to one another, as do those of reproductive success and mortality (Carnes et al. 2006). Figure 13.3 is a generalized portrayal of the decline in reproductive success for humans, with one curve reflecting the declining effectiveness of natural selection during the reproductive period, and with another curve reflecting the rise in mortality and the decline of natural selection in later life.
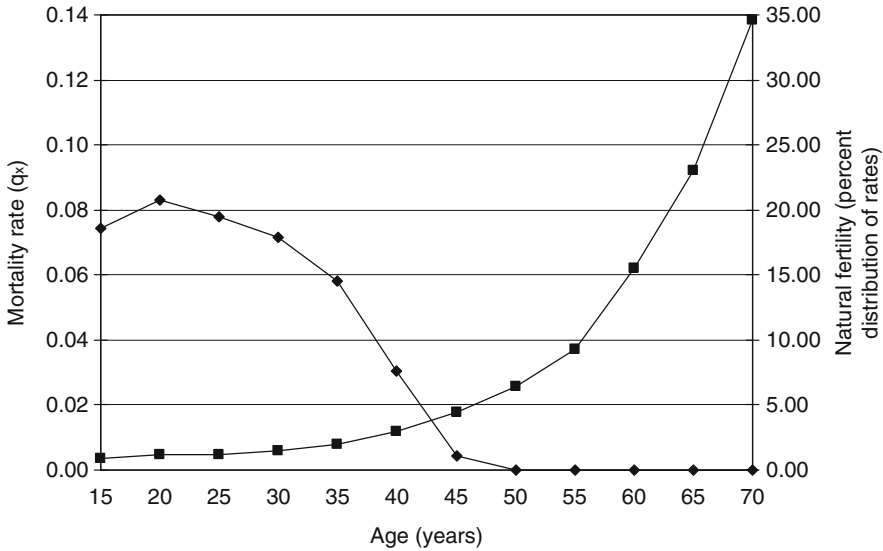
Fig. 13.3 Stylized representation of the age patterns of natural fertility rates and U.S. mortality rates for women (Note: Points are plotted at the initial ages of the 5-year age groups to which they apply;) Source: U.S. NCHS (2002a) and Table 13.2

Reproductive success is represented by the curve of natural fertility, as the latter term was defined in Chap. 9. As one curve falls, the other curve rises.

The lack, or near absence, of selection pressure in the postreproductive period suggests that there is no evolved aging process in this period of the life span. According to evolutionary theory, natural selection operates primarily on traits that affect an organism's ability to reproduce; accordingly, one would not expect evolution to favor genes that extend an organism's life much beyond its reproductive years.

Factors Accounting for Postreproductive Life

Evolutionary biologists have been trying to provide explanations in evolutionary terms as to why humans live as long as they do after the reproductive period. Postreproductive individuals are rarely found in nature except in a few species, and the period of postreproductive survival in nonhumans is relatively short (Austad 1997). In contrast, such individuals are common in captivity, especially among other primates. We seek to know whether the long postreproductive life of humans is an adaptive result of natural selection or is a non-adaptive artifact analogous to the postreproductive life of captive animals. According to Austad (1997), the commonality of postreproductive survival among captive animals does not mean that their increased longevity has evolutionary significance; these animals were simply not designed for such a long survival. Carey (2003) notes that various species have latent mechanisms, set in motion by certain environmental conditions, to

enhance their abilities at somatic maintenance and repair at the cost of reproduction. Among these environmental conditions that may contribute to their longevity is a scarcity of resources that may postpone certain physical developments in the species. Parents' raising younger generations and playing a role in intergenerational support may also prolong postmenopausal life. In contributing to the survival of their children and grandchildren, parents and grandparents serve a function in the evolutionary scheme.

