# The Cell Biology of Aging

## Introduction

The distinction between the effects of aging as a chronological process and diseases whose prevalence increase with advancing age remains blurred. Conditions once thought to be inevitable companions of old age are now known to in fact be pathological in origin and thus possibly treatable and preventable. One example is senile dementia, no longer the mysterious fate of the very old, but often a clinical manifestation of arteriosclerotic or biochemical brain disease.

Further research may elucidate the mechanisms underlying aging and their possible connection to age-related diseases, leading to the development of medical techniques that delay the onset and progression of symptoms. While it may not lead to actual extension of the human life span, such knowledge could reduce the prevalence and impact of chronic conditions that affect many elderly persons and drain our health care resources, allowing marked improvement in the general well-being and productivity of the growing elderly segment of the population.

The cell is the physiological building block in all higher organisms, including humans. Any investigation of mechanisms underlying the aging process must therefore look at how different cell types are altered over time to produce the structural and biochemical changes normally associated with aging. Numerous biological signs of aging have already been identified in cells both within the human organism and grown on artificial media. This section reviews the theories and evidence concerning mechanisms underlying biological aging.

## Theories about cellular mechanisms of aging

Theories about the cellular mechanisms underlying the aging process can be divided into two broad categories: 1) those involving a "biological clock" that orchestrates degenerative processes and determines life span; and 2) those involving accumulated damage, mutations, and waste products in certain cells.

### BIOLOGICAL CLOCK THEORIES

The biological clock theory proposes that an organism is inherently programmed to begin aging at a certain rate according to its chronological age. Evidence for this theory includes the observation that different species of higher vertebrates have very specific life spans that seem to be "programmed" into them according to species. Mechanisms underlying this programmed aging could involve an intrinsic genetic component of the tissues (24), and/or an extrinsic "neuroendocrine pacemaker" (16,17).

The genetic version of the biological clock is bolstered by the observation that the survival time of tissues grafted (or transferred) from an older animal into a younger one of the same species seems to depend on the age of the donor and is not influenced by the "younger" environment into which it has been introduced (24). Similarly, when nuclei from younger cells are transplanted into the cytoplasm of older cells, the recipients then live longer and regain the ability to replicate. These observations all suggest that a "clock" controlling aging does exist and may be located in the nucleus, possibly in the genetic material (24).

Genetic diseases that accelerate aging and abbreviate life spans further support intrinsic genetic control of aging, Werner's syndrome, for example, is a rare autosomal recessive disease (i.e., the gene for the disease is not carried on a sex chromosome and two copies of it must be present for the disease to appear) involving retarded growth, premature graying and loss of hair, cataracts, teeth loss, osteoporosis, aduh-onset diabetes, generalized atherosclerosis, and a median life span of 47' years. Cultured fibroblasts from people with Werner's syndrome exhibit a markedly abbreviated life span (23,53). Hutchinson-Gilford Progeria syndrome, another rare "age-accelerating" genetic disease, has similar symptoms that appear by age 1 and a median life span of 12 years. More than 80 percent of the deaths are due to heart disease (23). Localization of the exact gene lesions and their role in accelerating the aging process in these diseases could reveal genetic mechanisms involved in normal aging.

The control of aging by a "neuroendocrine pacemaker" extrinsic to the tissues involved is supported by evidence of progressive changes in neural and endocrine regulatory systems throughout adult life (17); such changes would produce a "cascade" of alterations in neural, endocrine, and tissue interactions, leading to the dysfunction of cells in the ovary, liver, and other target tissues (16). This neuroendocrine pacemaker could produce both cellular and physiological changes associated with aging. The mechanism driving these regulatory changes may involve the cumulative impact of specific hormones on the brain over time, After a certain amount of exposure, negative feedback at the hypothalamic level would cause changes in the homeostatic set points, causing ahered neuroendocrine out-

put and the observed functional and structural changes associated with aging.

This neuroendocrine pacemaker could also produce age-related disease by affecting genetic activity, leading to disturbances in immune function, proliferation of arterial walls, malignant growths, and other conditions that are associated with aging and limited life span in mammals (17).

It is not known, however, whether observed age-related changes in hormonal regulation and balance are a cause or an effect of the aging process (30). Furthermore, the biological clock may have both an intrinsic genetic and an extrinsic neuroendocrine component. Much research remains to be done before any conclusions may be drawn concerning programmed aging.

