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Future Directions in Aging Research (40959)[1]

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The future directions of research in biogerontology are inseparable from what is perceived to be the goals of gerontological research. Of all of the biomedical disciplines, biogerontology is unique in not having a clearly delineated objective. Who among us would ask "What is the goal of cancer research, cardiovascular disease investigations, or any research directed toward the understanding or amelioration of some specific disease?" The answers to such questions are self-evident but the goals of research in biogerontology are not agreed upon universally. Until goals are established, the future of research in aging will likely be directed toward resolving those diseases and pathological conditions that are generally believed to afflict the elderly more than they afflict our youth. If that is the goal then the mission of the National Institute on Aging becomes superfluous to the missions of all the other National Institutes.

The major causes of death in this country are cardiovascular diseases and cancer. Both of these conditions command the full attention of the best endowed of our National Institutes. The resolution of diseases, even those predominantly afflicting old people should not, per se, be the fundamental goal of research in biogerontology. The expression of disease in older people manifests itself as the result of an increased vulnerability caused by normal functional decrements that occur over time. This increased vulnerability to disease and death was first recognized by the actuary Benjamin Gompertz in the last century whose equations demonstrated that, for humans, after the age of 30 the likelihood of dying doubles every 7 years.

It is the nature of this normal age-related increase in vulnerability that should be the special province of biogerontologists and not the afflictions superimposed on that increased vulnerability. The study of normal age changes should represent the area of future research in biogerontology.

To argue that the physiological decrements occurring after sexual maturity and leading to old age in animals are normal may be anathema to some. Nevertheless these physiological decrements are normal and lead to physical conditions in older people that none of us would characterize as disease. Do we suffer from disease or abnormal pathology when our hair turns gray, our skin wrinkles, our athletic agility declines, or menopause occurs? I think not. Underlying these normal age changes and countless others, are the normal physiological age decrements no doubt demonstrable in virtually all of our organs, tissues, and cells. We are not diseased by these normal age changes but our increased vulnerability makes disease more likely.

Life expectation and life span. When considering aspects of gerontological research a distinction must be made between life expectation and life span (1).

It is generally believed that the human life span, of about 100 years, has not changed in the last million years, but what has changed is the larger number of people surviving to this apparent limit (Fig. 1). Medical achievements have simply resulted in the fact that more people are reaching the limit of what appears to be a fixed life span. Deaths in the early years are becoming increasingly less frequent, resulting in life tables that are simply becoming more rectangular as indicated by the direction of the arrow in Fig. 2. In many privileged countries, you can now reasonably expect to become old, which is a very new phenomenon, indeed.

In a utopian world where the two leading current causes of death would be resolved, the elimination of cardiovascular diseases

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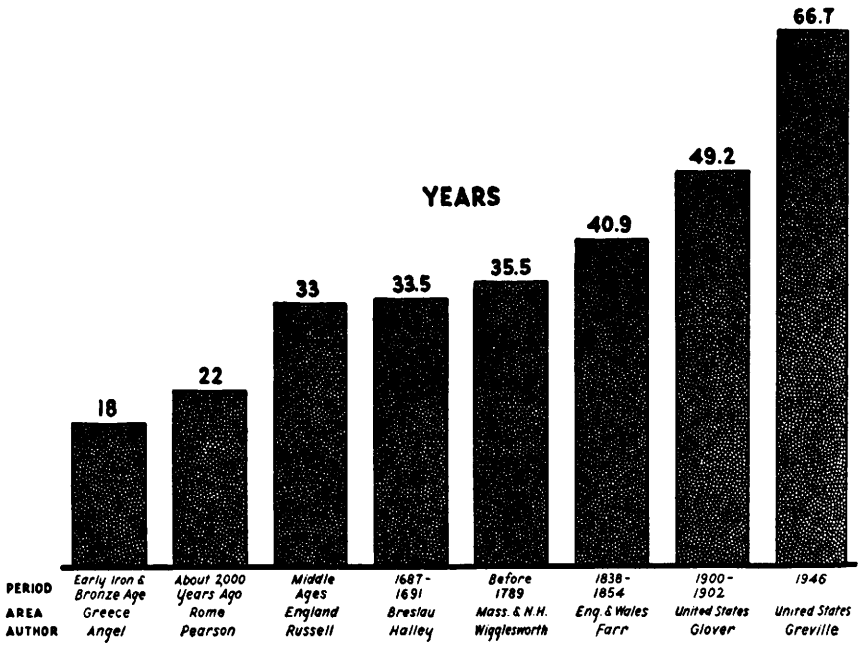

