Henry Ford Hospital Medical Journal

Volume 16 | Number 1 Article 5

3-1968

Aging: The Last and Greatest Challenge

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Henry Ford Hosp. Med. Journal
Vol. 16, No. 1, 1968

The Edsel B. Ford Memorial Lectures, which are sponsored jointly by the Edsel B. Ford Institute for Medical Research and the Henry Ford Hospital, have been held annually since 1952. The following is an adaptation of Dr. Strehler's lecture before staff doctors and guests, including pathologists, physiologists, biochemists, physicists, biologists and clinicians from Michigan and Ontario.—Ed.

Aging: The Last and Greatest Challenge

Sixteenth Annual Edsel B. Ford Memorial Lecture*

by

Bernard L. Strehler, Ph.D.**

Introduction

I welcome the opportunity to deliver the 1967 Edsel B. Ford Memorial Lecture. There is honor implicit in being in the company of so many distinguished biologists who have given previous lectures in this series. Also, it permits me to call attention to the opportunity which presently exists to make major inroads into the areas of ignorance surrounding the aging phenomenon. To the extent that my listeners and readers make known their interest, they may have an effect on the attack against mankind's oldest enemy.

Events of the last two years have revealed a new awareness of the importance of a more comprehensive, systematic (perhaps "systems") organization of research on the aging process, particularly at the cellular and molecular levels. Among these auguries are incisive symposia sponsored by the New York Academy of Sciences, the National Research Council, the Nuffield Foundation, the Society for Experimental Biology, the Society of Actuaries, the Interdisciplinary Communications Committee of the New York Academy, the Salk Institute and the Harvard Technology in the Future Series.†

Parallel to such spontaneous upwellings from within the scientific community are three other, somewhat related events:

*Given Nov. 7, 1967, under sponsorship of the Edsel B. Ford Institute for Medical Research and the Henry Ford Hospital. Portions of this text were presented at the Harvard Symposium on Technology in the Future and will appear in the published proceedings of that Conference. The author thanks the organizers of the Harvard Conference for their permission to adapt the material for presentation and publication at Henry Ford Hospital.

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†The proceedings of these symposia, particularly the Symposium on Interdisciplinary Perspectives on Time of the N. Y. Academy and the SEB symposium are extremely useful as documentary background for many of the concepts discussed here.

The emergence of systems research and bioengineering concepts in viable-hybrid form;

the very constructive and searching hearings and inquiries into the status of research on the aging process initiated by the Committee on Aging of the United States Senate (Harrison Williams, Chairman);

and the recent founding of the Association for the Advancement of Aging Research.

The latter reflects the belief by research leaders in this field and closely related areas that there is urgent need to involve more of the productive and imaginative segment of the scientific community and to apply to this problem the dissective-analytical approach that has been so successful in other problems of systems failure.

The AAAR can channel and translate the recommendations of the scientific community into more effective and systematic efforts. Its Board of Governors and Council of Advisors includes European and American scientists pre-eminent in the study of aging.

General Status of the Problem

Aging is, next to reproduction, the most universal of biological phenomena. In one expression or another, it affects the properties and permanence of members of all phyla, from protozoa to anthropoids, from bacteria to oak trees.[1,2]

There may be a few species that are immune to time-induced deterioration (e.g. the anemones studied by Asworth and Annandale),[3] but, by and large, life has not evolved in such a manner that its highest expressions, including particularly man, are immune to the slow deteriorative changes in structure and consequent function that lead to what we define as aging and that end in the death of the individual. As pointed out nearly 80 years ago by the brilliant biologist-essayist, August Weismann, this deterioration probably arose because natural selection operates largely before reproduction. Higher animals and plants may thus be viewed as huge lateral protuberances on the continuing thread of tiny, but all important, "germ cells" that have been propagated from the beginnings of cellular time. That some properties suited to the perpetuation of a biological line may lead, as a direct or accidental consequence, to the regular senescence of the individual carriers was stressed by Weismann and eloquently expanded and clarified by P. Medawar[5] and G. Williams.[6]

The problem to which we shall address ourselves, however, is not whether aging occurs, or even the unknown details of its evolution. Rather, we shall explore briefly how it expresses itself, summarize what we know of its mechanisms and (more important for the future) sketch in areas of ignorance. I believe much of the ignorance can be rapidly and effectively dissipated in the next decade or two — provided that plans are properly laid in the next year or two. For, I believe (and it is my opinion a consensus of leading knowledgeable biologists in the field would agree to) the following:

(1) that the process(es) of aging in man and his near and distant relatives is understandable in terms of general scientific concepts and laws.