### ACCUMULATION OF DAMAGE: FREE RADICALS AND OTHER HARMFUL AGENTS

The other major cellular theory of aging involves the accumulation of physical and biochemical damage to both genetic and nongenetic components of body cells over time. Such cumulative damage would most affect cells that do not normally divide, like liver, heart muscle, and nerve cells.

Free radicals are byproducts of cellular metabolism that are capable of generating chemical reactions destructive to parts of the cell. As the cell continues to metabolize over time, such damage may increase. Some evidence suggests that free-radical damage may be responsible for decomposition of certain cell parts and the subsequent accumulation of lipofuscin ("age pigments") in various body tissues. Accumulation of lipofuscin, and of partially digested materials that have also been found in aging cells, may impair cell function and contribute to cell aging (3,4). Thus, the metabolic process itself may damage the cell over time and contribute to aging.

Accumulated damage with age could also be manifested by genetic lesions produced by mutations or mechanical disruptions of the chromosomes (37,41,48). Such damage could be exacerbated by a possible age-related deficiency in genetic repair mechanisms (13,36) and could result in the manufacture of faulty proteins (e.g., enzymes, hormones, neurotransmitters) that cannot work properly **(18).**

Several of the genetic '(age-accelerating" diseases, including xeroderma pigmentosum and Cockayne's syndrome, seem to involve defects in the cells' genetic repair mechanisms (23)53). People afflicted with either disease show increased frequencies of chromosomal aberrations and their body cells are unusually sensitive to the mutation-inducing properties of ultraviolet light. The symptoms of both of these diseases include pre-

mature death and early onset of dementia and various age-related degenerative neurological disorders.

Aberrant proteins could also accumulate both inside and outside cells due to age-related defects in the genetic material or in other protein-manufacturing machinery in the cell. The chemicals and structures responsible for "decoding" and implementing genetic information could alter with age, resulting in structurally faulty proteins that would be unable to function normally (31).

Accumulated insults to the cell over time—whether metabolic, environmental, or viral--could thus lead to cellular degeneration, loss of function, cessation of division, and cell death with a diminution of function in various body organs. Such acquired lesions could also lead to the formation of malignant cells and cancer. The damage could be exacerbated by the aging immune system's decreasing ability to detect and destroy aberrant cells and materials in the body.

Much research remains to be done, however, on the accumulation of either genetic or nongenetic cellular lesions as a function of age, and on the role of such lesions in the aging process. Such knowledge could lead to preventive or therapeutic techniques that prevent or correct this age-related damage along with any associated debilitating symptoms.

## *Biological signs of aging*

Certain systemic changes are generally acknowledged to characterize "normal" aging. Those body functions that decline with age include: renal blood flow (44), cardiac output (especially during exercise; 20), glucose tolerance (1), vital lung capacity (27), and cellular immunity (2).

The great variation in the incidence and degree of such age-related changes and diseases between people of the *same* age suggests that individual behavior and physiology influence the aging process. Better understanding of causal factors underlying age-related conditions could thus lead to better preventive and therapeutic treatments.

This section briefly reviews what is known and not known about the cellular basis of these and other biological changes occurring with age, and what connections there might be between these changes and age-related disease. The etiology and clinical impact of many of these "signs" are not known.

### CELL LOSS

Cell death in certain tissues could contribute to the degeneration and death of the organism. In fact, while it is not the sole cause, the loss of cells in certain re-

gions of the body is thought to contribute significantly to the aging process. Such loss is particularly important in tissues whose cells are unable to renew themselves, such as nerve and heart muscle cells.

In certain regions of the brain, nerve cells appear to be lost with advancing age (5), reaching 20 to 40 percent loss in some areas (10). Age-related loss of neurons in the brain's cerebral cortex (5,7), cerebellum (21), and limbic system (45) could be involved in impairment of cognitive, motor, and learning/emotional behavior, respectively, in the elderly. Alzheimer disease, a type of senile dementia found mostly in older persons, is associated with substantial loss of cells from specific brain regions, perhaps leading to clinical disruption of learning and memory.

