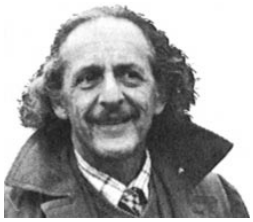
Current Comments®



The Dilemma of Prolongevity Research—Must We Age before We Die, or if We Don't, Will We?

Number 15 April 11, 1983

The prospect of aging concerns us all, whether we are coping with the death or debility of a loved one, examining a new wrinkle in the mirror, or just wondering, as children do, what it means to be old or to die. In past essays, I have discussed scientific approaches to some of the aspects of aging, both physical and psychological, that people fear most, such as senile dementia,[1] and coping with terminal illness.[2] We are told from birth that it is natural and right that we age and die, but the impulse to avoid death is strong indeed. It has manifested itself in various ways throughout recorded history, and transcended cultural boundaries. Medicine men and magicians, alchemists, sages, and physicians have searched for ways to ward off the effects of aging. But to date, scientists and their predecessors alike have been rebuffed. As far as physical immortality is concerned, we have not altered the life-to-death scenario in any significant way, so men and women continue to strive for immortality through their children, their creativity, or their religion.

It is easy to understand why Renaissance alchemists, who searched for the elixir of youth in much the same way as they pursued the transmutation of the elements, were unsuccessful. But some people may be surprised to learn that modern medicine, so adept at solving other problems, has found no way to slow down the basic aging process. It is true that, on the average, we live longer than our ancestors did. In ancient Rome, the average life expectancy was 20 years,[3] whereas babies born in the US today can expect to live about 73 years.[4] In fact, people aged 75 or older constitute the fastest-growing segment of the US population.[5]

This does not mean, however, that we have learned to delay old age. Rather, we have found ways to increase life expectancy at birth by controlling some of the diseases that used to kill us prematurely.[6] Since we cannot control the aging process, we must live with its consequences. Our susceptibility to death from disease, injury, infection, and other types of environmental insult rises exponentially after age 30.[7,8] It is sobering to think that the maximum life span, or uppermost age that humans can possibly expect to reach, has remained constant, at about 110 years, since antiquity.[6]

Why has the problem of aging been such an intractable one? Up until the middle of this century, the prevalent view of scientists had been that the task of controlling aging was fundamentally impossible.[9] But today, such a consensus no longer exists.[10] Many researchers now believe that their predecessors failed, not because their goals were misguided, but because the tools and the level of sophistication they could bring to the task were inadequate. Moreover, it is argued that progress has been hampered because funding has been scarce, and researchers concerned with aging have been too few and far between.[11]

Indeed, until recently, aging research had been plagued by all of these problems. During most of the first half of the twentieth century, while rapid progress

was being made in other areas of biomedicine, only a handful of scientists throughout the world were doing aging research.[9] One of these pioneers was Nathan Shock, who, according to Paul D. Phillips, Wistar Institute, Philadelphia, is considered by many to be one of the "fathers" of modern gerontology.[12] Many years ago, I met Shock on a train going from Baltimore to New York. I noticed that he was actually reading a copy of *Index Medicus*. This was before the days of *Current Contents*® (*CC*®).

For over 40 years, Shock did aging research at the Gerontology Research Center, Baltimore City Hospitals, where he is now scientist emeritus. In addition to being one of the first researchers to measure the effects of aging on a variety of body functions, Shock made an important contribution to his field as a bibliographer and reviewer of gerontology and geriatrics literature.[12] His bibliographies regularly appeared in the *Journal of Gerontology* for 30 years, between 1950 and 1980, and for six years he served as editor of that publication.

During the 1960s, scientific interest in aging grew slowly, and funding levels remained low, particularly in contrast with the amount of money expended in other areas of biomedical research. In the early-1960s, I began researching the subject of aging for a book I had hoped to write. I found that only one percent of the funds allotted by the US government to biomedical research was going to gerontology. I discontinued work on my book when Robert C.W. Ettinger's *The Prospect of Immortality*[13] appeared in print, and voiced many of my own concerns about the need for a more concerted, systematic approach to the problem of aging. This point has been made, incidentally, in other books on aging research as well. These include *The Immortalist*[14] by Alan Harrington, and *The Process of Ageing*[9] by Alex Comfort. A more recent book, *Prolongevity*[15] by Albert Rosenfeld, discusses some of the most promising advances which have been made in our knowledge of aging over the past two decades, and analyzes the impact that funding patterns have had on our progress.

After the 1960s, as Rosenfeld and others have pointed out, the funding picture began to improve. Still, until 1976, the National Institutes of Health (NIH), the major governmental funding agency for biomedical research in the US, administered money for aging research indirectly, through the Aging Branch of the National Institute for Child Health and Human Development.[11] In 1976, the National Institute on Aging (NIA) was established, and aging research escaped its "stepchild" status. Since that time, funding and interest in aging research have grown rapidly. In 1976, according to Karen Ross, NIA budget officer, NIA had only 19 million dollars to administer. In 1982 that figure had risen to more than 80 million dollars. And the estimate for 1983 is even higher.[16] The NIA, incidentally, has recently named a new director. T. Frank Williams, University of Rochester, will take over this post, which has been vacant since September 1982, on July 1.

Aging research has also acquired support from a variety of private sector organizations. The American Longevity Association, for example, is an organization of scientists and laypersons which raises funds from private sources and makes them available to scientists conducting promising research. Since 1981, I have served on the advisory council of this thousand-member organization, along with the chairmen of a number of major US corporations. In addition to an advisory council, the organization has a scientific board and a scientific advisory council. The scientists on these committees, ten of whom are Nobel laureates, help to channel resources where they are most needed.

The American Federation for Aging Research, headquartered in New York City, is another private organization which supports aging research. It was founded three years ago by Irving S. White, a preeminent cardiologist who helped to organize the American Heart Association, at the request of Robert

Table 1: A selected list of organizations devoted to aging research.

