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AGING

Introduction

Until a person is in their fourth or fifth decade of life, the finality of aging may not mean a lot, even though it's a lifelong process. Childhood, adolescence and young adulthood are typically filled with feelings of immortality. It's often only when a person starts to notice physical changes that they accept that they are actually getting older.

So what exactly is aging — what causes it, how does the body change and how long can a person expect to live?

Some of the physical effects of aging are wrinkles, gray hair and slower reflexes, but what else is going on that you're not seeing? As individuals age, time takes its toll on the organs and systems in the body. How and when this occurs is unique to the individual. And everyone doesn't undergo the same changes. Still, in general, some of the age-related changes that occur include changes in:

Bones - As one ages, the bones become less dense as they slowly lose mass and minerals. Gradual loss of density weakens the bones and makes them more susceptible to fracture.

Brain - The number of neurons (cells) in the brain decreases. However, in some areas of the brain, the number of connections between cells increases, perhaps helping to compensate for the cellular decrease and maintain normal brain function.

Cardiovascular system - The size of the heart increases slightly**.** The blood pressure increases, the maximum heart rate decreases and the heart may take longer to return to its normal resting state after physical activity.

Hearing - The normal wear and tear of sounds over the years can damage the cells of the inner ears. The walls of the auditory canals also thin, and the eardrums thicken. Some will have greater difficulty hearing higher frequencies.

Kidneys - The size of the kidneys shrinks, and the amount your bladder can hold decreases. The kidneys also become less efficient at removing wastes from the blood.

Muscles - Muscle mass and strength decrease, though increased physical activity can reduce this effect. As the amount of water in the tendons and ligaments decreases, stiffness increases.

Reproductive system - Women produce less estrogen, progesterone and testosterone as they age. The uterus and the vagina shrink, and there's less vaginal lubrication. Men produce less sperm, and their levels of testosterone decrease.

Skin - The skin thins, and the nails grow at about half the pace they once did. The sweat and oil (sebaceous) glands become less active, and the moisture in the skin decreases.

Vision - The eyes are less able to produce tears, the retina thins and the lenses yellow. In ones 40s, focusing on objects that are close-up becomes more difficult due to changes in the lenses. Later, the irises stiffen, making the pupils less responsive. This can make it more difficult to adapt to different levels of light. Further changes to the lenses can make an individual sensitive to glare.

Falls - In the United States, one of every three persons, aged 65 years and older, falls each year. Among older adults, falls are the leading cause of injuries, hospital admissions for trauma, and deaths due to injury. In 1999, about 10,097 seniors died of fall-related injuries. Fractures are the most serious health consequence of falls.

Approximately 250,000 hip fractures, the most serious fracture, occur each year among people over age 65. Many of these falls and resulting injuries can be prevented. Strategies to prevent

falls among older adults include exercises to improve strength, balance, and flexibility; reviews of medications that may affect balance; and home modifications that reduce fall hazards such as installing grab bars, improving lighting, and removing items that may cause tripping.
Driving - While rates of motor vehicle related death and nonfatal motor vehicle related injuries among older adults vary by state, there are some consistencies. In most states, the fatality rates for men are twice those for women. In all states, motor vehicle-related fatalities are higher among adults 75 years and older, as compared with adults between 65 and 74 years of age. Among older adult drivers, the number of motor vehicle-related fatalities increased 30% and the number of nonfatal injuries increased 21% between 1990 and 1997.
How Long Do People Live?
One hundred twenty-two years is the longest documented human life span. Though a life span this long is rare, improvements in medicine, science and technology in the last century have helped more people live longer, healthier lives. In the early 1900s the average life expectancy in the United States at birth was only about 50 years. Today, it's close to 77.
Moreover, the 85-plus group is the fastest-growing demographic segment in the United States, although the number of people 100 and older has exploded as well. The U.S. Census Bureau projects that the number of people age 85 and older could increase from 4 million in 2000 to 19 million by 2050. And the number of people age 100 and older is projected to more than quadruple from 65,000 in 2000 to 381,000 in 2030.
In the last 10 years, scientists have made great progress in the study of aging. Currently, thousands of research projects on how to slow aging are under way in numerous medical specialties throughout the world. Scientists are studying a variety of topics including everything from cloning for spare parts to how DNA mutations affect aging to fighting cancer with viruses. But longer lives also mean that some people may spend more time in an incapacitated state at the end of their lives, in part because the United States has done too little to promote healthy aging. Rates of obesity, sedentary lifestyle, smoking and alcohol abuse are still too high. However, researchers say it's never too late to clean up your act. For example, if an individual quits smoking, their risk of heart disease begins to fall almost immediately. Living a healthy lifestyle can improve how an individual ages. No matter the age, an individual can begin preparing now for their later years. An individual is the master of their own quality of life.
Clearly, old isn't what it used to be. And as more than 70 million baby boomers approach their retirement years, the definition continues to evolve.

ELDERLY, ALCOHOL AND ALCOHOLISM

While alcoholism has been increasingly diagnosed and treated in the general population as a whole, older persons, and 60 years of age and over, still constitute a "hidden" group with a significant number having medical problems associated with alcoholism and excessive drinking. The primary care physician can be the front line identifier of alcoholism and/or excessive drinking in the elderly. They need not be an expert or specialist in alcoholism or addiction medicine to assess the elderly patient, diagnose the disorder and provide for treatment. Physicians can update their own awareness in assessing and establishing a diagnosis, and in referring the elderly patient for on-going treatment for alcoholism and for any medical or psychiatric complications.

ELDERLY ALCOHOLIC/EXESSIVE DRINKERS DISPLAY:

Severe memory loss.
Inability to concentrate.
Defensiveness or irritation when asked even routine, general questions about alcohol use.

Extreme mood swings, even during a single office visit.
Undo concern about physical ailments, sometimes bordering on hypochondria.
Suicidal ideation.

ACUTE PRESENTING PROBLEMS IN THE ELDERLY

ALCOHOLIC/EXCESSIVE DRINKER PRESENTS:

Severe gastrointestinal complaints.
Loss of consciousness.
Panic attack.
Renal and bladder complications.
Hypoglycemia.
Aspiration of vomitus.
Angina and other cardiac involvement.
CNS intoxication effects, including ataxia and dyskinesia.
Blackouts.

Treatment of Alcoholism

The treatment of substance abuse and dependence in older adults is similar to that for other adults. Treatment involves a combination of pharmacological and psychosocial interventions, supplemented by family support and participation in self-help groups.

Pharmacotherapy for substance abuse and dependence in older adults has been targeted mostly at the acute management of withdrawal. When there is significant physical dependence, withdrawal from alcohol can become a life-threatening medical emergency in older adults. The detoxification of older adult patients ideally should be done in the inpatient setting because of the potential medical complications and because withdrawal symptoms in older adults can be prolonged. Benzodiazepines are often used for treatment of withdrawal symptoms. In older adults, the doses required to treat the signs and symptoms of withdrawal are usually one-half to one-third of those required for a younger adult. Short- or intermediate acting forms usually are preferred.

Alzheimer's Disease

Alzheimer's disease is one of the most feared mental disorders because of its gradual, yet relentless, attack on memory. Memory loss, however, is not the only impairment. Symptoms extend to other cognitive deficits in language, object recognition, and executive functioning. Behavioral symptoms, such as psychosis, agitation, depression, and wandering are common and impose tremendous strain on caregivers. Diagnosis is challenging because of the lack of biological markers, insidious onset, and need to exclude other causes of dementia. Alzheimer's disease is the most prevalent form of dementia. However, many of the issues raised also pertain to other forms of dementia, such as multiinfarct dementia, dementia of Parkinson's disease, dementia of Huntington's disease, dementia of Pick's disease, frontal lobe dementia and others.

Counseling Alzheimer's Patients and their Families

DURING THE EARLY STAGE

The first (mild) stage of AD generally lasts two to four years. Among the signs and symptoms (which may be mistaken for manifestations of aging) are loss of recent memory, inability to retain new information, subtle personality changes (including abandonment of interests and activities, and increasing stubbornness), and difficulty communicating. Depression is common and may be the presenting symptom; first-time depression in a patient older than 65 should be investigated as possible dementia. Patients begin to lack judgment and insight.

After diagnosis, the patient and family need straightforward information about the disease and the cognitive and functional changes to expect with each stage. Patients should be discouraged from driving, as even mild cognitive deficits are associated with increased risk of accidents.

Families will benefit from a list of community resources. The Alzheimer's Association, for example, offers invaluable information about support groups, respite care, individual and family counseling, and other services that can help ease the caregiver's physical, emotional, and financial concerns. The National Institute on Aging funds nearly 30 hospital- and university-based AD centers in the United States.