Three factors appear, then, to account principally for the extension of life expectancy of humans beyond the prime reproductive years. First, evolution has endowed the body with a reserve capacity so as to assure the completion of its reproductive mission. It would be inefficient to risk failure in this mission by not building in such a reserve capacity, given the ever-present extrinsic factors vying for the life of the person. This implies that survival well past the end of the reproductive period can occur because we are essentially living on our physiological reserves. Next, evolution may have a "reproductive" role for older people. Most parents become grandparents and are thus available to nurture and train the young, who may go on to achieve successful reproduction (Vaupel 2003; Austad 1997). The extended longevity of *homo sapiens* evolved in a socio-ecological context of favorable environments (e.g., extensive parental care and investment, a high level of sociality), similar to the experience of subhuman primates and eusocial insects (Carey 2002). Finally, trends in life expectancy suggest that human intervention may have contributed to the success of many people in approximating, and of some people in exceeding, their biological warranty period. Survival into the postreproductive years has been achieved by human ingenuity and self-discipline, including public health innovations, medical developments, environmental improvements, increased knowledge of how to care for oneself, and especially lifestyle changes (Carey 2003).

While traditional evolutionary theory maintains that there is a tradeoff between investment in children and a female's survival that distinguishes the various species (Kirkwood and Rose 1991), for given human societies older mothers appear to live longer. Selection for reproductive success may be a principal factor in selection for longevity. Perls et al. (1997) support this interpretation. Mueller (2004) disputes it. She believes that the greater longevity of older mothers can be explained by genetic heterogeneity between family lineages, by differences based on socioeconomic status (that is, the more affluent women are likely to sire their children at older ages and to have higher survival prospects as well), or by both.

Age-Trajectory of Mortality Rates

As noted in Chap. 3 and earlier in this chapter, where the data are reliable, the rise in the curve of mortality rates for humans tends to slow down after about age 85 or 90 and may even level off and reverse direction above age 110. The classical evolutionary theory of senescence generally supports the view that the mortality rates at the higher ages in most species rise steadily, possibly exponentially. However, Carey et al. (1992) and Curtsinger et al. (1992) have shown that the hazard rates at extreme

ages in several invertebrate species (e.g., medflies, nematode worms, and yeast) do not continue to rise exponentially. In numerous species the fundamental shape of the hazard curve is approximated by the Gompertz formula (that is, a pattern of unchanging rates of increase in the hazard rates from young adulthood) only up to a point, after which the hazard rates decelerate (Finch 1990). This interspecies similarity suggests that the same biological patterns apply to human and subhuman species. On the other hand, there is considerable variability among species and within species in the manifestations of aging, senescence, and death.

Summary of Evolutionary Role

In sum, an evolutionary approach to longevity posits that there is a tradeoff between the level of fertility and the level of survival, and links duration of life to the timing of sexual reproduction. Extended human survival in the postreproductive segment of the life span is determined by the excess physiological capacity available after the period of reproductive success. Natural selection and evolution operate only up through the reproductive period, but then other biological, cultural, technological, and social influences begin to dominate. Life expectancies at birth that extend beyond the reproductive years are a recent historical phenomenon. Large-scale survival into the postreproductive period and the associated ascendance of the intrinsic causes of death over the extrinsic causes in the mortality schedule reflect the triumph of human ingenuity over many extrinsic causes and the apparent success of human intervention over the evolutionary process. At present, evolutionary biologists cannot agree on a convincing and consistent explanation for the considerable postreproductive extension of human life, but the several factors noted appear to play important roles (Austad 1997).

