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ON AGING, OLD AGE AND SENILITY

Conrado S. Dayrit
Emeritus Professor of Pharmacology,
College of Medicine, U.P.
Vice President, Medical Affairs Division,
United Laboratories, Inc.
Philippines

"The study of aging is in its infancy"
(Ray and Barrette, 1973)

Introduction

"Aging" is defined by Webster as the process of growing mature or old. This definition is biphasic. On the one hand, the process of maturation is a positive process that includes growth and progressive attainment of the individual's maximum potentials in structure and function. The second part of the definition of aging, is the process of growing old – a negatively directed process where catabolism, degeneration, wasting and atrophy exceed building and repair. The individual may show structural regression as well as a slowing down of various bodily functions, decreased compensatory reactions and a general deconditioning (Fig. 1).

It will be in the regression-degeneration sense that "aging" will be used in this paper.

Life Span

All living organisms have a determinable life-span (1.1, 1.3). Man's average life-span is listed as 90 years (Table 1) but it appears to have been undergoing significant changes during his existence on planet Earth. According to the Bible's Old Testament (2, 3), Adam, the first man, lived 930 years and his immediate descendants lived similar life-spans, the longest being Methusela's 969 years (Table 2). Noah was 600 years at the time of the Deluge and he lived another 350 years afterwards. Interestingly, the life-spans of post-Deluge people shortened significantly. Abraham who lived circa 2100 BC attained only 175 years, Moses 120 years, and David and Solomon (circa 1000 BC) could not have lived more than 60 or 70 years for they both reigned as king for only 40 years each.

The pharaohs of Egypt (1.5) who lived at about this time (3,000 to 1,000 years B.C.) reigned for approximately the same number of years as David and Solomon (Table 3) and very apparently did not have the life span of their con-

Table 2. Biblical life spans

	Years				*Years*
Adam	–	930	Paleg	–	239
Seth	–	912	Reu	–	239
Enosh	–	905	Serug	–	230
Kenan	–	910	Nahor	–	148
Mahalalel	–	895	Abraham	–	175
Jared	–	962	Sarah	–	127
Enoch	–	365	Ishmael	–	137
Methusela	–	969	Isaac	–	180
Lamech	–	777	Jacob	–	147
Noah	–	950 (600 at time of Deluge)	Joseph	–	110
			Moses	–	120
Shem	–	600	Joshua	–	110
Arpachshad	–	438	David	–	? + 40 as king
Shelah	–	433	Solomon	–	? + 40 as king
Eber	–	464			

From: The New American Bible (Illustrated). Translated from the Original languages with Critical Use of All the Ancient Sources by Members of the Catholic Biblical Association of America, 1970.

Table 3.

Early Dynastic Period (c. 2686) – 414 years

1st Dynasty – kings
2nd Dynasty – 6 kings — Average reign = 34.5 yrs

Old Kingdom (c. 2686 – c. 2160) – 526 years

3rd Dynasty – 5 kings
4th Dynasty – 3 " — Average reign = 24 yrs.
5th Dynasty – 7 "
6th Dynasty – 4 "
(Pepi II, child king, reigned 94 years)

1st Intermediate Period (c. 2160 – c. 2040) = 120 years

7th Dynasty – ?
8th Dynasty – ?
9th Dynasty – ?
10th Dynasty – ?
11th Dynasty – 3 kings

Old Age or the "Elderly"

Victor Hugo (1802-85) was quoted as having said "forty is the old age of youth and fifty is the youth of old age." The U.S. Senate Special Committee on Aging (1985-86) has classified the elderly into four groups (6): the "near elderly" (55-64 years), the "young old" or "elderly" (65-74 years), the "old old" (75-84 years) and the "very old" (85 years and over). Chronologically, therefore, old age is defined to start in the 5th to the 6th decade of life with about a 10 year difference between what was considered old in Victor Hugo's time and what is old now (Table 4).

Table 4. The "Elderly"

*Old age of Youth	40 – 50	
Youth of Old Age	50 – 60	**
	55 – 64	Near Elderly
	65 – 74	Young Old or Elderly
	75 – 84	Old Old
	85 +	Very Old

*"Forty is the old age of youth, fifty is the youth of of old age" – Victor Hugo

**Aging America: Trends & Projections. Prepared by the U.S. Senate Special Committee on Aging 1985-86 ed., Wash. D.C.

Retirement at 65

Retirement from one's job at age 65 is said to have been started by Bismarck (Prince Otto-Leopold von Bismarck Schonhausen (1815-98). Actually it appears that he really picked this up from Krupp's Armaments that chose 65 because almost nobody reached that age and yet the illusion of retirement could still be given (7). Another version was that Bismarck asked for an age that will ensure that not too many will draw retirement benefits for too long. Roosevelt's Special Security then helped entrench it in 1930s (7).

Retirement is acceptance of aging with its decreased physical and mental capacity and increased disease propensity. It is the employers protection against age-induced loss of efficiency and debility. On the other hand, it is also an opportunity for the elderly to enjoy a well-earned rest and for the still-young to embark on other projects or even a new life. The increasing life-span of the U.S. population has caused the retirement age to be raised to 70 years with no age limit in many industrial and academic institutions. Except for our Justices, we still retire our people at 65.

The Aging Population

The improvements in medicine and public health including maternal and child care has been extending the life-span upwards and decreasing infant deaths and birth accidents. Hence, the average life expectancy has been rising together with the number of the "elderly" (Table 5). The Philippine population is still a young one with about 40% children 0-14 years and 10% in the 50 years-and-over bracket. These figures are expected to change. By 1992, the 0-14 bracket is predicted to decrease to 37.8% while the 50-and-over segment will increase to 11.2%. It will take the Philippines perhaps 3 or more generations of good health care and sanitation and population control before we will approach the present population mix of the developed countries of Europe and the U.S. where the population growth is zero or near zero, where children are seldom seen around and the nursing homes are full of the aged and the infirm. Now they worry that there are too many aged and too few children.

Table 5. Philippine vital statistics

Population	*54,668,332*	*57,356,042*	*64,258,611*
0 – 14 yrs.	40.3%	39.7%	37.8%
15 – 49	49.2	49.6	57.0
50 & over	10.5	10.7	11.2
Male	50.2	50.2	50.2
Female	49.8	49.8	49.8
Ave. Life Expectancy (yrs)	63.1	63.7	65.2
Crude Death Rate/000	7.9	7.6	7.0
Infant Mortality Rate per 000 Live Birth	56.59	54.07	47.74

DOH's Health Plan for People's Health 1987-1992.

Stages of Life

All living organisms go through 3 stages during their life-span: growth, reproductive and senescent. The relative durations of each stage varies (1.1). In the semelparous, reproduction takes place near the end of the life span. The salmon, for instance, from their spawning grounds in Canadian and Alaskan rivers that empty into the Pacific Ocean, swim out to sea and after spending almost their whole lifetime roaming the oceans of the world they return guided by their ins-

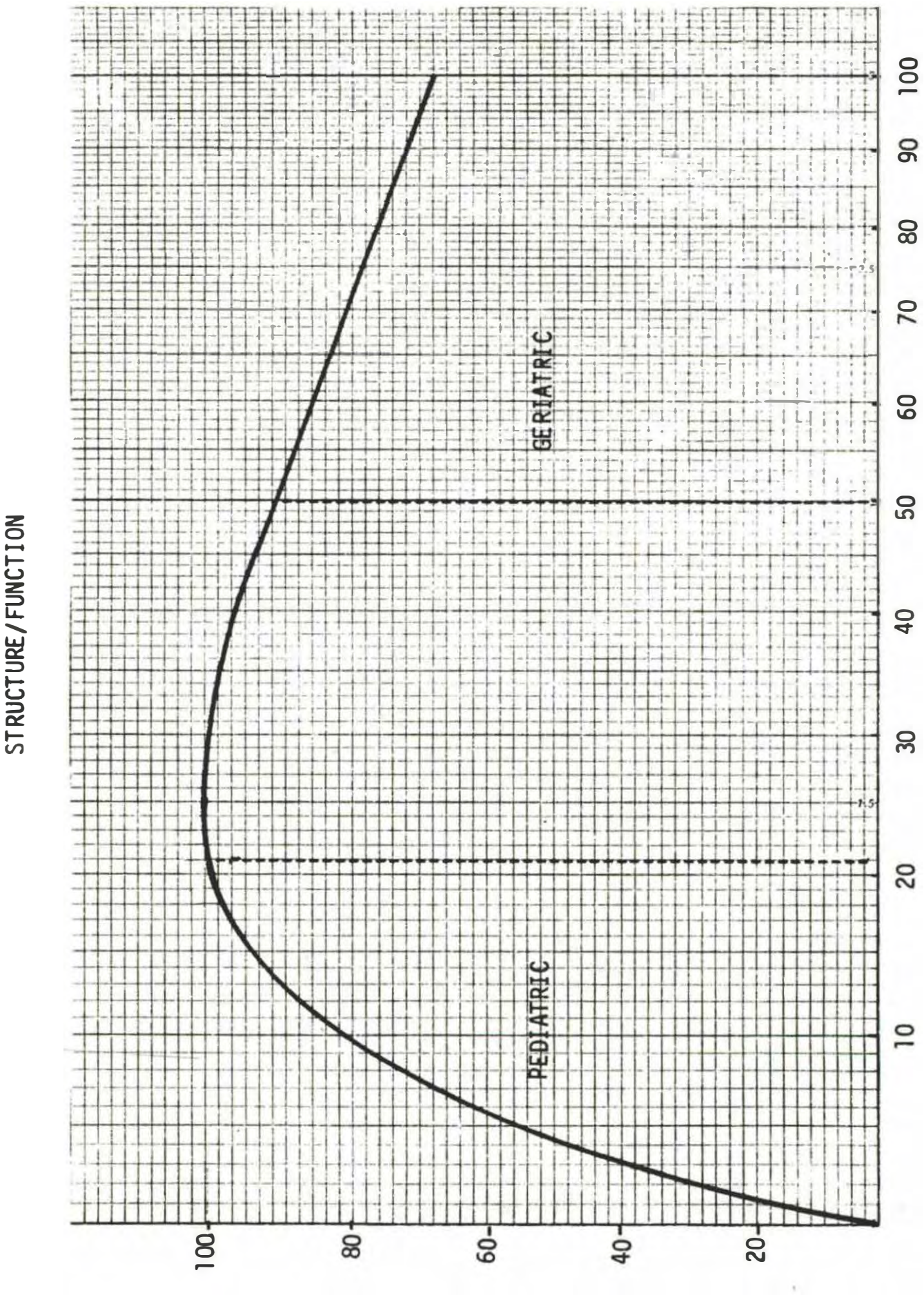

STRUCTURE/FUNCTION
100
80
60
40
20
GERIATRIC
PEDIATRIC
10
20
30
40
50
60
70
80
90
100
A G I N G (years)

Figure 1.

tincts, to the headwaters of their birth to deposit their eggs; after which they rapidly become senescent and quickly die. Man, on the other hand, is an iteroparous, and his reproductive period covers a major part of his total life-span. Senescence in the iteroparous is gradual in onset and progression, accompanied by a slow decline in reproductive performance, and accelerating with increasing age.