Argentina
Sociedad Argentina de Gerontología y Geriatría Buenos Aires, Buenos Aires

Australia
Australian Association of Gerontology, Sydney

Austria
Osterreichische Gesellschaft für Geriatrie, Vienna

Chile
Sociedad Chilena de Gerontología, Santiago

Denmark
Dansk Gerontologisk Selskab, Naestved

Federal Republic of Germany
Deutsche Gesellschaft für Gerontologie, Berlin
Forschungsgruppe Gerontologie, Giessen

France
Association de Gérontologie du 13e, Paris

German Democratic Republic
Gesellschaft für Gerontologie der Deutschen Demokratischen Republik, Berlin

Hungary
Magyar Gerontológiai Társaság, Budapest

Israel
International Association of Gerontology, Rehovoth
Israel Gerontological Society, Tel Aviv-Yafo

Italy
Associazione Gerontologica Italiana, Milan
Associazione Nazionale Italiana Medici ed Operatori Geriatrici, Florence
Società Italiana di Gerontologia e Geriatria, Florence

Japan
International Association of Gerontology, Tokyo
Nihon Ronen Igakkai, Tokyo

Romania
Societatea de Gerontologie, Bucharest

Switzerland
Forschungsgemeinschaft für Altersfragen in der Schweiz, Zurich
Institut für Experimentelle Gerontologie, Basel
Schweizerische Gesellschaft für Gerontologie, Basel

Union of Soviet Socialist Republics
USSR Gerontological and Geriatrics Society, Kiev

United Kingdom
British Geriatrics Society, Mitcham

United States
Alzheimer's Disease and Related Disorders Association, Chicago, IL
American Aging Association, Omaha, NE
American Federation for Aging Research, New York, NY
American Foundation for Aging Research, Columbia, MO
American Geriatrics Society, New York, NY
American Longevity Association, Torrance, CA
Fund for Integrative Biomedical Research, Washington, DC
Gerontological Society of America, Washington, DC
International Association of Gerontology, Durham, NC
National Institute on Aging, Bethesda, MD

Butler, who was then director of NIA. Since its inception, the organization has contributed substantial amounts of money to aging research, and it plans to accelerate its activities in the future. Some other organizations concerned with progress in aging research are listed in Table 1.

Growing public and private support for aging research reflects the scientific community's own increasing commitment. Today, aging research occupies unprecedented numbers of highly talented individuals, not only specialists in gerontology, but researchers from other disciplines as well. These include biochemistry, endocrinology, immunology, neurobiology, genetics, and cell biology, to name only a few. Since scientists in so many different disciplines are doing aging research, literature on aging is found in a wide variety of journals and is not confined to those which focus specifically on aging. Nevertheless, there are ten journals covered in *Science Citation Index®* which focus specifically on aging. These are listed in Table 2.

The variety and degree of specialization which now characterize aging research are revealed by the numerous research fronts on the subject in *Index to Research Fronts in ISI/BIOMED®*. The *ISI/BIOMED* research fronts concerned with aging are listed in Table 3. In previous essays, I have explained how our clustering techniques enable us to identify active research fronts.[17] The scientific literature on aging is massive and diverse, so the information provided by research fronts was helpful, both in identifying various areas in which research efforts are concentrated, and in locating those which may be most promising.

Table 2: A core list of journals covered in the 1982 *SCI*® devoted exclusively to aging and aging research.

Age
Age and Ageing
Experimental Aging Research
Experimental Gerontology
Geriatrics
Gerontology
Journal of Gerontology
Journal of the American Geriatrics Society
Maturitas
Mechanisms of Ageing and Development

Despite the growing momentum in aging research, we do not yet know what causes aging. Researchers, in fact, doubt that aging has any single cause. A great variety of changes occur with age in cells, tissues, and organs throughout the body, and some developments probably take place independently of others. On the other hand, there may be a set of primary events which, in turn, trigger a cascade of secondary ones. Many gerontologists believe that if we could discover what some of the primary aging processes are, we could defer a number of age-related health problems, and perhaps even postpone aging itself. The major problem, as Leonard Hayflick, University of Florida, Gainesville, has pointed out, lies in determining which of the many physiological "symptoms" of aging are its actual causes, and which are the results of "changes that may be occurring at a more fundamental level."[18]

Currently, a number of different theories of aging are being debated in the literature. These theories address not only the technical question of how we age, but also the more theoretical matter of why we age. These questions are related, because information on how aging evolved and what purpose it serves may offer clues to what sort of aging "clocks" we may possess, and how they might operate.[19]

Some researchers believe that after a specified period of time the body might actively sabotage itself. Such an active "self-destruct" mechanism might have evolved, they say, because death promotes variety in the gene pool and prevents excessive inbreeding.[20] Other researchers argue that death is *not* an adaptive advantage, but evolved merely because natural environmental hazards have tended to kill animals before they could grow old. If most members of the population succumbed to disease or predation before late adulthood, then there would be no reason for evolution to screen out health problems and genetic defects expressed after that time.[21] Only humans and the animals they have domesticated escape the vicissitudes of life in the wild. But we pay the price by aging.

One might wonder where these "bad genes" that undermine our health late in life come from in the first place. One

Table 3: A selected list of *ISI/BIOMED*® research fronts on aging. A=research front number. B=research front name. C=number of core papers. D=number of citing papers.

A	B	C	D
81-0027	Tissue culture in aging research	13	282
81-0826	Brain cholinergic mechanism alterations during aging	23	269
81-1017	Spiperone H-3 binding sites in the brain	6	261
81-1082	Lymphocyte activation in human aging	8	120
81-1243	DNA-repair in xeroderma pigmentosum	2	37
81-1774	Aging and catecholamine turnover	3	68
81-1903	Altered enzymes in aging cells	2	37
81-2012	Thyroid function in elderly patients	3	59
81-2027	Steroid hormones in aging women	2	69
81-2206	Cellular aging and DNA-repair	2	55
81-2233	Dopaminergic controls of fertility and aging	4	70
81-2871	Aging and biochemical changes in brain	2	19
81-2936	Sex steroid hormones and aging	2	44

proposed answer is the concept of "pleiotropism." A pleiotropic trait is one which may be beneficial early in life but detrimental later on. Richard G. Cutler, Gerontology Research Center, Baltimore City Hospitals, explains pleiotropism as the inevitable outcome of the trial and error manner in which life evolved. As Cutler notes, physiological features of living organisms evolved merely because "their advantage proved greater than their disadvantage."[19] Thus, the very same adaptations that help an animal grow, reproduce, and burn energy efficiently may also cause complications later in life. A hypothetical example might be a gene which helps young bones grow strong by absorbing calcium, but later promotes calcification of the joints.