Engineering Reliability Theory

Finally, I consider engineering reliability theory. This theory describes the age pattern of the failure rates of manufactured products and has been interpreted as a general theory of aging and longevity. It purports to explain the peculiarities of the age trajectory of mortality rates on the basis of users' experience with manufactured products as these products age. The theory has been adapted to explain the age pattern of living things (Gavrilov and Gavrilova 2004, 2001). The bimodal shape of the curve for human mortality shown in life tables is observed for the curve of failure rates of machines such as automobiles (Siegel 2002). The failure rate of machines follows the Weibull model rather than the Gompertz model:

$$\mu_x = \mu_a \, Bx^c \tag{13.5a}$$

$$\ln \mu(x) = \ln \mu_a + \ln B + c \ln x \tag{13.5b}$$

Here the age-pattern of the force of mortality is assumed to be a power function of x. This formula is applied widely in the analysis of the reliability of manufactured products and in the implementation of proportional hazard models (see Appendix 1):

While machines begin life with all new parts, some come out of the factory with defects. Human beings begin life with all new but many defective parts also. On the other hand, humans have the advantage of many redundant parts, unlike most machines. According to reliability theory this redundancy may help explain the extended life expectancy of human beings after menopause. As with living things, the failure rates of manufactured products show a deceleration of the rates of increase at the advanced ages. Reliability theory has been used to argue that, given that the curve of mortality rise more slowly or even levels off at the advanced ages, there is no fixed limit to life span. This interpretation of reliability theory also rejects mortality compression theory on the basis of the latter's assumption that there is a limit to human life span. On the other hand, some analysts apply the analogy of the "sudden death" of manufactured products (e.g., automobiles) to humans and thereby argue that humans have a fixed life span that cannot be exceeded without slowing the aging process.

Research Programs to Increase Longevity

Two opposing, but not entirely mutually exclusive, positions have been taken as to how to extend human life expectancy and life span. One view, that of clinical medicine and geriatrics, would primarily direct efforts at the reduction of the death rates for specific chronic diseases of later life, such as the heart diseases, malignant neoplasms, diabetes, and Alzheimer's disease. The other view, that of biogerontology, would primarily seek to maximize efforts at understanding the networks of molecules that comprise cells and tissues, the ways these networks are regulated and interact with each other, and the molecular events that lead to health or disease. By devoting resources to understanding the basic processes by which cells become dysfunctional, the dynamics underlying a range of diseases may be discovered and more years may be added to life expectancy than by trying to reduce the incidence of specific diseases.

Biogerontologists maintain almost with one voice that success in the research on the molecular changes in the human body that occur with increasing age could lead to greater extensions of life expectancy and life span than research on specific major causes of death. From their view, study of the individual causes of death as such contributes little to the understanding of the process of aging (Hayflick 2000). Research in understanding why cells age is expected to lead to the control of a number of chronic diseases, thus adding greatly to human longevity. To extend human life to any marked extent, the basic processes of aging have to be understood before any of the chronic diseases of later life can be eliminated. To do this,

we have to learn how to modify the processes that degrade the surveillance, maintenance, and repair processes of cells, cause disease, and ultimately cause the molecules needed for survival to lose their molecular fidelity. At present the only way to extend life is

through interventions that manufacture survival time by treating the manifestations of disease processes. Some of the interventions, like an appendectomy, cure the problem by eliminating it. Others like heart bypass surgery and dialysis treat the disease processes but do not eliminate it. There are limits to the number of years that can be added by such interventions (B.A. Carnes, 2004, Private e-mail communication,B.A. Carnes to J.S. Siegel, 2/23/04).

Carnes et al. (2003) maintain that human bodies are not designed for extended operation and the historical ascendence of the intrinsic/endogenous causes of mortality over the extrinsic/exogenous causes suggests that the individuals in the more developed regions may be rapidly approaching their life span potential.

Many approaches are now being pursued by molecular biologists and research geriatricians to extend human longevity. Several of these confront the very processes by which cells are formed, are repaired, and die. One such area of research is the process by which telomeres, the caps at the ends of the chromosomes in the cells, shorten, leading, by their excessive shortening, to cell death (apoptosis). Another such area of research is the process of autophagy, by which used-up proteins, invading microorganisms, and malfunctioning organelles are cleared away in order to keep cells healthy. A third area relates to the processes by which body tissues are regenerated, whether it is nerves (neurogenesis), blood vessels (angiogenesis), or bones (osteogenesis). Knowledge of how to control these processes might enable the researcher to slow the rate of cell death, maintain the efficacy of the "clean-up" operation, or replace tissues that have died.