Patients and family caregivers also need information and advice about available medical treatments. Although medications approved to treat AD are expensive, their early use is an important means of prolonging the first stage--and preserving the patient's ability to participate in creating an advance directive and making other important decisions. Effective early treatment may also make it possible to delay institutionalization.

At each contact, patients should be evaluated for depression. Short-term treatment with selective serotonin reuptake inhibitors that have limited anticholinergic effects (eg, citalopram, sertraline) may be indicated for AD patients with depression. The family should be told to watch for and report symptoms such as apathy, irritability, refusal to eat, and weight loss, with the understanding that these may simply be symptoms of the dementia itself.

Caregivers should be reminded that attending to the patient's comorbid conditions can help slow the progression of disability and maintain function. Hypertension, diabetes, congestive heart failure, chronic obstructive pulmonary disease, arthritis, genitourinary conditions, and hypothyroidism are common concerns, as are vision and hearing impairment.

Additional Considerations

Early attention to the patient's environment is important (ie, consistency and structure, safety, moderate stimulation, and contrasting colors). Familiar items, including photographs and souvenirs, and orientation cues, such as clocks and calendars, can help stimulate memory and cognition. Some patients benefit from therapy using music, art, exercise, or pets, reminiscence therapy, and psychotherapy (emotion-oriented, supportive, and/or interpersonal).

The earliest stage of AD is an ideal time to broach the subject of advance care planning with the patient in the presence of the family or caregiver. More than one study has found that patients with early dementia can participate in completing advance directives. Considerations should include use of artificial nutrition and hydration, hospitalization, antibiotic use, and do-not-resuscitate orders.

THE MIDDLE STAGE

The moderate second stage of AD may last from two to 10 years. Patients require full-time supervision because of increasing confusion, declining ability to care for themselves, wandering tendencies, belligerence, and, for many, psychotic episodes. Communication skills continue to decline and delusions, agitation, and paranoia are common.

As symptoms progress, many caregivers begin to think about placing their loved ones in a long-term care facility. Behavioral strategies and appropriate pharmacologic management (discussed below) may help to delay this step. Families should be made aware of the available adult day care and community-based programs. They should also be directed to contact the Alzheimer's Association or the appropriate constituent unit of the National Council on Aging for information on financial resources.

Practical Coping Strategies

A safe, predictable environment and a consistent daily routine are the mainstay of managing potentially troublesome behaviors and the starting point for all other interventions. Safety measures include removing throw rugs and other obstructions over which patients may trip, and securing medicine, firearms, keys, toxic substances, and dangerous tools and utensils. Also, caregivers should be taught specific techniques to maintain optimal communication with the patient, such as those outlined by the Alzheimer's Association.

Apathy--manifested as loss of interest, poor persistence, blunted emotions, and lack of social interaction--may occur in 90% or more of AD patients. Apathetic patients may be mistaken as lazy or resistant, because they seem to expect others to initiate activities they themselves are still capable of performing. Functioning may be improved by regular exercise, increased social stimulation, prompt encouragement to begin activities, a structured activity routine, and use of visual cues to expected behaviors.

About 90% of patients also experience psychiatric manifestations, particularly behavioral disturbances. These include agitation (aggressiveness, combativeness, repetitious questioning, shouting, cursing, disinhibition) and wandering. The caregiver should look for physical or environmental stressors--such as pain or discomfort, anxiety, lack of sleep, noise, clutter, and presence of large numbers of people--that may be triggering or exacerbating the behavior, and these should be removed wherever possible. Caregivers can calm the patient better with an easygoing attitude than by challenging him or her.

Spending time outside with the patient when the weather permits, incorporating exercise into the patient's daily routine, and limiting the patient's caffeine intake are ways caregivers can help the patient avoid sleeplessness. A regular sleep schedule should be maintained, with naps limited to 30 minutes and use of the bed restricted to sleep only.

Wandering is a significant problem because it can be persistent and is inherently dangerous. Yet ambulation is considered an important factor in maintaining the AD patient's quality of life. One strategy is to provide a controlled environment where the patient may wander safely, rather than to try to eliminate the behavior. Wandering can be restricted by using child-proof doorknobs, mounting locks or latches higher or lower than eye level, obscuring doors with a scenic poster or curtains, and placing signs on doors with the words "stop" or "do not enter." Another effective technique is to keep outdoor clothing (symbols of departure) out of sight.

Required Reading: Alzheimer's disease

PBS: A Portrait of Alzheimer's

Required Reading: Guidelines for Alzheimer's Disease Management

Mental Disorders and Aging

Older adults are encumbered by many of the same mental disorders as are other adults; however, the prevalence, nature, and course of each disorder may be very different. This section provides a general overview of assessment, diagnosis, and treatment of mental disorders in older people. Its purpose is to describe issues common to many mental disorders.

Sleep Disorders

Sleep disturbances are common and pharmacologic intervention should be considered only when other non-pharmacologic interventions have failed (American Psychiatric Association, 1997). The sleeping area should be free of distractions and might contain nightlights if helpful to the patient. Caregivers should be instructed to try to limit the amount of sleep during the day. Naps should be kept short and there should be increased exercise or activity in the morning/early afternoon. Patient should be dressed during daytime hours. Caffeine and nicotine should be avoided and nighttime fluids and diuretics should be restricted. Warm milk and tryptophan

before sleep may be successful, as may a tepid bath or light snack high in carbohydrates (Warshaw, et al., 1995). Pharmacologic treatment of other sleep disorders must take into account whether depressive symptoms, fear, pain, or side effects from other drugs underlie the insomnia (Warshaw, et al., 1995). Great caution must be exercised and caregivers warned because of reactions (incontinence, instability/falls, agitation) with major tranquilizers. Antidepressants (e.g. Trazadone), minor tranquilizers or benzodiazepines may suffice in intermittent short-term doses, but should be terminated at the earliest possible time (Warshaw, et al., 1995). Use of various dopamine agonists has been described in case reports, but the efficacy of these drugs has not been demonstrated in controlled studies. Simple remedies, such as use of melatonin, may help insomnia. For stronger sedation, a low dose of antipsychotic is preferable to a longer-acting benzodiazepine, which often has lingering effects. Diphenhydramine hydrochloride (over-the-counter) should be avoided because it may increase confusion due to its anticholinergic effects (Inouye, 1998).

Schizophrenia in Late Life

Although schizophrenia is commonly thought of as an illness of young adulthood, it can both extend into and first appear in later life. Diagnostic criteria for schizophrenia are the same across the life span, and DSM-IV places no restrictions on age of onset for a diagnosis to be made. Symptoms include delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, as well as affective flattening, alogia or avolition. Symptoms must cause significant social or occupational dysfunction, must not be accompanied by prominent mood symptoms, and must not be uniquely associated with substance use.

Prevalence and Cost

One-year prevalence of schizophrenia among those 65 years or older is reportedly only around 0.6 percent, about one-half the 1-year prevalence of the 1.3 percent that is estimated for the population aged 18 to 54.

Misuse of Prescription and Over-the-Counter Medications

Older persons use prescription drugs approximately three times as frequently as the general population and the use of over-the-counter medications by this group is even more extensive. Annual estimated expenditures on prescription drugs by older adults in the United States are $15 billion annually, a fourfold greater per capita expenditure on medications compared with that of younger individuals. Not surprisingly, substance abuse problems in older adults frequently may result from the misuse, that is, under use, overuse, or erratic use—of such medications; such patterns of use may be due partly to difficulties older individuals have with following and reading prescriptions. In its extreme form, such misuse of drugs may become drug abuse.

Pharmacological Treatment

The special considerations in selecting appropriate medications for older people include physiological changes due to aging; increased vulnerability to side effects, such as tardive dyskinesia; the impact of polypharmacy; interactions with other comorbid disorders; and barriers to compliance.

The aging process leads to numerous changes in physiology, resulting in altered blood levels of certain medications, prolonged pharmacological effects, and greater risk for many side effects. Changes may occur in the absorption, distribution, metabolism, and excretion of psychotropic medications.

As people age, there is a gradual decrease in gastrointestinal motility, gastric blood flow, and gastric acid production. This slows the rate of absorption, but the overall extent of gastric absorption is probably comparable to that in other adults. The aging process is also associated with a decrease in total body water, a decrease in muscle mass, and an increase in adipose tissue. Drugs that are highly lipophilic, such as neuroleptics, are therefore more likely to be accumulated in fatty tissues in older patients than they are in younger patients.

The liver undergoes changes in blood flow and volume with age. Phase I metabolism (oxidation, reduction, hydrolysis) may diminish or remain unchanged, while phase II metabolism (conjugation with an endogenous substrate) does not change with aging. Renal blood flow, glomerular surface area, tubular function, and reabsorption mechanisms all have been shown to diminish with age. Diminished renal excretion may lead to a prolonged half-life and the necessity for a lower dose or longer dosing intervals.

