A View of the Aging-Disease Relationship From Age 85

Herman T. Blumenthal

Department of Community and Family Medicine, St. Louis University School of Medicine, and the Aging and Development Program, Department of Psychology, Washington University, St. Louis, Missouri.

This essay posits a continuum between biological and pathological aging based on the following tenets: (i) Biological aging is not genetically programmed. (ii) Both biological aging and the diseases of the senescent period are caused by intrinsically generated random phenomena. (iii) The same phenotypic disease can occur in the juvenile, mature, and senescent periods of the life span, but with inherited genetic mutations having a progressively diminishing role with advancing age. (iv) The diseases of the juvenile period are of congenital or inherited origin. Those of the period of maturity derive from late-acting inherited genes or from so-called risk factors. During the senescent period, they derive from the same types of intrinsic random events that account for biological aging.

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.

N.W. Shock, 1961 (1)

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

J.G. Evans, 1988 (2)

When I joined the Gerontological Society (now the Gerontological Society of America [GSA]) about 50 years ago, two expressions dominated the discourse relevant to an aging-disease relationship: "the (singular) aging process" and "aging is not a disease." The first of these expressed the objective of finding a unifying mechanism that would account for the diverse manifestations of biological aging. "Aging is not a disease" was based on the concept that the direct causes of the aging-related diseases are independent of "normal" aging phenomena. It would appear that the central objective of both expressions was to establish gerontology as a discipline distinctively different from the disease-oriented ones.

I joined the biology and medical science sections because, as a pathologist, although my primary interest was in disease pathogenesis, I was also interested in ascertaining what the links might be between biological aging and the chronic diseases with peak morbidities and mortalities in older persons—cardio- and cerebrovascular disease, cancer, diabetes, hypertension, and osteoporosis. Alzheimer's disease, now a preoccupation of gerontologists of all stripes, was hardly on the horizon back then.

Shock's foregoing statement reflects the orientation of most members of GSA as well as of the medical community at large. However, for some time now it has been recognized that the many manifestations of aging cannot be accounted for on the basis of a single unifying mechanism. Indeed it is even acknowledged that an encompassing definition of biological aging is difficult, if not impossible, to formulate (3,4). The separation of normal aging from the diseases most prevalent in older persons, however, remains a subject of controversy. Although it appears that most gerontologists continue to hold to a separation of the aging-related diseases from biological aging as posited by Shock, there are some who subscribe to Evans's view of a continuum between biological and pathological aging.

Consonant with Shock's statement, Strehler (5) in 1977 offered the criteria of intrinsicity, universality, progressivity, irreversibility, and genetically programmed, intended to separate biological aging from disease. However, not all of these criteria fulfill that objective. Until definitive cures are discovered for the chronic aging-related diseases rather than therapies that slow their progress, the aging-related diseases will remain progressive and irreversible. And with respect to genetic programming, Martin (6) maintains: "There is no aging program, nor is there an aging gene." The criteria of intrinsicity and universality are addressed later in this essay.

From a medical perspective, the following tenets have been offered to separate biological aging from aging-related diseases:

Certain diseases have a high prevalence in older persons because the offending extrinsic agent(s) produce disease after a long latent period, or because repeated insults are required.

Any disease during the lifetime of an individual is capable of adding "injury" to the "insult" of biological aging.

Diseases with a high prevalence in older persons are the consequences of the aging-linked weakening of critical biological defense mechanisms which then permit the effects of extrinsic agents to take hold.

The Traditional Medical Model

The foregoing concept of the aging-disease relationship is in the tradition of the medical model that has its origin the era of Pasteur and Koch, when it was discovered that a specific microorganism caused a particular disease. Proof of causation was based on fulfilling Koch's postulates. And even back then it was recognized that the offending organism was a necessary but not a sufficient cause, because not all exposed individuals developed the malady.