Aspects of Aging

Aging has been divided into: a) biological or physiological, b) psychological or behavioral and c) sociological or economic aspects. A 4th and the most commonly used as reference in the chronological aging which underlies the preceding three and, in the end, becomes the ultimate determinant if we believe that life-span on earth has been predetermined. The more poetic Greeks had their Fates: Clotho who spun the golden thread of life, Lachesis who measured it and Atropos who severed it.

All these facets of aging interact and influence each other in a positive or negative manner (Fig. 2). An optimistic outlook, for instance, can definitely benefit the sociological and physiological reactions of a person – just as mental depression can hasten physiological or biological decline. This is partly why there are the "young at 90," and the "old at 30," and those who "die of a broken heart." A sick patient has better chances of recovering when he has optimism. When he loses the will to live he starts to die.

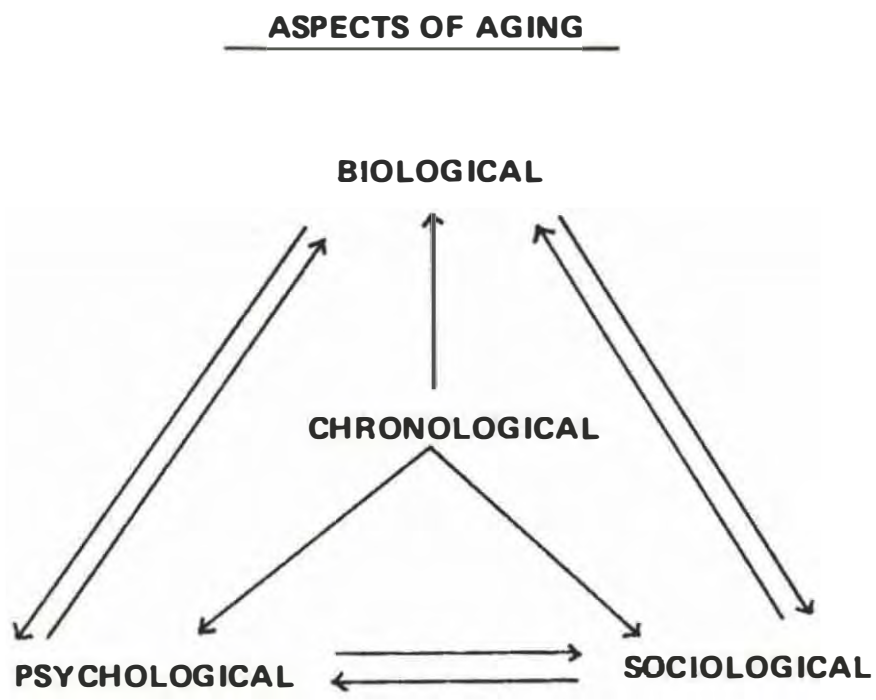


Figure 2.

Genes and Control of Growth and Development

All biological directions in living organisms are stored in the DNA and since all cells of an organism are the daughters, granddaughters and great granddaughters of a single fertilized ovum, they all contain the complete genetic material in their DNA. However, as cells differentiate and branch out towards more specialized cell types (e.g. neurones, muscle cells, white blood cells, connective tissue, etc.) and as they further mature into their specific target end-cell types (cortical pyramidal neurones, ventricular myocardial cells, T-killer lymphocytes, elastic or collagen fibers, etc.), they limit operation to selected genes. These genes are those that produce the characteristic proteins for the specific structures and functions of the cell at each stage of development. The amount of DNA information utilized by a fully mature cell is estimated to be only 0.4% of the total genetic information in the cell's DNA (8). The rest of the vast material in the DNA is repressed and may never be expressed for the life of the cell. Development of a cancerous state in a cell may derepress some genes and cause a cell to retrogress to a more primitive or immature state. Its specialized function is then lost but its rate of mitosis increased many many fold. In this state a cell line may survive in culture indefinitely without apparently being affected by aging, such as the HeLa cells which were obtained from the uterine cervical cancer of a patient named Helen Lane in 1952; these cells have been maintained in tissue culture up to the present as in their original state.

Normal cells, however, appear to be limited as to the number of divisions they can undergo. Hayflick's experiments (8) with fibroblast cells in tissue culture under carefully controlled conditions showed that human embryonic fibroblasts undergo a fixed 50 ± 10 population doublings within 7 to 9 months, at a doubling rate of about once per week, which slows down to 10 days as senescence develops. The cells finally fail to divide enough to reach confluence, show signs of degeneration, and die. The life-span of 50 doublings appears to be intrinsic to the embryonic fibroblast cells and they manifest this by a remarkable demonstration of "memory." For after interruption of cell division by freezing in liquid nitrogen for any length of time (in the case of one cell culture, 13 years) the cells when thawed out resumed their doubling to a lifetime total of 50 and no more. Fibroblasts obtained at autopsy from lungs of human adults 20 to 87 years, however, doubled only 14 to 29 times (8). Other cells, like those of the skin, liver, brain and smooth muscles have also been subjected to similar tissue culture studies by other workers and have been found to possess a similar limited capacity to divide. This is the genetic life span under experimental conditions. What it is in vivo, we do not know.

Tissue culture studies being essentially in vitro do not of course and cannot take into account all the in vivo factors, particularly bioamines and hormones, that may influence and delay the aging process. What these studies say is that there seems to be a built-in mechanism in every cell's DNA that counts the number of times it can divide and shuts off the whole machinery at the end of its pre-

determined critical limit. How far is men's present life-span from his genetic life span is the $64,000 question.

Some cell lines continue to divide for the duration of a man's life span; while others divide little if at all after reaching maturity (8, 9). Cells of the bone marrow, skin, connective tissues and the mucosal lining of the gut continue dividing and replacing the cells lost. Red blood cells, for instance, have a life span of 120 days and are replaced by new rbc from the bone marrow. Platelets live for only 10 days and are continuously replaced. Thus, the bone marrow is in a constant state of mitotic activity. Any depression of this activity leads to decreased number or count in the circulating blood: anemia, granulocytopenia, thrombocytopenia, agranulocytosis. This is not so with nerve cells, muscle cells, endocrine cells, and cells of the special senses. These cells stop dividing soon after birth, although they continue to grow in size up to maturity. The brain, cannot replace its neurones damaged by a stroke; nor can the heart replace its infarcted myocardium. Repair of these damaged areas is by scar tissue and the function lost may be compensated to greater or lesser degree only by hypertrophy of the remaining functional elements. And an eye lost is lost forever. A scarred cornea has to be replaced by a corneal transplantation. Malchus would have had to live the rest of his life without the ear Peter chopped off had Jesus not put it back.

It has been said that with the continuous division and replacement of cells, an individual is not the same individual he was a few years ago. This generalization appears to be untrue as far as cell identity is concerned – for the cells of the brain and nervous system, and those of the heart and endocrine glands are the self same ones that the individual had when he was born and the same ones that will age and die with him. From the molecular point of view, however, it has been argued that with the continuous replacement of the protein structures of the cell, it no longer is the same molecular identity. Perhaps so, but exception must have to be made for the cell's chromosomes and DNA strand and, more important, the genetic information and directions the DNA carries. Perhaps in the regulatory signals of the DNA, its operons, repressors, derepressors, etc. (Fig. 3) lie the secret of growth, aging and senescence.

Effects of Aging

The first evidences of aging are functional in nature, particularly those elicited under stress. They usually start slowly, imperceptibly about the age of 40, perhaps earlier in some, and are difficult to distinguish from the lows of normal function. The athlete tires a little more easily, performs less accurately and reacts more slowly a little more often than before. The executive has difficulty in reading the fine print and has to have reading glasses – and having acquired them he often forgets where he placed them. The audiophile complains that his fine HiFi stereo does not give out quite the same brilliance and presence as before. The males start complaining to their physicians about their sexual decline. The women, about half

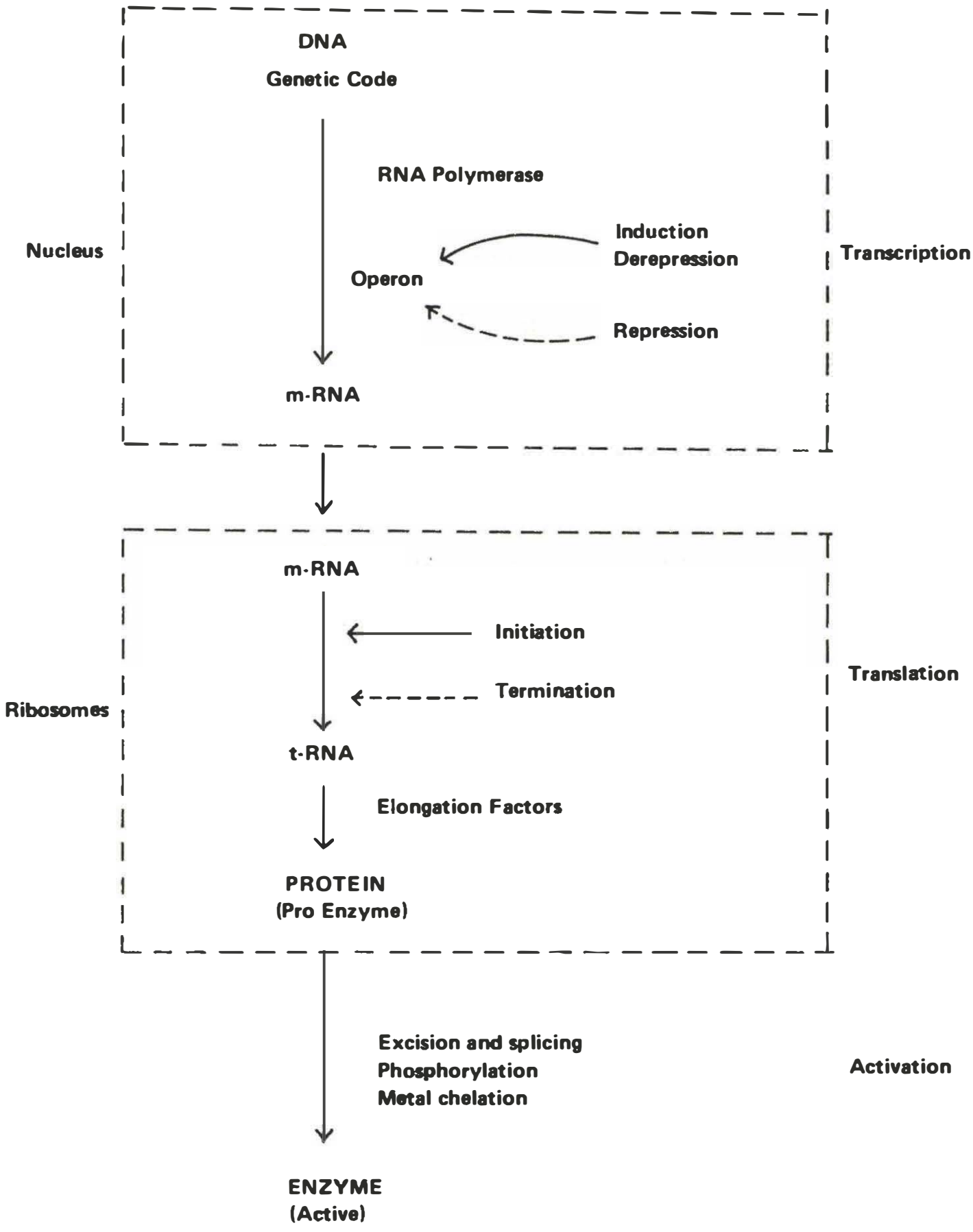

DNA
Genetic Code
RNA Polymerase
Nucleus
Induction
Derepression
Transcription
Operon
Repression
m-RNA
m-RNA
Initiation
Translation
Termination
Ribosomes
t-RNA
Elongation Factors
PROTEIN
(Pro Enzyme)
Excision and splicing
Phosphorylation
Metal chelation
Activation
ENZYME
(Active)

Figure 3.

of them, for their part, start to complain of hot flushes, increased nervousness or elevated blood pressure – signs of menopause.