The scattered loss of muscle fibers from the heart and their replacement with noncellular fibrous strands is observed in aging animals (29), along with a generally decreased proportion of muscle to connective tissue and fat, both in the heart and skeletal muscles. Alteration in the muscles controlling lung ventilation and their responsiveness to neural stimulation, although not necessarily involving cell death, may contribute to acute and chronic difficulty in breathing.

In the kidney, a deterioration of excretory function with age is accompanied by a steady decrease in the number of the organ's microscopic filtering units, or nephrons. Losses of 40 to 50 percent of the maximum number of nephrons can occur by age 70 (38). This loss and other age-related cellular changes could be related to functional decline of the kidney in the elderly, including a decrease in glucose resorption, water clearance, and total acid excretion. This reduces an elderly person's ability to maintain physiological balance of blood components, and can lead to excess circulating amounts of drugs if dosages are not adjusted to account for diminished kidney function.

Other organs undergoing appreciable atrophy with age include the thymus, ovaries, uterus, and testes (29). Hormonal changes in the elderly are suspected to contribute to these phenomena (see sections on cancer and hormonal changes for details and implications).

## CESSATION OF CELL DIVISION

The mechanisms that control cell proliferation and limit the replicative life span of normal cells are unknown, but could be significant in the aging process of the cell and the organism as a whole. Evidence based on observations first made by Hayflick (25) suggests that some cells in the body can reproduce for a limited number of generations; when grown in tissue culture (i.e., in laboratory dishes with a special mixture of nutrients), they cannot divide indefinitely. In fact, turnover of cells in areas where they are sloughed

off and renewed constantly (as in the skin or intestine) may decrease with age and lead to a net loss of cells. For example, there is a marked flattening and loss of cells in both the inner and outer skin layers of the elderly, along with impaired wound healing.

The relevance of a limited number of cell generations to the life span of the organism as a whole, however, has not been established. Study of cell lines that continue to proliferate indefinitely, like cancer cells, might yield clues to the mechanisms underlying the limited replicative life spans of normal cells.

## CHANGES IN CELL MORPHOLOGY

A decrease in the density of synapses (areas across which nerve cells signal each other) has been reported in certain regions of aging brains in humans (26,45) and animals (4,19,22). Loss of dendrites (signal receptors) from certain nerve cells has been observed in the cortex of elderly persons with senile dementia (8,45) and in several brain regions of aging laboratory animals (14,15)32,33)34,50). Degeneration of nerve cell axons (signal receivers) is also seen in the brains of old laboratory animals (l9,40). All of these changes could reduce connectivity between nerve cells in the brain and possibly cause impaired brain function in the elderly. For more detail, see the OTA background paper, *Impacts of Neuroscience,* published separately as part of this assessment.

In addition, the nerve cell's outer membrane often exhibits a loss of transmitter receptors and increased rigidity with age. Membrane rigidity reduces the active transport of ion exchange, thereby reducing transmitter efficiency. These changes may also inhibit cell signaling by altering sensitivity to hormones, growth factors, and neurotransmitters.

The increased rigidity observed in the surface membranes of cells other than neurons, including lymphocytes (immune cells) and liver cells, may be due to a generalized increase in the cholesterol: phospholipid ratio of the membrane, possibly leading to a decrease in cell motility and function. The clinical effects of this change are unknown.

The elastic properties of lung tissue also decline with age and could contribute to the impeded ventilation and reduced rate of metabolic gas exchange seen in the elderly. Degeneration of the lung parenchymal tissue and a reduction in its capillary bed has been associated with emphysema. Further research is needed into the effect of environmental pollutants, including tobacco smoke, on lung tissue. Chronic obstructive lung disease, including emphysema, is the fifth leading cause of death among the elderly today, has a rising mortality rate, and is increasing in prevalence as a debilitating chronic condition (see app. A).

## CHANGES IN MATERIALS INSIDE THE CELL

The possible accumulation of damage to the cell's internal machinery underlies one of the major theories of aging discussed earlier. Such a cumulative effect is especially important in cells that do not normally divide frequently (e.g., liver parenchymal cells) and those incapable of dividing at all (e.g., nerve, muscle, and egg cells). Such damage could be due to accidents, disease, and/or the effects of normal metabolism over time that may adversely affect such vital cell functions as protein synthesis.

