Aging and disease are not synonymous. There are processes of aging and etiologies of disease. The relationship between the two are important, but not inevitable. (1)

... to draw a distinction between disease and normal aging is to attempt to separate the undefined from the undefinable. (2)

HISTORIES of gerontology recount that centuries before there was a formal concept of biological aging or of definitive disease in its modern context, some philosophers and statesmen held opinions as to the nature of death in old age. Following are two examples that are particularly relevant to the subject of this essay.

The death that comes in old age is painless, for the aged die without any violent affection befalling them, and the parting of their soul is quite unfelt. (Aristotle, *On Respiration*)

Yet it may be urged, many old men are so feeble that they can perform no function that duty or indeed any position in life demands. True, but that is not peculiar to old age: generally it is characteristic of ill-health... Old age is an incurable disease. (Cicero, *De Senectute*)

Back then, most of what we now regard as manifestations of biological aging consisted of its external anatomical and behavioral manifestations. The earliest recorded descriptions of definitive disease (during the Medieval–Renaissance period) consisted of incidental observations in the course of anatomical dissections. Ancient anatomists such as Vesalius, Leonardo de Vinci, Benveni, and Serino were able to record only gross anatomical manifestations of the aging-associated diseases, including gangrene of the lower extremities; cancer of the stomach, large intestines, and bladder; and the tortuosity and hardening of the arteries that we now subsume under the term *atherosclerosis*.

With the advent of the microscope and the emergence of cellular pathology as a science, the autopsy became an almost routine postmortem procedure. The European founders of this discipline, such as Virchow, Rokitansky, Aschoff, Morgagni, and others, added descriptions of both gross and microscopic characteristics of diseases such as arteriosclerosis, myocardial infarction, patterns of metastases in cancers, cirrhosis of the liver, degenerative diseases of the joints, osteoporosis, endocrine disorders, vascular aneurysms, and senile amyloidosis. It was Virchow, in particular, who noted that all diseases are, in the final analysis, traceable to large or small groups of cells, the functional capacity of which is altered in accordance with the state of their molecular composition.

Despite these early anatomical observations of definitive pathological lesions, the late-18th-century publications on the theory of medicine by William Cullen at the University of Edinburgh Medical School in Scotland revealed that the clinical classification of disease was based solely on symptomatology. Concepts of disease etiology did not emerge until the late 19th and early 20th centuries, following the discoveries of Pasteur, Koch, and others that specific microorganisms cause particular diseases. Definitive proof of etiology was based on the verification of Koch’s postulates—the injection of a pure culture of the suspected microorganism into animals, and the demonstration that these animals develop a disease comparable with its human counterpart.

There followed recognition of the fact that malignancies can be induced by viruses, by the application of carcinogenic chemicals, or by exposure to radiation. Also during this period, Anitchkow demonstrated that animals fed a high-fat diet displayed vascular lesions similar to those of humans, later designated by the term *atherosclerosis*. These observations gave rise to the concept of disease etiology that we now call the medical model.

The concept of an aging–disease continuum seems to have been considered by Claude Bernard as early as 1865 (3), as evidenced by the following statement:

We shall never have a science of medicine as long as we separate the explanation of the pathological from the explanation of normal vital phenomena.

Although the foregoing provides a historical account of opinions regarding an aging–disease relationship, it also continues into the modern era. In addition to the contrasting views of Shock and Evans, an appendix at the end of my essay provides a diversity of opinions by others on the aging–disease relationship (4–29). These are classified as to whether they are in accord or in opposition to an aging–disease dichotomy, or whether they are ambiguous in this regard.

In keeping with the sectional division by disciplines represented in *The Gerontological Society of America* (GSA), the authors of these statements include biologists, physicians, psychologists, and social scientists. The dates provide a time frame that stretches from the advent of the medical model over a century ago to the present time.
Although this is by no means a complete list of those who have made statements regarding this conundrum, the number of authors in each category is, nevertheless, indicative of the fact that the spectrum of views has not changed substantially over the course of the past century. Furthermore, a reading of these statements provides a variety of reasons on which opinions have been based.