Pharmacodynamics, which refers to the drug's effect on its target organ, also can be altered in older individuals. An example of aging-associated pharmacodynamic change is diminished central cholinergic function contributing to increased sensitivity to the anticholinergic effects of many neuroleptics and antidepressants in older adults.

Because of the pharmacokinetic and pharmacodynamic concerns presented above, it is often recommended that clinicians "start low and go slow" when prescribing new psychoactive medications for older adults. In other words, efficacy is greatest and side effects are minimized when initial doses are small and the rate of increase is slow. Nevertheless, the medication should generally be titrated to the regular adult dose in order to obtain the full benefit. The potential pitfall is that, because of slower titration and the concomitant need for more frequent medical visits, there is less likelihood of older adults receiving an adequate dose and course of medication.

Increased Risk of Side Effects

Older people encounter an increased risk of side effects, most likely the result of taking multiple drugs or having higher blood levels of a given drug. The increased risk of side effects is especially true for neuroleptic agents, which are widely prescribed as treatment for psychotic symptoms, agitation, and behavioral symptoms. Neuroleptic side effects include sedation, anticholinergic toxicity (which can result in urinary retention, constipation, dry mouth, glaucoma, and confusion), extrapyramidal symptoms (e.g., Parkinsonism, akathisia, and dystonia), and tardive dyskinesia.

What is a Geriatric Psychiatrist?

A geriatric psychiatrist is a medical doctor with special training in the diagnosis and treatment of mental disorders that may occur in older adults. These disorders include, but are not limited to, dementia, depression, anxiety, and late-life schizophrenia. Older adults have special physical, emotional, and social needs. Understanding this, the geriatric psychiatrist takes a comprehensive approach to diagnosis and treatment, including listening and responding to the concerns of the older adult, helping families, and when necessary, working with other health care professionals to develop effective approaches to treatment. Co-existing medical illnesses, medications, family issues, social concerns, and environmental issues are integrated into a comprehensive program of care.

Ageism

Never has there been an era more conscious of chronological age than this one. People will go to extraordinary lengths to maintain a youthful appearance, from elaborate beauty preparations, to

plastic surgery, vitamin cocktails and much more besides. Retirement is often seen as a withdrawal from usefulness and active participation in communities.
Yet in some cultures (like the Hunza and Vicabamba), there seems to be no concept of retirement; people remain active in farming, teaching and walking long distances all their lives. In other cultures, especially where oral traditions are strong, older people have played an important role in society by passing on knowledge to younger generations. This suggests that in contexts, such as modern western culture, where the status of older people is low, it is because attitudes determine that it will be low, not because it is a natural consequence of the ageing process.
A definition of ageism is: 'a set of attitudes that generate fear and denigration of the ageing process and stereotyping presumptions regarding competence'. Ageism is reflected in unjustified age discrimination in employment, in patronizing or denigrating attitudes, negative (or non-existent) media images, and the widespread expectation that retirement from full-time employment means the end of usefulness and of active participation in society.

Cultural Competence

Long Term Care

Most elderly individuals are independent. But later in life, individuals in their 80s and 90s may begin to need help with everyday activities like shopping, cooking, walking and bathing. For many people, regular or “long-term” care may mean help from family and friends or regular visits by a home health aide. For others who are frail or suffering from dementia, long-term care may involve moving to a place where professional care is available 24 hours a day.
The good news is that families have more choices in long-term care than ever before. Today, services can provide the needed help while letting you stay active and connected with family, friends, and neighbors. These services include home health care, adult day care, and transportation services for frail seniors as well as foster care, assisted living and retirement communities, and traditional nursing homes.

Successful long-term care means planning ahead –

If a patient is having trouble with things like bathing, managing finances, or driving, make sure they consult with a doctor.
You probably will need to get other family members involved. A special type of social worker, called a geriatric case manager, can help the family through this complex time by developing a long-term care plan and locating appropriate services. Geriatric case managers can be particularly helpful when family members live a long distance apart.
Talk about the best way to meet his or her needs. For instance, if he or she is having trouble making meals, would they want meals delivered by a local program or would they like family and friends to help? Would they let a paid aide in their home? If they don’t drive, would they like a friend or bus service to take them to the doctor or other appointments?
Learn about the types of services and care in your community. Doctors, social workers, and others may have suggestions. The Area Agency on Aging and local and state offices of aging or social services can give you lists of adult day care centers, meal programs, companion programs, transportation services, or places providing more care.
Find out how they may, or may not, be covered by insurance. The Federal Medicare program and private “Medigap” insurance only offer short-term home health and nursing home benefits. Contact your state-run Medicaid program about long-term nursing home coverage for people with limited means. Also, your state’s insurance commission can tell you more about private

long-term care policies and offer tips on how to buy this complicated insurance. These agencies are listed in your telephone book, under "Government."

Be aware that figuring out care for the long term isn't easy. Needs may change over time. What worked 6 months ago may no longer apply. Insurance coverage is often very limited and families may have problems paying for services. In addition, rules about programs and benefits change, and it's hard to know from one year to the next what may be available.

Facts about long term care:

80% of Long Term Care is received in a home-like setting.

The average cost of a semi-private nursing home bed is $50,000 per year or more!

Home care costs average $20,000 per year or more!

Medicare will NOT pay for Long Term Care.

Medicare HMOs will NOT pay for Long Term Care.

Caring for the caregiver is just as important as caring for the aging adult.

Signs that one may need additional care:

Elderly adults often are reluctant to accept help from loved ones for fear of losing their independence.

Communicate with elderly patients in a non-threatening manner if you believe they need help for their physical or mental limitations. Ability, not age, is the best way to judge if a person needs daily assistance. Watch for these warning signs:

Difficulty doing basic tasks, such as walking, dressing, eating and cooking may be signs that one needs additional care.

Poor remembering skill are a sign that help may be needed. If the elderly person is unable to remember familiar names, places, or recent events he or she needs extra attention. Poor hygiene and/or an inability to fulfill responsibilities can be signs that extra help is needed. If you spot unopened mail, unpaid bills and bank account overdrafts, you should be concerned.

Changes in health including weight loss, incontinence, changes in appetite and bruising from falls can be signs.

Signs of isolation including lost of interest in friendships and activities are warning signs. You should be concerned with alcohol or drugs use. Paranoia and depression are common signs of dementia and other chronic disorders.

Residential Care:

At some point, support from family, friends, or local meal or transportation programs may not be enough. If they need a lot of help with everyday activities, they may need to move to a place where care is available around-the-clock. There are two types of residential care:

Assisted living - arrangements are available in large apartment or hotel-like buildings or can be set up as "board and care" homes for a small number of people. They offer different levels of care, but often include meals, recreation, security, and help with bathing, dressing, medication, and housekeeping.

Skilled nursing facilities – "nursing homes" – provide 24-hour services and supervision. They provide medical care and rehabilitation for residents, who are mostly very frail or suffer from the later stages of dementia.

Sometimes, health care providers offer different levels of care at one site. These "continuing care communities" often locate an assisted living facility next to a nursing home so that people can move from one type of care to another if necessary. Several offer programs for couples, trying to meet needs when one spouse is doing well but the other has become disabled.

Adult Day Care

Over the past few decades, adult day centers have developed as an important service delivery approach to providing community-based long-term care. Adult day centers, although heterogeneous in orientation, provide a range of services, usually during standard " 9 to 5" business hours, including assessment, social, and recreation services, for adults with chronic and serious disabilities. They represent a form of respite care designed to give caregivers a break from the responsibility of providing care and to enable them to pursue employment.

Over the past 30 years, adult day centers have grown in number from fewer than 100 to over 4,000, under the sponsorship of community organizations or residential facilities. A large national demonstration program on adult day centers showed that they can care for a wide spectrum of patients with Alzheimer' s disease and related dementias and can achieve financial viability. There also is evidence that adult day centers are cost-effective in terms of delaying institutionalization, and participants show improvement in some measures of functioning and mood.

Ombudsman Program

Long-term care ombudsmen are advocates for residents of nursing homes, board and care homes, assisted living facilities and similar adult care facilities. Since the Ombudsman Program began in 1972, thousands of paid and volunteer ombudsmen working in every state and three other jurisdictions have made a dramatic difference in the lives of long-term care residents. LTC ombudsmen advocate on behalf of individuals and groups of residents, provide information to residents and their families about the long-term care system, and work to effect systems changes at the local, state and national level. They provide an on-going presence in long-term care facilities, monitoring care and conditions and providing a voice for those who are unable to speak for themselves.

The Ombudsman Program is established under the Older Americans Act, which is administered by the Administration on Aging (AoA). Local ombudsmen work on behalf of residents in hundreds of communities throughout the country.

About one thousand paid and 14,000 volunteer staff (8,000 certified) investigate over 260,000 complaints each year. They provide information to more than 280,000 people on a myriad of topics including how to select and pay for a long-term care facility.