Body Changes Found in Old Age

Table 6 (1.2, 9, 10, 11) summarizes the salient features of aging. Almost every organ and system of the body is involved in the process of degeneration. The degree of involvement, however, and the time they occur, differ from person to person. They may appear earlier in life, or later, or perhaps not at all. Most however do show the tell-tale signs of aging of skin and/or hair. A progressive increase in body fat with aging (12.2) (Fig. 4) has been reported by many but the data comes from developed countries. This finding is true also of the segments of our society whose caloric intake is well in excess of their physical activity – which happens when strenuous physical activities cease with the athletics of youth and the one exercise that easily is within every one's physical capacity is not done – that of pushing one's self from the table. Those who eat well-within their caloric requirements do not become obese – as many members of this venerable Academy can show as living proof.

But perhaps one of the most striking evidence that aging is really a retrogressive process is the gradual decrease in height of both sexes (Table 7) (12.1). In male whites this decrease starts about the age of 35 and in the females as early as 30. The obvious obesity of the population in this Table is seen in the slower fall in their weight. In time, the weight also follows as a result of decrease in muscle mass (13) from disuse atrophy and loss of bone mass (calcium, phosphates and protein matrix). Both changes are basically due to protein loss possibly due to alteration of enzyme activity. Decalcification and bone resorption begins around age 35 and results in thinning of the cortical layer of bone by 20% and 30%, respectively in men and women surviving to 90 years of age (14). This explains the predisposition of the hip bone to be fractured by minor accidental falls and of the vertebral bodies, the weight bearers of the body, to be compressed and fractured.

Effects on Collagen. Collagen is a structural protein that is the most abundant in the body, comprising 25 to 30% of total body protein. It is the principal component of tendons, ligaments, basement membrane and all connective tissues; it is also present in bone and cartilage, blood vessels, intervertebral disks and the cornea and lens of the eye (Table 8). Aging appears to alter the levels and activities of various enzymes (hydroxylases, glycosyl transferases, pro-collagen peptidases, lysyl oxidases) that act on collagen and thereby cause the polypeptide chains of collagen to become increasingly cross-linked, inflexible, and less soluble. Collagen being an extracellular protein, is not turned-over like other proteins and cannot be renewed; so that when it is cross-linked, the organ affected suffers degeneration of function and structure (9). In arteries, for instance, collagen change is one of the mechanisms involved in the atherosclerotic process. Presbyopia and cataract of the lens of the eye are directly linked to collagen degeneration. And weakening of the interver-

tebral disk and its nucleus pulposus explains why the aged spine becomes rigid and deformed. The same can be said of the synovial membrane of joints and development of arthritis in the aging person.

Table 6. Body changes and disease conditions found in old age

Organ/System	*Pathological/Biochemical changes*	*Function changes and symptoms*
GENERAL		
Growth	Decreased Wt and Ht from about age 40	
Fat	Increasing fat deposition (in heavy eaters)	Obesity, increased abdominal size
INTEGUMENTAL		
Skin	Decreased collagen and elastic fiber. Increased cross-linking of collagen (Types I,III) fibers. Decreased interstitial fluid	Wrinkling, thinning of skin
Hair	Hair follicle degeneration and atrophy	Graying, thinning, falling off, balding
BONES/JOINTS	Osteoporosis – loss of bone matrix and mineral components	Tendency to fractures
	Spondylosis	Back pains, kyphois
	Arthritis	Joint pains, deformity Difficulty in bending, squatting, standing up
SKELETA MUSCLE	Atrophy from disuse (decreased physical activity)	Decreased muscular strength Decreased lean body mass
NEURO-MOTOR SYSTEM	Decreased number of neurones Decreased number and sensitivity of receptors	Weakness, slow reaction time, tremors Decreased proprioception difficulty in balancing Decreased muscular control for fine movements
CARDIOVASCULAR SYSTEM		
Arteries	Atheroma formation; loss of elastin and collagen narrowing calcification thrombosis, occlusion	Reduced blood flow to organs supplied; ischemia, infarction of heart, brain, kidneys, extremities High blood pressure, esp. systol

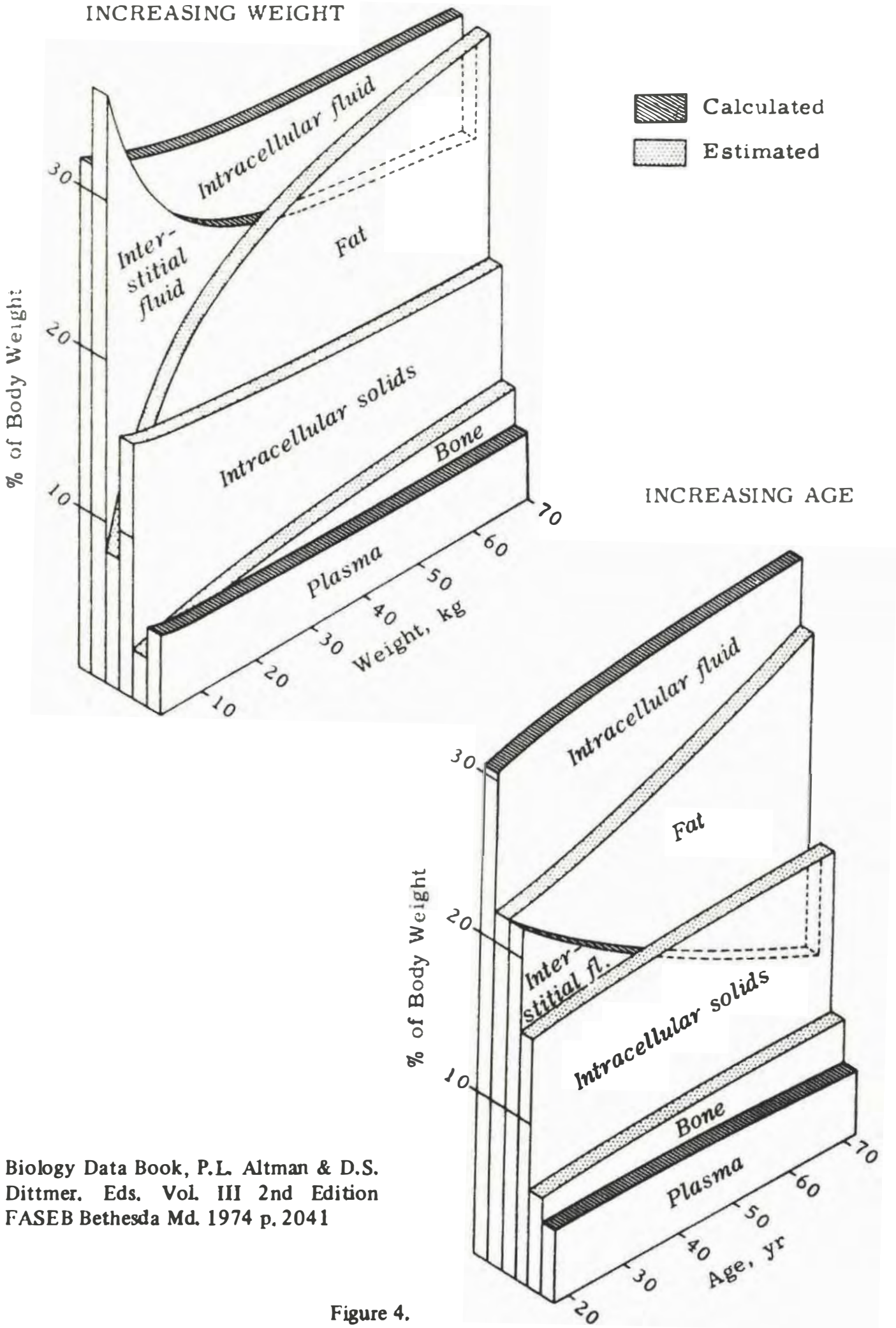
Heart	Myocardial ischemia, infarction	Angina pectoris
	Aortic and mitral valve thickening and calcification	Decreased stroke volume and cardiac output.
	Amyloid deposition	Arrhythmia, palpitations
	"Brown atrophy"	Weakness, shortness of breath congestive heart failure
Veins	Leg vein varicosities	Leg pain, edema
LUNGS/BRONCHI	Chronic bronchitis, bronchiectasis	Wheezing, dyspnea, cough
		Weakness
GUT	Decreased digestive enzymes	Appetite loss, indigestion
	Decreased bowel motility	Constipation
	Hemorrhoids	Anal pain, bleeding
LIVER	Decreased drug metabolizing enzymes	Increased drug toxicity
KIDNEYS	Decreased renal blood flow and glomerular filtration rate	Increased drug toxicity
PROSTATE	Benign prostatic hypertrophy	Urination problem
SPECIAL SENSES		
Eyes	Lens less elastic	Presbyopia
	Cataract	Blindness
Ears	Otosclerosis	Deafness, for high notes to total
	Vestibular hypersensitivity	Intolerance to tilting, tendency to faint
Olfactory Taste	Reduced number and sensitivity of receptors	Change in sense of smell and taste
ENDOCRINES	Cessation of ovarioan function; reduced estrogen secretion	Menopause; osteoporosis
	Decreased testosterone secretion	Decreased sexual potency
	Decreased insulin secretion	Late onset diabetes mellitus
	Decreased T_3 secretion	Overall decrease in metabolic activity
IMMUNOLOGIC SYSTEM	Thymus involution, Decreased Helper T-lymphocytes	Increased susceptibility to infections. Increased predisposition to cancer
	Decreased ability to distinguish "self" from "non-self"	Auto-immune diseases

BLOOD	Decreased erythropoiesis Increased total cholesterol and triglycerides Decreased fibrinolysis	Senile anemia Increased tendency to thrombosis
BRAIN	Decreased number of neurones Decreased number and sensitivity of receptors Cerebral ischemia and degenetion; stroke	Decreased reaction time Weakness Impaired memory Decreased learning solving ability Paralysis, paresis Parkinsonism Senile depression, psychosis Amyotropic lateral sclerosis Alzheimer's dementia

Table 7. Growth: height and weight by age

	Age	*WEIGHT*		*HEIGTH*	
		Male (kg)	*Female (kg)*	*Male (cm)*	*Female cm)*
U.S. (1960-62)	18-24	72.6	58.5	174.5	162.1
	25-34	77.6	61.7	175.5	161.8
	35-44	78.0	65.3	174.0	161.3
	45-54	78.0	66.7	173.2	159.8
	55-64	75.3	68.9	171.2	158.5
	65-74	72.6	66.2	169.9	156.2
	75-79	68.0	62.6	167.4	155.2
Caucasian	20-24	71.7	56.7	174.5	162.6
	25-29	73.9	57.6	174.5	162.8
	30-34	74.8	59.0	174.0	161.5
	35-39	75.3	61.7	173.7	161.0
	40-49	75.8	64.4	172.7	160.5
	50-59	74.8	67.1	170.9	159.5
	60-69	73.5	66.2	169.7	158.0
	70-79	71.2	65.3	168.9	157.0
	80-89	68.5		167.9	

From: PL Altam & DS Dittmer Eds. Fed. Am. Soc. Exptal Biol. 1972 Vol. 1 p. 201



Biology Data Book, P.L. Altman & D.S. Dittmer. Eds. Vol. III 2nd Edition FASEB Bethesda Md. 1974 p. 2041

Figure 4.