As cells metabolize they produce deleterious by-products. Free radicals, for example, are extremely reactive substances given off by the mitochondria (the cell's "energy generators") during respiration that can trigger chemical reactions destructive to cell structures. A major consequence of such oxidative damage is lipid peroxidation, (39) which has been implicated in the formation of lipofuscin, a yellow-brown "age pigment" found in some nerve, muscle, and liver cells of old animals and humans (29,30), It is not known whether lipofuscin interferes with cellular function, but drugs that inhibit the formation of lipofuscin in mice resulted in a mean extension of life span.

In old cells, damage to the intracellular sac that contains digestive enzymes may also occur, resulting in a leakage of destructive enzymes out into the cytoplasm that damages the cell (30). Other malfunctions could result from the accumulation of partially degraded cell parts that would normally be totally degraded into reusable components after they have "worn out."

Senescent nerve cells often collect abnormal filaments that progressively fill the cell body and dendrites, replacing the normal cellular "skeleton" thought to be vital to many cell functions. This condition is found in normal aging and, to a greater extent, in such diseases as Down's syndrome and senile dementia (12,28). Similarly, massive quantities of filamentous protein have been observed to accumulate in aging cells in tissue culture. The effect of such changes in cellular architecture is unknown, but they may interfere with some functions, including the internal movement of cell components.

Another vital class of cellular proteins is the receptor proteins that are specifically adapted to receive chemical signals from outside the cell in order to modify cell function. For example, cells in the adrenal gland are instructed by chemicals from another gland via such receptors to release stress hormones into the blood. Certain kinds of receptors in the cell cytoplasm (fluid interior) seem to undergo an age-related decrease in number that has been correlated with decreased responsiveness of the cell to certain hormones, including sex hormones, disrupting their usual regu-

latory functioning (43). It is possible that the age-related loss of hormonal function—implicated in disorders ranging from diabetes to immune deficiency (see section on hormonal changes) -could stem from a loss of available receptors, whether by a decrease in their production, an increase in their breakdown, or a "masking" of the receptors by a competing protein.

## CHANGES IN CELLULAR PROTEIN AND EXTRACELLULAR MATERIALS

There is evidence of changes in cell protein with age, both through changes in the amount and kind synthesized, and in their structural integrity over time (30). In general, there seems to be an overall decrease in rate of protein synthesis in most of the tissues of older animals (46). Protein synthesis is vital to the maintenance of cells, many parts of which "wear out" with time and are replaced continuously. Malfunctioning of the synthetic process could lead to the general disrepair and degeneration of a cell.

In several tissues, synthesis of structural proteins ceases in the adult (e.g., cartilage), child (tooth dentine), or even before birth (eye lens proteins). During aging, these proteins may be progressively altered, leading to diminished function. Structural changes in the lens proteins of the eye, for example, could "stiffen" the lens, hindering the ability to focus and resulting in the deterioration of near vision that is almost universal in the elderly. Cataracts, a clouding of the lens, may also result from structural changes in lens proteins (35).

One of the most well-known biological aging processes involves structural changes in certain extracellular proteins that are normally responsible for the structural integrity of many tissues. For example, cross-linking of collagens—proteins that lend strength and stability to joints, tendons, and the skin—reaches a constant level at maturation (49). The cross-links, however, seem to be damaged with advancing age (possibly by free radicals) to produce a stiffening of connective tissue and thickening of basement membranes, both of which may impede cell function. This may contribute to the loss of elasticity in the skin of elderly persons.

Cross-linking of collagen in joint cartilage may contribute to osteoarthritis (age-related degradation of the extracellular matrix that provides cartilage elasticity has also been implicated in degenerative arthritis). Cross-1inking may also contribute to the thickening of the basement membrane of the kidney's glomeruli (minute structures responsible for initial filtration of the blood). This could impede filtration and exacerbate the loss of excretory competence with age.

The protein mesh maintained on the surface of almost all cells also seems to be biochemically altered with age. The matrix is normally involved in cell attachment, shape, migration, and perhaps in cell division–functions that could be affected by alteration of its constituent proteins.