While the vast majority of frail and homebound older people receive quality care at home, abuse does occur. Estimates vary, but most studies find rates of abuse by caregivers, either family or non-family members, to range up to 5 percent. Abuse is generally defined in terms of being physical, psychological, legal or financial. The abuse is most likely to occur when the patient has dementia or late life depression, conditions that impart relatively high psychological and physical burdens on caregivers.

A recent report by the Institute of Medicine describes the range of interventions for protection against abuse of older people, including caregiver participation in support groups and training programs for behavioral management, especially for Alzheimer's disease, and social services programs (e.g., adult protective services, casework, advocacy services, and out-of-home placements). While there are very few controlled evaluations of these services, communities need to ensure that there are programs in place to prevent abuse of older people.

REPORTING?

Mandated reporters must report actual or suspected physical and sexual abuse, abandonment, isolation, financial abuse, mental abuse, or neglect of an elder or dependent adult. Failure of a mandated reporter to report abuse is a misdemeanor, punishable by a jail sentence or

fine. Report the abuse immediately by telephone followed by a written report within two working days using the standardized abuse reporting form.

Normal Life-Cycle Tasks

With improved diet, physical fitness, public health, and health care, more adults are reaching age 65 in better physical and mental health than in the past. Trends show that the prevalence of chronic disability among older people is declining: from 1982 to 1994, the prevalence of chronic disability diminished significantly, from 24.9 to 21.3 percent of the older population. While some disability is the result of more general losses of physiological functions with aging (i.e., normal aging), extreme disability in older persons, including that which stems from mental disorders, is not an inevitable part of aging.

Normal aging is a gradual process that ushers in some physical decline, such as decreased sensory abilities (e.g., vision and hearing) and decreased pulmonary and immune function. With aging come certain changes in mental functioning, but very few of these changes match commonly held negative stereotypes about aging. In normal aging, important aspects of mental health include stable intellectual functioning, capacity for change, and productive engagement with life.

Cognitive Capacity

Cognition subsumes intelligence, language, learning, and memory. With advancing years, cognitive capacity with aging undergoes some loss, yet important functions are spared. Moreover, there is much variability between individuals, variability that is dependent upon lifestyle and psychosocial factors. Most important, accumulating evidence from human and animal research finds that lifestyle modifies genetic risk in influencing the outcomes of aging. This line of research is beginning to dispel the pejorative stereotypes of older people as rigidly shaped by heredity and incapable of broadening their pursuits and acquiring new skills.

Retirement often is viewed as the most important life event prior to death. Retirement frequently is associated with negative myths and stereotypes. However, most people fare well in retirement. They have the opportunity to explore new interests, activities and relationships due to retirements liberating qualities. In the Retirement phase, new feelings of freedom, courage, and confidence are experienced.

Those at risk for faring poorly are individuals who typically do not want to retire, who are compelled to retire because of poor health, or who experience a significant decline in their standard of living. In short, the liberating experience of having more time and an increased sense of freedom can be the springboard for creativity in later life. People can change the course of an individual, family, community, or culture.

Prevention of Excess Disability

Prevention efforts in older mentally ill populations also target avoidance of excessive disability. The concept of excess disability refers to the observation that many older patients, particularly those with Alzheimer's disease and other severe and persistent mental disorders, are more functionally impaired than would be expected according to the stage or severity of their disorder. Medical, psychosocial, and environmental factors all contribute to excess disability. For example, depression contributes to excess disability by hastening functional impairment in patients with Alzheimer's disease. The fast pace of modern life, with its emphasis on independence, also contributes to excess disability by making it more difficult for older adults with impairments to function autonomously. Attention to depression, anxiety, and other mental disorders may reduce the functional limitations associated with concomitant mental and somatic

impairments. Many studies have demonstrated that attention to these factors and aggressive intervention, where appropriate, maximize function.

Prevention of Premature Institutionalization

Another important goal of prevention efforts in older adults is prevention of premature institutionalization. While institutional care is needed for many older patients who suffer from severe and persistent mental disorders, delay of institutional placement until absolutely necessary generally is what patients and family caregivers prefer. It also has significant public health impact in terms of reducing costs. A randomized study of counseling and support versus usual care for family caregivers of patients with Alzheimer's disease found the intervention to have delayed patients' nursing home admission by over 300 days. The intervention also resulted in a significant reduction in depressive symptoms in the caregivers. The intervention consisted of three elements: individual and family counseling sessions, support group participation, and availability of counselors to assist with patient crises.

Caregivers

What is caregiving?

Caregiving means caring for others, whether friends or relatives, who have health problems or disabilities and need help. Caregivers provide many kinds of help to care receivers, from grocery shopping to helping with daily tasks such as bathing, dressing, and eating. Most people who need help from caregivers are elderly.

Caregiver and Stress

Caregiver stress is a daily fact of life for many caregivers. Caregiving often takes a great deal of time, effort, and work. Many caregivers struggle to balance caregiving with other responsibilities including full-time jobs and caring for children. Constant stress can lead to "burnout" and health problems for the caregiver. Caregivers may feel guilty, frustrated, and angry from time to time. Caregivers often need help caring for an elderly or disabled care receiver. Sometimes other family members or friends and neighbors are able to help, but many caregivers do most or all of the caregiving for a loved one alone. Research has shown that caregivers often are at increased risk for depression and illness. This is especially true if they do not receive enough support from family, friends, and the community.

Caring for a person with Alzheimer's disease or other kinds of dementia at home can be overwhelming. The caregiver must cope with declining abilities and difficult behaviors. Basic activities of daily living often become hard to manage for both the care receiver and the caregiver. As the disease worsens, the care receiver usually needs 24-hour care.

What can caregivers do to prevent stress and burnout?

Caregivers can call upon others for support and assistance. Other family members, friends, and neighbors may be able to help in different ways. It may not be easy to ask for help, and they may need to make very specific requests. But getting help from others will benefit the caregiver and the person being caring for.

Respite care can be a good way to get a break (respite) from constant caregiving. If other caregivers aren't available to fill in for the main caregiver, respite care services may be available in the community.

Caregivers can take steps to take care of their own health: Caregivers should eat a healthy diet rich in fruits, vegetables and whole grains and low in saturated fat. They need to get enough sleep and rest. Caregivers need time for some exercise most days of the week. Regular exercise can help reduce stress and improve a person's health in many ways. They should see a health care provider for a checkup if they have symptoms of depression or illness. Caregivers should

seek counseling if needed. Caregivers should stay in touch with friends. Social activities can help keep a feeling of being connected and should help with stress. Faith-based groups can offer support and help to caregivers. Caregivers should find a support group for other caregivers in their situation (such as caring for a person with dementia). Many support groups are available online through the Internet.

What Is Aging? What Is Senescence?

Aging is a complex natural process potentially involving every molecule, cell, and organ in the body. In its broadest sense, aging merely refers to changes that occur during the lifespan. However, this definition includes some changes that aren't necessarily problematic, and usually don't affect an individual's viability. Gray hair and wrinkles, for instance, certainly are manifestations of aging, but neither is harmful.

To differentiate these superficial changes from those that increase the risk of disease, disability, or death, gerontologists prefer to use a more precise term—senescence—to describe aging. Senescence is the progressive deterioration of many bodily functions over time. This loss of function is accompanied by decreased fertility and increased risk of mortality as an individual gets older. The rate and progression of this process can vary greatly from person to person, but generally over time every major organ of the body is affected. As we age, for instance, lung tissue loses much of its elasticity, and the muscles of the rib cage shrink. As a result, maximum vital breathing capacity progressively diminishes in each decade of life, beginning at about age 20. With age, blood vessels accumulate fatty deposits and lose much of their flexibility, resulting in arteriosclerosis or "hardening of the arteries." In the gastrointestinal system, production of digestive enzymes diminishes, and as a result, tissues lose much of their ability to break down and absorb foods properly. In women, vaginal fluid production decreases and sexual tissues atrophy with increasing age. In men, sperm production decreases and the prostate enlarges.

Why these and other changes occur with advancing age both intrigues and perplexes gerontologists. In fact, senescence is one of nature's least understood biological processes. Gerontologists, for instance, disagree about when senescence begins. Some argue it begins at birth. Others contend it sets in after the peak reproductive years. But clearly, senescence, whether it begins at birth or age 20, 30, or 40, leads to an accumulating loss of bodily functions, which ultimately increases the probability of death, as we get older.

What is the Difference Between Life Expectancy and Lifespan?

When George Washington celebrated his 60th birthday in 1792, he had outlived all of his male ancestors, dating back for several generations. He

had outlived a typical Virginian of his era by about 15 years. To achieve this relative “old age,” he had survived smallpox, mumps, pneumonia, dysentery, typhoid fever, a staphylococcal infection of the hip, four bouts of malaria, and two nearly fatal encounters with influenza.