(2) that our society has the means to develop this understanding in 10 to 20 years.

(3) that such early description of the process and its components in basic terms will require a newly critical dissective examination, deliberate administrative planning and emphatic and adequate support of research on the problem.[A]

(4) that the present efforts along these lines are grossly inadequate to do the job well within the foreseeable future — certainly not within the lifetime of those reading this essay.

Whether research on this problem will receive the attention and support it deserves depends on those who have the power to influence policy relevant to the question. If the existing administrative, funding, educational, and manpower obstacles are allowed to persist one result will follow; if they are removed another result is likely.

Some Effects of Biological Aging

There are two related cardinal effects of time on animals and plants. They are:

(1) Following the attainment of reproductive maturity, most biological individuals tend to decrease in the rate or efficiency with which they carry out various functions. This change in a variety of functions of humans, abstracted from the studies of Shock and collaborators,[7] is shown in Figure 1.

(2) This deterioration in function results in a decrease in an individual's chances of staying alive, i.e. the probability of death per unit time increases. The mathematical equation describing the change in the probability of dying was derived empirically by Benjamin Gompertz, an English insurance actuary, about 140 years ago.[8] This equation is exceedingly simple: $R = R_o e^{\alpha t}$, where R is the chance of dying at any age, t; R_o is a mathematical constant related to the predicted chance of dying at age o; and α is a constant that describes the rate of increase of the mortality rate as a function of age. The closeness of the Gompertz equation approximation to real systems is shown in Figure 2.

One of the puzzles that appears to have been resolved recently is posed by the contrast between the large changes that occur in the mortality rate (1000 fold) (see Fig. 2) and the concurrent, quite small rate of loss of function that occurs (ca. 1% per year after age 30 for many functions) (see Fig. 1). Both Sacher's studies[9] and work reported from the author's laboratory[10] suggest that this is due to statistical aspects of so-called stochastic processes, processes in which small disturbing events are much more frequent than large ones. From mathematical models and the application of real and observed numbers to them, several things are apparent.

[A]See column F, Table I for suggested new investment if effective comprehensive, prompt progress is to be made in understanding basic aspects of the problem.