FIG. 1. Average length of life of humans at birth from the early Iron and Bronze Age until 1946. Today average length of life at birth in the United States is about 75 years. From L. I. Dublin, A. J. Lotka, and M. Spiegelman, "Length of Life," Ronald Press, New York (1949).

and cancer in this country would yield a net increase of about 14 years in life expectation at birth and only slightly less at age 65 (Table I). The net increase in life expectation achieved at birth in this country from 1900 to 1980 is about 25 years. The increase in life expectation at birth during the last 80 years largely resulted from the resolution of deaths which occurred before the age of 65.

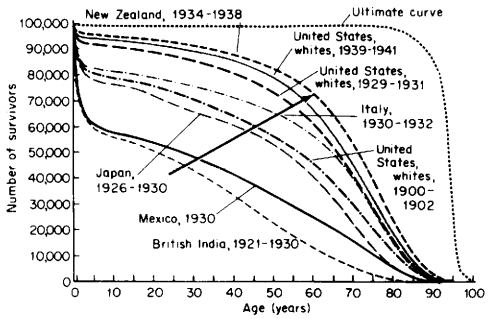

FIG. 2. Number of survivors from a cohort of 100,000 individuals born in diverse geographical areas and points in time. Modified from A. Comfort, "Ageing: The Biology of Senescence," Holt, Rinehart & Winstron, New York (1964).

The gain in life expectation at ages 65 and 75 from 1900 to 1975 was about 3 years for the former age and 1 year for the latter age.

If there is reason to believe that deaths from cardiovascular diseases and cancer will be resolved in the next 25 years, then life expectancy will show an increase of about half of that which has occurred since 1900. After that spectacular accomplishment, the leading cause of death will be accidents, which because of their statistical nature are not likely to be eliminated. Thus the social, psychological, political, and economic impacts of resolving the two leading causes of death on life expectation in the next 25 years can be reasonably assessed by studying like changes that have occurred in the early part of this century when a similar increase in life expectation occurred.

Let us also consider a world in which all causes of death resulting from disease and accidents are totally eliminated (Table I). What would be the effect on human longevity and the human life span? The effect on human longevity would be to realize

TABLE I. GAIN IN EXPECTATION OF LIFE AT BIRTH AND AT AGE 65 DUE TO ELIMINATION OF VARIOUS CAUSES OF DEATH (1969–1971)

Cause of death	Gain (years) in expectation of life if cause was eliminated	
	At birth	At age 65
Major cardiovascular–renal diseases	11.8	11.4
Diseases of the heart	5.9	5.1
Cerebrovascular diseases	1.2	1.2
Malignant neoplasms[a]	2.5	1.4
Motor vehicle accidents	0.7	0.1
All accidents excluding motor vehicles	0.6	0.1
Influenza and pneumonia	0.5	0.2
Diabetes mellitus	0.2	0.2
Infectious and parasitic diseases	0.2	0.1
Tuberculosis	Less than 0.05	

[a] Including neoplasms of lymphatic and hematopoietic tissues.

Source. U.S. Public Health Service, National Center for Health Statistics, "U.S. Life Tables by Causes of Death: 1969–71," by T.N.E. Greville, "U.S. Decennial Life Tables for 1969–71," Vol. 1, No. 5, 1976.

the ultimate rectangular curve (Fig. 2) in which citizens would live out their lives, free of the fear of premature death, but with the certain fate that death would strike somewhere in the ninth decade.