When Jeanne Calment was born in 1875, the illnesses that plagued Washington’s generation still took many lives, health care was still fairly primitive, and the life expectancy—the average number of years from birth that an individual can expect to live—was still less than 50 years worldwide. Yet Mme. Calment, perhaps because she was born with a set of extraordinary genes or was simply fortunate enough to elude many of the illnesses that claim so many others, beat the odds and set the benchmark for maximum human lifespan—the greatest age reached by any member of a species.

Life expectancy in the United States rose dramatically in the 20th century, from about 47 years in 1900 to about 73 years for males and 79 years for females in 1999. This increase is mostly due to improvements in environmental factors—sanitation, the discovery of antibiotics, and medical care. Now, as scientists make headway against chronic diseases like cancer and heart disease, some think life expectancy can be extended even further in the 21st century.

As part of this quest, gerontologists are studying a variety of life forms including yeast, fruit flies, nematodes, mice, and primates in search of clues applicable to human aging. As they explore the genes, cells, and organs involved in aging, they are uncovering more and more of the secrets of longevity. As a result, life extension may some day be more than the stuff of myth. In addition, as gerontologists apply their expanding knowledge to medicine, the prevention or retardation of the onset of some age-related diseases and disabilities may become realistic goals.

Why Do We Age?

Gerontologists have proposed many theories to explain the diversity of the aging process in nature. Pacific salmon, for instance, reproduce only once and die within hours of spawning, while at the other end of the spectrum, sea anemones, which reproduce asexually, show few, if any, outward signs of deterioration until the very end of their long lives. Most gerontologists now agree that no single theory can account for this wide spectrum. In fact, with the tools of biotechnology and an influx of new knowledge, all-encompassing theories of aging are giving way to a more diverse perspective.

Aging today is viewed as many processes, interactive and interdependent, that determine lifespan and health, and gerontologists are studying a

multitude of factors that may be involved. The rest of this booklet describes what we know and don't know about many of these factors, and where we think scientists are likely to find answers to questions about aging and longevity.

Theories of Aging

Theories of aging fall into two groups. The programmed theories hold that aging follows a biological timetable, perhaps a continuation of the one that regulates childhood growth and development. The damage or error theories emphasize environmental assaults to our systems that gradually cause things to go wrong. Many of the theories of aging are not mutually exclusive. Here is a brief and very simplified rundown of the major theories.

PROGRAMMED THEORIES

Programmed Longevity. Aging is the result of the sequential switching on and off of certain genes, with senescence being defined as the time when age-associated deficits are manifested.

Endocrine Theory. Biological clocks act through hormones to control the pace of aging.

Immunological Theory. A programmed decline in immune system functions leads to an increased vulnerability to infectious disease and thus aging and death.

ERROR THEORIES

Wear and Tear. Cells and tissues have vital parts that wear out.

Rate of Living. The greater an organism's rate of oxygen basal metabolism, the shorter its life span.

Crosslinking. An accumulation of crosslinked proteins damages cells and tissues, slowing down bodily processes.

Free Radicals. Accumulated damage caused by oxygen radicals causes cells, and eventually organs, to stop functioning.

Somatic DNA Damage. Genetic mutations occur and accumulate with increasing age, causing cells to deteriorate and malfunction. In particular, damage to mitochondrial DNA might lead to mitochondrial dysfunction.

Each year on her birthday, Jeanne Calment sent her lawyer a note, which read, “Excuse me if I’m still alive, but my parents didn’t raise shoddy goods.” Her brother, who died at age 97, apparently wasn’t too “shoddy”

himself. When another super centenarian, Sarah Knauss of Allentown, Pennsylvania, died in 1999 at age 119, her daughter was 96.

Some families seem blessed with long lives. In fact, siblings of centenarians have a four times greater chance of living into their early nineties than most people, according to researchers at the New England Centenarian Study in Boston. A coincidence? Hardly. What likely helps set these hardy individuals apart are extraordinary sets of genes, the coded segments of DNA (deoxyribonucleic acid), which are strung like beads along the chromosomes of nearly every living cell. In humans, the nucleus of each cell holds 23 pairs of chromosomes, and together these chromosomes contain about 30,000 genes.

There is little doubt that genes have a tremendous impact on aging and longevity. Based on studies of identical twins, who share the exact same set of genes, scientists now suspect that lifespan is determined by both environmental and genetic factors, with genetics accounting for up to 35 percent of this complex interaction. Although different animal species vary up to 100 times in lifespan—humans live five times longer than cats, for instance—scientists are discovering some surprising similarities between our genes and those of other species. Even single-celled yeast, one of nature's simplest organisms, may provide scientists with important genetic clues about human aging and longevity.

Tracking Down a Longevity Gene

Investigators are finding clues to aging and longevity in yeast, one-celled organisms that have some intriguing genetic similarities to human cells. In a laboratory at Louisiana State University Medical Center in New Orleans, Michal Jazwinski, Ph.D., has found genes that seem to promote longevity in these rapidly dividing, easy-to-study organisms.

Yeast normally have about 21 cell divisions or generations. Jazwinski observed that over the course of that lifespan, certain genes in the yeast are more active or less active as the cells age; in the language of molecular biology, they are differentially expressed. So far, Jazwinski has found 14 such genes in yeast.

Selecting one of these genes, Jazwinski tried two different experiments. First, he introduced the gene into yeast cells in a form that allowed him to control its activity. When the gene was activated to a greater degree than normal, or overexpressed, some of the yeast cells went on dividing for 27 or 28 generations; their period of

activity was extended by 30 percent.
In his second experiment, Jazwinski mutated the gene. When he introduced this non-working version into a group of yeast cells, they had only about 12 divisions.
The two experiments made it clear that the gene, now called LAG-1, influences the number of divisions in yeast or, according to some researchers' ways of thinking, its longevity. (LAG-1 is short for longevity assurance gene.) But how it works is still a mystery. One small clue lies in its sequence of DNA bases—its genetic code—which suggests that it produces a protein found in cell membranes. One next step is to study the function of that protein. Similar sequences have been found in human DNA, so a second investigative path is to clone the human gene and study its function. If there turns out to be a human LAG-1 counterpart, new insights into aging may be uncovered.
In another laboratory, Leonard Guarente, Ph.D., of the Massachusetts Institute of Technology found that mutation of a silencing gene—a gene that "turns off" other genes—delayed aging 30 percent in yeast. The gene, which is also found in *C. elegans* and other animals, produces an enzyme that alters the structure of DNA, which, in turn, alters patterns of gene expression.

Longevity Genes

Researchers have found evidence of several genes that seem to be related to longevity determination. Longevity-related genes have been found in tiny roundworms called nematodes, in fruit flies, and even in mice. Like yeast, nematodes and fruit flies have attracted a lot of attention from gerontologists because their short lifespans and their well-characterized genetic composition make them relatively easy to study. Investigators, for instance, can perform nearly 2,000 roundworm studies in the time it would take them to do one human study.
Under normal conditions, some genes are thought to manufacture proteins that limit lifespan. But when these same genes are mutated, they either produce defective proteins or no proteins at all. The net effect is these mutations promote longevity.
For instance, a mutation of a gene whimsically named "I'm Not Dead Yet" or INDY, can double the lifespan of fruit flies. In studies supported by the NIA, these fruit flies not only lived longer, they thrived. By the time that 80 to 90 percent of normal flies were dead, many of the INDY flies were still

vigorous and capable of reproduction. At least two other life-extending genetic mutations have been detected in the fruit fly genome.

In *C. elegans*, a nematode (roundworm), researchers have found yet another treasure trove of genetic clues about the aging process. By altering certain genes, researchers can substantially extend the normal 2-to-3-week lifespan of these tiny worms. One of these genes, called *daf-2*, controls a special stage in the worm's development called dauer formation. A dauer forms, if, in the first few hours of its brief life, a worm finds food scarce. In this state, *C. elegans* grows a cuticle for protection and can go into hibernation for several months. When the food supply is ample again, the worm emerges from this metabolically slowed, non-aging state and continues its normal life cycle. The protein produced by the *daf-2* gene drives the worm's development past or out of the dauer state. But Cynthia Kenyon, Ph.D., and her colleagues at the University of California, San Francisco, found that *daf-2* does much more. It also can regulate the lifespan of normal, fertile adults. By altering this gene so that its activity is reduced, Kenyon's team found lifespan of well-fed worms, which did not form a dauer, could be doubled. Other investigators have detected mutations in similar *daf* genes that increase nematode lifespan three or even four-fold.

Age-related Traits Are All in the Family

Finding longevity genes is only one of many goals for gerontologists. An equally important mission is unraveling the genetic processes involved in age-related traits and diseases.