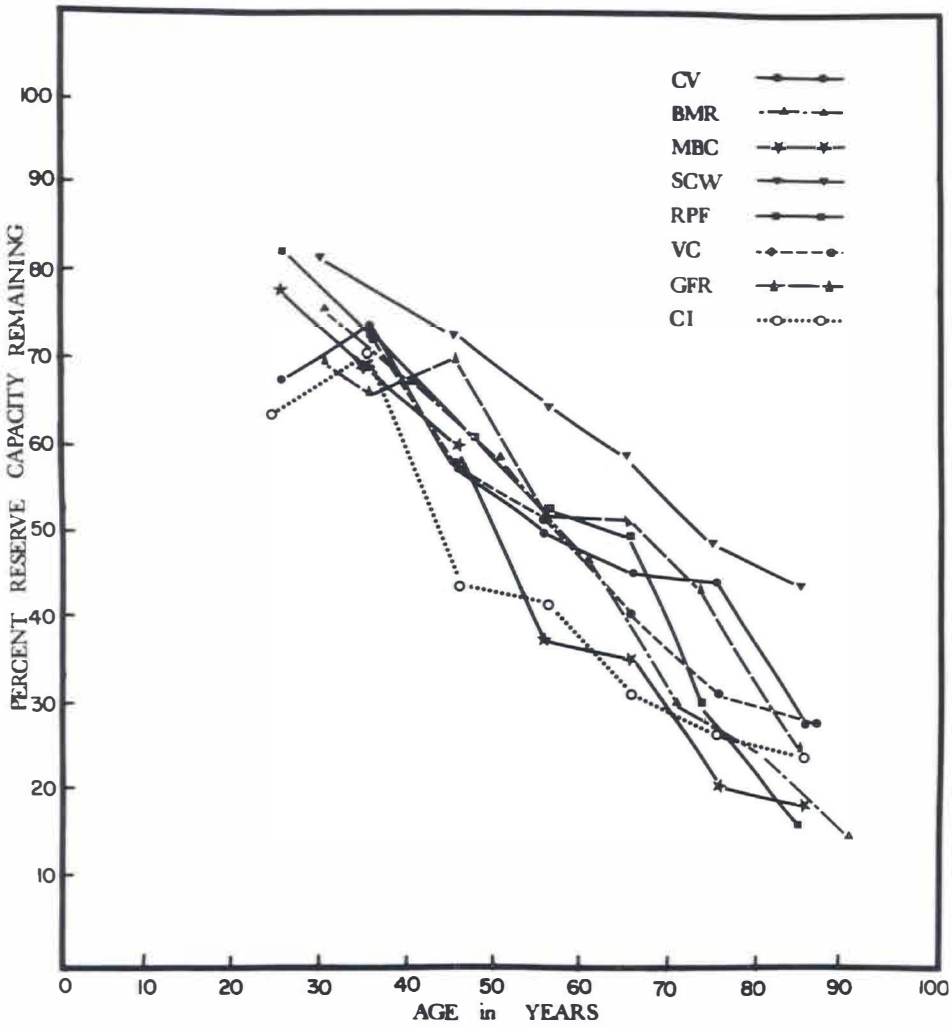

Figure 1

Composite diagram of the percent of the reserve capacity at age 30 remaining after various ages are attained. The limiting value (on the lower side) for any capacity as estimated from the lowest individual value for the parameter in any subject at any age, was subtracted from the mean value of the parameter at each decade and the results plotted. Symbols indicate as follows: CV—Nerve Conduction Velocity; BMR—Basal Metabolic Rate; MBC—Maximum Breathing Capacity; SCW—Standard Cell Water; RPF—Renal Plasma Flow; VC—Vital Capacity; GFR—Glomerular Filtration Rate; CI—Cardiac Index.

First: while the average length of life has increased dramatically during the last century, the maximum life span has not been significantly changed, i.e. more people approach the limit, but the limit itself is not greater.

Second: man's rate of aging is not appreciably altered by changing his environment. "Bad" environments may saddle him with more disease and kill off some indivi-