Other extracellular components varying with age contribute to the development of diseases more prevalent in the aged. Deposition of lipid-containing plaques along the inner walls of arteries, or atherosclerosis, occurs mostly in the elderly and underlies many forms of cardiovascular disease. Deposition of amyloid (a waxy substance consisting of proteins and sugars) in blood vessels, characteristic of a variety of diseases, is found consistently in the elderly and mainly in the kidneys, heart, pancreas, adrenal gland, and central nervous system (29). The clinical impact of such deposits is undetermined but could involve impaired function of these organs.

Disorders involving decrease in bone mass (osteoporosis) or in the calcium content of the bone (osteomalacia) account for a large portion of chronic disabilities in the elderly, including increased susceptibility to fracture due to a weakening and brittleness of the bones (see ch. 3). Defects in vitamin D metabolism, hormone imbalances, and inactivity have all been implicated in disturbing the complex balance between the continual absorption and deposition of bone by specialized cells.

## ABNORMAL CELL PROLIFERATION AND CANCER

Hyperplasia, or the abnormal proliferation of cells in certain body tissues, is often observed in the elderly. Cancer, or malignant neoplasia, is second only to cardiovascular disease as a cause of death in the United States (see app. A). The chances that a person will develop cancerous growths within a 5-year period rise from 1 in *700* at age *25* to 1 in **14 at age 65.** The overall incidence of cancer peaks between ages 40 and 80, although certain forms of cancer (e.g., leukemia, lymphoma, and prostatic cancer) are more prevalent in older age groups.

Hyperplasia is found in a variety of localized regions in the elderly, including hyperplastic and malignant growths in the endocrine glands and various types of cancers in the skin, bladder, gastrointestinal (particularly the colon), urinary, and reproductive tracts. Some formations, like "polyps" or small growths in the colon and bladder, may be a localized reaction to generalized cell loss and seem to presage local cancer formation (29). Cancers in the fatty and fibrous tissues are also often found scattered throughout the aging body. Malignant growths in the elderly also commonly involve the breasts, lymphoreticular system, and lungs.

Although usually not malignant, age-related proliferation of smooth muscle cells in the arteries may contribute to atherosclerosis (47).

Cancerous growths seem to be largely triggered by interactions between noxious agents (e.g., radiation, chemical exposure, and viruses) and characteristics of the host, including genetic factors, hormonal balances, immunological responsiveness, and nutritional status—all of which are more likely to be impaired in the elderly (see ch. 4 and relevant sections of this appendix).

An inherited or acquired genetic component, including a possible age-related decrease in ability to repair mutated and otherwise damaged DNA, may predispose an individual to the birth and spreading of malignant growths. Several "age-accelerating" genetic disorders, like Werner's syndrome, Bloom's syndrome, and xeroderma pigmentosa, involve increased incidence of certain cancers that are suspected to stem from faulty DNA-repair mechanisms.

Altered hormone levels in the elderly have been linked to some cancers: postmenopausal cancer of the uterus has been associated with continued presence of estrogen, both in its natural and ingested forms; increased breast cancer with a rise in prolactin; and increased prostate cancer with the drop in testosterone observed in elderly men.

Finally, the loss of immune function in the elderly (discussed in the following section) may include a decreased ability to detect and kill aberrant or cancerous cells after they have formed, thus facilitating the birth and growth of cancers.

Although these genetic, endocrine, environmental, viral, hormonal, and immunologic factors are all suspect, the relationship between the aging process and the markedly increased incidence of cancer in the elderly compared to the general population remains largely a mystery.

## THE AGING IMMUNE SYSTEM

When the body is invaded by a potentially harmful foreign substance, or "antigen," including bacteria and viruses, an immune reaction is triggered. The immune reaction involves the binding and "deactivating" of the antigen by one of two agents present in the blood and body tissues: immune cells (T-lymphocytes or T-cells) produced by the lymph tissue that directly attack the antigen, or proteins in the blood known as antibodies produced by specialized immune cells (B-lymphocytes or B<ells) that are present in the spleen, lymph nodes, and blood.

The T-cell is dependent on the thymus (a ductless glandlike structure found in the neck or upper chest of all vertebrates) and, in addition to its ability to

directly "neutralize" antigens, helps regulate the production of antibodies by B-ells. Antibody production is aided by "helper" T-ells and hindered by "suppressor" T-ells. T-ells can also directly kill cancerous, transplanted, or otherwise aberrant cells and are thought to be responsible for cell-mediated or acquired immunity (e.g., the resistance to a specific disease acquired after vaccination).