NIA and Italian investigators are focusing their attention on Sardinia, a secluded Mediterranean island. Since settlers first occupied the island thousands of years ago, the population has grown without much immigration from the outside world. Because they are more closely related than people living in other societies, Sardinians share much of

The genes isolated so far are only a few of what scientists think may be dozens, perhaps hundreds, of longevity- and agingrelated genes. But tracking them down in organisms like nematodes and fruit flies is just the beginning. The next big question for many gerontologists is whether counterparts in people—human homologs—of the genes found in laboratory animals have similar effects. The *daf-2* gene in *C. elegans*, for instance, is similar to a gene found in humans that functions in hormone control.

In the worm, this gene makes a protein that looks much like the receptor for the hormone insulin. In humans, this hormone controls functions including food utilization pathways, glucose metabolism, and cell growth. These and other genetic linkages are under intense scrutiny, and ultimately could yield clues about how genes interact with environmental factors to influence longevity in humans and other species. Caloric restriction, for example, is the only known intervention shown to prolong life in species ranging from yeast to rodents. Scientists suspect this intervention works in yeast, worms, and other species, in part, because it triggers alterations of genetic activity. Caloric restriction also may work, partially, by altering metabolic pathways involved in energy utilization. (See The Next Step: Caloric Restriction in Primates).

the same genetic information, which makes it easier to track genetic effects through generations.

When a particular trait exists in a genetically isolated “founder” population such as Sardinia, it is likely that the same few genes are responsible for the trait in most or all affected individuals. Once the genes for a certain complex trait are identified within the founder population, researchers can use this information to isolate interacting genes and assess their importance in more genetically diverse cultures, like the United States. Other large founder populations exist in Finland, Iceland, and French-speaking Quebec.

In a study called the Progenia project, gerontologists are studying Sardinians for evidence of genetic influences on two traits: severe arterial stiffness and frequent positive emotions. Vascular stiffness may be an important predictor of heart disease mortality. Reports also suggest that joyfulness and other positive emotions can have profound impact on life satisfaction and health as we age. Gerontologists suspect these traits have strong genetic components. As the project progresses, investigators plan to conduct genetic analysis on individuals who share extreme values of these traits and will attempt to identify the underlying genes.

Many investigators, however, interpret these findings cautiously because there are important differences between human genes and those of lower animals. In fact, the structural similarity is only about 30 percent, which means that comparing yeast genes to human genes, for instance, is like comparing a go-cart to a high-performance racing car. The basic machinery may be similar, but one is far less complex than the other. So while yeast, worms, and other simple organisms are helpful models of aging, they probably don't completely mimic the process that occurs in humans. For this reason, gerontologists study the genetics of mice, primates, and other mammals that are more closely related to us. Some researchers are also studying human cells for more precise clues about how genes regulate human longevity and aging.

Other unanswered questions concern the roles played by these genes. What exactly do they do? How and when are they activated? On one level, all genes function by transcribing their "codes"—actually DNA base sequences—into another nucleic acid called messenger ribonucleic acid or mRNA. Messenger RNA is then translated into proteins. Transcription and translation together constitute the process known as gene expression.

The proteins expressed by genes carry out a multitude of functions in each cell and tissue in the body, and some of these functions are related to aging. So, when we ask what longevity or aging-related genes do, we are actually asking what their protein products do at the cellular and tissue levels. Increasingly, gerontologists also are asking how alterations in the process of gene expression itself may affect aging. Technological advances, which allow researchers to observe the expression of thousands of genes at once, are speeding the investigation of this process. In time, this emerging technology could help clarify what changes are occurring simultaneously in diverse cells, as they get older. (See Microarrays in Action, at right).

For now, investigators have found evidence that some proteins, such as antioxidant enzymes, prevent damage to cells, while others may repair damaged DNA, regulate glucose metabolism, or help cells respond to stress. Other gene products are thought to influence replicative senescence.

Cellular Senescence

During the process of cell division or mitosis, a cell's nucleus dissolves, and its chromosomes condense into visible thread-like structures that replicate. The resulting 92 chromosomes separate, migrating to opposite sides of the cell where new nuclei—each with 46 chromosomes—are formed. Once this occurs, the original cell, following the chromosomes' lead, pulls apart and

forms two identical daughter cells. It is this process that allows us to grow from a single cell into 100 trillion cells, composing the organ systems that make our bodies.

Early in life, nearly all of the body's cells can divide. But this process doesn't go on indefinitely. Researchers have learned that cells have finite proliferative lifespans, at least when studied in test tubes—*in vitro*. After a certain number of divisions, they enter a state in which they no longer proliferate and DNA synthesis is blocked. For example, young human fibroblasts—structural cells that hold skin and other tissues together—divide about 50 times and then stop. This phenomenon is known as the Hayflick limit, after Leonard Hayflick, who with Paul Moorhead described it in 1961 while at the Wistar Institute in Philadelphia. At least four genes involved in this process have been identified. This special aspect of cellular senescence is known as replicative senescence.

However, we do not die because we run out of cells (even the oldest people have plenty of proliferating fibroblasts and other types of cells). In fact, most senescent cells are not dead or dying. They continue to respond to hormones and other outside stimuli, but can't proliferate. Evidence suggests they can continue to work at many levels for some time after they cease dividing. Senescence, however, can cause radical shifts in some important cellular functions. For instance, senescent cells are resistant to dying and, as a result, they occur more often in aging bodies. Cellular senescence also triggers important changes in gene expression. Normally, fibroblasts are responsible for creating an underlying structure, called the extracellular matrix, which controls the growth of other cells. But senescent fibroblasts secrete enzymes that actually degrade this matrix.

Gerontologists suspect the breakdown of this structure may contribute to the increased risk of cancer as we age. So, cellular senescence may be critical early in life because it limits cell proliferation and helps suppress cancer. But as we get older, senescent cells might be harmful because changes in the genes they express might actually promote unregulated growth and tumor formation. This concept that genes, which have beneficial effects early in life, can also have detrimental effects later is known as antagonistic pleiotropy. Some gerontologists speculate that a better understanding of antagonistic pleiotropy might reveal much about what aging is, and how cellular senescence contributes to it.

But for now, many major questions about cellular senescence remain unanswered. Investigators, for example, are uncertain whether senescent cells accumulate in all tissues and organs with increasing age, thus contributing to the gradual loss of the body's capacity to heal wounds,

maintain strong bones, and fend off infections. Accumulation of senescent cells, if it does occur, could, in turn, indirectly increase an individual's vulnerability to the diseases and disabilities often associated with aging. However, no feature of aging has yet been unequivocally explained by *in vitro* cellular senescence.

Proliferative Genes

Searching for explanations of proliferation and senescence, scientists have found certain genes that appear to trigger cell proliferation. One example of such a proliferative gene is *c-fos*, which encodes a short-lived protein that is thought to regulate the expression of other genes important in cell division.

Proliferative genes, such as *c-fos* and others of its kind, are countered by anti-proliferative genes, which seem to interfere with division. The first evidence of an anti-proliferative gene came from an eye tumor called retinoblastoma. When one of the genes from retinoblastoma cells—later called the RB gene—became inactive, the cells went on dividing indefinitely and produced a tumor. But when the RB gene product was activated, the cells stopped dividing. This gene's product, in other words, appeared to suppress proliferation. Another well characterized gene of this type is the *p53* gene, which produces a protein that also limits cell proliferation. These genes are called tumor suppressor genes.

Limited proliferation is the norm in the world of human cells. In some cases, however, a cell somehow escapes this control mechanism and goes on dividing, becoming, in the terms of cell biology, immortal. And because immortal cells eventually form tumors, this is one area in which aging research and cancer research intersect. When tumor suppressor genes are inactivated, investigators theorize it turns on a complex process that leads to development of a tumor. So replicative senescence apparently has been retained through evolution as a defense against cancer.

Scientists are unraveling how the products of these genes promote and suppress cell proliferation. There are indications that a multi-layer control system is at work, involving a host of intricate mechanisms that interact to maintain a balance between the two kinds of genes. Some genes, for instance, appear to suppress or silence other genes. Mutations in these silencing genes have been shown to affect the lifespan of *C. elegans* and yeast. Many gerontologists are studying how silencing and other mechanisms such as telomere shortening influence replicative senescence.

Oxygen Radicals

Oxygen sustains us. Every cell in the body needs it to survive. Yet, paradoxically, oxygen also wreaks havoc in the body and may be a primary

catalyst for much of the damage we associate with aging. This damage occurs as a direct result of how cells metabolize it.

Oxygen is processed within a cell by tiny oganelles called mitochondria. Mitochondria convert oxygen and food into adenosine triphosphate (ATP), an energy-releasing molecule that powers most cellular processes. In essence, mitochondria are furnaces, and like all furnaces, they produce potentially harmful by–products. In cells, these by–products are called oxygen free radicals, also known as reactive oxygen species.