THE MODERN CONCEPTUALIZATION OF A DICHOTOMY

In the early years of the GSA, over a half-century ago, two slogans dominated the discourse—“The (singular) aging process,” and “aging is not a disease.” The first was based on the belief that a single mechanism would eventually be discovered that would account for the many and varied manifestations of aging. Since it later became clear that there was no single molecular or cellular cause of aging, this view was abandoned. However, the singular expression is still frequently encountered.

Over a half-century ago, Strehler (7) offered the following five criteria posited to distinguish biological aging from aging-associated diseases: intrinsicality, universality, irreversibility, progressivity, and genetic programming. Several of these criteria were subsequently abandoned in recognition of the diversity of the manifestations of biological aging, the fact that manifestations of aging are not genetically programmed (in fact, aging is associated with genetic instability), and the fact that diseases (as is the case in biological aging), if cures are not available, are progressive and irreversible. Acknowledging the fact that defining biological aging is difficult, other authors (30,31) offered a less restrictive definition—biological aging as the result of failure of homeostatic systems, resulting in an increasing probability of death.

Intrinsicality and Universality

Although a 1996 symposium on aging theories as applied to all of the subdisciplines of gerontology (32) acknowledged the fact that there is no definitive theory of aging, Strehler’s criteria of intrinsicality and universality merit attention because they might serve as a basis for distinguishing between biological aging and aging-associated diseases.

Intrinsicality remains important for those who believe that aging-associated diseases derive from extrinsic causes in accord with the above-noted medical model. Opposing this concept is the view that there are intrinsically generated phenomena that can account for both biological aging and aging-associated diseases. Universality in regard to biological aging and aging-associated diseases can be applied in two ways—across species or within species. As to biological aging across species, Finch (33) provides the following observation:

(There is) an enormous range of rates... There are species that may experience negligible degrees of senescence in certain environments, and some in which advanced age may not compromise reproductive function.

Although biological aging may be universal in mammalian species, it has also been argued that no single disease can account for the termination of the life span in all aged individuals, although coronary and cerebrovascular disease, cancer, and dementia, taken together, may approach universality. Furthermore, there are autopsy studies that suggest that amyloidosis alone may approach universality in very old subjects (34).

The expression “aging is not a disease” may have initially been based as much on the objective of establishing aging as an independent discipline as on the existence of convincing evidence that aging and aging-associated diseases are separable entities. Be that as it may, the separation of biological from pathological aging is based on the following tenets. First, any disease during the lifetime of an individual is capable of adding “injury” to the “insult” of biological aging. Second, certain diseases have a high prevalence among the aged population because the offending extrinsic agent(s) produce disease after a long latent period, or because repeated insults are required. Third, the diseases with a high prevalence in the aged population are the consequence of the aging-linked weakening of critical biological defense mechanisms, which then permit the effects of extrinsic agents to take hold.

THE CONUNDRUM OF CAUSALITY

For over a century, concepts of disease causation have undergone an evolutionary process. It began with Koch’s postulates that provided the infectious disease model while recognizing that the immune system could provide protection. Like the infectious disease model, the current medical model holds that the immediate causes of non-infectious diseases are also of external origin. In regard to aging-associated diseases, the above-noted tenets hold that they are caused by unspecified external agents in combination with an aging-related waning of defense systems to confer susceptibility.

The Morass of Risk-Factor Etiology

Because definitive causal agents comparable with those that are operative in infectious diseases are not applicable, so-called risk factors have become popular proxies for causation. Hill (35) has listed a number of criteria for validating a causal link that extends beyond a statistical correlation. In the context of the causation of aging-associated diseases, the following questions appear to be particularly relevant: Does the causal relationship make biological sense? Is it at least biologically plausible? Is the causal association compatible with present knowledge of the disease?