Aging is accompanied by a marked decrease in the immune system's ability to respond to invasion by harmful substances, as well as an increase in autoimmune reactions (immune reactions to the body's own materials). The B-cells that produce antibodies decrease in number and activity with age. T-cell function exhibits the sharpest decline: direct T-cell attack of antigens decreases with age along with helper T-cell activity, while activity of the suppressor T-cells increases (46,52). As a result, the strength of immune response to infectious agents and aberrant cells is reduced in the elderly.

The aging immune system is also less able to distinguish foreign invaders from native materials, leading to injury of the patient's own tissues by autoimmune reactions (9,42). Age-related deposits of antibody-antigen complexes are often found in organs with extensive capillary beds like the kidneys, lungs, liver, and the brain, and may contribute to localized tissue damage (29,52). There is speculation that rheumatoid arthritis may be due to some type of autoimmune reaction to tissues in the joints.

Age-related morphological changes in the immune system have been associated with the above functional abnormalities seen in the elderly. In particular, the thymus undergoes a progressive decrease in size with age, accompanied by a loss of function. Involution of the thymus begins at puberty and leads to an approximate 85-percent decrease in mass by age so in humans (29). In addition, bone marrow is increasingly replaced by fat and fibrous tissue in the elderly, with a general reduction of both immune and red blood cell production in peripheral tissues.

Such age-related decreases in immune function could render the elderly more vulnerable to infectious diseases, including pneumonia and influenza, which remain fourth in leading killers among the elderly today (see app. A), and could contribute to the age-related increase in the prevalence of cancer.

### AGE-RELATED CHANGES IN HORMONES

Endocrine glands (e.g., the thyroid, pancreas, pituitary, and testes) tend to shrink with age and exhibit age-related declines in the secretion of some hormones. The sharp drop of estrogen secretion in women during menopause, for example, is well documented. The metabolism of many hormones also declines with age, however, resulting in no net change in the basal levels.

The age-related decrease in function of many hormones could be alternatively explained by an age-related decrease in the effect of some hormones on their target tissues or organs. Glucose intolerance, for example, is more prevalent among the elderly and may be due to a reduction in insulin sensitivity (and therefore reduced ability to metabolize glucose) in peripheral tissues of older persons (11), coupled with an inherited disposition towards the illness. Behavioral changes associated with aging, including an increase in obesity and decrease in exercise, may also contribute to these changes.

This decreased effect of hormones on their target tissues may also provide a basis for age-related changes in presentation of illnesses, response to treatment, and ability to respond to stress. For example, the heart of an older person is generally less responsive to stimulation by catecholamine, a hormone that normally causes the heart to pump harder and faster. As a result, elderly people are less able to maintain adequate blood pressure in response to postural stress or bleeding.

## Conclusion

The aging process probably involves a complex interaction of several mechanisms, possibly including both a '(biological clock" and accumulated cellular lesions with age. Examination of aging on the cellular level, however, is only part of the integrative approach necessary to a full understanding of the process. Much work remains to be done on the biochemical, cellular, systemic, organismic, and even population levels before a viable theory may be developed to explain why and how people age. Such knowledge could, in turn, lead to medical techniques that prevent or mitigate the symptoms of aging and age-related diseases that afflict many elderly people and drain the Nation's medical and social service resources.

## Appendix B references

1. Andres, R., "Aging and Diabetes," *Med. Clin. North Amer.* 55(4):835-846, 1971.
2. Besdine, R., et al., *Handbook of Geriatric Care,* 1982.
3. Bjokerund, S.,"Studies of Lipofuscin Granules in Human Cardiac Muscle, H. Chemical Analysis of Isolated Granules, " *Exp. Molec. Path.* 3:377-389, 1964.
4. Bondareff, W., and Geinisman, Y., "Loss of Synapses in the Dentate Gyrus of the Senescent Rat, " *Nat. Amer. J. Anat.* 145:129-136, 1976.
5. Brody, H., and Vijayashankar, N., "Anatomical Changes

in the Nervous System, " *Handbook of the Biology of Aging, C.* E. Finch and L. Hay flick (eds.) (New York: Van Nostrand Reinhold Co., 1977).