Table 8.

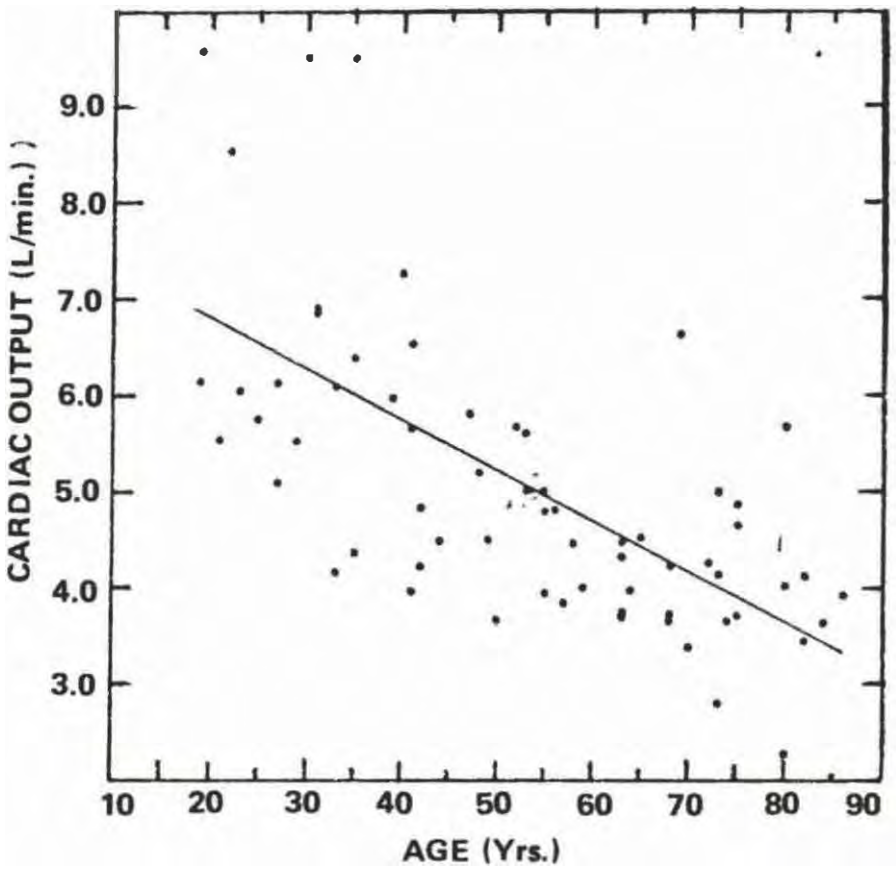
Collagen type	*Chain structure*	*Distribution*
I	$[\alpha 1(I)]_2 \alpha_2$	Bone, tendon, skin, connective tissue, intervertebral disk, blood vessels
II	$[\alpha 1(II)]_3$	Hyaline cartilage, eye lens, cornea, nucleus pulposus of the intervertebral disk
III	$[\alpha 1(III)]_3$	Skin, blood vessels, smooth muscle, synovial membrane of joints
IV	$[\alpha 1(IV)]$	Basement membrane

Modified from: MS Kanungo: Biochemistry of Aging. Acad. Press 1980 p. 137

Effects on the Cardiovascular System: The principal effects of aging are probably exerted mostly on the arteries, while the effects on the heart are secondary in nature. Microscopy may indeed show increase in collagen and elastic fibers in the old heart, and atrophy or hypertrophy of myocardial cells in different areas (11); but although these could be part of a senile cardiomyopathic process, the more probable is that they are due to the coronary sclerosis that invariably is present in these old hearts. The aphorism that "one is as old as one's arteries" still stands. Arteries carry life's sustenance to every organ in the body and it is inevitable that any interference with this conduit will cause damage and dysfunction of that organ.

The aging of the cardiovascular system starts very insiduously as early as the prime of life. Brandfonbrener *et al.*, (15) report a steady decline in the basal cardiac output of 67 males without cardiovascular disease starting about the age of 30, with the regression line of the cardiac output decreasing by 1.0% per year of age (Fig. 5). The regression line of the cardiac index (L/min/m body surface) decreases 0.79% per year of age. The arterial pressure, on the other hand, shows a rather steep increase of both average systolic and average diastolic pressures from infancy till age 20-24; whereupon, while the average systolic BP continues to increase more slowly till age 70-74 to hypertensive levels, the average diastolic BP curve remains fairly flat and normal at around 80 mm Hg (Table 9 and Fig. 6). The result is a systolic type of hypertension characteristic of the elderly and attributed to increasing rigidity of the large arteries of the body as a result of atherosclerosis. This is the simple picture when average systolic and diastolic pressures are examined. But when the upper ranges of BP readings per age group are studied (Table 9) it is evident that, considering the recently established BP standards of 135/85 as the

upper limit of normal and 140/90 as the lower limit of hypertension, the subjects in the studies of 1940s-50s cited in Table 9 and Fig. 6 unfortunately include systolic and diastolic hypertensives both male and female even from the age of 20-24 years. Does this vitiate the studies? The problem is a little like the chicken and the egg dilemma. Should subjects showing up readings of 140/90 or higher be excluded from the survey because they have hypertensive disease and will confuse the effects of aging? or should they be included for the reason that hypertension is a part of aging? Are hypertension and atherosclerosis a part of aging? The question is still moot.



The relationship between cardiac output and age in 67 males without circulatory disorder and during "basal" state. The line indicates the simple linear regression for the data. (From Brandfonbrener, M., Landowne, M., and Shock, N.W.: Changes in cardiac output with age, Circulation 12:557, 1955).

Figure 5.

Atherosclerosis causes hardening, narrowing and blocking of arteries resulting in myocardial infarction, stroke and death. These diseases are most often found in old age and thus have been considered as almost intrinsic to the aging process. Since the 1950s, however, concerted efforts of the world's scientists focused on this problem as it was reaching epidemic proportions. The strong predisposing causative roles of saturated fats, cholesterol and blood lipids, lack of exercise, smoking, hypertension, diabetes, etc. (Table 10) were one by one established. In the U.S. more than

Table 9. Arterial blood pressure

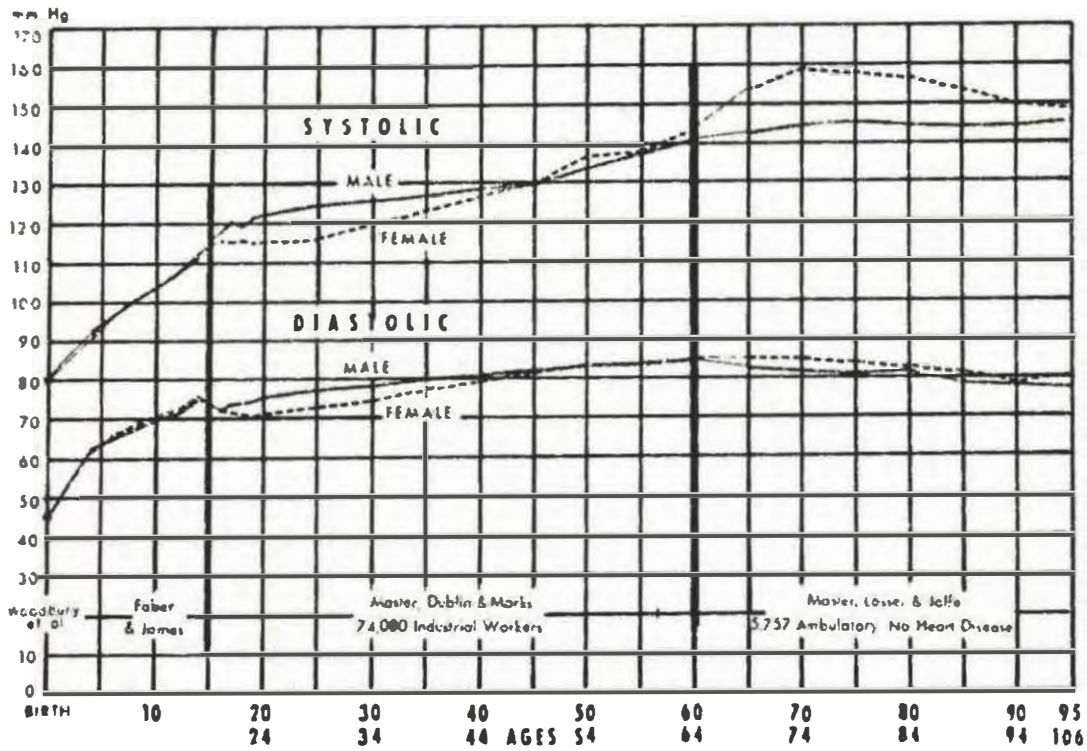
	Male		*Female*	
Age	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*
20-24	123 (96-150)	76 (57- 96)	116 (93-139)	72 (53- 91)
25-29	125 (100-150)	78 (60- 95)	117 (94-139)	74 (56- 92)
30-34	126 (99-153)	79 (60- 98)	120 (92-147)	75 (54- 96)
35-39	127 (99-155)	80 (60-101)	124 (97-151)	78 (58- 98)
40-44	129 (100-159)	81 (63-100)	127 (94-161)	80 (59-100)
45-49	130 (97-163)	82 (51-103)	131 (92-169)	82 (59-104)
50-54	135 (97-172)	83 (61-106)	137 (96-179)	84 (59-108)
55-59	138 (101-175)	84 (62-106)	139 (97-180)	84 (61-106)
60-64	142 (100-183)	85 (60-109)	144 (100-188)	85 (60-110)
65-69	143 (92-194)	83 (64-102)	154 (97-211)	85 (58-112)
70-74	145 (93-197)	82 (52-112)	159 (108-210)	85 (55-115)
75-79	146 (104-188)	81 (56-106)	158 (106-210)	84 (58-110)
80-84	145 (95-195)	82 (63-101)	157 (102-212)	83 (57-109)
85-89	145 (98-192)	79 (50-108)	154 (99-209)	82 (48-116)
90-94	145 (99-191)	78 (54-102)	150 (104-196)	79 (55-103)

Ref.: AM Master, HA Lindsay, WS Hartroft (in Biology Data Book 2nd ED 1974 Vol. III p. 1714)

Table 10. Atherosclerosis: predisposing factors

1. Time and Aging – "wear and tear"
2. Genetic (hereditary)
3. Lack of exercise – sedentary
4. High caloric, high fat diet
5. High serum total cholesterol and LDL, low HDL
6. Hypertension
7. Diabetes
8. Smoking
9. Psychic, emotional stresses, Type A personality

half (51.4%) of all deaths in the 1950s were due to heart disease, principally arteriosclerotic-coronary (slide). Now, as a result of the drastic changes in the national diet (from about 3,300 daily calories with 40-45% animal fats to a much leaner diet) and the promotion of exercise, as jogging and walking (16), and the serious campaign against smoking (17), the cardiovascular mortality rate has come down to only 30% of total deaths and the average life-span has been increased to 74.5 years. Much still remains to be done but the important lessons to be derived is the differentiation possible between the aging itself and those diseases found in aging whose control can enable us to modify the aging process.