There are examples of correlations that comply with these criteria and others that do not. The risk factors most commonly studied include dietary indiscretions, obesity, tobacco consumption, a sedentary lifestyle, and exposure to harmful environmental pollutants and insecticides. An example of the latter are the estrogenic effects of some pesticides with the potential for causing mutations leading to several types of human cancers (36). As to other causal relationships that make biological sense, tobacco consumption has been statistically linked with lung cancer, and it makes sense in that tobacco tars are mutagenic. However, the majority of lung cancers occur in nonsmokers. Obesity
and hyperlipidemia are statistically associated with some types of diabetes, and this association can be explained on the basis of their metabolic link with insulin resistance.

Studies on the beneficial effects of exercise have been questioned on the basis that those who exercise may be healthier at the outset than those who do not (37). In addition, although the short-term benefits of exercise are clear (38,39), there is a question of whether these benefits can be sustained (40).

In contrast, studies by sociologists have revealed that the effect on mortality of low socioeconomic status is greater than that of such risk factors as cigarettes, hypertension, and hypercholesterolemia combined. In this regard, the mortality gap between the rich and poor has been growing wider (41).

There are confounding features that also have to be considered. One disease may serve as a risk factor for another, such as hypertension or diabetes for heart disease and stroke. Furthermore, some risk factors are associated with more than one disease; for example, smoking cigarettes is associated with experiencing both heart attacks and cancer, diseases that have little in common in their pathogenesis. In contrast, some of the risk factors linked with coronary artery disease do not apply to cerebrovascular disease, although the two are similar in their pathogenesis.

Some correlations do not survive the test of time. Recommendations based on earlier observational studies on hormone replacement therapy in postmenopausal women, most lacking randomized control clinical trials, have had to be revised because a later more comprehensive study proved them to be in error. On the basis of earlier findings it was concluded that estrogen therapy in menopausal women would reduce the risk of coronary artery disease but increase the risk of breast, endometrial, and cervical cancer. The risk of these cancers could be reduced by using a combination of estrogen and progesterone. A more recent randomized control study (42) involved 16,608 postmenopausal women aged 50–79 years with intact uteri who were tested in a study using a placebo compared with an estrogen–progesterone mixture design. The study was halted after a mean of 5.2 years because of the increased risk of breast cancer despite or because of the inclusion of progesterone. Moreover, it also showed an increased risk for heart attacks, stroke, and pulmonary embolism. Similar correlations have been drawn between low testosterone and loss of muscle mass and cardiovascular disease in older males (43–46). This condition of andropause represents a classical example of the disease-aging continuum, with longitudinal studies showing a fall in testosterone levels in all men (47), but treatment studies suggesting that it is only at disease levels of testosterone that symptoms occur and are reversed by treatment (48–50). There is a major need for a Men’s Health Study similar to the Women’s Health Initiative to determine the validity of these claims.

Current risk assessment is, in a sense, a throwback to the period when disease was attributed to the cumulative effects of a variety of harmful environmental factors. An important difference now, however, is that risk assessment is disease specific and based on clinical criteria. In these actuarial times, statistical correlates have become the new ciphers for disease phenotypes. To emphasize the absurd lengths to which some correlations have been carried out, McCormick noted in a 1993 report (51) that over 300 risk factors have been associated with coronary heart disease.

Statistical analyses are also often incomplete because they do not distinguish between the causal connection as a necessary one comparable with an infectious agent, or one that only confers susceptibility. In diseases with age at onset in the senescence period of the life span, it is particularly important to distinguish between direct causal mechanisms and the indirect impairment of defense mechanisms.

With regard to aging-associated diseases, chronological age provides the strongest statistical correlate. Moreover, Forbes and Gentleman (52) have identified putative similar pathways between smoking-induced life shortening and biological aging, suggesting that smoking may, in effect, be an accelerator of aging.