This situation is occurring and will continue to evolve because biomedical research has directed its efforts almost exclusively to the disease-associated causes of death. Scant attention has been paid to the underlying causes of biological aging that are unrelated to disease but which, in clock-like fashion, dictate for each species a specific maximum life span. To be sure, the physiological decrements that occur in advancing years increase vulnerability to disease but unless more attention is paid to the fundamental non-disease-related biological causes of aging, then the fate of all inevitably will be death on or about our 95th birthday.

Prospects for increasing human longevity. As a consequence of these considerations there are two ways in which the efforts of biomedical researchers can be expected to extend human longevity in the next 25 years. The first is to reduce or eliminate the major causes of death, in particular, cardiovascular diseases and cancer. The results of ameliorating minor diseases will be minimal. For example, if all of the remaining infectious diseases were to be completely eliminated, there would be a mere 0.2-year gain in life expectancy at birth (Table I). Thus it could be argued that if an increase in life expectation is the main goal of biomedical research, most research should be directed toward the elimination of the two major causes of death. This position is not likely to attract many adherents, but is nonetheless the most logical conclusion to be derived from life-table studies and the projections dealt with in Table I. Table I however is based on data presupposing that causes of death are accurately recorded on death certificates. That supposition cannot, however, be made without challenge.

If one can measure the current effort put forth toward these two approaches by the expenditure of funds for each, then funds spent on cardiovascular disease and cancer research are more than 15 times greater than those funds spent in gerontology. It is also probable that the number of researchers, and consequently the amount of effort, in both of these areas also differs by 15-fold. Consequently, the liklehood that any significant increase in human longevity will occur in the next 25 years depends upon (1) significantly better cure rates for cardiovascular diseases and/or cancer, and/or (2) significant advances in our understanding and ability to manipulate the biological clock that sets for each species a mean maximum life span.

If potential success in either of these endeavors can be measured by the current at-

titudes and priorities of the biomedical research establishment, then it is clear that the search for cardiovascular disease and cancer cures are much more likely to effect human longevity than is gerontological research. Notwithstanding this is the further conclusion that by resolving these two diseases a maximum of 14 years of additional life expectancy could be attained but with successful efforts to increase the life span itself no fixed end point is ruled out. Furthermore the resolution of the two leading killers will in no way reverse or halt the decline in physiological decrements characteristic of age changes whereas efforts to increase the life span could lead to such a reversal. Clearly research in cardiovascular diseases and cancer should not be stopped but if our goal is to maximize opportunities to effectively increase human longevity then our current priorities are seriously out of balance. If this imbalance continues unchanged then the likelihood that the research accomplishments of a handful of underfunded gerontologists will affect the human life span is very small indeed.

Tampering with our biological clock. If the goal of biogerontology is to understand and then manipulate our biological clock then one profoundly important question arises: How desirable is it to be able to manipulate our biological clocks? The answer to this question is not simple. The fact that it must be asked is further evidence for the distinction that must be made between disease-oriented biomedical research and gerontological research. The goals of gerontological research are quite a different matter because we are not certain whether the "resolution" of the physiological decrements of old age will indeed benefit the individual or society as a whole. Many different scenarios that might result from the control of age changes are possible and each has an important negative side effect. Take, for example, the possibility that research into the biology of aging might result in the total elimination of all age-related physiological decrements. If this were achieved and no control were had on the biological clock itself, the result might be a society whose members would live full, physically vigorous, youthful lives until the ninth decade when death would suddenly strike. If, on the other hand, we were to learn how to tamper with our biological clock, with what goal in mind would one choose to reset this clock? Surely one wouldn't choose to spend an additional 10 years suffering from the infirmities of old age—yet that might, initially, be the only way to intervene. Is society prepared to cope with individuals whose only choice might be between naturally occurring death and 10 or more years spent with the viscissitudes of old age? We can hardly deal with a mean maximum life span of, say, 90 years to say nothing of the further social, economic, and political dislocations that might occur if we add a decade to this figure. Aside from this possibility, it is also worth considering the prospect of clock tampering in which the choice would be to spend more years at a particular developmental stage of our lives than we now do. The clock might be stalled for 10 years at, for example, a chronological age of 20. Is this desirable? Each of us, after pondering this provocative question would likely agree that the time at which we would like our biological clocks arrested should correspond to those years in which maximum life satisfaction and productivity occurred. Yet if we were forced to make such a decision it would probably have to be made prospectively. Even more complex is the question of when in the human life span individuals are most productive. An interesting and exhaustive study of this question was made by Dr. Harvey C. Lehman in 1953 (2). The conclusion to be reached from these data is that, depending upon the particular area of human endeavor, the time of maximum productivity can occur throughout the human life span. Thus clock tampering becomes a game that very few of us are capable of playing.