Improvements in health and increases in longevity could come from further progress in a variety of technical fields: Regenerative medicine, genetic engineering, tissue engineering, nanotechnology, and sonocytology. Regenerative medicine refers to the use of human and other organic materials to stimulate the body's healing power and replace defective parts, and includes such procedures as bone marrow transplantation, joint replacement, organ transplantation, and cartilage cell transplantation. Genetic engineering includes recombinant DNA applications (e.g., gene splicing), in which drugs based on human proteins, such as recombinant human insulin (for diabetes) and interferon alpha (for boosting the immune system in the treatment of hepatitis and cancer) are used to treat common diseases. Engineers in the relatively new field of tissue engineering are working on ways to help the body grow new cartilage, bones, organs, and other tissues damaged by injury or disease. Nanotechnology involves the application of engineering at the molecular level, including the creation of biological robots that can visualize the human body at the subcellular level and identify and prevent disease before symptoms appear. Robots may someday be programmed to maintain homeostasis, keeping body cells in a state of equilibrium. Sonocytology would advance the practice of ultrasonography by providing sonograms for the internal organs at the subcellular level, thus making possible the detection of abnormalities at a very early stage.

Other possible developments include new drugs and medical devices, such as improved medical imaging devices, sensor-driven drug delivery, remote monitoring devices, and implantable neurostimulation systems. We can envision, in addition,

expansion of such areas of research as caloric restriction, preservation of heat-shock proteins, hormone treatments, and control of lifestyle risk factors (e.g., diet and exercise).

For further discussion here I select six promising approaches that may be expected to contribute to human longevity during the next half century: Improvements in the functioning of the immune system, genetic alterations, caloric restriction, organ regeneration and replacement, technological advances in robotics and imaging, and pharmacological interventions. These approaches are generally more consistent with the broad-spectrum view of the molecular biologist than the single-cause approach of the geriatric researcher.

Improving the Functioning of the Immune and Endocrine Systems

Research into the study of the change in the functioning of the immune system as the body ages is driven by the fact that the aging process is associated with a reduction in the ability of the immune system to respond to the demands made on it and that this reduced response contributes to more infections, more inflammatory diseases, more uncontrolled growths, and slower recovery from attacks by external microbial agents. The evidence of the consequences of the reduced efficiency of the immune system is widespread. For example, the elderly are far more likely to contract infectious diseases such as influenza, pneumonia, and gastroenteritis than persons of middle age.

Research is aimed at ways of strengthening the aging immune system, as by modifying the diet, pursuing appropriate exercise programs, reducing stress, avoiding environmental assaults, securing recommended vaccines, and adopting other lifestyle changes. Efforts are being made to achieve more widespread acceptance of existing vaccines for adults, such as the pneumococcal pneumonia vaccine, the HPV vaccine (human papillomavirus vaccine), the adult pertussis/diphtheria/tetanus vaccine, and the new vaccine for shingles; and to develop a new vaccine for HIV/AIDS. Because HPV infections cause most cases of cervical cancer, this disease may be eliminated soon in the industrial countries. These vaccines deal with microbial diseases, however, rather than with the endogenous/intrinsic diseases of later life.

Two other physiological systems, the endocrine system and the neurological system are also extremely important in the aging process, and collaborate closely with the immune system in directing and monitoring the other physiological systems of the body and in maintaining homeostasis of body processes. They are involved in metabolism and waste discharge (i.e., via the gastrointestinal system and urinary system), locomotion and coordination (i.e., via the musculoskeletal system and circulatory system), and sensory responses.