**Genetic Risks**

In lieu of risk factors, Williams (53) stresses the role of germline genetic factors, and he notes that only ~20% of cigarette smokers develop lung cancer whereas the mechanisms that protect the other 80% remain largely unknown. Familial aggregation has been observed for disorders such as cardiovascular disease and cancer. Of men with coronary heart disease occurring before the age of 55, 50–60% have a strong family history of this disease. With regard to hypercholesterolemia, although the inherited forms represent only ~5% of the general population, they account for more than 50% of cases with onset before the age of 55. Total cholesterol as a risk factor for cardiovascular disease progressively declines with advancing age, and in those over 85, high cholesterol concentrations are associated with longevity (54), although the prevalence of coronary heart disease continues to rise in this group of advanced age.

In sum, the determination of causality involves complex processes, whether applied to biological aging, to risk factors, to genetic determinants, or to aging-associated diseases. The further identification of single nucleotide polymorphisms (SNPs) linked with particular disorders should provide additional information regarding genetic risk. It may even be that the diseases with age at onset during the senescence period of the life span involve fewer complexities, because the role of risk factors and of genetic risks plays a progressively diminishing part with advancing age, and the oldest old appear to represent an elite population relatively invulnerable to these risks (55). Nevertheless, the prevalence of these same phenotypic diseases continues to rise in the oldest old, because, as noted elsewhere (56), the advent of techniques for analyzing the molecular biopathology of aging and aging-associated diseases has led to the conclusion that more than one pathogenetic pathway may lead to the same phenotypic lesion.

**The Relevance of Longevity Extension to a Resolution of the Aging–Disease Dichotomy**

Longevity extension, also regarded as a retardation of biological aging, might be viewed as an opportunity to
clarify the aging–disease relationship. There are three major lines of activity directed at either extending human longevity or at identifying determinants of the human life span. The first, as noted by Olshansky and colleagues (12,57), and in an editorial in the Journal (58), is an ill-considered expansion of hormone replacement therapy conducted under the auspices of The American Academy of Anti-Aging Medicine. It promotes the administration of such agents as pituitary growth hormone, testosterone, and adrenal dehydroepiandrosterone (DHEA), despite the possibility that there may be harmful consequences comparable with those already noted with regard to hormone replacement therapy in menopausal women.

The second is a study conducted by Perls (59), the goal of which is to identify the genetic and phenotypic markers characteristic of centenarians. The third line of activity consists of the ongoing studies on longevity extension by caloric restriction (CR) in rodents, but now also extended to primates (60–63).

The changes in CR rodents associated with increased longevity, some of which are also present in centenarians and tentatively in CR primates, include a reduction in triglyceride and melatonin levels, in oxidative damage, in glucose tolerance, in plasma insulin, and a reduction in the rate of decline in DHEA. The search is already on for an antiaging pill that would have effects similar to CR and be more acceptable to humans (64).

In a review of CR studies that extend the life span of mice and rats, Masoro (65) has concluded that CR does not eliminate aging-associated diseases; it only postpones their age at onset, thereby providing support for the role of reactive oxygen species and advanced glycation end (AGE) proteins in the generation of diseases in this model, albeit at a slower rate (66).

In presenting studies dealing with genes that can be manipulated to extend longevity in yeast, Caenorhabditis elegans and Drosophila melanogaster, Guarante and Kenyon (67) further blur the distinction between biological aging and aging-associated diseases. They state:

When single genes are changed, animals that should be old stay young. In humans these old mutants would be analogous to a ninety year old who looks and feels forty-five. On this basis we begin to think of ageing as a disease that can be cured or at least postponed.

Conclusions

First an explanatory note on terminology. In this essay I have used the term aging-associated disease rather than age-related disease. This choice is to emphasize that the primary focus here has been on diseases with age at onset in the senescent period of the life span, the oldest old, rather than through progressive periods of the total life span.

