All of these theories assume that natural selection has negligible or negative influences on aging. Some postmodern ideas propose that aspects of aging might be adaptive and raise the possibility that evolution can act on the aging process in a positive way. These include the following:

- *Grandmother hypothesis.* The grandmother hypothesis proposed by Hamilton in 1966 describes how evolution can enhance old age. In some animals, including humans, the survival of multiple, dependent offspring is beyond the capacity and resources of a single parent. In this situation, the presence of a long-lived grandmother who shares in the care of her grandchildren can have a major impact on their survival. These children share some of the genes of their grandmother including those that promoted their grandmother's longevity.
- *Mother's curse.* Mitochondrial dysfunction is a key component of the aging process. Mitochondria contain their own DNA and are only passed on from mother to child because sperm cells contain almost no mitochondria. Therefore, natural selection can only act on the evolution of mitochondrial DNA in females. The "mother's curse" of the maternal inheritance of mitochondrial DNA might explain why females live longer and age more slowly than males.
- *Adaptive senectitude.* Many traits that are harmful in younger humans such as obesity, hypertension, and oxidative stress paradoxically appear to be associated with greater survival and function in very old people. Perhaps driven by the grandmother effect, this might represent "adaptive senectitude" or "reverse antagonistic pleiotropy," whereby some traits that are harmful in young people become beneficial in older people.

CELLULAR PROCESSES THAT ACCOMPANY AGING

There are many cellular processes that change with aging. These are generally considered to be degenerative and stochastic or random changes that reflect some sort of time-dependent damage (Fig. 94e-3). Whether any of these is the root cause of aging is unknown, but they all contribute to the aging phenotype and disease susceptibility.

Oxidative Stress and the Free Radical Theory of Aging Free radicals are chemical species that are highly reactive because they contain unpaired electrons. Oxidants are oxygen-based free radicals that include the hydroxyl free radical, superoxide, and hydrogen peroxide. Most cellular oxidants are waste products generated by mitochondria during the production of ATP from oxygen. More recently, the role of oxidants in cellular signaling and inflammatory responses has been recognized. Unchecked, oxidants can generate chain reactions leading to widespread damage to biological molecules. Cells contain numerous antioxidant defense mechanisms to prevent such oxidative stress including enzymes (superoxide dismutase, catalase, glutathione peroxidase) and chemicals (uric acid, ascorbate). In 1956, Harman proposed the "free radical theory of aging," whereby oxidants generated by metabolism or irradiation are responsible for age-related damage. It is now well established that old age in most species is associated with increased oxidative stress, for example to DNA (8-hydroxyguanosine derivatives), proteins (carbonyls), lipids (lipoperoxides, malondialdehydes), and prostaglandins (isoprostanes). Conversely, many of the cellular antioxidant defense mechanisms, including the antioxidant enzymes, decline in old age. The free radical theory of aging has spawned numerous studies of supplementation with antioxidants such as vitamin E to delay aging in animals and humans. Unfortunately, meta-analyses of human clinical trials performed to treat and prevent various diseases with antioxidant supplements indicate that they have no effect on, or may even increase, mortality.

Mitochondrial Dysfunction Aging is characterized by altered mitochondrial production of ATP and oxygen-derived free radicals. This leads to a vicious cycle mediated by accumulation of oxidative injury to mitochondrial proteins and DNA. With age, the number of mitochondria in cells decreases, and there is an increase in their size (megamitochondria) associated with other structural changes including vacuolization and disrupted cristae. These morphologic aging changes are linked with decreased activity of mitochondrial complexes I, II, and IV and decreased ATP production. Of all of the complexes involved in ATP production, the activity of complex IV (COX) is usually reported to be most impaired in old age. Reduced energy production is linked with generation of hydrogen peroxide and superoxide radicals leading to oxidative injury to mitochondrial DNA and accumulation of carbonylated mitochondrial proteins and mitochondrial lipoperoxides. As well as being implicated in the aging process, common geriatric syndromes including sarcopenia, frailty, and cognitive impairment are associated with mitochondrial dysfunction.

Telomere Shortening and Replicative Senescence Cells that are isolated from animal tissue and grown in culture only divide for a certain number of times before entering a senescent phase. This number of divisions is known as the Hayflick limit and tends to be less in cells isolated from older animals compared to younger animals. It has been suggested that aging in vivo might in part be secondary to some cells ceasing to divide because they have reached their Hayflick limit. One mechanism for replicative senescence relates to telomeres. Telomeres are repeat sequences of DNA at the end of linear chromosomes that shorten by around 50–200 base pairs during each cell division by mitosis. Once telomeres become too short, cell division can no longer occur. This mechanism contributes to the Hayflick limit and has been called the cellular clock. There are some studies that suggest that the length of telomeres in circulating leukocytes (leukocyte telomere length [LTL]) decreases with age in humans. However, the aging process also occurs in tissues that do not undergo repeated cell division such as neurons.

Altered Gene Expression, Epigenetics, and microRNA There are changes in the expression of many genes and proteins during the aging process. These changes are complicated and vary between species and tissue. Such heterogeneity reflects increasing dysregulation of gene expression with age while appearing to exclude a programmed and/or uniform response. With old age, there are often reductions in the expression of genes and proteins associated with mitochondrial function and increased expression of those involved with inflammation, genome repair, and oxidative stress. There are several factors controlling the regulation of gene and protein expression that change with aging. These include the epigenetic state of the chromosomes (e.g., DNA methylation and histone acetylation) and microRNAs (miRNA). DNA methylation correlates with age, although the pattern of change is complex. Histone acetylation is regulated by many enzymes including SIRT1, a protein that has marked effects on aging and the response to dietary restriction in many species. miRNAs are a very large group of noncoding lengths of RNA (18–25 nucleotides) that inhibit translation of multiple different mRNAs through binding their 3′ untranslated regions (UTRs). The expression of miRNAs usually decreases with aging and is altered in some age-related diseases. Specific miRNAs linked with aging pathways include miR-21 (associated with target of rapamycin pathway) and miR-1 (associated with insulin/insulin-like growth factor 1 pathway).

Impaired Autophagy There are a number of ways that cells can remove damaged macromolecules and organelles, often generating cellular energy as a byproduct. Intracellular degradation is undertaken by the lysosomal system and the ubiquitin proteasomal system. Both are impaired with aging, leading to the accumulation of waste products that alter cellular functions. Such waste products include lipofuscin, a brown autofluorescent pigment found within lysosomes of most cells in old age and often considered to be one of the most characteristic histologic features of aging cells. They also include aggregated proteins characteristic of age-related neurodegenerative diseases (e.g., tau, β-amyloid, α-synuclein). Lysosomes are organelles that contain proteases, lipases, glycases, and nucleotidases that degrade intracellular macromolecules, membrane components, organelles, and some pathogens through a process called autophagy. The lysosomal process most impaired with aging is macroautophagy, which is regulated by numerous autophagy-related genes (ATGs). Old age is associated with some impairment in chaperone-mediated autophagy, whereas the effect of aging on the third lysosomal process, microautophagy, is unclear.