Mean blood pressure levels in apparently healthy people from birth to old age. (From Master, A.M., and Lasser, R.P.: Blood pressure elevation in the elderly. *In:* Hypertension: Recent Advances, Brest, A. N., and Moyer, J. H., editors. Philadelphia, 1961, Lea & Febiger, pp. 24-34.)

Figure 6.

Unfortunately, the process of atherosclerosis (Fig. 7) is much more complicated than just lipid deposition as proposed in the Insudation Theory of Rudolf Virchow and supported by the cholesterol-feeding studies in rabbits of N. N. Anitschkow. Firstly, even without formation of an atherosclerotic plaque, there is a wear-and-tear type of degeneration of the arterial wall seen with aging. This consists of (Fig. 8): a gradual thickening of the intima, a thinning of the muscular layer, disruption of the internal elastic membrane, increase in fibrous and collagen fiber deposition and an overall hyaline degeneration of structures.

In 1976, Benditt (18) found that even preceding any sign of lipid deposition, special smooth-muscle-like cells from the muscular layer migrate to the intima and initiate the plaque formation (Monoclonal Migration Theory). What induces those cells to migrate is not known but one plausible explanation is that endothelial injury may attract platelets to adhere and aggregate and to release, among other known substance, a migration or growth factor. The deposition of cholesterol and other lipids in the plaque appears to be in a later development. The lipids in lipoprotein form enter the wall of blood vessels from the blood stream and are deposited in the intima if they can not pass out thru the lymphatic channels of the vasavasorum (19). The formation of the plaque at this stage is complicated by stimulation of the clotting process – formation of layers of fibrin clots or thrombus over the plaque, together with calcification of the plaque, which further narrows and finally occludes the artery, choking off the circulation to the heart, brain,

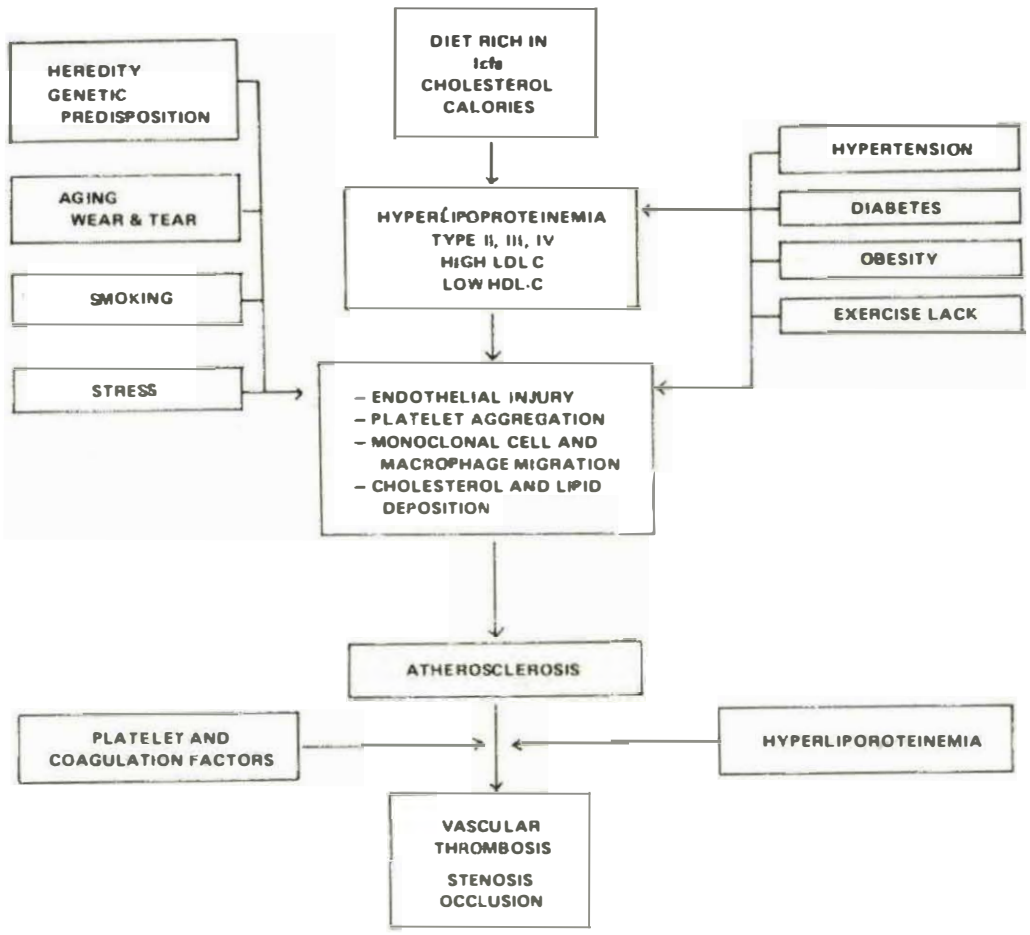


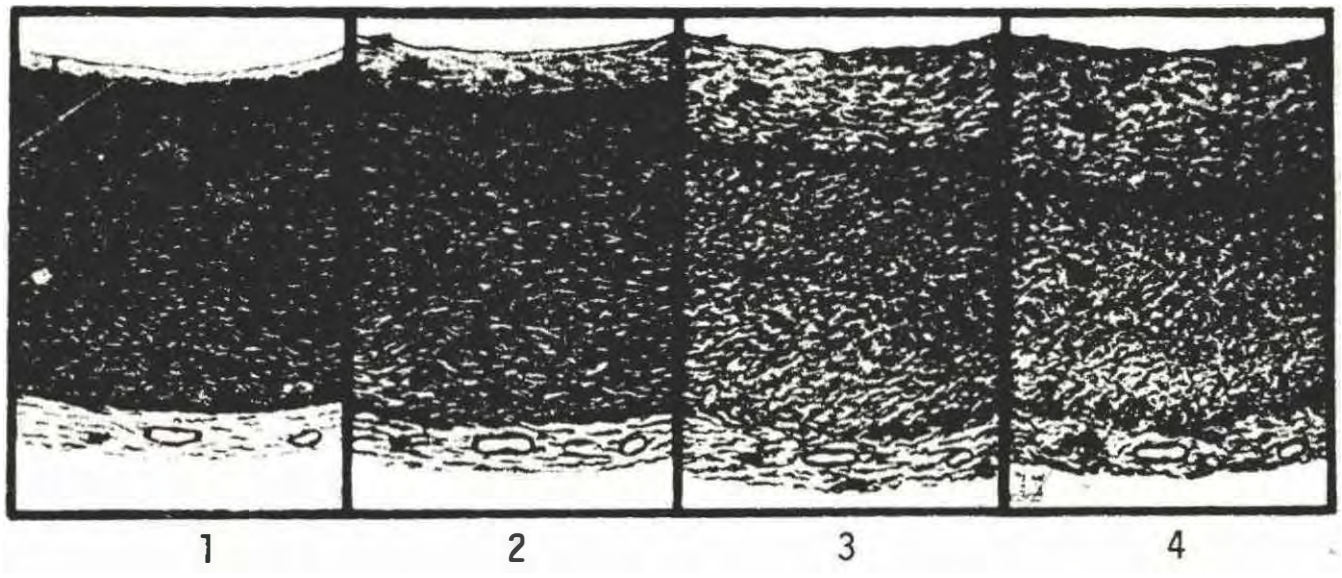
Figure 7.

kidneys or leg (Fig. 7). This last process, the clotting, also appears to be controllable to some extent now with antiplatelet aggregation agents, such as aspirin. Hence, the only process still beyond our control in what we know about atherosclerosis is the initiation of the plaque by these migrating monoclonal cells and the understanding of how the genes do it – why some persons develop atherosclerosis very early in life and some do not and are able therefore to break the age barrier.

Effects on the Communications System

On the Adrenergic System: The adrenergic system is the "fight or flight" division of the autonomic nervous system. Together with the adrenaline it causes to be released from the adrenal medulla, it prepares the body for action. Thus it makes the heart beat stronger and faster, the bronchi to dilate, the blood vessels to constrict, the blood pressure and the blood glucose to rise. Aging depresses the adrenergic control over these various organ systems (20-25). The heart rate at rest becomes slower and the ability of the heart rate to increase in response to exogenous adrenaline or isoproterenol is reduced. So also is the ability of the blood pressure to respond to baroreceptor reflexes, resulting in the well-known tendency of old persons to orthosthatic hypotension. The effects of aging on the heart and its nerves have been demonstrated in rats by electron micrography (Table 11). The older the rat is (and rats are old at 12 months and ancient at 24 months) the more degenerative findings are seen involving not only the structures of the myo-

Degenerative changes due to aging: Four states in the aging process of the aorta



1. Adolescent (thirteen to nineteen years of age). The intima A and subintima B are relatively fine and thin. The internal elastic lamina C is fine in texture. The medica D consists of good fleshy muscle. The adventitia E is loose and delicate in texture.
2. Young adult (twenty to thrity-nine years of age). The subintima has increase in size and become denser. The internal elastic lamina has become thicker. The media shows evidence that fibrous connective tissue has supplanted some of the smooth-muscle fibers, and there is progressive disorganization of elastic tissue. The adventitia is denser.
3. Older adult (forty to fifty-nine years of age). The subintima is the seat of diffuse and focal deposition and general fibrous thickening. The internal elastic lamina has split. In the media, the disorganization of elastic tissue has become more marked. A great deal of muscle tissue has been replaced by connective tissue and, on gross examination, seems to have lost much of its color. The adventitia has become cloudy, thick and tendinous.
4. Senile (sixty to eighty years of age). In senescence, the submintima is very thick and fibrous and now has a glassy opacity due to hyalinization. The internal elastic lamina has become frayed and fragmented, with tag ends in the adjacent media. The media has had most of its muscle fibers replaced by connective tissue and has the appearance of gristle. The adventitia is very coarse and tendinous.

From: Physician's Bulletin 23: 1:9 (Eli Lilly & Co.)

Figure 8.