Goals for biogerontology. Having presented here only a few of the possible goals of biological research in aging it should be clear that a simple answer to this question cannot be given. Although simple to state and conceptually easy to understand, I have purposely avoided the notion of biological immortality. I have done this for one principle reason—that to attain it is so

far beyond any practical realization that any discussion of it would be more science fiction than likely science fact.

Furthermore, one of the most serious effects of even a modest success by biological gerontologists in increasing human life expectancy is the societal consequences. Most gerontological sociologists are persuaded that even as little as a 5-year increase in life expectancy at, say, age 75 would be so profound as to rupture our present economic, medical, and welfare institutions.

In spite of the apparent dilemma in stating goals for gerontological research there is, I believe, one goal that appears to be wholly desirable and even attainable as a short-range objective. That would simply be to reduce the physiological decrements associated with biological aging so that vigorous, productive, nondependent lives would be led up until the mean maximum life span. Implicit in this notion is that the quality of life is more important than its quantity.

The goal of gerontological research in the future should be to understand the biological basis of aging in order to extend the number of vigorous and productive years and to reduce the time spent in senility and the infirmities of old age.

Of what value is immortality, if by achieving it one extends the infirmities? Two modern versions of this theme exist in Aldous Huxley's "After Many a Summer Dies the Swan" and Oscar Wilde's "The Picture of Dorian Gray." In fact the Gerontological Society itself has as its motto: "To Add Life to Years Not Just Years to Life." I would therefore challenge the view that the goal of research in aging is simply to increase longevity.

If longevity is to be increased merely by extending the years of our infirmities, then the goal is not worth seeking. This indeed is the modern dilemma faced by many physicians who are torn between using every means for prolonging the terminal stages of disease in the name of prolonging life but at the expense of continuing the agony of certain death. The goal that appears to be not only more desirable but indeed more attainable is not the extension of longevity per se, but the extension of our most vigorous and productive years. If tampering with our biological clocks ever becomes a reality, I believe that it would be tragic in the extreme if such clock-tampering would result only in the extension of those years spent in declining physical and mental health. Having said this, what are the prospects of achieving it? I believe that the prospects are beginning to brighten.

Changing attitudes. It is sometimes observed that there are no gerontologists, just biochemists, cell biologists, and immunologists working in gerontology. Many serious biologists with an interest in aging still hold at arm's length the appelation "gerontologist" either because of the attitude that the problem is simply too complex to seriously believe that it will yield to experimentation or because the many pseudoscientific fringe groups still in search of biological immortality have had such a pervasive influence on the field that to formally associate oneself with it would be to suffer an unseemly stigma.

Happily these convictions have become less tenable in the past few years and a significant change in attitude toward the science of gerontology has occurred. There is now developing the realization that biological aging is no more complex than are problems in embryology, development, neurobiology, cancer research, or genetics. The attitude that efforts by gerontologists to reverse the aging process are akin to medieval alchemy is untenable in view of the fact that all successful biomedical research has the net effect of prolonging life. Thus there is no rational reason to discourage research on the fundamental causes of age changes. Established gerontologists are no longer apologetically explaining their interest in aging and young scientists are beginning to appreciate that the fundamental problems are less intractable than their predecessors thought. Public awareness of this neglected field has, commendably, resulted in its recognition to the extent that an Institute on Aging has finally been created at the National Institutes of Health.