In considering the basis for a separation of the degenerative changes in “normal aging” from an aging-associated disease, how does one define a disease? Philosophers, ethicists, clergy, social scientists, and physicians have wrestled with this definition (68). Some define it as a default value—the absence of a state of proper or ideal functioning. Others regard disease as any condition associated with discomfort, pain, disability, or death—or an increased liability to these states. By some of these criteria, even “normal aging” would qualify as a disease.

How, then, does one distinguish between a biological aging lesion and a disease?

For the dichotomists, the challenge is to delineate a defineable border that separates biological from pathological aging. Although the notion of a dichotomy between the two dates from antiquity, in the modern era it dates from approximately 1929 to the present. Most recently, it has been addressed by Olshansky and coworkers (12,57). They comment as follows (57):

Until we better understand aging processes and discover how to manipulate them, these intrinsic and currently immutable forces will continue to lead to increasing losses in physiological capacity and death, even if age-associated diseases could be totally eliminated. (p. B293)

Nothing is really new here. Of the criteria proposed in the modern era of gerontology for separating biological from pathological aging, Olshansky and colleagues again apply the criteria of intrinsicality and universality—and ultimately a biological death at the end of the life span in the absence of disease.

In this paradigm, what are the causes of disease? Because direct causation in compliance with the Pasteur–Koch model is not applicable to noninfectious degenerative diseases, the medical model presently in vogue employs risk factors as proxies for the extrinsic causation of aging-associated diseases—accompanied by germline genetic risks. Although there may be applications in which the risk factors make biological sense and germline mutations have been identified as causal, they are not applicable to the causation of the degenerative diseases of the oldest old. As Perls (55) has recorded, the oldest old, including centenarians, have escaped the risk factors and genetic risks, whereas the prevalence of aging-associated diseases continues to rise.

For those supporting a continuum between the two, it is necessary to delineate the paths leading from a biological aging phenomenon to a disease. In short, we must demonstrate that aging is not simply just another risk factor for disease, but that the two are more intimately connected. A resolution of this conundrum rests on the identification of disease causation in the context of biological aging.

What has changed the dialogue between those supporting a dichotomy and those supporting a continuum are concepts that have evolved in the modern era of gerontology with the potential for linking the two. As more knowledge about aging has been acquired, it has become evident that the manifestations of biological aging are so diverse that they cannot be attributed to one or only a few causes, thereby blurring the distinction between biological and pathological aging of possible intrinsic origin. A classical example is frailty, which appears to be a combination of multiple diseases leading to a decline in functioning (69–72). A paradigm shift in concepts of biological aging took place with the advent of the stochastic theory of biological aging.
Particular landmarks include Harman’s demonstration of the effects of intrinsic free radical generation (73), followed by Cutler’s (74) introduction of the concept of intrinsic errors in transcription, translation, and posttranslational modification of proteins; and, related to the generation of free radicals, the role of AGE products by Brownlee and associates (75). These advances provided the basis for a continuum between biological and pathological aging. Holliday (18) subsequently provided a list of causes and defenses of biological aging that apply equally to the intrinsic genesis of aging-associated diseases.

Senile amyloidosis is a long-recognized phenomenon in both rodents and humans (76). Its genesis has recently been identified as a posttranslational misfolding of proteins (77). Amyloidosis is generally recognized to be a disease, and autopsy studies (34) place its prevalence at 80–100% in subjects of advanced age, thereby approaching universality. A major cause of Alzheimer’s disease is thought to be overproduction of beta-amyloid. An animal model of beta-amyloid overproduction, the SAMP8 mouse, has early memory disturbances directly attributable to beta-amyloid overproduction, but in many ways it otherwise resembles senescent mice (78–81).