Table 11. Electron micrographs of atria of fischer 344 rats

	3 months old	*12 months old*	*24 months old*
Cell membrane	Intact	Discontinuous in nerve & muscle	Lack of cell boundary definition
Sarcoplasmic Reticulum	Intact		Swollen
Mitochondria	Intact	Disrupted cristae	Empty
Myocardium	Intact		Degeneration
Axoplasms	Clear	Dark inclusions – cellular debris	
Noradrenergic Terminal	Dark Vesicle		Some still contain many & clearly identifiable NE vesicles. Many showed extensive vacuolization, advanced type lamellar degeneration.
Interstitium	Fibrous material		Collagen – packed

cardial fibers, but also the adrenergic nerves; the latter shows extensive vacuolization and lamellar degeneration (21). The decrease in adrenergic activity during aging may be explained by changes involving practically the whole of the system from the brain to the periphery (see Figs. 9 and 10). In the brain, there is loss of Alpha and Beta receptors from different centers as well as dopaminergic receptors from the corpus striatum; the loss is attributed to impaired synthesis (24, 25). Degeneration of peripheral adrenergic nerves has been reported (21). There is diminished norepinephrine content of the heart and various organs and impaired NE synthesis in the adrenergic neurone endings (22). These can best be explained by lack or decreased enzymatic activity of the hydroxylases or decarboxylases that convert tyrosine to DOPA, dopamine and NE. There is no change seen in NE release mechanisms and there is no decrease in the number of Beta receptors in the heart nor of alpha 2 receptors in the arterioles. But the responsiveness of these receptors to their agonist, NE, is decreased. Adenyl cyclase activity is also decreased. The explanation appears to lie in a change in interaction between the Beta receptors and the guanine nucleotid regulatory protein (Fig. 10), causing an impaired ability to form a high affinity state necessary for adenyl cyclase activation (22, 23). Furthermore, and contributing to loss of adrenergic control by aging is a decreased translocation in the membrane-bound phosphokinase (23). Basically, therefore, a change in the protein configuration of these structures must be occurring in aging.

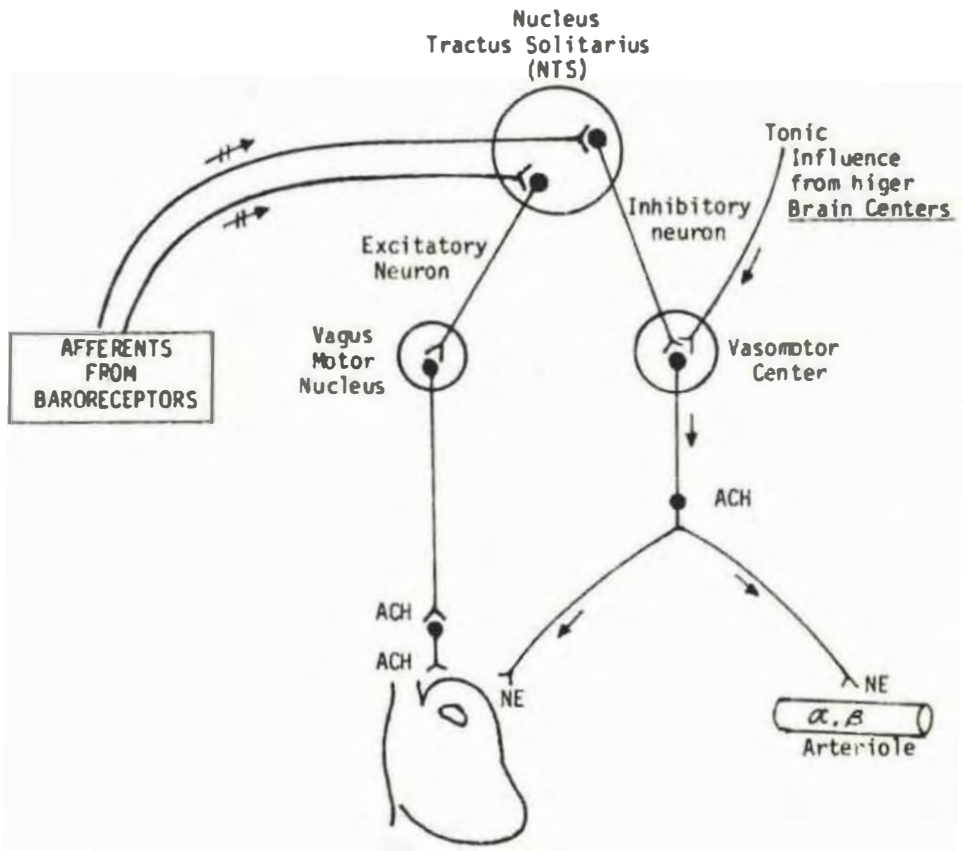


Figure 9.

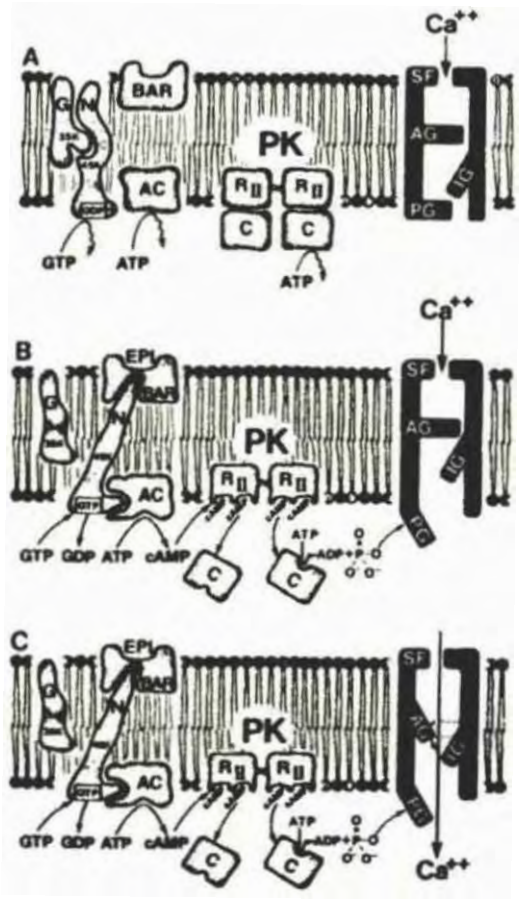


Figure 10.

On the Endocrines. A sharp fall in estrogen secretion occurs with menopause in females; in males the fall in androgens is gradual, extending well into old age (Table 12). These are the most important changes seen in the endocrines in aging (9). Being anabolic, the loss of sex hormones contribute significantly to the osteoporosis and loss of lean muscle mass that accelerates after age 40. Of lesser significance are the decreases in parathormone leading to calcium loss, of triodothyronine (T3) leading to a general metabolic decline, and alteration in insulin activity or secretion leading to decreased sugar tolerance.

Table 12. Changes in hormones blood levels in old age (human)

Testosterone	↓
Estrogen	↓
Al dosterone	↓
Glucocorticoids	↔
Growth Hormone	↔
Gonado tropin	↑
TSH	↔
Parathormone	↓
Insulin	↔
Glucagon	↔
T_4	↔
T_3	↓

On the Humoral System of the Body. The magnitude and scope of the body's system for intercommunication and control is still being unravelled. It is not only inter-organ and inter-tissue, as with the well-studied endocrine-hormones and secretogogues; it is even and inter- and intra-cellular. It utilizes its own neurotransmitters and chemical messengers which vary from the simple cAMP and cGMP to highly complicated peptides and proteins. It includes the blood clotting factors, chemotactic factors, prostaglandins, leukotrienes, kinins, renin-angiotensin-aldosterone, lymphokines, ANH (Atrial Natriuretic Factor), TNF (Tumor Necrosis Factor), MAF Macrophage Activating Factor) TIMP (Tissue Inhibitor or Metalloproteinases), and hosts of other active substances not to mention the antibodies for every specific antigen. These substances are produced by different cells and tissues, usually in situ where they are needed. The endothelium, that single layer of flat cells lining the intima of blood vessels which can barely be seen by the light microscope is not just a mechanical lining, but is now known to perform multiple functions of resisting or promoting thrombosis, vascular repair and active protection; in the process it manufactures and secretes at least 9 different substances such as proteoglycans, thrombomodulin, Protein C, prostacyclin, endothelial growth factor, Factor S.

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The effects of aging on this big family of hormones and humoral agents is not fully understood but will surely be elucidated as they are better understood: e.g. the role of the platelet factors, particularly that which has to do with atherosclerotic plaque formation; the role of the lymphokines, such as the interleukins 1 and 2 which may play a role in resistance to infection and cancer; the leukotrienes and asthma, chronic bronchitis and pulmonary aging.

Effects on Enzymes

Enzymes are the catalysts that make the whole body machinery function. They are synthesized by every cell, and apparently as needed or called for. Lactase is needed for the lactose of milk; and tends to disappear in non-drinkers of milk, hence their diarrhea with milk. The lever is the organ that detoxifies and metabolizes many substances including drugs. The production by the liver of drug metabolizing enzymes (DME) may be induced or inhibited by specific drugs resulting in faster or slower metabolism of those drugs that need the enzyme. Table 13 compares the biologic half-lives (T 1/2) and clearance rates of representative drugs in young and old persons (27). All drugs in the list are metabolized more slowly by the elderly and may therefore cause toxicity which explains the well known observation that old persons are more susceptible to drugs and should be given smaller doses. The reason that oral propranolol does not differ in its T 1/2 in the young and the old is because it is metabolized so very fast that barely 10% of the ingested dose can survive this first pass to reach the systemic circulation. Old age therefore can be seen to cause significant decrease in the liver's DMEs such as the oxidases, decarboxylases, deaminases, etc. The enzymes of the aorta, brain, and striated (skeletal) muscles also show some decreases on aging but the studies are still insufficient Table (14). Oxido-reductases of the aorta are definitely reduced as shown by 9 out of 10 reported studies. Hydrolases and lyases appear not to be decreased by aging (9).

Effects on the Brain

The early manifestations of aging on the brain, namely difficulties with memory and learning of new things, have been mentioned and listed (Table 6). Also already mentioned are the effects of disturbed circulatory flow leading to cerebral ischemia and strokes (cerebral thrombosis, embolism and hemorrhage). Degeneration of various parts of the brain may be explained by localized circulatory disturbances such as degeneration of the basal ganglia leading to Parkinsonism. Studies of the cerebral blood flow by Doppler Ultrasonic Technique has shown a discontinuous pattern in the elderly suggestive of increased cerebral vascular resistance (28). These are all effects of aging on the brain, part of senility. Senile, however, is a word that more specifically refers to, as Hayakawa puts it,

Table 13. Age-related pharmacokinetic data

	Age (yrs)	*T 1/2 (hrs)*	*% Change*	*Clearance Rate ml/min/kg*	*% Change*
ANTIBIOTICS					
Penicillin G (i.v.)	25	0.55			
	77	1.0	+82		
Procaine Penicillin G	25	10			
(i.m.)	77	18	+80		
Tetracycline	25	3.5			
	75	4.5	+29		
Dihydrostreptomycin	27	5.2			
	75	8.4	+62		
Amoxycillin	Young	1-1.5			
	89	2.67	+116		
Cefazolin (i.v.)	24-33	1.57			
	70-88	3.15	+101		
TRANQUILIZERS					
Diazepam	30	32			
	65	70			+118
Phenobarbital	20-40	71			
	70	107			+51
CARDIAC DRUGS					
Propranolol (oral)	29	3.58			
	80	3.61	0		
Propranolol (i.v.)	29	2.53		13.2	
	80	4.23	+67	7.8	−69
Metoprolol	23	3.5			
	67	5.0	+43		
Digoxin	27	51		1.11	
	72	73	+43	0.88	−26
	34-61	36.8		1.7	
	72-91	69.6	+89	0.8	−113
Quinidine	23-34	7.25		4.04	
	60-69	9.7	+34	2.64	−53
Lidocaine	24	1.34		7.6	
	65	2.33	+74	8.1	+7=0
ANALGESICS					
Morphine (i.v.)	26-32	2.9		14.7	
	61-80	4.5	+55	12.4	−19
Aspirin	21	2.38			
	77	3.71	+56		
Indomethacin	20-50	1.53			
	71-83	1.73	+13		