A free radical can be produced from almost any molecule when it loses an electron from one or more of its atoms. In cells, they are commonly created when mitochondria combine oxygen with hydrogen to form water. This transformation releases energy into the cell, but it also can shred electrons from oxygen. When this happens it leaves the oxygen atom—now an unstable oxygen free radical—with one unpaired electron. Because electrons are most stable when they are paired, oxygen free radicals steal mates for their lone electrons from other molecules. These molecules, in turn, become unstable and combine readily with other molecules.

This process, called oxidation, can spark a chain reaction resulting in a series of products, some of which are actually beneficial. The immune system, for instance, uses free radicals to destroy bacteria and other pathogens. Another oxidizing molecule, called nitric oxide, helps nerve cells in the brain communicate with each other.

Free radicals, however, also can be vandals that cause extensive damage to proteins, membranes, and DNA. Mitochondria are particularly prone to free radical damage. The major source of free radical production in the body, they are also one of its prime targets. As the damage mounts, mitochondria become less efficient, progressively generating less ATP and more free radicals. Over time, according to the free radical theory, oxidative damage accumulates in our cells and tissues, triggering many of the bodily changes that occur as we age. Free radicals have been implicated not only in aging but also in degenerative disorders, including cancer, atherosclerosis, cataracts, and neurodegeneration.

But free radicals, which also can be produced by tobacco smoke, sun exposure, and other environmental factors, do not go unchecked. Cells utilize substances called antioxidants to counteract them. These substances including nutrients—the familiar vitamins C and E—as well as enzymes produced in the cell, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, prevent most oxidative damage.

Nonetheless, some free radicals manage to circumvent these defenses and do harm. As a result, cellular repair mechanisms eventually falter and some internal breakdowns are inevitable. These breakdowns can lead to cellular senescence, and eventually may trigger apoptosis, a form of programmed cell death.

The discovery of antioxidants raised hopes that people could retard aging simply by adding them to the diet. So far, studies of antioxidant-laden foods and supplements in humans have yielded little support for this premise. Further research, including largescale epidemiological studies, might clarify whether dietary antioxidants can help people live longer, healthier lives. For now, however, the effectiveness of dietary antioxidant supplementation remains controversial. In the meantime, gerontologists are investigating other intriguing biochemical processes affected by free radicals, including protein crosslinking.

Protein Crosslinking

Blood sugar—glucose—is another suspect in cellular deterioration. In a process called non-enzymatic glycosylation or glycation, glucose molecules attach themselves to proteins, setting in motion a chain of chemical reactions that ends in the proteins binding together or crosslinking, thus altering their biological and structural roles. The process is slow and complex, but crosslinked proteins accumulate with time and eventually disrupt cellular function.

Investigators suspect that glycation and oxidation are interdependent processes since free radicals and crosslinks seem to accelerate the formation of one another.

Crosslinks, also known as advanced glycation end products (AGEs), seem to “stiffen” tissues and may cause some of the deterioration associated with aging. Collagen, for instance, the most common protein molecule in our bodies, forms the connective tissue that provides structure and support for organs and joints. When glucose binds with collagen—as it tends to do as we age—this normally supple protein loses much of its flexibility. As a result, lungs, arteries, tendons, and other tissues stiffen and become less efficient. In the circulatory system, AGEs may help trap LDL (the so-called “bad”) cholesterol in artery walls, and thus contribute to the development of atherosclerosis. They also have been linked to clouded lenses (cataracts), reduced kidney function (nephropathy), and age-related neurological disorders including Alzheimer’s disease.

These conditions appear at younger ages in people with diabetes, who have high glucose levels (hyperglycemia). Glycosylated hemoglobin in red blood cells, for instance, is an important marker doctors use to measure hyperglycemia. While the physiological effects of glycosylated hemoglobin are unclear, the disease it helps doctors detect—diabetes—is sometimes considered an accelerated model of aging. Not only do the complications of diabetes mimic the physiologic changes that can accompany old age, but people with this condition have shorter-than-average life expectancies. As a result, much research on crosslinking has focused on its relationship to diabetes as well as aging.

Just as the body has antioxidants to fight freeradical damage, it has other guardians, immune cells called macrophages, which combat glycation. Macrophages with special receptors for AGEs seek out and engulf them. Once AGEs are broken down, they are ejected into the blood stream where they are filtered out by the kidneys and eliminated in urine.

The only apparent drawback to this defense system is that it is not complete and levels of AGEs increase steadily with age. One reason is that kidney function tends to decline with advancing age. Another is that macrophages, like certain other components of the immune system, become less active.

Why this happens is not known, but immunologists are beginning to learn more about how the immune system affects, and is affected by aging (See The Immune System). And in the meantime, diabetes researchers are investigating drugs that could supplement the body's natural defenses by blocking AGEs formation.

Crosslinking interests gerontologists for several reasons. It is associated with disorders that are common among older people, such as diabetes and heart disease; it progresses with age; and AGEs are potential targets for drugs. In addition, cross-linking may play a role in damage to DNA, which is another important focus for research on aging.

DNA Repair and Synthesis

In the normal wear and tear of cellular life, DNA undergoes continual damage. Attacked by oxygen radicals, ultraviolet light, and other toxic agents, it suffers damage in the form of deletions, or deleted sections, and mutations, or changes in the sequence of DNA bases that make up the genetic code. In addition, sometimes the DNA replication machinery makes an error.

Biologists theorize that this DNA damage, which gradually accumulates, leads to malfunctioning genes, proteins, cells, and, as the years go by, deteriorating tissues and organs.

Not surprisingly, numerous enzyme systems in the cell have evolved to detect and repair damaged DNA. For repair, transcription, and replication to occur, the double-helical structure that makes up DNA must be partially unwound. Enzymes called helicases do the unwinding. Investigators have found that people who have Werner's syndrome (WS), a rare disease with several features of premature aging, have a defect in one of their helicases. George Martin, M.D., of the University of Washington and other investigators are exploring the mechanisms involved in DNA repair in WS and similar disorders, collectively known as progeroid syndromes. This research could help explain why DNA repair becomes less efficient during normal human aging.

The repair process interests gerontologists for many reasons. It is known that an animal's ability to repair certain types of DNA damage is directly related to the lifespan of its species. Humans repair DNA, for example, more quickly and efficiently than mice or other animals with shorter lifespans. This suggests that DNA damage and repair are in some way part of the aging puzzle.

In addition, researchers have found defects in DNA repair in people with a genetic or familial susceptibility to cancer. If DNA repair processes decline with age while damage accumulates as scientists hypothesize, it could help explain why cancer is more common among older people.

Gerontologists who study DNA damage and repair have begun to uncover numerous complexities. Even within a single organism, repair rates can vary among cells, with the most efficient repair going on in germ (sperm and egg) cells. Moreover, certain genes are repaired more quickly than others, including those that regulate cell proliferation.

DNA

DNA, the double helix cellular molecule that contains thousands of genes necessary for life, is constantly being damaged and repaired. Gerontologists suspect DNA repair mechanisms become less efficient with age. Accumulating DNA damage, including breaks in its structure or changes in its

nucleotide sequences, can lead to some of the physical changes we associate with aging.

Especially intriguing is repair to a kind of DNA that resides not in the cell's nucleus but in its mitochondria. These small organelles are the principal sites of metabolism and energy production, and cells have hundreds of them. Investigators suspect mitochondrial DNA is injured at a much greater rate than nuclear DNA, possibly because the mitochondria produce a stream of damaging oxygen radicals during metabolism. Adding to its vulnerability, mitochondrial DNA is unprotected by the protein coat that helps shield DNA in the nucleus from damage.

Research has shown that mitochondrial DNA damage increases exponentially with age, and as a result, energy production in cells diminishes over time. These changes may cause declines in physiological performance, and may play a role in the development of age-related diseases. Investigators are examining how much mitochondrial DNA damage occurs in specific parts of the body such as the brain, what causes the damage, and whether it can be prevented.

Heat Shock Proteins

In the early 1960s, investigators noticed fruit flies did something unusual. When these insects were exposed to a burst of heat, they produced proteins that helped their cells survive the temperature change. Intrigued, researchers looked for these proteins in other animals, and found them in virtually every living thing including plants, bacteria, worms, mice, and yes, humans. Today, the role of these substances, known as heat shock proteins, in the aging process is under scrutiny.

Despite their name, heat shock proteins (HSPs) are produced when cells are exposed to various stresses, not only heat. Their expression can be triggered by exposure to toxic substances such as heavy metals and chemicals and even by behavioral and psychological stress.

What attracts aging researchers to HSPs is the finding that the levels at which they are produced depend on age. Old animals placed under stress—short term, physical restraint, for example—have lower levels of a heat shock protein designated HSP-70 than young animals under similar stress. Moreover, in laboratory cultures of cells, researchers have found a striking decline in HSP-70 production as cells approach senescence.

