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Special Report from the Challenging Views of Alzheimer's Disease

What is aging? What is its role in Alzheimer's disease? What can we do about it?

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1. Introduction

Here we present a summary of the round-table discussion entitled "What is Aging, What Is its Role in Alzheimer's Disease and What Can We Do About It?" from the recent conference, Challenging Views of Alzheimer's Disease – 2004, held in Philadelphia, July 2004. Eight scientists specializing in aging, Alzheimer's disease, and neurobiology discussed the definition of aging, how aging theory relates to understanding Alzheimer's disease, and what insights from understanding this relationship could be applied to developing means to treat or prevent this disease.

2. Alzheimer's disease is an integral part of the aging process (**Ashford**)

A fundamental principle of aging in all species of complex, celled living beings is that mortality (annual hazard of dying), after an initial developmental period, increases at an exponential rate as a function of chronological age [9,23,25]. This principle is known as the Gompertz Law [14]. There appear to be few exceptions to this principle, and limitations occur only at the extremes of old-age [19]. The Gompertz function suggests that there is a relatively consistent aging pattern that is optimized for each cellular species, probably related to the instability of each constituent cell of the organism and massive redundancy [12]. The universality of this principle indicates that evolution and phylogenetic pressures operate on the genome of each species to bring the energetic forces subserving living system design [18] and repair into balance within the context of the resources and stresses of the ecological niche [25]. This concept leads to the systems perspective that the driving issue in survival is not an aging program (see [29]) but the individual's effort to stay alive as long as is optimum for the success of the species. The survival of each system of the body must be coordinated for a similar survival quality to optimize the energy expended by evolution both for developing the individual and for the individual to survive as long as is feasible. Life span ranges between various species over several orders of magnitude, for example from fruit

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flies to turtles [11]. This law even applies to humans, explaining over 99.7% of the variance of human death, separately for men (doubling time of 8.2 years) and women (doubling time of 7.5 years), between ages 30 and 95 years in the United States for the year 2000 [1]. Each gene of the genome of a species has some role in the development and survival of members of the species in the full ecological niche to which that species has adapted. Various specific genes may persist acoss generations and act on individuals with a range of degrees of positive or negative effects on longevity even after completion of reproductive competence [16]. However, after the completion of development, the net effect of the interaction of the genome and the environment on survival time across the individuals of a species is predominantly an exponential increase of mortality. This exponential mortality increase, which begins at about age 10 in humans, appears to be a fundamental property of all celled organisms and provides the definition of aging (as opposed to decay, a steady mortality risk).

Alzheimer's disease (AD) has been characterized clinically as a disease of the elderly that causes a dementia with an insidious onset and slowly progressing course that is well defined [3]. Based on its clinical pattern, AD can best be conceptualized as a disease that fundamentally affects memory (e.g., information processing and storage), and analysis of its attack on the mind and brain suggests that it is most basically a disease of neuroplasticity [27]. There has been considerable attention to the relationship between AD and the aging process. Since the incidence of AD increases with age in a pattern most closely described by an exponential function (doubling every 5 years from ages 60 to 90 [15]), the Gompertz Law appears to apply to the risk of the development of AD. There also appears to be a leveling off of AD incidence at later age [17,20], just as is seen with mortality in the extreme of aging. Because the doubling time for the increase of dementia risk is shorter than that for the increase of mortality, the direct conclusion is that the process of developing dementia is more closely associated with aging than even mortality rate. These observations clearly indicate that AD is indeed an age-related condition, and more so than most causes of death. The vulnerable system which becomes progressively more susceptible to assault by the AD process with the aging of an individual is presumably machinery that would be vulnerable to deterioration over time, and that underlying mechanism is neuroplasticity, the organism's system for information storage. The identification of AD as an aging condition which follows the Gompertz Law provides models and frameworks to understand the dynamics of the neural systems which AD affects. Using the theoretical analysis of Gavrilov and Gavrilova [12], the neurons of the brain associated with neuroplasticity can be conceptualized as a system with a large number of redundant and imperfect components. As the neurons and their connections progressively fail [4], so memory will fail.