Among mammals, the rate of aging typically depends on the rate of metabolism—the quicker the metabolism, the shorter the life span. Metabolic rate, in turn, is usually inversely proportional to size, since the larger an animal, the less it has to work to replace heat lost through its skin, and to maintain the normal body temperature of 37° Celsius which is common to mammals.[19] But there are exceptions. Humans are smaller and have faster metabolisms than elephants, yet we live longer. The explanation for this may be that humans have an unusually large brain and depend on their intelligence for survival.[19] Thus, some researchers speculate, humans stood to benefit from a long life span, which gave them time to accumulate experience.

Gerontologists do not know which of the differences between us and our primate ancestors lengthened our life spans. But many now believe that a relatively small number of adaptations, caused by mutations in key genes, may have done the job. They deduce this from how quickly, in evolutionary time, the necessary alterations were made. It took three million years for our life spans to double over those of our prehominid ancestors.[22]

The idea that longevity is linked to a finite number of genetic characteristics has gained support from studies involving closely related strains of mice. Roy L. Walford, University of California, Los Angeles, and others have found that extremely minor genetic differences between otherwise identical strains of mice can be correlated with significant differences in life span.[23] Walford believes that a discrete series of genes called the major histocompatibility complex (MHC) may control physiological traits which play an important role in determining our longevity.[6] Findings like these are promising because the fewer biochemical, structural, and genetic factors involved in regulating aging, the greater the likelihood that they will one day be understood and brought under control.

At present, scientists know of only two ways to extend the maximum life spans of animals. The lives of cold-blooded animals can be prolonged if they are kept at cold temperatures.[6] Some warm-blooded animals can be kept alive beyond their typical maximum life spans if their food intake is restricted.

The effect of food restriction on life span was first discovered in the 1930s by Clive M. McCay, Cornell University.[24] McCay fed rats nutritionally sufficient, but calorically restricted, diets. These underfed rodents grew, developed sexually, and consumed oxygen more slowly than the controls. They also lived 50 percent longer.[24] Subsequent research has supported McCay's findings. Morris H. Ross, Institute for Cancer Research, Philadelphia, imposed a regimen of severe dietary restriction on his rats immediately after weaning and found that some of them lived 1,880 days. "For a human this would correspond to 180 years," Ross comments.[25]

Unfortunately, as yet, there is no evidence that fasting prolongs life in humans.[26,27] Moreover, it is not clear that food restriction would have a positive effect on rodent life span except under carefully controlled laboratory conditions, where exposure to a variety of health risks is minimized.[25] In the laboratory, however, underfed rodents not only stay younger longer than controls,

but develop cancer and other age-related diseases much less frequently.[25,28-30]

Workers in a number of laboratories are using variations of McCay's experiments to determine which of the physiological effects of fasting influence longevity, and which of these might have analogous effects in humans.[28,29] For example, one variation of the experiment, restricting food intake after, rather than before, adulthood may minimize complications, and thus be applicable to humans. Walford and Richard Weindruch, University of California, Los Angeles, Medical Center, have found that careful food restriction begun during adulthood may extend the maximum life spans of rodents.[30] The benefits of adult dietary restriction remain a subject of controversy. Nonetheless, if adult restriction works, the significance of this finding could be enormous.

One important difference between food-restricted and normal rats may be in oxygen consumption and metabolic rate. For virtually all forms of life, oxygen is used to fuel metabolism. Pure oxygen molecules go through a series of reactions in which they are ultimately transformed into water. Oxygen is a very strong hydrogen "magnet," particularly in its intermediate forms as a single O atom or an ^{-}OH hydroxyl ion. Its ability to attract hydrogen atoms away from other molecules means that it will oxidize almost anything it comes in contact with.[31]

According to Denham Harman, University of Nebraska, all forms of life on earth have been forced to "strike a balance"[31] between efficient metabolism and impermissible oxidation. Harman and a number of other researchers believe that aging may actually be the accumulation of damage inflicted throughout our bodies by volatile oxygen molecules called "free radicals."

One way that the cells of the body protect themselves from being oxidized by these free radicals is by segregating the oxidation reactions needed for respiration into specialized organs in each cell known as mitochondria. Another is by manufacturing chemicals which deactivate free radicals, called antioxidants. Harman postulated that supplementing the body's supply of these free radical "scavengers" might decelerate aging. Indeed, in one experiment, mice fed large quantities of antioxidants had an average life span 30 percent longer than controls.[32] As Harman points out, "This increase is equivalent to raising the human life span from 73 to 95 years."[32] Other researchers are performing similar experiments and investigating free radicals in connection with many types of damage found in aged tissues and cells.[11] Some researchers believe that a variety of chemicals generated by the body may be useful in deactivating free radicals. Uric acid, found in all mammalian urine, is one of these.[33] Vitamin E, found in nuts and some other foods, also helps "mop up" free radicals, although large doses of supplemental vitamin E have not affected longevity in humans or other animals.[11]

Although administering some types of antioxidants to laboratory animals has extended their average life expectancy, it has not extended their maximum life span, as one would expect if free radicals were the sole cause of aging. On the other hand, it is possible that supplemental antioxidants can stop only certain types of free radical damage. For example, the mitochondria, or cellular respiratory organs, themselves may be damaged by oxidation, and because of their outer membranes, they may not be able to absorb supplemental antioxidants.[32] The role of the mitochondria in aging is under investigation in a number of laboratories.[11]