Because concepts of causation of the aging-related diseases...
are not readily applicable to the infectious disease model, risk factors such as smoking, a sedentary lifestyle, dietary indiscretions, obesity, and so forth, have served as proxies for etiology, based largely on risk assessment by statistical analyses. However, there are several confounding features of the risk-factor model of disease causation. One disease may serve as a risk factor for one or more other diseases, such as diabetes and hypertension for cardio- and cerebrovascular disease. Some risk factors are associated with more than one disease, as in the case of cigarettes with heart disease and cancer, diseases that have little in common in their pathogenesis. And some risk factors linked with coronary heart disease appear not to apply to cerebrovascular disease, although the two are similar in their pathogenesis. Moreover, Forbes and Gentleman (7) have identified putative similar pathways between biological aging and smoking-induced life shortening, suggesting that smoking may, in effect, be an accelerator of aging. Furthermore, these risk factors appear not to have a significant role in diseases with age-at-onset after about age 75, although the prevalence of the aging-related diseases continues to rise in the oldest-old (8). And these risk factors are largely inapplicable to the genesis of Alzheimer’s disease at any age-at-onset. Finally with regard to the risk factor concept, age provides the best statistical correlate.

BIOLOGICAL AGING—CAUSES AND DEFENSES

Contrary to Shock’s distinction between processes of aging and etiologies of disease, Martin’s (6) contention that there is no aging program nor aging genes rests on a body of evidence showing that intrinsically generated random phenomena over the life span play a causal role in the genesis of many of the manifestations of biological aging and of the aging-related diseases. As Cutler (9) has recorded: “All mammalian species express the same temporal patterns of physiological aging and onset frequency of disease.”

Among the spontaneous random events now regarded as causes of biological aging are DNA and RNA coding errors, errors in transcription, microsatellite instabilities, failure of appropriate epigenetic methylation, oxygen free radicals and advanced glycosylation end (AGE) products (10). It is also of note that oxygen free radicals and AGE products can induce errors in transcription and translation, and that chromosomal aberrations associated with biological aging and some aging-related diseases may be the result of errors in the proteins of the cytoskeletal fibrils to which chromosomes attach, separate, and migrate during mitosis. To these can be added the post-translational misfolding of proteins, as discussed below with regard to the genesis of amyloidosis.

Holliday (10) also provides a list of defense mechanisms. They include apoptosis, suppressor genes, redundancy of genetic information, DNA and RNA editing mechanisms, DNA repair enzymes, free radical scavengers, mechanisms for the removal of defective proteins, and the immune system. But as Holliday also notes, these defense mechanisms deteriorate with advancing age by virtue of the same causal mechanisms as those noted above. Moreover, he posits that these causal mechanisms, and the failure of the defenses against them, apply to both biological aging and the intrinsic genesis of aging-related diseases.

A DIFFERENT AGING-DISEASE PARADIGM

A demographic perspective of disease causation and attendant mortalities over the life span is provided by Figure 1. Several investigators (11-14) have offered interpretations of this bi-modal plot. They are all in agreement that the trough, roughly covering the span between ages 15–30, represents the period during which evolution has endowed the human species with its maximum reproductive capacity, and with the maximum capacity of its defense mechanisms against aging and disease. Although Burnet (11) does not take into account the diseases of early age-at-onset, Childs and Scriver (12) interpret these diseases to be of inherited or congenital origin.

Interpretations differ, however, as to the meaning of the ascending curve. Burnet (11) posits that as the defenses progressively weaken in subsequent years, intrinsically generated mutations accumulate and give rise to diseases with a mortality rate essentially in compliance with the Gompertz plot, whereas Childs and Scriver (12) regard the diseases of this segment to be of extrinsic origin, with inherited genes playing a progressively diminishing role. Brody and Schneider (13) posit that if the prevalence of a disease does not decline at an advanced age, then that disease derives from biological aging. They show that coronary heart disease complies with this interpretation. Furthermore, Brody (14) provides epidemiological evidence that the age-at-onset of the dementias also complies with this interpretation.