Paracetamol	24	1.82	
	81	3.03	+66
Phenylbutazone	26	81	
	78	105	+30

Ref.: DP Richey: Pharmacokinetics & Drug Disposition in Handbook on Pharmacology of Aging by PB Goldberg & J. Roberts p. 7, CRC Press 1983

the enfeebling effects of age on the mind; the second childhood (28). There is not only a serious loss of memory but also of cognition and reasoning. It may be accompanied by depression, psychosis, or dementia. However, ordinary senile psychosis which appears after age 65 years must be differentiated from Alzheimer's dementia which is familial and may start even as early as age 40. The neuropathological findings are similar but those of Alzheimer's Diseases are more severe and more extensive (30). In Alzheimer's the primary cellular degeneration consists of neurofibrillatory tangles, granulovacuolar changes, senile plaques between cells composed of enlarged nerve fibers and synaptic endings with degenerated mitochondria and with an amyloid core (31). The regional cerebral blood flow and metabolic rate of glucose as measured by Positron Emission Tomography (PET) are reduced throughout the brain in relation to the severity of the dementia and neuropsychometric deficits (32). The neurotransmitters in the brain are markedly reduced, starting with acetylcholine of the hippocampus, later followed by the monoaminergic, GABA-ergic and peptidergic systems (30). Unfortunately, simple replacement of the acetylcholine by choline containing compounds like lecithin is of no therapeutic value in preventing or delaying the progress of the disease. The enzyme choline acetyl transferase that synthesizes the acetycholine is somehow not produced in adequate amounts. Alzheimer's Disease is familial and recently (Newsweek 3/2/87) reported that a genetic marker for Alzheimer's has been located in chromosome 21 and that a gene also located in chromosome 21 has been identified as directing the manufacture of the amyloid protein deposited in Alzheimer brain plaques.

Lipofuscin in Aging

Lipofuscin is a pigment found deposited in the cytoplasm of aging hearts (11) and in neurones (33). The dark brown type is seen in the substantia nigra of the brain by age 3 years and does not increase by age. The light yellow type is chemically related to lipids, first detected in the cells of Clarke column in the brain by age 20 years and increases linearly with chronologic age. Lipofuscin appears to be nothing more than a waste product of mitochondrial degeneration and its removal by phagocytes can be enhanced by antioxidants and pigment-mobilizing drugs like meclofenoxate (33).

Genes, Enzymes and Proteins

It is evident that the aging process exerts its effects primarily on the proteins and peptides of the body and most importantly the enzymes. Almost nothing in the body can function, be synthesized or metabolized, without the intervention of one or several enzymes. Hormones depend on enzymes for their synthesis. The thyroid hormones T3 and T4, and the medullary adrenal hormones, epinephrine and norepinephrine, are synthesized from tyrosine by enzymes. The adrenal corticosteroids and the sex hormones are synthesized from cholesterol by enzymes, while cholesterol itself is built up from acetate by enzymes. Energy cannot be stored in ATP without enzymatic help, and ATP releases its tremendous store of energy only by enzymatic action. There are enzymes that bond or break up, enzymes that add or subtract, that transfer or transform, that regulate transport or act as receptors. In short, there are enzymes for every imaginable chemical and physiological process. Even the genes in the double-stranded DNA cannot be expressed without an RNA polymerase enzyme that separates the strands and transcribes the message into the messenger RNA. The mRNA then migrates to the ribosomes for translation of its base sequence according to the genetic code to determine the amino acid sequence of the protein. When the genes, through wear and tear, or the destructive effects of ultraviolet rays, free radicals, toxic materials or oxygen lack become damaged, again there are enzymes to repair and restore the DNA's integrity (34,35). There is an enzyme to reverse thymine dimerization photochemically; enzymes that incise the DNA strand and excise the damaged segment (specific endonocleases); enzymes that synthesize a new complementary strand (35) and insert it into the deleted region (DNA polymerases): and an enzyme that seals the DNA incisions (ligase). Because of such repair maintenance, bacterial genes can be duplicated as many as 100 million times before there will be a 50% chance that even one gene will be altered (34). The DNA polymerase has a special repair activity – that of a 3' – 5' proof-reading exonuclease activity which enables it to backtrack and edit or proofread any incorrect base-pair that may have been inserted and remove it. The average error frequency for base-pair substitution has been estimated to be in the order of 10^{-8} to 10^{-10} errors per base pair replicated in T4 bacteriophage and *E. coli*, respectively (37).

What are enzymes? Enzymes are proteins or polypeptides and, like all amino acid-composed substances, the information for their synthesis resides in the genes of the DNA. One enzyme may have its messages encoded in one or several genes that may not even be adjacent to each other.

Since the DNA cannot be transcribed without enzymes and enzymes are dependent on DNA for their synthesis, a chicken-and-egg question may be posed at this point: which came first – the DNA or enzymes?

The whole of the DNA of a person, as discussed before, is present in every cell of every organ of that person. Every cell's DNA contains all the information for the manufacture of every protein and peptide needed in that person's whole

life. Furthermore, the DNA is extravagantly redundant. Its genetic material is repeated, some as many as a million times (36). These repeated segments (which are identical or near copies of the gene) appear to be scattered throughout the DNA and could be transcribed into mRNA. As mentioned before, however, only about 0.4% of a cell's DNA may expressed or operant; the rest is unexpressed or suppressed; and that which is operant is not continuously expressed but is switched on and off depending on need. Hence, the control mechanisms of the DNA play a most important and as yet poorly understood role. What dictates the level of each enzyme in the cell and how are the constantly changing needs signaled "upstairs"? With the more than 2,000 enzymes in the human system, how does each signal its lack or excess? The post-translational controls, such as the phosphorylase reaction to activate a pro-enzyme to active form is most helpful in enabling the stocking up of raw material pro enzymes near where they will be needed. But what about the phosphorylase supply – since the half lives of enzymes is short? There is much still that is not known. Could the effect of aging be on the control or regulatory mechanisms? Unfortunately, while very much is now known about the DNA's "hardware" very little is known about its "software" – i.e. the programs that run it. Localizing the site of the aging program on the DNA regulatory mechanism is an attractive and logical hypothesis.

Table 14. Enzyme changes on aging (human)

Enzymes	*Organ*	*No. of studies showing*		
		Dec	*No change*	*Inc.*
Oxido reductases	Aorta	9	1	
Transferases	Aorta	1	1	1
	Brain	–	1	–
	Striated muscle	1	–	–
Hydrolases	Aorta	2	–	4
	Brain	–	1	1
Lyases	Aorta	1	2	2
	Skeletal muscle	1	–	–
Ligases	Aorta	1	–	–

Modified from M.S, Kanungo, Biochemistry of Aging, 1980

There are two principal effects of aging on proteins (a) decreased synthesis, whereby muscle and bone mass is lost and adrenergic receptors are decreased; and (b) structural alteration, leading to such changes as increased collagen cross-linking and alterations of enzyme activity. Enzyme lose their potency resulting in diminished biochemical reactions and metabolic processes, consequently, decreased physiologic functions (Table 6). Other proteins such as receptors are similarly

altered rendering them insensitive i.e. incapable of reacting with or accepting their agonists. Such alterations occur when critical changes in the tertiary conformations of the protein occur. The tertiary structure of a protein is that which is most thermodynamically stable for the primary structure and interactions of its side chains. Under proper conditions, proteins have been shown to spontaneously assume their tertiary foldings, which structure is stabilized by formation of disulfide bridges. Reduction of the disulfide bridges in a protein denaturates the protein and results in its losing both its native conformation as well as its biological activity (38). Many enzymes are composed of two or more subunits and take on a quarternary structure with a specific binding site for its substrate. Alteration in this quartenary structure will change the affinity of the binding site for substrate.

These alterations in proteins, enzymes and receptors with aging were at first attributed to errors in DNA transcripton or RNA translation (Orgel's Error Theory of Aging). More recent studies (on unaltered and altered enolase) have shown that alteration in enzyme activity cannot be due to errors in translation. Furthermore, cell-free studies indicate that the fidelity of translation does not decline with age (39). The alteration of enzyme activity in aging is probably a post translational event and may be the result of a subtle denaturation from what Rothstein calls an increased "dwell-time" of proteins in an aged cell that has a diminished protein turn-over (40).

Promotion of Health and Longevity

The present life span of human beings is markedly disease-limited, – limited particularly by infections, malnutrition, cardiovascular diseases, cancer, senility (Fig. 11). If there were no diseases to shorten life, life span will surely be much longer, although there still must be limits to man's longevity, since genetic determination is probably what controls the life spans of all creatures of this earth – whether flora or fauna, vertebrates or invertebrates, fish or fowl, one-celled or multicellular organisms. The important question we should like to answer, however, is not, how long can man's life span be lengthened but rather how can a healthy life be extended? By so doing, life span inevitably should also be increased and this is well and good – provided that the longer life span of people can be fruitfully integrated into the social life and economic practices of human society. Our ideal goal in other words, should be the attainment of a state of health for the majority of society where even the aged would be in full possession of his faculties and not a burden to his family or society but capable still of contributing his share in terms of physical or mental output – till the end of his life whether such will be 100 or 150 years, or perhaps even longer. (Although I would not personally like to live that long unless this world gets a whole lot better!). This scenario with an abrupt terminus is just like what Oliver Wendell Homes' logically related in "The Deacon's Masterpiece (or the Wonderful One-Hoss Shay"):

That was built in such a wonderful way
For the wheels were just as strong as the thills
And the floor was just as strong as the sills
And the panels just as strong as the floor
And the back-cross bar as strong as the fore

Seventeen hundred and fifty five
It ran a hundred years to a day
Eighteen hundred and fifty five
Just the hour of the Earthquake shock
What do you think the parson found
The poor old chaise in a heap or mound
As if it had been to the mill and ground.
How it went to pieces all at once
All at once and nothing first
Just as bubbles do when they burst.

Present man is not built that most logical way. There is always some *locus minoris resistentiae,* some weak spot, or organ – the brain, the heart, the kidney, the killer T-lymphocyte – that fails ahead of the others. And the cause of such failure is recognized as a disease of the organ. Seldom can we refer to a person as "dying of old age" – dying because he is too old and not because he was sick. But in some places that were visited by Alexander Leaf (41) in Ecuador, Pakistan and the Caucasus, there were more old old and very old people than most other places in the world; and these old people were still doing hard physical work although eating much less food than we do. Their food intake we would in fact rate as mal – or under-nourishment (Table 15). Unfortunately, Leaf's account was not a real epidemiological survey. We do not know if these old people were really all that healthy although so many were indeed very old – in Vilcamba, Ecuador, they comprised 16.4% of the population, and 1% of the population were centenarians!