Aside from oxidation, there are many other types of chemical reactions carried out by the body which are necessary to maintain life, but which could also be potentially disruptive. These chemical reactions are regulated and kept in balance by the endocrine system. Hormonal signals trigger many events in the life cycle such as growth and reproductive

maturity. Researchers believe that they may also play a role in aging. Until the early part of this century, scientists suspected that aging might simply result from chronic shortages of sex hormones. Many nineteenth-century gerontologic experiments involved grafting the testes of young animals onto old men, often the scientists themselves.[34] We now know that aging is probably not caused by insufficient hormone production.[34]

On the other hand, in some species, fluctuations in hormonal output may trigger aging. The Pacific salmon, for example, dies shortly after it spawns. This is because the hormonal changes which prepare these fish for spawning also undermine their ability to regulate their metabolic processes. Within two weeks after spawning, both male and female salmon die, apparently of "old age." During those two weeks, they undergo deterioration comparable to the kind that humans would experience over a 40-year period.[5]

A progressively destabilized hormonal balance may work in an analogous way in humans. In order to adjust the levels of hormones circulating in the body, the endocrine system depends on feedback mechanisms. There is some evidence that these grow less sensitive over time. Vladimir M. Dilman, Petrov Research Institute of Oncology, Leningrad, USSR, has proposed that the hypothalamus, the "control center" where feedback signals are converted to hormonal responses, may act as an aging "clock." According to Dilman, if ever higher concentrations of particular hormones are necessary to "register" in the hypothalamus, then the balance of hormones will shift over time. This shift may trigger growth, sexual maturation, and aging.[35]

The enormously complicated system that regulates our hormonal balance involves not only chemical signals, but electrical ones as well. Nervous impulses from many parts of the brain travel directly to the hypothalamus, where they can activate a broad spectrum of hormonal responses.[36] Thus, some aging changes mediated by hormones may actually begin in the brain.

One such change is menopause. In two different experiments, female rats that had stopped having reproductive cycles were injected with a chemical called L-dopa. L-dopa acts on the brain by stimulating the production of neurotransmitters called catecholamines, which are less plentiful in old brains than in young ones. As their catecholamine levels rose, their reproductive cycles resumed.[37,38] Since reproductive senescence may be controlled by timing mechanisms similar to the ones which govern other aspects of aging, the discovery that it is influenced by the chemical balance in the brain was an important one.[36]

Some researchers theorize that hormone receptors, rather than the hormones themselves, are to blame for some disruptions caused during aging. For a hormone to take effect, it must attach itself to the appropriate hormone receptors located in or on the cells of target organs. This, in turn, initiates the specified biochemical reactions in the cells. George S. Roth and colleagues, Gerontology Research Center, Baltimore City Hospitals, have found that the concentrations of certain key receptors may diminish substantially with age. For instance, receptors for hormones that regulate the way many types of cells absorb and metabolize nutrients appear to decline markedly between maturity and senescence.[39] This may be one reason why the aged utilize nutrients differently than young people. Less efficient nutrient use could produce subtle types of deterioration throughout the body. Researchers have recently discovered that the concentrations of receptors for the various hormones are regulated by other sets of hormones. This suggests that hormone therapy could perhaps restore receptor concentrations to their youthful levels.[39]

In addition to affecting hormone receptors, certain hormones may interfere with other hormones by blocking their

action in ways that we do not yet understand. W. Donner Denckla, Institute of Alcohol Abuse and Alcoholism, NIH, believes that a hormone secreted by the pituitary gland beginning at the time of puberty may interfere with the body's ability to use thyroxin, the hormone of the thyroid gland. Indeed, as Denckla and others have observed, hypothyroidism, or a shortage of thyroid hormones, does mimic some of the symptoms of aging. In Denckla's experiments, elderly rats whose pituitary glands were removed showed a partial rejuvenation.[20] Denckla's "death hormone" has not yet been isolated, and its existence still remains a matter of speculation.[40]

Eight of the research fronts in Table 3 pertain to changes in the endocrine system which have been observed during aging. These are numbered 81-0826, 81-1017, 81-1774, 81-2012, 81-2027, 81-2233, 81-2871, and 81-2936. These areas of aging research are promising, not only because the neuroendocrine system could act as an aging clock, but also because of emerging evidence that changes in specific components of this system, particularly in the brain, could cause a large number of age-related disorders. Examples of such disorders include memory loss, senility, Parkinson's disease, insomnia, and many others.[36] Let me make it absolutely clear that the selected list of research fronts on aging does not represent the limit of the information on aging that can be retrieved in this data base. The entire content of 1,400 journals is indexed. However, thousands of "topics" are extremely specialized and do not necessarily accumulate enough core or current papers to define a research front. We can, however, by variable-level clustering, increase the number of these specialties almost indefinitely. I'll examine this question in a future discussion of the ISI® Search Network.

Immunology is another field which may yield insight into the aging process. The difficulty that the aged have both in fighting off and in recovering from disease suggests that their immune systems are no longer functioning properly, and that the immune system may initiate some aspects of aging. A healthy immune system protects the body against invasion by viruses, bacteria, fungi, and many other substances the body recognizes as foreign. It may also seek out and destroy budding cancer cells and other body cells which are diseased, damaged, or otherwise abnormal.

Two types of white blood cells, T cells and B cells, are produced in bone marrow and are mobilized during an attack. B cells manufacture custom-made antibodies, while T cells kill antigens on contact. In order to "learn" how they must mature and differentiate to cope with any threat at hand, these white blood cells, or lymphocytes, depend on a gland called the thymus, located in the lymphatic system, at the base of the neck. In older persons, the thymus no longer functions properly. By the age of 50 it has usually shrunk to 15 percent of its former size, and by the age of 60 it has stopped secreting thymic hormone. This could be one reason why immune responses of the aged are inadequate.[41]

In addition to failing to ward off infection and disease, an aging immune system may begin to attack the body's own healthy cells and tissues, because it can no longer distinguish them from foreign or sick ones. Autoantibodies, or antibodies which attack the body's own tissue, are more preponderant in old people than in young people. Between the ages of 40 and 80, the proportion of various kinds of autoantibodies in the body can increase six- to eightfold.[41]