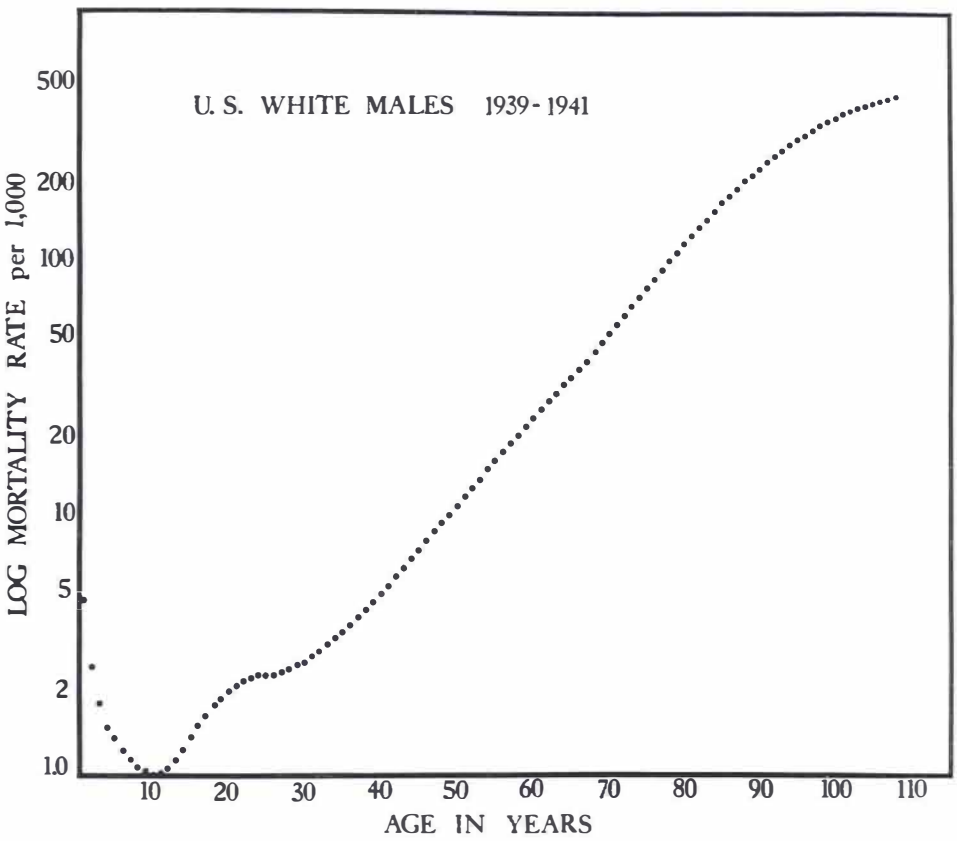

Figure 2

Gompertz Plot of Age Specific Mortality Rate (Male, white, U.S., 1940. Age in years vs. log mortality rate).

duals early, but this damage is largely independent of an underlying deteriorative process that marches inexorably toward a fixed limit.

Third: the possible or probable elimination of the major specific infections and deteriorative diseases will not drastically change the age distribution of future populations and generations.[11] Any major alteration of this distribution will depend upon future understanding of the fundamental biological basis and mechanisms of aging.

On the Sources of Biological Aging

Entire volumes can be dedicated to the detailed description of functional change but to describe it is not to understand its origin.

Obfuscators and particulatists may take refuge in and stoutly defend the truism that aging is a complex process, expressing itself in many confusing ways; that it may be different in cell types A and B, or in species X and Y, or individual M and N. But the essence of science is to reduce a complex phenomenon to its basic elements,

to derive the rules that make such complex systems understandable as composites of simpler systems, and to decide which set of rules or laws is appropriate to a specific natural phenomenon.

It is my belief that a large portion of research in gerontology is not sufficiently focused on these general procedures and that what is needed is a re-evaluation of the existing general approach to the problem. Specifically, what is almost universally lacking in gerontological research is the testing of specific hypotheses (of aging) in terms of their qualitative and quantitative contribution to the debilities of age.

This deficiency is probably a more telling commentary on the workers in the vineyard than on the quality of the grapes growing there; for, although literally thousands of specific theories of aging could be proposed, those theories fall into a relatively small number of discrete categories that can be succinctly stated and which represent scientific sub-problems of manageable proportions.

Thus, in one such reasonably inclusive formulation, (see Table I) the *major* theories of the molecular origins of senescence represent some 23 different hypotheses. Some of these hypotheses have already been tested extensively (cross linkage, somatic mutation); other are currently under examination; others are essentially unexplored.

Some of the salient lines of evidence, obtained during the past decade and summarized in the table, include findings that somatic mutations (specifically, chromosomal abberations and blood group antigen changes) are not a dominant cause of aging, that the so-called age pigments accumulate in substantial amounts (6 to 25% of the intracellular volume), that human cells in culture are limited to only about 50 divisions (doublings, to be exact), that denaturative reactions are not a key part of the aging of cold blooded animals, that different cell types lack certain machinery presumably necessary for the translation of certain genetic code words, that the incidence of autoimmune reactions increases with age, that the predominant protein of the body, collagen, becomes more insoluble and cross-linked with aging, that senescence of leaves can be induced by a specific substance, abscisin, found in old leaves, and that the ability of collagen in old animals to yield energy (glycogenesis) is drastically reduced in older animals.

These and other findings represent important progress. Nevertheless, it is apparent that the problem could be substantially simplified if certain important general information were available. Examples of such informational loopholes are represented by the following questions:

(1) What chemical components of adult animals (especially humans) are not replaced or replaceable?

(2) If cells are transplanted from a young animal to an old one (or vice versa) are the properties of the transplants and their constituent cells (particularly their physiological age) determined by the host age or by the donor age?