There is no doubt that disease hasten the aging process and there are disease-producing factors that can deleteriously affect the DNA and its regulatory mechanisms for aging, as will be discussed below. Contrawise, health and the absence of disease undoubtedly can prolong life, perhaps even to the biologic genetically-determined limit. Whether the latter can be extended further is something for the future to decide as to feasibility and desirability.

How then can we live healthier longer lives? Before we can talk about the health problems of the industrialized society, we still have to mention that the Philippines is still in the Age of Infection. Our leading causes of morbidity and mortality are the infectious diseases – TB, bronchopneumonia, diarrhea, El Tor, intestinal worms – fortunately not yet AIDS! Our TB incidence is, according to our own Secretary of Health "a national calamity" and it is, since our ASEAN neighbors have all controlled theirs and we still have not! El Tor is endemic, diar-

Table 15.

	Ecuador Vilcamba Village	*West Pakistan Hunza Valley*	*USSR Caucasus*
Age			
Over 100 yrs.	9 of 819		4,500 – 5,000 1,844 (39/100,000) live in Georgia 2,500 (63/100,000) live in Azerbaijan 15,000
Over 80 yrs.			
Over 60 yrs.	16.4%		
Oldest	121 yrs.	110 & 105 yrs.	
Work	Hard – Agriculture	Intense – agriculture & mountain climbing	70% of 15,000 who are over 80 work in farms
Diet			
Total Calories*	1,200	1,923	
Proteins	35-38 g	50 g	
Fats*	12-19 g	36 g	40-60 g
Carbohydrates	200-250 g	354 g	
Animal type Protein & Fats	Very low	1%	
Alcohol	Yes-Moderate		Yes
Tobacco	Yes		

From: A. Leaf. Scientific Amer. Sept. 1973 pp. 45-52
*U.S. Diet (1960): Total Calories – 3,300/day
Fats (mostly animal) –157 g - 42% of daily caloric intake

rhea periodically epidemic and intestinal worms infecting more than 90% of our public school children. The control measures for these diseases are known. They are all taught in Hygiene and Sanitation classes. Yet water is not potable, sewage and garbage strewn about and flies, cockroaches and rats abound. Of 132 water samples tested from Manila, Legaspi City, Quezon, La Union, the Igorot Provinces, only 18(13.6%) were found potable. La Union and Kalinga-Apayao had no potable water among the samples tested (43,44).

Malnutrition, of the undernutrition type, is the lot of many of our poor people and their children. Many children will suffer irreparable brain cell loss and doomed to an IQ of a moron. One does not talk of a ripe old old age and longevity when there are obstacles like these. Control and remedy of these diseases and the

conditions that bring them about must be our highest health priorities. Continuing campaign to instill healthy habits and cleaning of surroundings and environments should reap untold benefits. Chlorination of wells and drinking water should be studied and applied all over the country. Garbage and sewage disposal, etc, etc. How can we talk of aging when our people never even have a chance to reach old age or reaching it are already in a stage of senility!

Control of Chemical Pollution: The world is in the midst of a chemical revolution and chemical pollutants abound: in the air, lakes, rivers, ground; in the food we eat and the water we drink and the air we breath, out in the open as well as in our homes, offices, not to mention conference rooms. Nicotine and cigarette tar have been proven to cause not only cancer of the lungs and coronary attacks but also cancer of the mouth and pharynx, urinary bladder, pancreas (44.1) not only in the smoker himself but also the people who inhale his smoke – side stream or passive smokers. Asbestos boards making up our ceilings or lining our air conditioning ducts should be now have all been removed and replaced after demonstration of the carcinogenicity of asbestos fibers on the lungs. Lead and mercury poison the central nervous system and cause tremors. Cadmium, nitric acid, nitrous acid, formaldehyde, hydrogen sulfide cause irritation of the eyes, nose, respiratory passages and mucous membranes. Carbon monoxide from car exhaust, gas ranges, wood stoves, bind hemoglobin and make it unavailable for oxygen transport. Ozone from automobile emissions and copying machines is irritant to lungs and eyes and nose although beneficial once it reaches the stratosphere where it shields the world from the carcinogenic ultraviolet rays (45). The recent reports of a hole in the ozone layers over Antartica caused by chlorofluorohydrocarbons should cause universal alarm because UV is not only carcinogenic especially to the skin but UV can produce immediate formation of pyrimidine dimers on DNA strands which if not repaired may result in failure or mis-transcriptions of genetic messages (44.2). The use of persistent bioaccumulative pesticides like DDT may be good for increasing the harvest but ensure that all our fishes in our rivers and the cattle who roam our fields will not get enough DDT to eventually poison us who eat their meat and the vegetables (44.3). And speaking of air pollution, Manila should rank among the top cities for this, what with our leaded gasoline, decrepit cars, buses and jeepneys emitting thick black smoke oblivious of the police who periodically announce to the public that smoke belchers will be apprehended but never do. The city dwellers' lungs at autopsy are significantly blackened with carbon. The provincial dwellers' lungs may probably look better because the dust and carabao and horse dung may not show up. But the high rate of respiratory infections is a sure sign that our lungs are insulted enough to keep our average life span where it now is – 65 years.

Diet and Exercise: "Man should eat to live, not live to eat". Malnutrition of the over-eating variety has long been shown to lead to hyperlipidemia, atheroschlerosis, hypertension, heart disease and strokes. This is particularly true if the high caloric intake is contributed to by a high saturated animal-type fat content and accompanied by a sedentary habitus. A low caloric diet below 2,000 /Cal. per day

with a low fat content is now known to produce the reverse effect – lowered blood lipids, cholesterol and blood pressure and decreased tendency to atherosclerotic complications and death. In laboratory animals, food restriction or undernutrition but not malnutrition, is said to be the most effective and reproducible method for increasing longevity, and for decreasing and delaying the occurrence of myocardial degeneration and fibrosis, periarteritis, spontaneous tumors, age-induced diminution of immunologic response as well as auto-immune diseases (39). In male Fischer F344 rats, the age related decrease in protein synthesis was suprisingly prevented by diet restriction – as if dieting acts as a physiological stress to stimulate gene expression (Lindell) (39). Leaf's report on the diets in the 3 regions he visited would appear to support these findings on experimental animals (Table 15). The Ecuadoreans ate a bare 1,200 calories with only 10% as fat, mostly vegetable. The Pakistanis ate more, 1,900 calories, but the fat was also mostly vegetable and formed only 17% of the daily diet. The Caucasian diet was not reported but the fat content was similar to that of the Pakistanis. And all 3 peoples did hard physical work. Perhaps those who say that exercise does not prolong life do not exercise enough. But it does look like that many of us are eating too much for our own good and smoking too much. That is why cardiovascular disease incidence among Filipinos is rising fast; it is now No. 2 as a cause of death (46).

How to Delay Aging

As can be gleaned from the previous discussion, the factors of aging are many. Looming over all would be one's inherited genes – how good are they and how efficient are their regulatory and repair mechanisms. Good genes can often resist or overcome all the insults and damages inflicted by pathogenes, toxins, toxic metabolites to which a person may be exposed and good genes can carry a person to a ripe old age in surprising good state of health. This means that the enzyme systems for repair of the cells of the important organ-systems must be good. Some enzymes are synthesized from relatively simple compounds like the vitamins; hence vitamins should be given in adequate amounts to ensure that the enzyme levels of all cells in the body are adequate. Other enzymes are peptides or polypeptides and require DNA-RNA activity. Control of this activity is beyond our present capabilities although gene splicing (genetic engineering) is developing very fast and soon science may be knocking on the door of genetic control of the aging process and perhaps uncover issues with legal or moral complications (47). Professors Niehans of Switzerland and Wiedeman of Germany practice injection of sheep embryo cells with the idea of "rejuvenating" the DNA of cells. Embryonic cells are used because they are said to be still non-antigenic and will not be rejected. Many famous people, some aging presidents and artists are said to have undergone this therapy and "were rejuvenated". The treatment is expensive and requires a long preparation and stay at the clinic isolated in beautiful scenic little towns; and the therapy has to be

repeated after every so many years. However, the rejuvenation appears to be more psychological than physical – but then psychology is a potent rejuvenating force.

The antioxidant and free-radical scavenging properties of Vitamin E appear most suited as protector from the damaging effects of free radicals on the phospholipids of cell membranes. This vitamin as well as selenium which can detoxify lipid peroxides, are becoming attractive in geriatric therapeutics.

Mind over Matter

The mind is the seat of intelligence, reason, cognition, memory and will. It is also the abode of wisdom. It must be in the brain but its location can not be found. It could be diseased and age prematurely as in Alzheimer's Disease. In many people it remains healthy till very late in life and may continue to develop even when the other body systems have started to retrogress. Such people grow in intellect and wisdom and create their greatest works and masterpieces at ages of 60, 70, 80 or 90. The power of the mind over the body has long been recognized and practiced by the peoples of the east. The fakirs of India walk on live coal of 2000°C temperature but do not suffer any burns; or stick long needles through various parts of their anatomy with no bleeding or apparent pain. An article in the *American Heart Journal* in the 1950s reported a "holy man" buried alive for 3 days as pre-planned, with continuous ECG monitoring of the cardiac activity. The ECG complexes gradually became smaller and disappeared for 3 days only to reappear and return to normal configuration when the subject was exhumed alive. Such control of the mind over the body is manifested in many other ways a little less spectacular. The karate artist who splits a concrete block with a blow of his hand delivered with the concentrated force of all the energies of his mind – and without suffering any injury. In a negative way, the power of the mind can also be seen in the sufferings of the hypochondriac who experiences pain and dysfunction of every organ in her body on which her fearful mind focuses. I treated a shell-shocked patient with complete hemiplegia during the entire duration of the Japanese Occupation 1941-45, only to see him get up and walk normally after the Liberation of Manila. There is no doubt that the mind can control the body reactions. The mind can control even the effectiveness and reactions of drugs. A patient who believes in his physician gets well or at least feels better with his medicines; while a patient distrustful of his doctor does not get any better and may develop adverse reactions.

"One is as old as he thinks he is". Can the mind control aging? The old young man is a defeatist, a pessimist and a perennial worrier. His stresses increase his corticosteroid levels, the breakdown of proteins by enzymes, formation of peptic ulcers, hypertension, anxieties and later depression. He is old at 40. The young old man on the other hand thinks positively and is not easily fazed by difficulties; an optimist, he seldom worriers and is seldom stressed. Mental, cardiovascular,

gastrointestinal, immunologic diseases, consequently have little opportunity to take a foothold on him. His active mind continues to seek for challenges. George Zukor at the age of 103, was asked to write the history of the movie industry of which he was a participant and innovator since the industry's infancy. He retorted – don't bother me, I'm very busy. As long as the mind keeps young and meets challenges positively, aging's effects are held back. When a man retires for a well-earned rest, or worse, if forcibly retired for any reason, then aging proceeds or may even be accelerated. One of these days, studies may show that indeed the DNA's regulatory mechanisms can be turned on or off by the mind, which already controls so many functions of the body.

Prescription for Youth in Old Age

Old age is chronologically dependent and time marches on and no one can hold back its hands (The time capsule going to negative time is another story).

Youth is prevention of aging by preservation of health, avoidance of pollution, prevention of disease, toning-up of the body and exercise of the mind and spirit. These having been achieved, our genes can take care of the rest.

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