Some researchers believe that the low-grade, generalized deterioration we associate with aging may be brought on by an autoreactive immune system.[6] Walford and Weindruch have found some evidence linking the immune system with the overall aging process. In their rodent dietary restriction experiments they observed that, in addition to lengthening maximum life span, food restriction forestalls a variety of immune disorders.[30]

One problem with the immune theory of aging is that treatments, other than dietary restriction, which bolster the im-

mune responses of older animals have not extended their maximum life spans. As Marc E. Weksler, Cornell University, points out, however, the immune system is very complex and we still do not understand the details of how it is regulated. This may make our efforts to rejuvenate it somewhat crude. By tampering with the levels of thymic hormone, for instance, we may reinvigorate our overall immune response, but with the indirect result of aggravating autoimmune disease.[41]

It is probable that the defects in an aged immune system stem not only from the thymus, but from subtler changes in the lymphocytes themselves. To test this possibility, researchers cultured lymphocytes from donors of various ages and grew them in sterile media. If an antigen was added to the media, the lymphocytes responded by proliferating. But this response was weaker in lymphocytes from aged donors.[41] Thus, factors intrinsic to the white blood cells themselves may cripple the aged immune system.

Lymphocytes are not the only cells in the body that may proliferate more slowly as we age. When other cells that have the capacity to divide in our bodies are cultured, they continue to proliferate for a time. But after a finite number of divisions, or "population doublings," the process slows down and stops, and all the cells in the sample eventually die. This has led to speculation that aging stems not merely from changes in crucial organ systems, but also from gradual alterations within each individual cell. Prior to the 1960s, the death of normal human cells in culture was attributed to contamination or other procedural problems.[42,43] If ideal experimental conditions could be maintained, it was thought, then human cells could live forever. Indeed, cells derived from tumors and some other types of cells showed no signs of aging in culture.[42,43]

In 1961, collaborating at Wistar Institute, Hayflick and Paul S. Moorhead, who have since gone to the University of Florida and Children's Hospital, Philadelphia, respectively, ran a large study of fetal cells in culture and observed that the cells had a definite life cycle. All of them died after roughly 50 population doublings.[43] Hayflick and Moorhead interpreted this as evidence of aging at the cellular level, and published their findings in a landmark paper, entitled "The serial cultivation of human diploid cell strains."[43] Several years ago this paper was featured in *CC* as a *Citation Classic*.[44] Subsequently, to prove that the cells were not being killed by experimental conditions, Hayflick performed other experiments. In one, he mixed young and old cells in the same media and found that they died in two distinct stages. Hayflick published this, and other evidence of intrinsic cellular aging, in a 1965 article[45] which became his most-cited article between 1965 and 1978. Incidentally, Hayflick was one of the 1,000 most-cited contemporary scientists for the period 1965-1978.[46]

The relationship between cellular aging in culture (*in vitro*) and in the body (*in vivo*) has been demonstrated in other experiments. George M. Martin, University of Washington, Seattle, took fibroblasts from donors ranging from embryos to individuals 90 years of age. He and his co-workers found that the older the donor, the fewer times the cells would double in culture.[47,48] Martin and his colleagues also cultured cells of individuals with a variety of life-shortening diseases and found that their cells had a shorter life span than controls.[49]

Normal human cells do not reach the limit of their proliferative capacity in the body, where they divide much more slowly than they do in culture. But before cells in culture stop dividing, they develop the same kinds of deficiencies as those found in the cells of aged persons. By studying accelerated "aging under glass,"[8] as Hayflick calls it, we can learn a great deal about changes in aging cells that could contribute to functional losses throughout our bodies. Therefore, it is not surprising that research front 81-0027, "Tissue culture in aging research," is one of the most active aging research fronts. Core documents for this research front are listed in Table 4, and a

Table 4: These are the core documents which were cited by the papers in *ISI/BIOMED®* research front #81-0027, "Tissue culture in aging research."

Absher P M, Absher R G & Barnes W D. Genealogies of clones of diploid fibroblasts. *Exp. Cell Res.* 88:95-104, 1974.

Bell E, Marek L F, Levinstone D S, Merrill C, Sher S, Young I T & Eden M. Loss of division potential in vitro: aging or differentiation? *Science* 202:1158-63, 1978.

Cristofalo V J & Sharf B B. Cellular senescence and DNA synthesis. *Exp. Cell Res.* 76:419-27, 1973.

Goldstein S, Littlefield J W & Soeldner J S. Diabetes mellitus and aging: diminished plating efficiency of cultured human fibroblasts. *Proc. Nat. Acad. Sci. US* 64:155-60, 1969.

Hayflick L. The limited *in vitro* lifetime of human diploid cell strains. *Exp. Cell Res.* 37:614-36, 1965.

Hayflick L & Moorhead P S. The serial cultivation of human diploid cell strains. *Exp. Cell Res.* 25:585-621, 1961.

Holliday R, Huschtscha L I, Tarrant G M & Kirkwood T B L. Testing the commitment theory of cellular aging. *Science* 198:366-72, 1977.

Martin G M. Cellular aging—clonal senescence. A review. (Part I.) *Amer. J. Pathol.* 89:484-511, 1977.

Martin G M, Sprague C A & Epstein C J. Replicative life-span of cultivated human cells. *Lab. Invest.* 23(1):86-92, 1970.