Genetic factors associated with Alzheimer's disease are also critical [1,2,21]. Just as with specific genetic factors inducing partial syndromes of aging [16] as mentioned above, those genes associated with development of AD in younger individuals (usually autosomal dominant) are relatively rare and affect the particularly vulnerable amyloid pre-protein metabolism [24]. Such deleterious genes that currently exist in the human species have probably survived because they exert their negative effects, in this case the induction of AD, after reproduction.

The complex issue of the long-term evolutionary condition of Alzheimer's disease is more closely linked with apolipoproteinE (APOE) [2,27,28]. The APOE gene appears to mediate an important aspect of cholesterol metabolism in the brain associated with neuroplasticity [1,27]. The AD risk associated with APOE can be seen simply as a factor affecting the location of the Gompertz curve [21]. However, there are numerous energy system dynamics involved in the control of this genotype. For example, the role of longevity beyond the usual reproductive years, an individual able to maintain cognizance in the elderly state would be able to continue to contribute meaningfully to the survival of progeny and the greater tribe [10]. Since information itself is integrative, the longer a brain can survive and function well, the more complex the analyses that that brain may make to benefit the survival of the species. Another issue is that the human brain, with the survival advantage of being able to analyze and store tremendous quantities of information, has critical demands for cholesterol to form new interneuronal connections, the substrate of the stored information; consequently the environmental availability of adequate lipid nutrients and the genetic machinery to manage these nutrients represent a critical evolutionary concern.

The study of aging and AD suggests that AD is in principle an age-related condition, subject to a subset of the genetic and evolutionary pressures that affect aging in general. Analysis of AD as an age-related condition should lead to a better understanding of the implications of this devastating disorder, approaches to its treatment, and potential avenues to its prevention.

3. New choices for a definition and mechanistic understanding of aging (Atwood/Bowen)

A valid theory of aging should be able to identify a logical point in the life history of an organism that represents the onset of the aging process. Currently aging is described as beginning when there is an increase in the probability of mortality, or, put more simply, when there is a progressive decrease in functional ability. By this definition, aging is thought to commence at $\sim$ 10 years of age [6,9]. However neither of these definitions is consistent with observed phenomena. Importantly, there is not a smooth linear or logarithmic relationship between the chronological age of an organism and its probability of mortality. In humans the probability of mortality is much greater during fetal life and the first year after birth than it is during much of the remainder of one's life. It is equally difficult to determine when aging begins using the "loss of function" definition. This is because some physiological functions begin to decline while others are still developing. For instance, flexibility begins to decline as soon as we are born and hearing begins to decline after age 10, a time when some functions, such as reproduction, have not even begun. For these reasons we feel a better definition of aging is required and propose that aging is *any change in an organism over time* [8]. This definition can best be illustrated by imagining that an organism is nothing more than a multitude of molecular interactions. If these interactions were to all of a sudden stop, then there would be no aging as there is no change, as is the case with cryopreservation of embryos. However, reestablishment of these reactions, such as following the thawing of an embryo, allows for change and therefore for aging.