Exactly what role HSPs play in the aging process is not yet clear. They are known to help cells dismantle and dispose of damaged proteins. They also facilitate the making and transport of new proteins. But what proteins are involved and how they relate to aging is still the subject of speculation and study.

While at the NIA, Nikki Holbrook, Ph.D., and other researchers investigated the action of HSP-70 in specific sites, such as the adrenal cortex (the outer layer of the adrenal gland). In this gland as well as in blood vessels and possibly other sites, the expression of HSP-70 appears closely related to hormones released in response to stress, such as the glucocorticoids and catecholamines. Eventually, answers to the puzzle of HSPs may throw light on some parts of the neuroendocrine system, whose hormones and growth factors might have an important influence on the aging process.

Hormones

Hormones are powerful chemicals that help keep our bodies working normally. Made by specialized groups of cells called glands, hormones stimulate, regulate, and control the function of various tissues and organs. They are involved in virtually every biological process including sexual reproduction, growth, metabolism, and immune function. These glands, including the pituitary, thyroid, adrenal, ovaries, and testes, release various hormones into the body as needed.

As we age, production of certain hormones, such as testosterone and estrogen, tends to decrease. Hormones with less familiar names, like melatonin and dehydroepiandrosterone (DHEA) are also not as abundant in older people as in younger adults. But what influence, if any, these natural hormonal declines have on the aging process is unclear.

Hormone Replacement

In the late 1980s, at Veterans Administration hospitals in Milwaukee and Chicago, 12 men age 60 and older began receiving injections three times a week that dramatically reversed some signs of aging. The injections increased their lean body (and presumably muscle) mass, reduced excess fat, and thickened skin. When the injections stopped, these changes reversed, and the signs of aging returned. What the men were taking was recombinant human growth hormone (hGH), a synthetic version of the hormone that is produced in the pituitary gland and plays a critical part in normal childhood growth and development. At the same time, evidence was accumulating that menopausal hormone therapy with estrogen (alone or in combination with a progestin in women with a uterus) could benefit postmenopausal women by reducing cardiovascular disease, colon cancer, and other diseases of aging. Further studies have indicated that, although estrogen remains an effective way to control hot flashes, long-term use of these hormones may increase risk for several major age-related diseases in some women, especially then treatment is started years after menopause. The finding that levels of testosterone in men decreased with

aging raised the question of whether they too might benefit from sex hormone treatment.

As a result of these preliminary observational findings, the NIA launched a series of research initiatives to clarify what influence hormone replacement therapy might have on the aging process. So far, most of these studies have been inconclusive, but have led many investigators to question whether the risks of hormone replacement may outweigh any benefit. Supplements of hGH, for instance, can promote diabetes, joint pain, carpal tunnel syndrome, and pooling of fluid in the skin and other tissues, which may lead to high blood pressure and heart failure. Studies in mice have raised other concerns about the hormone. Investigators have found that mice deficient in growth hormone production live substantially longer than normal mice, while mice overproducing growth hormone live shorter than average lives. This finding suggests that even if hGH replacement therapy is initially beneficial, ultimately it may be harmful and actually might curtail longevity.

Similarly, there is scant evidence that testosterone supplementation has any positive impact in healthy older men. In fact, some studies suggest supplementation might trigger excessive red blood cell production in some men. This side effect can increase a man's risk of stroke.

Estrogen is perhaps the most well studied of all hormones. Yet results from the Women's Health Initiative (WHI), the first major placebo-controlled, randomized clinical trial of estrogen therapy with or without progestin to prevent some chronic diseases of aging, surprised the medical community. There were more cases of stroke, blood clots, heart disease, and breast cancer in postmenopausal women using estrogen and progestin in the study, and more cases of possible dementia in women over age 65, than in those using the placebo. But, there were also fewer bone fractures and cases of colon cancer. In postmenopausal women using estrogen alone, there were more cases of stroke and fewer bone fractures than in those women on placebo. Other studies indicate that menopausal hormone therapy is effective in controlling moderate-to-severe menopausal symptoms, so research is ongoing to evaluate benefits and risks in menopausal and younger postmenopausal women.

As research continues, the pros and cons of hormone replacement may become more precisely defined. These hormonal supplements appear to increase risk and provide few clear-cut benefits for healthy individuals and do not seem to slow the aging process.

Hormones and Research on Aging

Produced by glands, organs, and tissues, hormones are the body's chemical messengers, flowing through the blood stream and searching out cells fitted with special receptors. Each receptor, like a lock, can be opened by the specific hormone that fits it and also, to a lesser extent, by closely related hormones. Here are some of the hormones and other growth factors of special interest to gerontologists.

ESTROGEN > Although it is primarily associated with women, men also produce small amounts of this sex hormone. Among its many roles, estrogen slows the bone thinning that accompanies aging. In premenopausal women the ovaries are the main manufacturers of estrogen (see image). After menopause, fat tissue is the major source of smaller amounts and weaker forms of estrogen than that produced by the ovaries. While many women with menopausal symptoms are helped by hormone therapy during and after menopause, some are placed at higher risk for certain diseases if they take it. The results of the WHI are prompting further studies about the usefulness and safety of this therapy when used by younger menopausal and postmenopausal women to control symptoms, such as hot flashes, and to prevent chronic diseases.

GROWTH HORMONE > This product of the pituitary gland appears to play a role in body composition and muscle and bone strength. It is released through the action of another trophic factor called growth hormone releasing hormone, which is produced in the brain. It works, in part, by stimulating the production of insulin-like growth factor, which comes mainly from the liver. All three hormones are being studied for their potential to strengthen muscle and bones and prevent frailty among older people. For now, however, there is no convincing evidence that taking growth hormone will improve the health of those who do not suffer a profound deficiency of this hormone.

MELATONIN > Contrary to some claims, secretion of this hormone, made by the pineal gland, does not necessarily diminish with age. Instead, a number of factors, including light, can affect production of this hormone, which seems to regulate various seasonal changes in the body. Current research does indicate that melatonin in low dosages may help some older individuals with their sleep. However, it is recommended that a physician knowledgeable in sleep medicine be consulted before self-medication. Claims that

melatonin can slow or reverse aging are far from proven.

TESTOSTERONE > In men, testosterone (see image) is produced in the testes (women also produce small amounts of this hormone). Production peaks in early adulthood. However, the range of normal testosterone production is vast. So while there are some declines in testosterone production with age, most older men stay well within normal limits. The NIA is investigating the role of testosterone supplementation in delaying or preventing frailty. Preliminary results have been inconclusive, and it remains unclear if supplementation of this hormone can sharpen memory or help men maintain stout muscles, sturdy bones, and robust sexual activity. Investigators are also looking at its side effects, which may include an increased risk of certain cancers, particularly prostate cancer. A small percentage of men with profound deficiencies may be helped by prescription testosterone supplements.

DHEA > Short for dehydroepiandrosterone, DHEA is produced in the adrenal glands. It is a precursor to some other hormones, including testosterone and estrogen. Production peaks in the mid-20s, and gradually declines with age. What this drop means or how it affects the aging process, if at all, is unclear. Investigators are working to find more definite answers about DHEA's effects on aging, muscles, and the immune system. DHEA supplements, even when taken briefly, may cause liver damage and have other detrimental effects on the body.

Growth Factors

Some types of hormones can be referred to as growth or trophic factors. These factors include substances such as insulin-like growth factor (IGF-I), which mediates many of the actions of hGH. Another trophic factor of interest to gerontologists is growth hormone releasing hormone, which stimulates the release of hGH. Growth factors might have an important role in longevity determination. In nematodes, for instance, mutations in at least two genes in the IGF-I pathway result in extended lifespan.

The mechanisms—how hormones and growth factors produce their effects—are still a matter of intense speculation and study. Scientists know that these chemical messengers selectively stimulate cell activities, which in turn affect critical events, such as the size and functioning of skeletal muscle. However, the pathway from hormone to muscle is complex and still unclear.

Consider growth hormone. It begins by stimulating production of IGF-I. Produced primarily in the liver, IGF-I enters and flows through the blood stream, seeking out special IGF-I receptors on the surface of various cells, including muscle cells. Through these receptors it signals the muscle cells to increase in size and number, perhaps by stimulating their genes to produce more of special, muscle-specific proteins. Also involved at some point in this process are one or more of the six known proteins that specifically bind with IGF-I; their regulatory roles are still a mystery.
As if the cellular complexities weren't enough, the action of growth hormone also may be intertwined with a cluster of other factors—exercise, for example, which stimulates a certain amount of hGH secretion on its own, and obesity, which depresses production of hGH. Even the way fat is distributed in the body may make a difference; lower levels of hGH have been linked to excess abdominal fat but not to lower body fat.

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