There are other relevant connections between biological aging and disease that support a continuum. Two examples follow: the first is based on a homeostatic system gone awry, and the second is based on events linked to the stochastic concept of biological aging. First, people who develop type 2 diabetes pass through three phases. The first phase, as demonstrated by the Baltimore Longitudinal Study (82), is the long-recognized biological aging phenomenon in which there is a progressive deterioration in glucose tolerance with advancing age. It then may progress to a state designated as “impaired glucose tolerance” and insulin resistance. In a final progression, overt diabetes emerges. Accompanying this process is a progressive increase in the production of AGE proteins that gives rise to the vascular complications of diabetes (83). Second, Ames and associates (66) argue as follows:

Metabolism, like other aspects of life, involves tradeoffs. Oxidant by-products of normal metabolism cause extensive damage to DNA, protein and lipid. We argue that this damage (the same as that produced by radiation) is a major contributor to aging and to degenerative diseases of aging such as cancer, cardiovascular disease, immune-system decline, brain dysfunction and cataracts.

Is the dichotomy issue only a philosophical one, or will its resolution have consequences? Hayflick calculates (11) that successful eradication of cardiovascular and cerebrovascular disease and cancer would add only 15 years to our average life expectancy. Although eradication of these diseases has yet to appear on the horizon, the studies on longevity extension in rodents, now extended to primates, indicate that this strategy would postpone these diseases to a later age at onset, but not eliminate them. In addition, although the effect on disease (postponement or elimination) of an antiaging drug that would mimic CR is not known, there are serious reasons to question the advisability of the longevity extension enterprise.

As documented in a previous essay (56), it has been projected that, even without a longevity extension program, by the year 2050 we will have approximately 70 million Americans over the age of 65 and approximately 50 million over the age of 85. Centenarians will number around 300,000, and they would still be dying of disease, not of old age. According to Kevels (84), “elderly women will make up a disproportionately large fraction of society, and our society will be burdened with a huge cadre of people beyond reproduction or work.” Disease prevention using already available knowledge appears to decrease morbidity associated with aging (85). Our system for providing for the health care needs of the aged population is already under severe stress, and future planning should place a much higher priority on providing for an even larger population of the aged than on extending the human life span and further intensifying this problem.

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REFERENCES
In Accord With a Dichotomy

“Death from senescence alone can occur.” (4)

“To me, ‘pathological’ actually means something which is added on to the normal changes in the life history of an organism.” (5, p. 81).

“If aging is an illness, this is true only in the sense of its limitations rather than the purity of its syndromes susceptible to special medical influences. In this view it can be concluded that the forces of aging are not a sickness in the accepted sense of the word, but that aging is irreversible…” (6)

“These three events (coronary artery occlusion, cerebrovascular accident, the initiation of a tumor) which incidentally account for the majority of deaths in the older age group in Western countries, are not themselves considered to be part of the aging process even though they might occur universally.” (7)

“Of the letters and editorials you (The Lancet) have published on aging, none explains the difference between aging phenomena (genetically programmed) and age-associated pathological phenomena (acquired or initiated by external events). This distinction must be made or there will be no progress.” (8)

“On the one hand we must distinguish between aging and disease; on the other hand the interaction between them is of considerable and theoretical interest…” (9)

“The term ‘biological aging’ should, in my judgment, be reserved for characteristics and processes that occur universally with aging in all members of a given species. Conversely, factors that impinge upon and influence aging in varying degrees, separate from the universal genetically programmed factors, include lifestyle factors, exposures to environmental influences, and disease.” (10)

“Advances in our knowledge of age-associated diseases have far outpaced advances in our understanding of the fundamental ageing processes that underlie the vulnerability to these pathologies. If we are to increase human life expectancy beyond the fifteen year limit that would result if today’s leading causes of death were resolved, more attention must be paid to basic research on ageing. Determination of longevity must be distinguished from ageing to take us from the common question of why we age to a more revealing question that is rarely posed; why do we live as long as we do? But if the ability to intervene in ageing ever becomes a reality, it will be ripe with unintended consequences.” (11)