This new definition has several implications, not the least of which is that growth and development are part of the aging process. The new definition would also imply that the rate of change would equal the rate of aging and that the rate of aging varies throughout life (unlike the current linear aging concept). Under this scenario the fetal period represents the period of most rapid aging and we propose that the mechanism(s) underlying growth and development is (are) also responsible for senescence. Growth and development are a consequence of cell division, cell differentiation and apoptosis, and whatever regulates this process is also likely responsible for regulating aging, and therefore, senescence. Reproductive hormones, specifically the hormones of the hypothatlamic-pituitary-gonadal (HPG) axis, are known to be intimately involved in the growth and development of an organism. We propose that some of the HPG hormones primarily promote mitosis while others regulate differentiation and apoptosis. Gonadotropin releasing hormone (GnRH), luteinizing hormone (LH), and follicle stimulating hormone (FSH), likely represent the mitogenic hormones and activins the differentiation hormones. The serum concentrations of these hormones correlate well with the rate of change/aging throughout life (see Fig. 1). During fetal life they are produced in high concentrations by the placenta. The serum concentrations plummet at birth with the loss of the placenta but soon increase again during the first year of life. After this time during the remainder of childhood they remain at low concentrations until puberty when they again increase. During the reproductive period of life we believe their mitogenic and differentiation properties are countered by the sex steroids and inhibin. The age-related loss of reproductive function and therefore sex steroids and inhibin synthesis and secretion results in a significant increase in serum concentrations of LH FSH, and activins. We propose that this hormonal milieu causes cells to undergo senescence by a process we term "dyosis" – dysregulated mitosis. The consequences of dyosis are tissue dependent and in susceptible individuals are responsible for the neuropathological changes associated with Alzheimer's disease (AD). All the biochemical, pathological and functional changes associated with AD can be explained by abnormalities in cell cycle signaling (reviewed in [5]). This aberrant cell cycle signaling results in the apparent re-entry of neurons into the cell cycle, and leads to the characteristic changes observed in the AD brain: chromosomal replication leading to polyploidy, up-regulation of cell cycle markers, tau phosphorylation, AβPP metabolism and Aβ deposition, oxidative stress, increased mitochondrial DNA and Cox-1 expression, up-regulated growth factor signaling pathways, synapse loss, and death of differentiated neurons. This is supported by the fact that the gene mutations associated with early-onset AD are genes with important cell cycle functions (i.e. PS1, PS2 and AβPP). Interestingly, the AD brain displays many of the neuropathological and biochemical changes observed in the fetal brain, namely the presence of Aβ [26], hyperphosphorylated tau [13] and presenilin expression [7].

We have incorporated the above ideas into a comprehensive theory of aging which we named the "Reproductive-Cell Cycle Theory of Aging" [8]. This theory is able to explain: 1) the timing of the onset of puberty which is closely tied to longevity; 2) two phenomena that are closely related to species lifes-

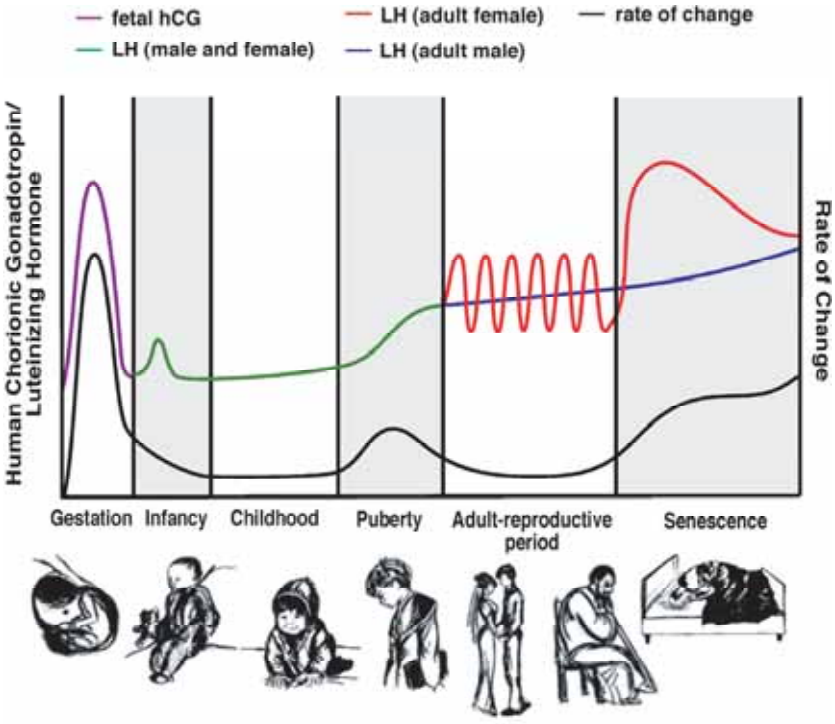

Fig. 1. Reproductive hormones drive cellular change throughout life. Large increases in mitogenicity (mitogenic index) occur during the growth and development of the mammalian fetus, infant, and pubertal adolescent. The equilibrium between mitogenesis and differentiation-apoptosis becomes dysregulated, initiating dyosis, which drives senescence [22].