6. Brody, H., "Structural Changes in the Aging Nervous System," *Interdisciplinary Topics in Gerontology*, vol. *7*, H. T. Blumenthal (cd.) (Munchen: Kayer, Basel, 1970).

7. Brody, H., "Organization of the Cerebral Cortex, HI: A Study of Aging in the Human Cerebral Cortex," *J.Comp. Neur.*102:511-5567, 1955.

8. Buell, S., and Coleman, P., "Dendritic Growth in the Aged Human Brain and Failure of Growth in Senile Dementia," *Science* 206:854-856, 1979.

9. Burnet, F. M., *Immunological Surveillance* (Oxford, England: Pergamon Press, 1970).

10. Curcio, C. A., Buell, S. J., and Coleman, P. D., "Morphology of the Aging Nervous System: Not All Downhill, " *Aging Motor Systems*, F. J. Pirozoli, and J. G. Malletas (eds.) (New York: Praeger, 1983), pp. 7-35.

11. DeFronzo, R. A., "Glucose Intolerance With Age: Evidence for Tissue Insensitivity to Insulin, ''Diabetes 28:1095-1101, 1979.

12. DeJong, R. N., and Pope, A., "Dementia," *The Nervous System*, D. B. Toner and T. N. Chase (eds.) (New York: Raohn Press, 1975).

13. Esptein, J., et al., "Rate of DNA Repair in Progeric and Normal Human Fibroblast, " *Biochem. Biophy's Res.Com - mun.* 59:850-857, *1974.*

14. Feldman, M. L., "Aging Changes in the Morphology of Cortical Dendrites, " *Neurobiology of Aging, R.* Teny *and S.* Gershon (eds.) (New York: Raven Press, 1976), pp. 211-227.

15. Feldman, M. L., and Dowd, C., "Loss of Dendritic Spines in Aging Cerebral Cortex ," *Anat. Embry. 148:279-301, 1975.*

16. Finch, C. E., "Emergent Issues in Neurogerontology, " *Roche Seminars on Aging, No. 1,* Section l/The Scientific Aspects, 1980.

17. Finch, C. E., "The Regulation of Physiological Changes During Mammalian Aging," *Quart. Rev. Biol.*51:49-83, *1976.*

18. Gallant, J., "The Error Catastrophe Theory of Cellular Senescence," *Biological Mechanisms in Aging,* R. T. Schimke (cd.), 1981.

19. Geinisman, Y., "Loss of Axosomatic Synapses in the Dentate Gyrus of Senescent Rats, " Soc. *Neuro. Abstr.*5:5, 1979.

20. Gerstenblith, G., "Cardiovascular Aging, " *Biological Markers of Aging,* M. E. Reff and E. L. Schneider (eds.), 1982.

21. Hall, T. C., Miller, A. K. H., and Corsellis, J. A. N., "Variations in the Human Purkinje Cell Population According to Age and Sex, " *Neuropathology and Applied Neurology* 1:267-292, *1975.*

22. Hasan, M., and Glees P., "Ultrastructural Age Changes in Hippocampal Neurons, Synapses and Neuroglia," *Exp. Ger.*8:75-83, *1972.*

23. Hay flick, L., "Genetic Disparities of Senescence, " *Bio- cultural Aspects of Disease,* H. R. Rothschild (cd.) (New York: Academic Press, 1981).

24. Hayflick, L., "The Cell Biology of Aging," N. *Engl. J. Med.* (Dee.):1302-1308, 1976.

25. Hayflick, L., "The Limited *In Vitro* Lifetime of Human Diploid Cell Strains," *Exp. Cell Res.*37:614-636, 1965.

26. Huttenlocher, P. R., "Synaptic Density in Human Frontal Cortex—Develop Mental Changes and Effects of Aging," *Brain Res.* 163:195-205, *1979.*

27. Kannel, W. B., and Hubert, H., "Vital Capacity as a Biomarker of Aging," *Biological Markers of Aging,* M. E. Reff and E. L. Schneider (eds.), 1982.

28. Katzman, R., et al. (eds.), "Alzheimer's Disease: Senile Dementia and Related Disorders," *Aging,* vol. 7 (New York: Raven Press, 1977).