“Aging, in our view, makes us ever more susceptible to such ills as heart disease, Alzheimer’s disease, stroke and cancer, but these age-related conditions are superimposed on aging, not equivalent to it.” (12)

In Accord With a Continuum

“The textural changes which old age induce in the organism sometimes attain such a point that the physiological and pathological states seem to mingle by an imperceptible transition and to be no longer sharply distinguishable.” (13)

“It is my conviction that death in human beings never occurs, or only in rare instances, without pathological changes to which death might be attributed…. Autopsies which have been made in the very old always show a pathological cause (of death).” (14)

“Can the effects of aging be distinguished from those of pathology? To attribute to aging all time associated changes to which no specific cause can be found is at best a temporary holding tactic which will suffice only as long as we are ignorant of the mechanism involved. Time alone causes nothing.” (15)

“…. man will never die of old age but always from disease. However, terminal disease of the future will be different from that we are faced with now and presumably more diversified.” (16)

“Attempts have been made by numerous workers to separate physiological from pathological aging. The two are, however, so interrelated as to make attempts relatively abortive. It would be far more relevant to accept the existence of a continuum of ageing phenomena.” (17)

“. . . the distinction between so-called natural ageing and the pathologies that are common in old people is artificial. What we see is an increasing likelihood of many diseases in individuals as they age, which does not, of course, mean that all individuals develop all the pathologies.” (18)

“If one defines disease as ‘reaction to injury’ there is no clear distinction between aging and other diseases.” (19)

“. . . we are told at the outset that we should focus on distinguishing changes in the elderly due to disease or disease from changes due to true aging, thus the ‘usual versus successful’ ideology was imposed a priori. What if the ‘aging vs disease’ dichotomy is an unsuccessful way of conceptualizing research problems in gerontology?” (20)

“Although it is well known that most diseases show marked increases with age, the connection between the ageing process and the incidence of age-related diseases is highly underestimated. Recent developments in gerontology
are unearthing the molecular link between ageing and disease.” (21)

*Ambiguous Views*

“Research to control aging and to treat aging will, whether we like it or not, turn aging into a disease—for if aging or death occur at a time when it could have been postponed, it comes to be regarded as a disease.” (22)

“Why do we die? Although manifest senescent disease is primarily a medical problem, its roots are biological, and the intractability of the problem of death arises from the difficulty of bringing the immense variety of clinical and pathological phenomena into relation with the parsimonious thought processes of biological science.” (23)

“The diseases with which large numbers of aging individuals die can be classified in three ways in regard to aging: 1. Diseases that are aging processes themselves. 2. Diseases that show an increasing incidence with age. And 3. Diseases that have more serious consequences with increasing age.” (24)

“. . . there is no reason in principle why some of the disagreeable changes that accompany aging should not be diminished or annulled—particularly those which are clearly secondary in nature. These are physical changes, no different in principle from other disease processes and no less amenable to investigation and treatment.” (25)

“Autopsy studies indicate that the concept of pure physiological aging as a cause of death is observed rarely, if ever, and that with age the individual shows an increasing number of organic lesions of the cardiovascular, cerebral and other systems. Thus as far as can be foreseen, extension of the life-span depends essentially on retardation of pertinent pathological processes.” (26)

“In the future studies of aging must better attempt to capture the interplay between diseases and aging phenomena.” (27)

“Many basic factors about senescence in even the best studied specimens are still being revised as the multifarious confoundings of age-related diseases are best understood. It is noteworthy diseases of adult humans have been considered in isolation from the larger manifold of changes in this age group; this narrow view may have limited progress.” (28)

“Scientific evidence is rapidly accumulating to suggest the hypothesis that the fundamental age-related changes that ultimately result in the functional deficits, pathologies and diseases of the aged are based, in part, on specific age-related changes in gene expression.” (29)