TABLE I
A SUMMARY AND EVALUATION OF EVIDENCE BEARING ON BASIC HYPOTHESES OF BIOLOGICAL AGING

A Statements of Hypothesis	B Model Experiments or Questions	C Relevant Findings	D Tentative Conclusions	E References	F Recommended Additional Annual Research Support
Senescence is due to: Class I: Loss of Cellular Syntheses Due To:					
A. Genetic Damage 1. DNA Mutation (Base substitution, strand breakage or deletion)	Do treatments (e.g. x-ray) which cause an increase in the number of accumulated mutations decrease lifespan proportional to increased load of mutation?	No (For chromosome abberations)	Less than 10% of aging is due to this type of effect	12, 13, 14	$700,000
2. Cross-Linkage (of DNA)	Does cross linkage of DNA occur with age?	Perhaps to slight extent	Need experiments		$300,000
	Do substances which cause RNA cross-linkage agents accelerate aging?	No clear evidence	Need experiments		$200,000
B. Loss of Message Synthesis					
1. Inhibitor-repressor. Accumulation (e.g. histones)	Are there substances in old cells that repress message synthesis by young DNA (+ enzymes)?	Histones are bound to DNA	The small extent of Young/Old difference in histone binding suggests mechanism is unlikely	15, 16	$1,000,000
		Metal ions are bound to DNA			$300,000
2. Absence of adjunct factors (e.g. sRNA, sRNA polymerase)	Are ribosomes, sRNAs activating enzymes of old tissues capable of sustaining synthesis with young DNA as template?	None	Need experiments		$200,000
C. Loss of Message Translating Ability					
1. Unspecific loss of protein synthetic capacity	Similar to above	None	Need experiments		$100,000
2. Loss of ability to translate certain messages because of loss (codon restriction hypothesis)	Are there tissue differences in specific sRNA acylases?	Yes	May be of considerable importance	17, 18	
	Do these differences result: in tissue specific synthetic losses?	Not known	Need experiments		$300,000
	Are these losses codon-specific?	Not known			
a. Specialized products	Do cells of different types differ in codon reading specificities?	Probably	This model may account for large percentage (60 to 95%) of decline	17, 18	$300,000
b. Unspecialized cell components (membranes) c. Mitotic Components	Do specialized syntheses repress type b and c syntheses?	Usually	Active exploration needed	19, 20, 21, 22	$300,000

TABLE I (Continued)

A Statements of Hypothesis	B Model Experiments or Questions	C Relevant Findings	D Tentative Conclusions	E References	F Recommended Additional Annual Research Support
Senescence is Due To: Class II: Loss of Cellular Function Due To:					
A. Deterioration of semi-autonomous or symbiotic organelles					
1. Mitochondria	Are mitochondria of old tissues identical with young?	No, they are more readily uncoupled. However, P/O ratios of fresh mitochondria unaltered during aging (rat)	Unlikely source of senescence. Evidence not available	23, 24, 25, 26	$100,000
2. Plastids	Do plant organelles change with age?	Yes, loss of chlorophyll, change in protein complement, rRNA, etc.	May be key site of deterioration of plants		$200,000
B. Insufficiency of promoter substances e.g. hormones, growth factors, etc.	Do systemic promoting factors limit old organisms? Does parabiosis, transplantation, or transfusion alter cellular age effects?	Yes, in some cases, e.g. growth hormone factors in serum or embryos 11-keto 17-deoxy steroids, pituitary changes evident in rats. Diabetes increases vs age.	Probably important. May account for 20-80% of decrement in mammals: important in plants	27, 28, 29, 30, 31, 32	$200,000 $400,000
C. Accumulation of Inhibitors					
1. Systemic (soluble components)					
a. Serum factors (lipid peroxides)	Do inhibitory substances accumulate?	Probably, according to Carrel	Suggestive: may contribute substantially	33, 34	$200,000
	Does transfusion of old to young shorten life or vice versa?	Probably: e.g. plasmaphoresis			
b. Auto antibodies	Do old animals have increased auto-immune antibodies?	Yes	Specific lesions	35, 36	$200,000
	Is this universal?	No	Not a general process		
2. Extra or intracellular residues					
a. symbiotic viruses	Do viruses occur intracellularly during aging?	Many tissues are virus-laden at advanced ages	Need further experiments	37, 38	$400,000
	Do symbiotic viruses decrease function of mammals?	Not known	Need experiments		
b. exogenous precipitates (e.g. Ca salts)	Do such precipitates occur?	Yes, in certain diseases but probably not in normal aging	Unlikely to be basic important cause	39, 40	$300,000
c. cross linkages	Do cross-linked materials occur during aging?	Yes, age pigments	May be important impairment because of volume displacement (10-30%)	41, 42, 43, 44, 45	$1,000,000
	Is there a consequent effect on function?	Collagen is cross-linked; old collagen is not readily mobilized by aged rats (cortisol)	Reduces energy reserve available		
d. thermal denaturation	Are there accumulations of denatural materials?	No evidence	Need experiments		$600,000
1. uncatalysed	Does heat shock decrease life expectancy of survivors?	No, in Drosophila	Probably not important	46, 47, 48	
2. catalysed	Are enzymes damaged *in vivo* by reactions they catalyse?	Probably in some cases; but extent *in vivo* unknown	Need evidence		
e. Hydrolyses	Are partially hydrolysed, long-lived residues present?	No evidence	Need experiments; may be important		$150,000
f. Isomerization	Does old protein contain excess D-Amino acids?	Probably not	Unlikely source; more testing needed	49	$50,000