For the first time the discipline of gerontology has been given a degree of national recognition at the biomedical level to make

real the possibility that meaningful efforts will be made to understand the biology of aging. The field has now been given a level of national visibility that is almost compatible with the magnitude of the problem. Even more important is the implied notion that something can and should be done about biological age changes. The period of utter disregard of the field has now, hopefully, passed and recognition that the problem is not intractable has finally been appreciated.

In my view the goals of research into the biology of aging will be as clouded 10 years from now as they are today, nevertheless, it is a virtual certainty that research in the field will continue. Until the objectives are better dealt with, I take the cynical view that I am confident that the fallibility of those of us engaged in gerontological research is such that there is little likelihood that a full understanding of the aging process will be revealed soon.

Granting the premise that even in the absence of clearly delineated goals for biogerontology, the discipline will continue to flourish, what are the most likely research trails that will lead to a better understanding of the phenomenon? It seems clear that the trail should take us into the cell and terminate with information-containing molecules.

Theories of aging. Most gerontologists agree that there is probably no single cause of aging. A generalization that probably comes closer to a unifying theory consists of concepts based on genetic instability as a cause of aging (3). The genetic contribution to the aging process is likely to be foremost in the determination of a life span that is characteristic of each species. The genetic basis for age changes is tenable for many reasons (4) among which is the wide range of variation in maximum life spans among different animal species. It is obviously much greater than the range of individual life spans within the species. One fundamental problem in relating genetic processes to aging is the attempt to separate the genetic basis of differentiation from the genetic basis for aging, or the concept of "first we ripen, then we rot."

Genetic instability as a cause of age changes might include the progressive accumulation of faulty copying in dividing cells or the accumulation of errors in information-containing molecules.

The progressive accumulation of errors in the functions of either fixed postmitotics or in actively dividing cells could act as a clock. This process would initiate secondary types of mischief, which would ultimately be manifest as biologic aging as it is known. Thus, aging could be a special case of morphogenesis: cells may be programmed simply to run out of program.

Probably no other area of biologic inquiry is susceptible to so many theories as is the science of biogerontology. This proliferation of theories has occurred not only because of a lack of sufficient fundamental data but also because manifestations of biologic changes with time affect almost all biological systems, from the molecular level up to that of the whole organism. It is therefore easy to construct a theory of aging based on a biological decrement that may be observed to occur in time in any system at the level of the cell, tissue, organ, or whole animal. The important question will always be: Is the change observed a direct cause of aging, or is it the effect of changes that may be occurring at a more fundamental level?

If as modern concepts have it, biological development is based on signals originating from information-containing molecules, postdevelopmental changes can be reasonably attributed to a similar system of signals at the molecular level. This notion assumes that the switching on and off of genes during developmental processes also determines age changes; that is, age changes, like developmental changes, are "programmed" into the original pool of genetic information and are "played out" in an orderly sequence just as developmental changes are.

Aging might be attributed to a series of orderly programmed genetic events that shut down or slow down essential physiological phenomena when postreproductive age is reached. The programming may be the result of specific gene determi-

nants that, like the end of a tape recording, simply trigger a sequence of events to shut the machine down.