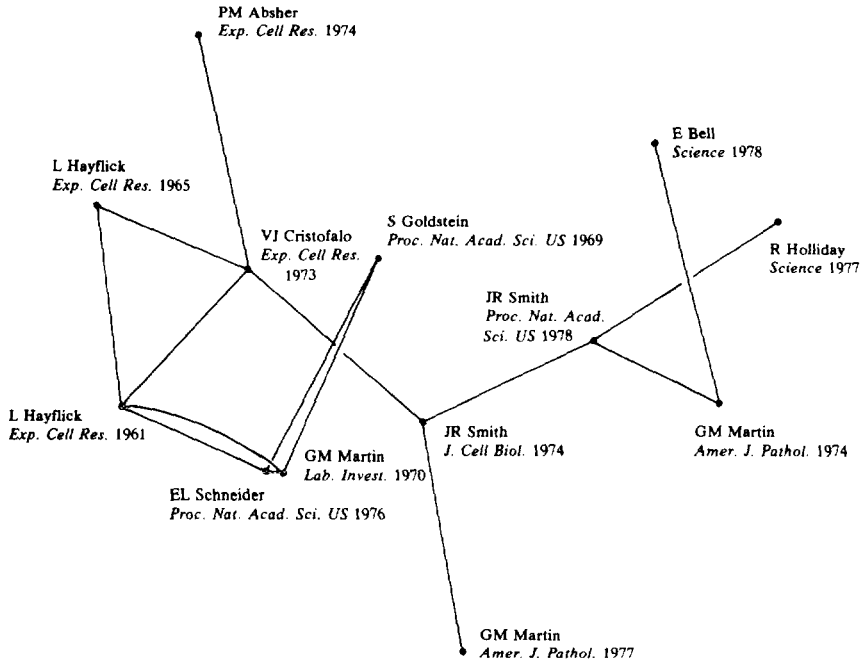
Martin G M, Sprague C A, Norwood T H & Pendergrass W R. Clonal selection, attenuation and differentiation in an *in vitro* model of hyperplasia. *Amer. J. Pathol.* 74:137-54, 1974.

Schneider E L & Mitsui Y. The relationship between *in vitro* cellular aging and *in vivo* human age. *Proc. Nat. Acad. Sci. US* 73:3584-8, 1976.

Smith J R & Hayflick L. Variation in the life-span of clones derived from human diploid cell strains. *J. Cell Biol.* 62:48-53, 1974.

Smith J R, Pereira-Smith O M & Schneider E L. Colony size distributions as a measure of *in vivo* and *in vitro* aging. *Proc. Nat. Acad. Sci. US* 75:1353-6, 1978.

Figure 1: A cluster map of the highly cited core documents which make up *ISI/BIOMED®* research front #81-0027, "Tissue culture in aging research." An active area of research can be identified through examining which papers are frequently co-cited. The distance between documents is a measure of relatedness.



cluster map appears in Figure 1. Table 5 is a sample of the papers retrieved by a search of this research front.

In addition to studying immune aging at the cellular level, researchers are investigating the effects of free radicals and hormones on isolated cells.[11,42] They are also exploring the possibility that aging is promoted by the deterioration of cellular membranes. These membranes play a crucial role in regulating the cell's internal environment.[11] Other questions concern the role of cellular enzymes in aging. Enzymes are necessary for carrying out a huge variety of chemical reactions on which cells depend, and there appear to be differences between some enzymes found in old and young cells.[11] Rather than resulting from errors in synthesis, as was once believed, alterations in enzymes may occur in the cells of old animals because they do not "turn over" or replace their enzyme molecules as quickly as young cells.[11] Or alternatively, as suggested by Morton Rothstein, State University of New York, Buffalo, a cell may deliberately stop producing one enzyme after a certain point, and start producing another.[50] In either case, changes in enzymes could gradually place burdens on cells that cause them to age.

Finally, in addition to these and many other types of investigations, researchers are performing experiments in which they fuse a nucleus containing genetic

Table 5: Selected documents in *ISI/BIOMED®* research front #81-0027, "Tissue culture in aging research," ranked in descending order according to the number of core documents they cite. A=number of documents in the group. B=number of core documents the group cited. C=bibliographic data.

A	B	C
1	11	**Group I** **Mitsui Y, Smith J R & Schneider E L.** Equivalent proliferation potential different size classes of human diploid fibroblasts. *J. Gerontol.* 36:416-9, 1981.
2	10	**Group II** **Hayflick L.** Recent advances in the cell biology of aging. *Mech. Age. Dev.* 14:59-79, 1980. **Kirkwood T B L & Cremer T.** Cytogerontology since 1881: a reappraisal of August Weismann and a review of modern progress. *Hum. Genet.* 60:101-21, 1982.
5	8	**Group III** **Macieira-Coelho A & Taboury F.** A re-evaluation of the changes in proliferation in human fibroblasts during ageing *in vitro*. *Cell Tissue Kinet.* 15:213-24, 1982. **Paz M A, Torrello B M & Gallop P M.** X-linked processes in serially passaged aging human diploid cells. *J. Gerontol.* 36:142-51, 1981. **Reff M & Schneider E L.** Cell culture aging. *Mol. Cell. Biochem.* 36:169-76, 1981. **Rosen E M, Mueller S N, Noveral J P & Levine E M.** Proliferative characteristics of clonal endothelial cell strains. *J. Cell. Physiol.* 107:123-37, 1981. **Schneider E L & Smith J R.** The relationship of *in vitro* studies to *in vivo* human aging. *Int. Rev. Cytol.* 69:261-70, 1981.
5	7	**Group IV** **Johnson L K & Longenecker J P.** Senescence of aortic endothelial cells *in vitro*: influence of culture conditions and preliminary characterization of the senescent phenotype. *Mech. Age. Dev.* 18:1-18, 1982. **Mets T & Verdonk G.** *In vitro* aging of human bone marrow derived stromal cells. *Mech. Age. Dev.* 16:81-9, 1981. **Mets T & Verdonk G.** Variations in the stromal cell population of human bone marrow during aging. *Mech. Age. Dev.* 15:41-9, 1981. **Röhme D.** Ageing and the fusion sensitivity potential of human cells in culture: relation to tissue origin, donor age, and *in vitro* culture level and condition. *Mech. Age. Dev.* 16:241-53, 1981. **Salk D, Bryant E, Au K, Hoehn H & Martin G M.** Systematic growth studies, cocultivation, and cell hybridization studies of Werner syndrome cultured skin fibroblasts. *Hum. Genet.* 58:310-6, 1981.

material of one cell with the components of another cell. By combining cells of different ages, and observing the survival time of the fused cell, researchers hope to find the location of the cellular aging clock. The results of some of these experiments indicate that the age of a cell is recorded in its nucleus.[51]

Gerontologists have long agreed that genetic factors influence our rate of aging. The genes we inherit determine that our maximum life span will be roughly 110 years, 50 times longer than the shortest-lived mammals.[7] The question that remains is, how do our genes regulate our life spans? Some gerontologists believe that the mechanism is an indirect one. Our genes determine our size, metabolic rate, and other physiological characteristics, and these, in turn, affect our susceptibility to disease and damage.[7] Others believe that the mechanisms which control aging are far more direct and "deliberate." For example, there may be certain "aging genes" that slow or shut down crucial biochemical pathways in a sequential manner, leading directly to the manifestations of aging.[51] In nature there are some examples of death-inducing genes. During the development of an embryo, for instance, certain tissues appear and then vanish, due to massive cell death.[51] In this case, the death of the cells is genetically programmed.