Taking these various views into account, the following interpretation (15) of this bi-modal plot has been proposed:

![Figure 1. The bi-modal plot of mortality versus age with a linear age scale and when the age scale is changed to a logarithmic one to show the approach to the straight line of a Gompertz plot.](https://academic.oup.com/biomedgerontology/article-abstract/54/6/B255/691608)
Segment 1 represents mortalities from diseases of early age-at-onset and of inherited or congenital origin, including juvenile neoplasms and the syndromes of precocious aging, some of which exhibit diseases comparable to the aging-related diseases of later life.

Segment 2 represents the period of maximum reproductive capacity, of maximum capacity of defense mechanisms, and a nadir in mortalities from disease.

Segment 3, the lower half of the ascending curve, represents mortalities from diseases of maturity-age-at-onset deriving from late-acting inherited genes or from those attributable to risk factors.

Segment 4, the upper portion of the ascending curve, represents mortalities from diseases of senescence-age-at-onset, and posited to derive from biological aging mechanisms.

The Amyloidosis Model

As Fogle (16) has written with regard to the genotype-phenotype relationship: "DNA dictates the information necessary to delineate the phenotypic structure, and the cellular machinery is the mode through which it is expressed. In this model, all the information in the phenotype is encoded in the genotype." This concept is in accord with the definition of phenotype as an observable expression of a trait affecting structure, physiology, or behavior that results from activity of RNA or protein molecules transcribed from DNA. But Fogle also observes that small changes in the cellular machinery may alter its ability to make sense of the genetic program. The amyloidosis model provides an example that the same phenotypic lesion can derive from a variety of pathogenetic pathways.

The Amyloid Phenotype

Amyloid is a proteinaceous substance deposited between cells in various tissues and organs in a wide variety of clinical settings, ultimately producing pressure atrophy of the parenchymal cells (17). In a landmark review, Glenner (18) detailed the phenotypic characteristics as displaying a pink-orange coloration with congo red stain with conventional light microscopy, a pink fluorescence with ultraviolet light, and apple green crystals with polarized light. On electron micrographs amyloid exhibits branched and unbranched fibrils of varying length, 40-120 Å in diameter, with the fibrils composed of paired helical filaments. On x-ray crystallography it displays a beta pleated configuration from which characteristics Glenner has designated all the amyloids as the beta fibrilloses.

The Amyloid Genotypes

The amyloid gene designates and their derivative proteins have been classified as follows:

AL—Gamma-type light chain immunoglobulin
AA—Nonimmunoglobulin apolipoprotein
AF—Familial hereditary amyloidoses (gamma trace, beta protein, and transthyretin variants)
AE—Endocrine amyloids (amylin of the islets of Langerhans, precalcitonin of the C cells of the thyroid, prolactin of the pituitary, and atrial natriuretic peptide of the heart)

Beta-2—Microglobulin in patients on hemodialysis
ASC—Senescence-related transthyretin variants and beta proteins

To emphasize the diversity of pathogenetic pathways, Saraiva (19) has identified 40 variants of transthyretin linked with the familial and senile amyloidoses. In accord with the prevalence of two or more concomitant diseases in aged subjects, there are also patients with combinations of two or more amyloid types.

Nongenetic aging-related enhancers such as free radicals and AGE proteins have also been linked with amyloidogenesis (20,21), including the observation that senescence-accelerated mice exhibit an enhanced oxidative stress due to an impaired transport of Cu-Zn superoxide dismutase (22,23). These mice develop a universal accelerated senile amyloidosis.

The Final Commonality

The post-translation folding of proteins that provide them with their highly specific three-dimensional configuration has been designated the second half of the genetic code (24). Misfoldings of proteins appear to constitute a commonality of all the amyloids, although they are not identical in their molecular composition. As Tauben (25) notes, when normal protein folding goes awry, incompletely folded protein molecules coalesce and form insoluble fibril aggregates. Disorders attributable to protein misfolding have been designated conformational diseases (26).