Alternatively, the universality of aging might be attributed to functional failures arising from the random accumulation of "noise" in some vulnerable parts of the system that ultimately interferes with optimum function and produces all the well-known physiological decrements. But, if the "noise" is randomly accumulated, why do members of each species appear to age at specific, highly predictable times? One may call the span of time during which "noise" accumulates and becomes manifest in some functional decrement, "the mean time to failure." This concept is applicable to the deterioration of mechanical as well as biological systems and can be illustrated by a consideration of the mean time to failure of, for example, automobiles. The mean time to failure of the average machine may be 5 to 6 years, which may vary as a function of the competence of repair processes. Barring total replacement of all vital elements, deterioration is inevitable. Similarly, failure of cell function may occur at predictable times that depend on the fidelity of the synthesizing machinery and the degree of perfection of cellular repair systems. Because biological systems do not appear to function perfectly and indefinitely, one is led to the conclusion that the ultimate death of a cell or loss of function is genetically programmed and has a mean time to failure. The mean time to failure may be applicable to a single cell, tissue, or organ, or to the intact animal itself. If the genetic apparatus simply runs out of accurate programmed information, that might result in different mean times to failure for all the dependent biological systems. The existence of different life spans for different species may reflect more perfect repair systems in animals of greater longevity.

Areas of biogerontological research. As to specific areas of research emphasis that might broaden our understanding of basic aging processes, my list is biased toward studies on specific genetic signals at the cellular level for the reasons just discussed.

Research should focus on identifying specific genes controlling aging or, conversely, on longevity genes. If the life spans of animals have increased as species evolve one might think in terms of a positive effect on longevity by genes that decrease vulnerability. It might not be foolish to ask, "Why are babies young?" Rates of gene expression should vary with species longevity. Repair processes and rates may play a role. The quality and quantity of information flow at the molecular level seems to be a particularly attractive field for exploration of fundamental age changes. Altered proteins, particularly enzymes, exist in the cells of aging organisms. How these alterations occur is not clearly understood. We might emphasize research on regulation and synthesis of nucleic acids, enzymes, and other specific proteins including post-translational modifications of newly synthesized protein molecules.

Little is known about the effect of age on cell membranes, mitochondrial synthesis, and the accumulation of age pigments or lipofuscin in neurons and other cells.

Alterations in chromatin composition are known to occur in cells as they age. This is expressed as a decrease in transcriptional activity possibly resulting from changes in the quantity and kind of genes being expressed.

At the whole-cell level, cultured normal human and animal cells have been shown to have a finite capacity to replicate and this has been interpreted as aging at the cellular level (5–7). The number of population doublings that cultured cells undergo is inversely related to donor age (6, 8–13) and may be directly related to species life span (14). Other cell culture phenomena related to aging include the inverse relationship between donor age and cell migration from explanted normal tissue (7). The cell biology of aging, called cytogerontology, has yet to be fully exploited. In recent years a plethora of functional decrements have been reported to occur in cultured cells before proliferation ceases (15). Many of these changes are similar to changes that occur in the whole organism as it ages. The salient question in this field is the location

and identification of the mechanism that limits the functional and replicative capacity of cultured normal cells. Utilizing cell enucleation and fusion technology to create reconstructed cells composed of old nuclei and young cytoplasms (and the reciprocal), studies in our laboratory have tended to implicate the nucleus as the site in which the governing elements are located (16–18). Further studies in this area should explore the loss of functional capacity in cultured nondividing or slowly dividing epithelial cells, neurones, muscle cells, and other specialized elements. It is likely that the functional capacity of these cultured cells will be found to decline in direct proportion to donor age and not found to be attributable to imperfect culture conditions as has been believed in the past.

Further studies at the cell level should include a reassessment of the role of dying cells. Cell death on a massive scale is a normal process during embryogenesis and early development. Is cell death to be considered pathological when it occurs in old tissue? What is the disposition of cell products from dying cells? Are there changes in cell cycles and turnover times in aging cell populations? Nerve cell loss is known to occur in regions of the aging brain. Better quantification is required as is information on the effects of this loss on brain function.

Further clarification of the formation of lipofuscin pigment and its relation to neuronal activity is required as is the identification of neuroendocrinologic deficiencies. Of particular importance are studies on the role of slow or latent viruses in senile dementia. Several neurological pathologies are now known to be caused by slow viruses and the incrimination of such agents in the dementias of old age could provide a quantum leap in our understanding of this widespread delibitating condition.