On the other hand, rather than deliberately sabotaging the body's vital functions, the genes may merely lose their ability to direct these activities properly, possibly due to damage that accumulates within the DNA. DNA damage can result from exposure to a variety of agents. Some, such as free radicals, are generated inside the body, and others, including radiation, ultraviolet light, and chemical mutagens, come from the environment.[7] When a cell's DNA is damaged it may no longer be able to function normally. For this reason, we have evolved systems for repairing damaged DNA.

Some researchers speculate that our ability to repair damaged DNA is an important factor controlling how fast we age. It is unlikely that repair systems themselves act as a "clock" by shutting down over time. Cell culture experiments indicate that the rate of repair remains constant in aging cells.[7] On the other hand, the longer a cell lives, or the more times it divides, the more opportunity it has to accumulate types of damage which can elude or overwhelm its repair apparatus.[7]

Studies comparing the repair capabilities of different species have shown a correlation between an animal's ability to repair certain kinds of DNA damage and its longevity.[52] In 1974, Ronald W. Hart and Richard B. Setlow, Oak Ridge National Laboratory, grew fibroblasts from various mammals in culture and exposed them to irradiation from ultraviolet light, which damaged their DNA. The researchers then measured the rate at which new pieces of DNA were being manufactured for insertion into damaged sites. Long-lived species such as humans, elephants, and cows synthesized DNA for repair five times as fast as certain short-lived species, including rats, mice, and shrews.[52] This correlation does not apply as well for all species, however.[50]

All of the theories I have mentioned—genetic, cellular, immune, neuroendocrine, and free radical—contain speculation. On the other hand, each of them has played an important role in stimulating research. Not only is more literature on aging being published than ever before, but many researchers feel that more "high caliber" work is being produced.[50] According to Jack Rowe, Beth Israel Hospital, Boston, "The new information that has been identified relating to several of these theories makes us optimistic that, around the corner, there is a breakthrough where we will substantially increase our understanding of the aging process and what controls it."[5] Researchers are generally somewhat cautious about predicting whether we will ultimately be able to extend the human life span. Bernard L. Strehler, University of Southern California, says, "At this

point in time, 80 percent through the 20th century, we still are unable to predict with any degree of certainty the extent to which the aging process will be retarded or arrested for future generations of humans."[53] Viewed from the perspective of history, it is important to note that, until recently, very few researchers expressed this type of optimism.

The social and demographic consequences of a major breakthrough in aging research are mind-boggling. The effects of modern medicine on average life expectancy have already placed new demands on our social and political institutions. If we were someday able to double our average life span, one can imagine that the effects on the world population, for example, would be catastrophic. The political implications of raising the retirement age from 65 to, say, 100 would be interesting. But these effects are also related to birth rates and their control. Rather than adding to some of our problems in caring for the elderly, aging research may help to solve them. Many of the diseases which cripple and debilitate us late in life might be prevented if we could find a way to decelerate the basic aging process.[6,10] Thus, aging research may offer hope, not only that we may someday delay death, but also that more of us will live out our lives in a healthier state. But there is always that nagging question—what happens in that 110th year?

* * * * *

My thanks to Kathleen Nell Schalch and Amy Stone for their help in the preparation of this essay.

REFERENCES

1. **Garfield E.** Senility: a major health problem in need of a solution. *Current Contents* (24):5-9, 15 June 1981.
2. **----------.** Death be not proud—meeting the needs of the dying through thanatology. *Current Contents* (12):5-13, 23 March 1981.
3. **----------.** Is death the last best friend or the ultimate enemy—conferences on thanatology and prolongevity signal increased research with seemingly contradictory objectives. *Essays of an information scientist.* Philadelphia: ISI Press, 1977. Vol. 1. p. 229-30. (Reprinted from: *Current Contents* (33):5-6, 18 August 1971.)
4. **US Bureau of the Census.** *Statistical abstract of the United States: 1980.* Washington, DC: US Department of Commerce, 1980. p. 72.
5. **PBS NOVA.** *Aging: the Methuselah syndrome.* (Television program.) Boston: WGBH Educational Foundation, 28 March 1982.
6. **Walford R L.** Immunology and aging. *Amer. J. Clin. Pathol.* 74:247-53, 1980.
7. **Brash D E & Hart R W.** Molecular biology of aging. (Behnke J A, Finch C E & Moment G B, eds.) *The biology of aging.* New York: Plenum Press, 1978. p. 57-81.
8. **Hayflick L.** The biology of human aging. *Plast. Reconstr. Surg.* 67:536-50, 1981.
9. **Comfort A.** *The process of ageing.* New York: Signet, 1964. 144 p.
10. **Rosenfeld A.** First word. *Omni* 5(5):6, 1983.
11. **Rothstein M.** *Biochemical approaches to aging.* New York: Academic Press, 1982. 314 p.
12. **Phillips P D.** Telephone communication. 28 February 1983.
13. **Ettinger R C W.** *The prospect of immortality.* New York: Doubleday, 1964. 190 p.
14. **Harrington A.** *The immortalist.* New York: Random House, 1969. 324 p.
15. **Rosenfeld A.** *Prolongevity.* New York: Knopf, 1976. 250 p.
16. **Ross K.** Telephone communication. 27 January 1983.
17. **Garfield E.** ABCs of cluster mapping. Parts 1 & 2. Most active fields in the life and physical sciences in 1978. *Essays of an information scientist.* Philadelphia: ISI Press, 1981. Vol. 4. p. 634-49. (Reprinted from: *Current Contents* (40):5-12, 6 October 1980 and (41):5-12, 13 October 1980.)
18. **Hayflick L.** The cell biology of aging. *J. Invest. Dermatol.* 73:8-14, 1979.
19. **Cutler R G.** Evolutionary biology of senescence. (Behnke J A, Finch C E & Moment G B, eds.) *The biology of aging.* New York: Plenum Press, 1978. p. 311-60.
20. **Deneckla W D.** A time to die. *Life Sci.* 16:31-44, 1975.
21. **Kirkwood T B L & Holliday R.** The evolution of ageing and longevity. *Proc. Roy. Soc. London Ser. B* 205:531-46, 1979.
22. **Cutler R G.** Evolution of human longevity and the genetic complexity governing aging rate. *Proc. Nat. Acad. Sci. US* 72:4664-8, 1975.
23. **Smith G S & Walford R L.** Influence of the main histocompatibility complex on ageing in mice. *Nature* 270:727-9, 1977.
24. **McCay C M, Crowell M F & Maynard L A.** The effect of retarded growth upon the length of life span and upon the ultimate body size. *J. Nutr.* 10:63-79, 1935.
25. **Ross M H.** Nutrition and longevity in experimental animals. (Winick M, ed.) *Nutrition and aging.* New York: Wiley, 1976. p. 43-57.