Amyloidosis and the Criterion of Universality

The criterion of universality has been applied in two ways as an aging-life-terminating mechanism applicable across all species, or as a mechanism limited to all individuals within a species. As to the first, aging itself does not comply with the criterion of universality because not all species exhibit senescence (27), and the application of universality across species does not take into account that as evolution has progressed there has been an increasing complexity of biological mechanisms with more opportunities for the latter to go awry, thereby providing a diversity of life-terminating events.

Death certificates are notoriously unreliable as to causes of death in humans, and although autopsies provide more reliable data, they too have limitations, including a current decline in the autopsy rate, particularly in aged subjects, and even more so in nursing home patients. Even when autopsies are performed, analyses for the presence of amyloid deposits are generally carried out only when there are clinical indications of an amyloid-related disease.

Nevertheless, a composite of several reports representing several hundred aged subjects (28-30) showed senescence-related (ASC) amyloid atrial deposits in 80-100% of cases. A single study (31) of 100 aged subjects revealed that 91 had amyloid deposits in the heart. Amyloid deposits in the heart, whether of immunoglobulin light chain, transthyretin variants, atrial natriuretic polypeptide (ANP), or of ASC derivation are particularly relevant to cause of death in old age. ANP level is an independent predictor of mortalities in the oldest-old (32).

There are two consequences of amyloid deposits in the heart. They can be the cause of a clinically undetected lethal arrhythmia or of heart failure. Deposits of atrial amyloid can also produce a restrictive cardiomyopathy that results in heart failure (33). Deaths from amyloid deposits such as these are often erroneously attributed clinically to heart failure from coronary artery...
disease or as death from so-called natural causes. Although such observations do not preclude death in the absence of disease at the end of the human life span, they support the conclusion that few of advanced age may be vouchsafed such an end.

Amyloidosis and the Bi-Modal Plot

Because the life-span distribution of the amyloid genotypes in accord with the bi-modal plot has been previously detailed (15), it is not repeated here. Suffice it to note that the presence of some diseases and their derivative amyloids in both the maturity and senescence onset categories reflects the fact that there is no sharp age demarcation between these two periods of the life span.

The Amyloidogenic Dementias

Alzheimer’s disease (AD) provides an example of the application of the tenets noted in the abstract to a single clinical and pathological entity. Moreover, AD appears to represent the most prevalent disease of those of advanced age. There are no identifiable risk factors except for head trauma. The life-span distribution of this category of the dementias conforms to the bi-modal plot and to the principle of diverse pathogenetic pathways leading to the same endpoint lesion. There is also a strong connection with biological aging, and the amyloidogenic dementias provide an example of a progressively diminishing role of genetic markers with advancing age.

As to the life span distribution, the amyloid plaques of AD are present at an early age in the Down syndrome (DS). As discussed below, genetic markers for this disease identified thus far apply mostly to AD of maturity age-at-onset. AD, with its highest prevalence in the oldest-old, appears to have few, if any, genetic markers.

As to the diversity of pathogenetic pathways, whereas the amyloid plaques of DS derive from the overproduction of the amyloid precursor protein (APP), which derives from the trisomy 21, the plaques in AD of maturity age-at-onset derive from several mutations of APP or other late-acting genes. As also discussed below, the plaques of AD of senescence age-at-onset may derive directly from biological aging phenomena.

The lesions of the amyloidogenic dementias consist of the deposits of beta protein plaques in the hippocampus and a cerebral amyloid angiopathy (CAA), the two often taking place together. But CAA with dementia also occurs in the absence of plaques. The beta protein of CAA has a different amino acid composition from the plaques of AD (34).

The principal genetic markers thus far identified in AD are overexpression and mutations of APP, two presenlin gene mutations, and mutations of APOE4. APOE is a 299-amino acid lipid transport protein that plays an important role in plasma cholesterol homeostasis. In humans there are three common alleles designated APOE 2, 3, and 4. The three alleles differ by only a single amino acid. The APOEs are highly expressed in the liver and brain. In the brain they are synthesized by astrocytes and some microglia.