The endocrine system produces hormones that are needed for the effective functioning of all the other systems of the body. Like the immune system, the

endocrine system functions less efficiently with advancing age. Some research has been directed at the effects on health and mortality of different levels of hormones and the effect of supplementing the body's natural production of various hormones. For example, DHEAS (i.e., dihydroepiandrosterone sulphate), the major sex steroid produced by the adrenal glands, is claimed to have anti-aging effects. DHEAS levels decline greatly with age. Low DHEAS has been associated with increased cardiovascular mortality in older men. The relation of DHEAS and mortality in older women has not been firmly established, but a U-shaped relation between the level of the hormone and adverse effects in women has been tentatively shown (Cappola et al. 2006). A U-shaped relation has commonly been seen by researchers in endocrinological conditions. Such a pattern of pathology with deficiency and excess is seen in hyperthyroidism and hypothyroidism, and Cushing's syndrome and adrenal insufficiency. Understanding this relation is important in order to determine whether dietary supplementation of DHEAS is desirable for prevention of premature mortality.

Genetic Alterations

Success in mapping the human genome has opened up a multitude of possibilities for research in associating particular genes with particular diseases and with aging. Some molecular biologists are researching the possibility of the existence of a "longevity gene" or combination of such genes. They hope to find a longevity gene or genes in humans equivalent to those found in a few invertebrates. C. Kenyon, L. Guarenti, M. Rose, and other molecular biologists are anticipating success here and have teamed up with genomic production companies. L. Hayflick, J. Olshansky, and B. Carnes, among others, strongly discount this possibility. The former researchers are trying to find common genetic pathways to aging across species by exploring biologically conserved mechanisms of senescence. They believe that aging is caused, or substantially influenced, by a limited number of critical "gateway" genes, and that if the existence of these genes can be discovered and a way can be found to manipulate their gene products, life in all the species, including humans, can be dramatically extended.[5]

Genetic alterations can now add many days to the life of a mouse. Experiments with mice carried out by Rose suggest that the longevity of mice can be increased by selectively breeding the mice that have offspring late in the reproductive period. There is also evidence that women who have children late in life live longer than

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[5]Some scholars oppose calling the genes that influence the duration of life "longevity genes," principally because the use of this term implies that such genes are the direct product of natural selection. They maintain, rather, that these genes are an inadvertent by-product of genetic programs for growth, development, and reproduction, and that manipulating them to extend life will also influence these early life processes.

other women (Doblhammer 2004). If the genetic paths that lead to longer life in humans can be determined, drugs could be devised by which the aging process could be manipulated.

Genetic alterations can also be achieved by gene therapy[6] and by stem-cell therapy.[7] Gene therapy and stem cell research hold promise for treating and even curing a wide range of chronic illnesses. The sequencing of the human genome poses new possibilities for progress through gene therapy, even though at present the functions of most genes, and the combinations of genes that oversee most cellular and tissue functions, are unknown. Gene therapy is being widely explored. For example, gene therapy is being used to stimulate bone growth (i.e., osteogenesis). It is being evaluated for its effectiveness in stimulating the growth of blood vessels (i.e., angiogenesis) and reducing, for example, the effects of peripheral artery disease. Alternatively, gene therapy is being evaluated for its effectiveness in suppressing angiogenesis (i.e., anti-angiogenesis) and thus cutting off the blood supply to unwanted body growths. Anti-angiogenesis therapy in the form of anti-angiogenic drugs is being experimentally used to treat macular degeneration. Scientists have already found genes that are tied to particular diseases, such as Alzheimer's disease, and scores of genes linked to cancers, and they have identified genes that support particular functions, such as angiogenesis.