29. King, D. W., et al., "Morbidity, and Mortality in the Aged," *Hosp. Prac.* (Feb):97-107, 1982.

30. Knook, D. L., "Aging of Cells: Accident or Programmed?" *Endeavour* 6(4):162-167, *1982.*

31. Linn, S., et al., "Decreased Fidelity of DNA Polymerase Activity Isolated From Aging Human Fibroblasts," *Proc. Nat. Acad. Sci. USA.* 73:2878-2822, *1976.*

32. Machado-Salas, and Scheibel, A. B., "Limbic System of the Aged Mouse, " *Exp. Neur.*63:347-355, *1979.*

33. Machado-Salas, et al., '(Morphologic Changes in the Hypothalamus of the Old Mouse, "*Exp. Neur.*57:102-111, 1977.

34. Machado-Salas, et al., "Neuronal Changes in the Aging Mouse: Spinal Cord and Lower Brain Stem, " *Exp. Neur.* 54:504-512, 1977.

35. Masters, P. M., "Senile Cataracts: A Model for Studying Post-Translational Changes in Structural Proteins, " *Biological Markers of Aging, M.* E. Reff and E. L. Schneider (eds.), 1982.

36. Mattern, M. R., and Cerutti, P. A., "Age-Dependent Excision Repair of Damaged Thymine From Gamma-Irradiated DNA by Isolated Nuclei From Human Fibroblasts," *Nature* (Lend). 254:450-452, 1975.

37. Medvedev, Zh. A., "The Nucleic Aids in Development and Aging, " *Advances in Gerontological Research, vol. 1,* B. L. Strehler (cd.) (New York: Academic Press, 1964), p. 181-206.

38. National Research on Aging Planning Panel, *A National P/an for Research on Aging,* Nat. publication No. 82-2453, September 1982.

39. Nohl, H., and Hegner, D., '(Do Mitochondria Produce Oxygen Radicals In Vivo?" *Em. J. Biochem.*82:563-567, *1978.*

40. Nuranjo, N., and Green, E., "Use of Reduced Silverstain to Show Loss of Connections in Aged Rat Brain, " *Brain Res. Bull.* 2:71-74, *1977.*

41. Orgel, L. E., "The Maintenance of Accuracy of Protein Synthesis and Its Relevance to Aging)" *Biochem. 49:517- 521, 1963.*

42. Phillips, S. M., and Wegman, T. G., "Active Suppression as a Possible Mechanism of Tolerance in Tetra Parental Mice, " *J. Exp. Med.* 137:291-300, *1973.*

43. Roth, G. S., "Age-Related Changes in Hormone Action: The Role of Receptors, " *Biological Mechanisms in Aging,* R. T. Schimke (cd.), 1981.

44. Rowe, J. W., "Renal Function and Aging," *Biologial Markers of Aging,* M. E. Reff and E. L. Schneider (eds.), 1982.

45. Scheibel, M. E., et al., "Progressive Dendritic Changes in the Aging Human Limbic System, " *Exp. Neur.* 53(2): 420-430, November 1976.

46. Schimke, R. T., and Agniel, M., "Biologic Mechanisms in Aging: Summary of Conference Proceedings," *J.* Amer. *Ger. Soc.* 31:40-44, Jan. 1983.

47. Stemerman, M. B., and Maciag, T., "Age-Related Aberrations in Proliferative Homeostasis," *Biological Mechanisms in Aging,* R. T. Schimke (cd.), 1981.

48. Szilard, L., "On the Nature of the Aging Process, " *Proc. Natl. Acad Sci. USA* 45:30-45, *1959.*

49. Tanzer, M. L., "Collagen Cross-Linking: Relationship to Theories of Aging," *Biological Mechanisms in Aging,* R. T. Schimke (cd.), 1981.

50. Vaughan, D. W., "Age-Related Deterioration of Pyramidal Cell Basal Dendrites in Rat Auditory Cortex," *J. Comp. Neur.* 171:501-516, 1977.

51. Weksler, M., "Age-Associated Changes in the Immune Response, " *J. Amer. Ger. Soc.* 30(11):718-723, *1982.*

52. Weksler, M., "The Senescence of the Immune System," *Hosp. Pract. 53-64, 1981.*

53. Williams, J. R., and Dearfield, K. L., "Introduction and Repair of DNA/Chromatin Alteration s," *Biological Mechanisms in Aging,* R. T. Schimke (cd.), 1981.