Mutations of APP and of the two presenlin genes are directly involved in the amyloidogenic process, whereas APOE4 is a risk factor for AD and the most common genetic marker. But the mutations of these genes account for less than 35% of AD cases, and with the exception of DS, they fall mostly in the maturity-onset category, although a few cases are in the senescence-onset group (35). Thus they do not account for the vast majority of AD cases, nor for the dementias of CAA, both of which occur mostly after age 80.

With regard to the life-span distribution of APOE4 in AD cases, a study by Asada and colleagues (36) on 224 demented Japanese subjects over age 90, including 47 centenarians, revealed that the APOE4 allele was present in 38% of the demented subjects under age 60, in 22% of those aged 80-89, and in none of the of the centenarians with dementia in whom the prevalence rate of AD was 70%. Thus, in accord with the progressive disappearance with age of genetic markers, the frequency of the APOE4 allele appears to decline with age and to have no impact on AD in centenarians. As yet, no genetic markers have been identified in AD in centenarians. The observation that random-frameshift or assembly-line mutations in the genetic code (37) result in a build up of beta-protein plaques provides an example of a disease deriving directly from a biological aging phenomenon.

As has been noted (38), “typically Alzheimer’s disease has a gradual onset, arising by minute degrees over a period of time. Prevalence and incidence estimates will vary greatly according to where along a continuum from normality to severe disease one places a diagnostic cut-point between nondisease and disease.” But the same conundrum confronts the pathologist because the presence of amyloid plaques in clinically nonmented aged subjects (39) leads to the necessity of subjectively correlating the number and distribution of plaques with the clinical manifestations of AD.

CONCLUSION

In accordance with the tenor of the time, when the National Institute of Aging (NIA) was created, its assigned mission was to support the study of biological and other aspects of aging, thereby distinguishing it from the disease-oriented institutes. Its support of AD has been viewed by some as a departure from this mission. It may be that initially the support of AD research was adopted by the NIA as a tactical measure to increase its funding, but as subsequent research has evolved, and as has been demonstrated here, there are valid biological reasons for extending this policy to the support of studies on other aging-related diseases.

The concept of causation of the aging-related diseases proposed here rests on the four tenets noted in the abstract and amplified in the text. They represent a significant departure from the traditional medical model of disease causation on which the aging-disease relationship has heretofore been based. The amyloidotic diseases, including the amyloidotic dementias, have been presented as models of causation of the aging-related diseases. They are particularly appropriate because, for the most part, conventional risk factors do not apply to their pathogenesis, and many of the amyloidotic diseases are of intrinsic origin. Moreover, in humans, amyloid lesions of the heart come close to complying with the criterion of universality.

It remains to be demonstrated that other major aging-related diseases such as vascular disease, cancer, diabetes, hypertension, and osteoporosis also conform to this paradigm—a process in which I am now engaged.

The paradigm presented here also has implications for the future planning of our health care system. The demographic projections of the future growth of our elderly population are based largely on current concepts of causation of the aging-re-
related diseases and on preventive and therapeutic strategies based on these concepts. The manipulation of genes associated with these diseases is widely viewed as the most promising approach to new preventive and therapeutic measures. However, if the paradigm presented here is validated for other aging-related diseases, then a strategy based on genetic manipulation, like the strategy of risk-factor avoidance, although eminently desirable, if successful, would not assure that the same or another aging-related diseases would not emerge in the period of senescence. In this scenario, the future growth of our aged population, and the required changes in our health care system, would be greater than current projections. The importance of conducting research that leads to an understanding of the aging-disease relationship poses a challenge that gerontologists of all stripes should address.

ACKNOWLEDGMENTS
Address correspondence to Herman T. Blumenthal, PhD, MD, Department of Community and Family Medicine, St. Louis University School of Medicine, 1402 South Grand Blvd., St. Louis, MO 63104.

REFERENCES

Received July 7, 1998
Accepted January 20, 1999