Like gene therapy, stem cell research holds promise for treating and even curing a wide range of chronic illnesses. Stem cells, particularly embryonic stem cells, can be programmed to grow into a variety of specialized cells and tissues. There is widespread hope, therefore, that embryonic stem cell therapy will make possible cures for Alzheimer's disease, Parkinson's disease, spinal cord injuries, and many other leading chronic diseases. Stem cells are now being experimentally injected into hearts to determine their regenerative capability and their ability to improve the function of hearts that are not receiving enough blood. Stem-cell therapy is now being used in the form of bone marrow transplantation for some types of cancers. It may eventually be used to replace the damaged nerve cells in the brains of Alzheimer's-disease patients.[8] The transplantation of blood-forming stem cells combined with an immune-suppressing drug (rapamycin) is being used to test the

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[6]Gene therapy has been made possible by the development of recombinant DNA technology, the process by which DNA can be split into pieces, recombined in new ways, and reinserted in new places in the body.

[7]Stem cells come in several types but all are pluripotent, that is, they can turn into many types of tissue–muscle, bone, skin, and so forth. The most versatile and promising stem cells are embryonic stem cells, but there is a controversy over their use because, in being harvested from embryos, the embryos are destroyed. This issue is discussed further in Chap. 17. I imagine that this controversy will be resolved shortly and that embryonic stem cell research will soon be widely employed in the pursuit of cures for the major illnesses of later life.

[8]For example, M. Tuszynski (Univ. of CA, San Diego) injected the brains of eight early-stage Alzheimer's patients with their own skin cells. These cells had been genetically engineered to produce nerve growth factor, a chemical that boosts repair and regeneration of the brain's nerve cells. The preliminary results showed the technique to be safe and somewhat beneficial (*AARP Bulletin*, July-Aug. 2004:13).

possibility of reversing sickle-cell anemia in adults. A combination of gene therapy and stem cell therapy is currently being tested on diabetic mice in the hope of improving blood flow, with considerable success to date.

Organ Regeneration and Replacement

We have arrived at the era of regenerative medicine and tissue engineering, with the expectation of replacing most organs, tissues, and cells. A continuing problem in medical care is the shortage of body organs for transplant. This is motivating a research effort to determine the conditions under which body organs can be regenerated or humans can receive organs from animals. One research protocol now under way is to transplant the hearts of pigs into baboons, with the intent that at some future time the pig hearts can be transplanted into humans. The process of transplanting animal organs into humans is called xenotransplantation.

Attention is being directed to the study of salamanders, a lizardlike amphibian, that can naturally regenerate its appendages when they are amputated. This is the only vertebrate that has this ability and further understanding of it may give clues as to the ways that regeneration in humans might be accomplished.

Caloric Restriction

Calorie restriction (CR) stands as the single method now known than can increase human longevity, or at least is a reasonably promising device for increasing human longevity. Numerous animal experiments have shown that a nutrient-dense diet, low in calories and low in fat, promotes health, retards aging, and extends life span (Fig. 13.4). It seems to postpone many age-related pathologies in animals. Physiological gains have been firmly demonstrated for rats and mice, but not yet for humans and other primates. A study conducted by Walford et al. (1992) concluded that drastic reductions in blood pressure, cholesterol, triglycerides, and other major risk factors for heart disease, along with reductions in risk factors for diabetes (e.g., "overweightness," high blood sugar levels, low body response to insulin) and possibly other leading causes of death such as cancer, may be achieved in normal individuals by their pursuit of a carefully chosen restricted diet. Specifically, the study showed that a low-calorie nutrient-dense regime produces physiological gains in humans similar to those in other animal species.[9]

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[9]According to Walford, daily-caloric intake should be cut to 2000 for average-sized men and 1800 for average-sized women. The goal is to reach a weight that is 10% to 25% below one's "set point." The set point is one's characteristic weight when not overeating or undereating. (Internet, *Bottom Line/Health* interview with Dr. Roy Walford, 1992.)