26. **Garfield E.** To fast or not too much fast. Part 1. The claims for fasting in the popular literature. *Current Contents* (46):5-11, 16 November 1981.
27. ----------. To fast or not too much fast. Part 2. A controversial question gets some scientific answers. *Current Contents* (47):5-11, 23 November 1981.
28. **Masoro E J, Yu B P & Bertrand H A.** Action of food restriction in delaying the aging process. *Proc. Nat. Acad. Sci. US—Biol. Sci.* 79:4239-41, 1982.
29. **Weindruch R, Gottesman S R S & Walford R L.** Modification of age-related immune decline in mice dietarily restricted from or after midadulthood. *Proc. Nat. Acad. Sci. US—Biol. Sci.* 79:898-902, 1982.
30. **Weindruch R & Walford R L.** Dietary restriction in mice beginning at 1 year of age: effect on life-span and spontaneous cancer incidence. *Science* 215:1415-8, 1982.
31. **Harman D.** Telephone communication. 15 February 1983.
32. ----------. The aging process. *Proc. Nat. Acad. Sci. US—Biol. Sci.* 78:7124-8, 1981.
33. Uric acid—the elixir of youth. *New Sci.* 94:79, 1982.
34. **Davis P J.** Endocrinology and aging. (Behnke J A, Finch C E & Moment G B, eds.) *The biology of aging.* New York: Plenum Press, 1978. p. 263-76.
35. **Dilman V M.** Hypothalamic mechanisms of ageing and of specific age pathology—V. A model for the mechanism of human specific age pathology and natural death. *Exp. Gerontol.* 14:287-300, 1979.
36. **Finch C E.** The brain and aging. (Behnke J A, Finch C E & Moment G B, eds.) *The biology of aging.* New York: Plenum Press, 1978. p. 301-9.
37. **Aschheim P P.** Résultats fournis par la greffe hétérochrone des ovaires dans l'étude de la régulation hypothalamo-hypophyso-ovarienne de la ratte sénile. (Results provided by the heterochronous transplant of the ovaries in the study of hypothalamo-hypophyso-ovarian regulation in the elderly rat.) *Gerontologia 10(2/3):65-75, 1964/65.*
38. **Huang H H & Meites J.** Reproductive capacity of aging female rats. *Neuroendocrinology* 17:289-95, 1975.
39. **Roth G S & Hess G D.** Changes in the mechanisms of hormone and neurotransmitter action during aging: current status of the role of receptor and post-receptor alterations. Review. *Mech. Age. Dev.* 20:175-94, 1982.
40. Your body and mind as the years go by. *Changing Times* 36(4):54-7, 1982.
41. **Weksler M E.** The senescence of the immune system. *Hosp. Pract.* 16(10):53-64, 1981.
42. **Cristofalo V J & Stanulis-Praeger B M.** Cellular senescence *in vitro.* (Maramorosch K, ed.) *Advances in cell culture.* New York: Academic Press, 1982. Vol. 2. p. 1-68.
43. **Hayflick L & Moorhead P S.** The serial cultivation of human diploid cell strains. *Exp. Cell Res.* 25:585-621, 1961.
44. **Hayflick L.** Citation Classic. Commentary on *Exp. Cell Res.* 25:585-621, 1961. *Current Contents* (26):12, 26 June 1978.
45. ----------. The limited *in vitro* lifetime of human diploid cell strains. *Exp. Cell Res.* 37:614-36, 1965.
46. **Garfield E.** The 1,000 contemporary scientists most-cited 1965-1978. Part I. The basic list and introduction. *Current Contents* (41):5-14, 12 October 1981.
47. **Martin G M, Sprague C A & Epstein C J.** Replicative life-span of cultivated human cells. *Lab. Invest.* 23(1):86-92, 1970.
48. **Martin G M.** Cellular aging—clonal senescence. A review. (Part I.) *Amer. J. Pathol.* 89:484-511, 1977.
49. **Epstein C J, Martin G M, Schultz A L & Motulsky A G.** Werner's syndrome: a review of its symptomatology, natural history, pathologic features, genetics and relationship to natural aging process. *Medicine* 45:177-221, 1966.
50. **Rothstein M.** Telephone communication. 10 March 1983.
51. **Hayflick L.** The cell biology of human aging. *Sci. Amer.* 242(1):58-65, 1980.
52. **Hart R W & Setlow R B.** Correlation between deoxyribonucleic acid excision-repair and life-span in a number of mammalian species. *Proc. Nat. Acad. Sci. US* 71:2169-73, 1974.
53. **Strehler B L.** Aging research: current and future. *J. Invest. Dermatol.* 73:2-7, 1979.