TABLE I (Continued)

A Statements of Hypothesis	B Model Experiments or Questions	C Relevant Findings	D Tentative Conclusions	E References	F Recommended Additional Annual Research Support
Senescence is Due To: Class III: Loss of Intercellular Coordination Due To:					
A. Physical alterations in:					
1. Membrane permeability	Does membrane permeability decrease with age?	In some cases permeability increases	Unlikely source of aging	50	$400,000
	Will agents that reduce permeability cause life shortening?	Radiation causes arterior-capillary fibrosis, shortens life	May be highly important Both above need critical tests	51	$200,000
2. Spatial relations between cells	Does cell slippage occur?	Evidently. Old tissues frequently recognizable by irregularity of spacing	Probably of some import	52	$200,000
	Does increased cell movement or dislocation shorten life?	Not known	Needs study		
3. Diffusion path or viscosity of diffusion medium	Is diffusion rate altered?	Not clearly known Conflicting evidence	Need experiments on tissue diffusion rates vs. age; measurements of tissue "viscosity" needed		$200,000
B. Decreased cell responsiveness					
1. Loss of receptor sites on cells	Do old cells show decreased responses?	Yes	Probably important	29, 53, 54, 55	$800,000
2. Loss of transducing machinery	Is specific enzyme machinery decreased?	Not known	Need experiments		$200,000
3. Loss of energy reserves	Are reserves decreased?	Free fatty acid release via epinephrine decreased	Important sources of decreases in sustained response		$500,000
		Collagen mobilization via cortisol decreased vs. age	Information in glycogen mobilization and resynthesis needed	44	
C. Cell Loss	Do cell losses occur?	Yes, 10-40% in some tissues			$500,000
1. Accidental	Does increased cell loss increase mortality?	In extreme cases, yes; quantitative relationships unexplored Not known without complicating factors	Probably not main source of dysfunction of muscle, heart, skin, liver, kidney; may be significant in nervous tissue and endocrines	56, 57, 58, 59, 60, 61	$200,000
2. Programmed	Is death of cells in adults "programmed" or "accidental?"	Embryological studies suggest yes: Death is part of life cycle of replenishing tissues Programmed death of non-dividing cells unknown	Studies on mechanisms of cell death needed		
				Total:	$10,700,000
				plus overhead	$14,800,000

(3) What is the effect of body temperature on the rate of aging of warm-blooded animals?

(4) Do mammalian cells have the capacity to divide indefinitely under the proper environmental conditions *in vivo?*

(5) What is the mechanism that controls the selective expression of a given genetic trait in one cell and of another trait in another; i.e. through what molecular-biochemical mechanism does embryonic differentiation occur?

Some of the answers will be derived from work not directly related to aging; some of them will fall out of descriptive work; but, the most potent force in the rapid development of the field would be the early and adequate financing of deliberate tests of the hypotheses listed in Table I and of such additional ones as may appear to be desirable as the field unfolds.

Research Requirements

Competent basic scientists charged with recommending the most ideal course of action have suggested that initial additional research support at the rate of $50 million per annum would be adequate not only to begin a critical test of hypotheses ($15 million/annum)[B] but would also permit a greatly increased rate of descriptive study and related basic studies ($15 million/annum each). Collateral biomathematical, demographic and methodological resource improvement is recommended at the rate of $5 million/annum.

Future Problems and Possibilities

The validity of predictions of lengthening life for humans from 20 to 500 years hence is contingent upon the factors that enter the equation. Two such factors are paramount. The first is: what are the real sources of age deterioration? the second is: what can be done to retard or reverse them? Obviously, the answer to the second hinges on the first. We can, therefore, begin to prophesy with accuracy only when we know more about the molecular and cellular origins of senescence.