A small sample of members of the Calorie Restriction Society, an informal association of people presumably observing the Walford-type diet, has been followed for 3 to 15 years by
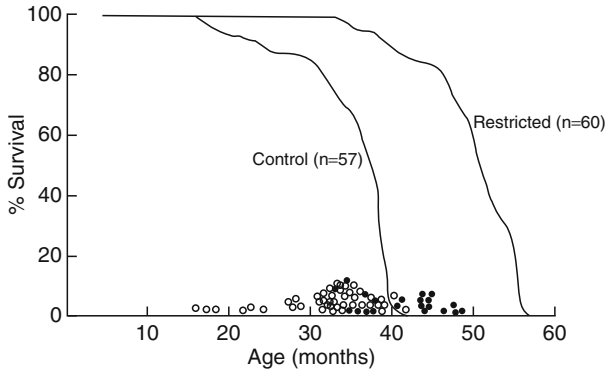
Fig. 13.4 Percent surviving of two groups of mice, one calorically restricted and the second a control group not calorically restricted (Source: R. J. Hodes, Director, U.S. National Institute on Aging, National Institutes of Health, public lecture, Nov. 2005)

A drastic reduction in calories may reduce damage from the harmful byproducts of oxygen metabolism. It may initiate metabolic changes that strengthen the immune system and increase the body's ability to produce new healthy cells. Thereby the process of aging is slowed. Caloric restriction (CR) seems to work the same way as the genetic manipulation of yeast, worms, flies, and mice; this device has been used to extend their life spans. On the other hand, it is questionable whether humans will tolerate on a routine basis the drastic caloric restriction required to achieve substantial benefits. People on these diets are known to feel cold, suffering from a dysregulation of their body temperatures, to feel very hungry, and to be subfecund. A study by Racette et al. (2006) showed that CR was feasible for one year, but the level of CR achieved was less than prescribed. In this study CR and exercise were equally effective in reducing weight and adiposity.

The importance of these studies is that a plan following drastic caloric restriction over many years may significantly extend longevity. If this finding is sustained, the practical application is to encourage more people to eat low calorie diets or, more realistically, to encourage pharmaceutical firms to develop a safe medication that suppresses appetites.

Pharmacological Interventions

Pharmacological interventions have long proved their efficacy in reducing disease and adding to life expectancy. A drug may be the mechanism by which the goal

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J. Holloszy of Washington University, St. Louis. This study shows "profound and sustained beneficial" effects in various biomarkers of health (e.g., low cholesterol, low blood pressure, low C-reactive protein) from drastic caloric restriction (1150 to 1950 calories per day).

of caloric restriction is finally achieved. Thousands of drugs are now being tested for their possible efficacy in turning off genes that are involved in cancer, diabetes, heart disease, and other diseases. With respect to cancer, the design of research is to profile cancer genes, determine the basis of their abnormality, and then try to disrupt these abnormal processes by developing appropriate medications. In the case of colon cancer, one drug now available works to starve the cancer cells while another aims to block a protein on the surface of the tumorous cells. With respect to Alzheimer's disease, current drugs deal only with its symptoms, but several clinical trials are under way designed to treat or cure the disease itself, either by preventing the formation of the amyloid beta protein responsible for the short-circuiting of neural transmissions in the brain of Alzheimer's patients, limiting its further growth, or ending the toxicity that it causes.

Developments in human genomic research may make it possible within a few decades to personalize the composition, selection, and administration of various drugs. Genomic profiling of an individual may reveal a given genetic predisposition and suggest a different composition of a medication from the general standard composition. This is the concern of pharmacogenomics. Drugs may be made available for categories of individuals fitting particular genomic profiles. This could result in fewer medication errors and increased efficacy of the medications that are prescribed for an individual. Certain persons have adverse reactions to certain drugs and others do not have such reactions because of their distinctive DNA profile; pharmacogenomics is dedicated to distinguishing these individuals.