In the field of endocrinology alterations in hormone responsiveness may be a major cause of the deterioration of physiologic function during aging. Nondividing cells lose hormone receptors with time with consequent reduction in hormone-mediated enzyme induction. We need to elucidate the cellular, molecular, and neuroendocrine mechanisms involved in hormone receptor changes during aging.

As normal functions decline in old age there is a concomitant rise in immunologically related diseases such as autoimmune disease, cancer, and reduced tolerance to infectious diseases. The decline in normal immune functions seems to derive from (1) the inability of T cells to proliferate maximally, (2) an increase in T cells with suppressor activity, and (3) a decrease in normal T cells. The goals here should include a determination of the etiology of these changes in the immune system at the cellular and molecular level with the hope of restoring declining immune function.

Some of the research areas in biogerontology that require attention include some specific disease states or studies on the intact organism. A high age-related disease is diabetes mellitus whose milder forms seem to be difficult to distinguish from normal age changes. This difficulty in distinguishing normal age changes from pathologic changes is not limited to diabetes and offers particularly important challenges for future research.

Thirty percent of postmenopausal women have major orthopedic problems related to osteoporosis. Falls with accompanying bone injury are the leading cause of all accidental deaths in elderly white females. Osteoporosis is four times more common in women than in men. Hip fracture surgery is the third most common procedure over age 65.

Most forms of cancer are more prevalent in the elderly, yet the inclusion of old age as a factor by cancer researchers is, even today, a rare consideration.

Little is known about the nutritional requirements of the elderly and the role nutrition might play in normal aging. Even the pharmacological effects and dosimetry of drugs used by old people is virtually unknown. Most drug action and dosage schedules derive from studies on young adults yet most drugs are administered to the aged.

Despite the current exercise craze there is no persuasive evidence that it increases longevity, slows declines in physiological

function, or is even good preventive medicine.

Finally, there is a particularly important need for a quantitative measurement of biological aging in man. We have come to depend too much on chronological determinations which are, for most purposes, meaningless. Does some biological change really take place at the stroke of midnight on our 65th birthday that makes us old? The rates of age changes certainly vary among individuals as they undoubtedly do among different organs or tissues in the same individual. Much could be learned from a simple test that would tell us the rate of aging in specific organs, tissues, or cells.

This catalog is by no means intended to be complete. I have mentioned only some major areas that are currently favored areas for research. In 5 years fashions will surely dictate another list.

The future of aging research. The future of aging research is really a function of the quality and quantity of young investigators who are encouraged to enter this field. Biogerontology has long been regarded as an impractical pseudoscience dealt with only by eccentrics and charlatans. Research on aging has been neglected by qualified scientists who perceive the field to be lacking in scientific respectability brought on, no doubt, by the fact that no area of biology has been more deceptive to the gullible or more profitable to the unscrupulous.

As a consequence of these considerations biogerontology has attracted few scientists willing to risk their reputations by working in a field that suffers such a stigma. The notion that the biology of senescence is too complex to yield to experimentation is a myth. How much more complex is it than developmental biology? When the continuum of life is perceived from conception, biologists call it developmental biology. When perceived from its terminus gerontologists call it aging.

Happily, several of the attitudes of scientists toward gerontology have changed in the past few years. Much of that change has come about as a result of the establishment of the National Institute on Aging for which so many of us worked. I might say that the official position of FASEB (not SEBM) was to oppose the establishment of the NIA. I was asked to rebut FASEB's position, and I am pleased to say that my position prevailed. Changes have come about because the sudden availability of grant funds has great magnetic qualities. I do not deplore this development, but like inflation, we now find too many dollars being chased by fewer qualified people. The result is an expanding population of instant gerontologists. Some would argue that this is the way to attract new talent to the field but much of this new talent is qualified only because they can design experiments with a temporal parameter. Is it possible to design an experiment without a temporal parameter? If not then all biologists qualify as gerontologists.

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