[B]The attainment of this limited goal (critical hypothesis testing) could be assured within the next 5 to 10 years if Congress or the administration establishes an Institute, Agency or Commission for basic research in aging funded initially at the rate of $50 million/annum.

The function of this institute should be, among other things:

(1) To establish a study section to sponsor and promote research capable of critically evaluating the alternative basic sources of senescence outlined in Table I. Such a review group should be charged with responsibility to initiate negotiations for contracts or grants in such areas as are currently not receiving adequate attention. Imaginative workers in these areas should each be funded at least at the rate of an additional $100,000/annum, in a manner perhaps closely resembling the successful VA Aging Research Satellite Program. Recommended additional annual research support is itemized in Table I.

(2) To sponsor regular opportunities to exchange research findings and to discuss progress and concepts in special meetings, symposia and conferences.

(3) To set up training programs in suitable academic environments in relevant areas of biology and aging.

(4) To initiate direct international research cooperation on this subject among scientists, both East and West.

(5) To promote studies directed toward anticipating and ameliorating social problems arising from alterations in age distribution.

Aging: Challenge

A. Reversing the Aging Process

If senescence is primarily due, as many believe, to the deterioration of non-replaceable cells or of subcellular structures, and if such structures become fixed and final when growth and differentiation cease, then suitable compensations can only be found by reversing whatever the controlling events may be. This seems a monumentally difficult task, but when embryogeny is fully understood, the job may not be so difficult. Much depends on whether the "operons" programming development can readily be guided or misguided from outside the cells in which they act.

B. Slowing the Aging Process

Much more likely of achievement than outright reversal of aging is the slowing of the process. Several procedures are known drastically to extend life in experimental animals; thus, starved rats live nearly twice as long as well fed ones, according to McKay's studies; rotifers, insects, fish, and reptiles live substantially longer at low body temperatures than at higher ones; high doses of ionizing radiation can double the life expectancy of the marine hydroid, *Campanularia flexuosa*. Of these regimens, the possible lowering of body temperature of humans through judicious manipulation of our hypothalamic thermostats might very appreciably change our life expectancy. For example, a 2-3° drop in body temperature would add about 20 years to life (if we follow the same rule that applies to cold blooded animals.)

C. Replacement Parts

Toupees, false teeth, spectacles, cosmetics, girdles and arch supports, are accepted means of compensating for time's unkind arrows. Recently, corneal transplants, plastic arteries, and whole transplanted kidneys, even artificial hearts and kidneys, have received much attention and will no doubt solve some acute medical problems. However, the picture of a patched and pasted bicentenarian being transported by pneumatic tube from heart-lung machine to artificial kidney to artificial liver, perhaps feebly twitching his servo-musculature or enjoying direct 3-dimensional video tape transmission to his occipital cortex (because of blindness) is not presently an attractive alternative to an extended sleep. I doubt that man will move with much satisfaction in that direction.

More likely is the transplantation of the essence of identity and attendant memories into some mind-analogue computor that can be programmed to replace all of its parts regularly; or even, a la Frankenstein, into another body whose mind has been deprived of all those experiences that make self and non-self recognizable. These may be possible solutions for a few; I doubt that they are satisfactory ones for many.

Rather, I would predict that, if we fail (as we may well do) to find a suitable mechanism whereby metazoan man can be made to replace all of his parts autonomously on a regular schedule, that the solution will lie somehow in another insight (perhaps a sort of scientific mysticism) in which the relatedness or even identity of man with men becomes a subjectively compelling reality rather than the partly objective awareness of this identity, sonnetized thus:

THE THIRD CERTAINTY

The first light I, who lay asleep had seen
Formed caricatures of noisy disarray:
Then one by one the web that lay between
Created self: "I am" — unique display.

To fear, to hate, to love, to dream, to grow
And know prophetic door that guards the sleep,
As sinews leather, vessels rock, topped snow:
We slide so slyly, glide to trench so deep.

Then where go "I", mystic collection? Night?
No more to taste the sea or feel the sky?
No more to dream on earth-locked starry height
Nor hear again a birdsong new Spring cry?

Or will some other world-bit's shape decree:
Indulge the grand illusion "I am me!"

from: THE PROMETHEUS EXPERIMENT
Perspectives in Biology and Medicine
Fall Issue 1967

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