We could consider the taking of special foods and dietary supplements as a form of drug intervention, just as we could the taking of vaccines. The virtues of one "food" or another are heralded from time to time as a general magic bullet for health. An ingredient in red wine, resveratrol, has recently been selected for this role, one which was previously assigned to some other widely used dietary supplements, such as echinacea and ginkgo. The putative beneficial health effects of resveratrol for humans include its anti-cancer, anti-viral, anti-inflammatory, and life-extension effects (Sinclair 2006). Such effects have been demonstrated for mice, but they have not been fully demonstrated for humans. The amount of red wine consumed in France may contribute to an increase in longevity, but it is not enough to explain the "French paradox," that is, the low incidence of heart disease in parts of France where the diet includes lots of saturated fats.[10]

Robot-Assisted Surgery and New Uses of Imaging Devices

Technological advances in surgery using guidance techniques are reducing the types of surgery requiring the need for large incisions, and so are reducing the risks of

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[10]I have omitted discussion of the fringe movement known as anti-aging medicine. It presumes to prolong life by administering selected dietary supplements and hormones. For a review of this topic, see National Academy on an Aging Society (2004).

surgical complications and the length of stay in the hospital. Minimally invasive surgery gains access to the body through natural orifices, the belly button, or small incisions. Other advantages include minimal blood loss, lower risk of infection, less scarring, and more rapid recovery time.

New research using guided imaging in cardiac surgery is intended to obviate the need to open the chest and stop the heart. One research protocol uses magnetic resonance imaging to guide the cardiac surgeon in operating on a heart requiring an aortic valve. Image-guided radiation therapy in the treatment of lung cancer gives radiologists a clearer, more accurate picture of the lung tumor, allowing a more precise targeting of the tumor and reducing the number of treatments needed for early-stage lung cancer.

Robot-assisted surgery has been introduced in cardiothoracic surgery, gynecological surgery, and urological surgery. It offers greater visualization of the operating site for the surgeon, makes possible greater dexterity and precision in the procedure, and allows a quicker recovery for the patient. A computer manipulates tiny "hands" holding surgical tools inserted in a small incision in the body. A camera also inserted through this incision provides a 3-D view of the site on a large monitor while the surgeon sits at a console controlling the movements of the robotic instruments. Robot-assisted surgery is now being used in the diagnosis and treatment of prostate cancer, ovarian, cervical, and uterine cancer, and kidney diseases.

Electronic Medical Record-Keeping and Bioinformatics

Electronic medical record-keeping is being introduced into medical practice but is still in its infancy. At the least, it would integrate the medical records of an individual so that any of the health-care providers attending an individual would have immediate access to them. At its best, it would integrate both the medical records on persons from all their health-care providers, including the medical records of all major health-care providers, such as the Mayo Clinic, Kaiser-Permanente, and the Veterans Administration, the research results obtained by such organizations as the National Health Interview Survey on self-reported health conditions and self-assessed health, and the findings in innumerable research publications. The new system would add to the safety of treatment by medication since it would reduce, if not eliminate, the risk of drug interactions. It would add to the effectiveness of medical treatment since physicians would have immediate, accurate, and complete information about the patient's history and the latest research findings on the patient's condition. Other alleged advantages of implementing electronic medical record-keeping are the reduction, if not elimination, of the ordering of duplicate medical tests and procedures and hence savings in the cost of medical care. Questions have been raised, however, whether there would be economies and whether privacy could be maintained.

Among the nascent fields of study that are supporting new developments in genetics is bioinformatics. Bioinformatics involves sorting through biological databases by use of the computer and providing data that could be used for genetic

research, genetic counseling, and the new developments in medical research. It does this by furnishing the tools needed to classify, track, and analyze the data developed by geneticists. Among these tools are microarrays, which are grids composed of bits of DNA that are complementary to the messenger RNAs the geneticist finds in a cell. They allow analysts to determine immediately which genes are at work in a particular cell and the strength of their activity. Microarrays are a valuable tool for gene discovery and mapping and are being used to screen thousands of genes rapidly in order to identify mutations that cause diseases. Nanotechnology, the technology used in the study of "supertiny" elements, can be used in conjunction with microarrays to detect diseased genes.

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