pan – the rate of growth and development and the ultimate size of the animal; 3) the apparent paradox that size is directly proportional to lifespan and inversely proportional to fertility between species but vice versa within a species; 4) the simultaneous regulation of the rate of aging and reproduction as evidenced by the fact that environmental conditions and experimental interventions known to extend longevity are associated with decreased reproductive-cell cycle signaling factors, thereby slowing aging and preserving fertility in a hostile reproductive environment; 5) how differing rates of reproduction between species are associated with differences in their lifespan; 6) why species that have adapted certain predator avoidance attributes such as a shell or the ability to fly exhibit exceptional longevity for their size; and 7) an evolutionarily credible reason why and how aging occurs- the hormones that regulate reproduction act in an antagonistic pleiotrophic manner to control aging via cell cycle signaling; promoting growth and development early in life in order to achieve reproduction, but later in life, in a futile attempt to maintain reproduction, become dysregulated and drive senescence.

4. Aging and disease (Blass)

The distinction between aging and diseases of aging is theoretical, not empirical. "Aging per se" is a poor subject for experimental study, because of the lack of well-documented biological markers of aging. Chronological age is only a surrogate – and theory-bound surrogate if one excludes older animals with recognized diseases. Before the 1980s, AD was considered an excellent paradigm for studying aging – specifically aging of the brain. In AD, one has a clear biological marker (the neuropathology) and can identify controls matched for chronological age, sex, and other variables who do not suffer from this form of "accelerated brain aging." Describing Alzheimer disease as an age-related disease distinct from aging itself has been very useful in many ways but is not necessarily the most useful way to think of this condition scientifically.

5. Demographics, inflammation, and aging (Finch)

Demographically, aging is the inexorable increase of mortality rates after maturation with a doubling rate

every 8 years in all human populations. The main cause of death and during aging is vascular disease. Because the demographic mortality doubling rate is about the same as the increasing incidence of Alzheimer's after 60, one may infer a deep relationship between aging and AD. This suspicion is also consistent with many shared inflammatory processes in AD and vascular disease, including the apparent reduction of AD risk by statins, anti-inflammatory, and anti-angiogenic drugs.

6. Alzheimer disease and aging (**Iqbal**)

Brain aging becomes noticeable when the ability to learn new tasks and time to respond to intellectual stimuli and to recall past events becomes reduced in a progressive and time dependent manner. These changes occur slowly over a period of several decades and probably start in a significant way after the peak of neurogenesis, i.e. both the formation of new neurons and as well as their differentiation, is over and the gain of new neurons is surpassed by neurodegeneration. This imbalance appears to become more severe and at an accelerated rate with a variety of brain insults resulting in Alzheimer disease. These insults, the etiological factors of Alzheimer disease, include both genetic and non-genetic causes, all of which appear to involve metabolic changes. The scientific challenges to prevent, inhibit and reverse Alzheimer disease include recognition of the polyetiology of this disorder and identification and selections of the therapeutic targets. Downstream targets like abnormal hyperphosphorylation of tau are likely to result in therapeutic drugs, which will help most Alzheimer disease patients.

7. Aging and cognition (**Joseph**)

Aging can be defined as a condition where stressors are not counteracted by protective functions, leading to a dysregulation in development. In the neurosciences it is characterized by losses in neuronal function accompanied by behavioral declines (decreases in motor and cognitive performance) in both humans and animals. These "stressors" include oxidative stress and inflammation, and a great deal of research has shown that during aging the brain becomes increasingly sensitive to both. These increases in sensitivity coupled with progressive declines in age- and calcium-sensitive signaling molecules associated with memory, especially the conversion of short- to long-term memory, provide a fertile environment for the superimposition of genetic changes indicative of Alzheimer disease (AD) on the brain resulting profound losses in cognitive ability. If this is the case, then it could be surmised that interventions designed to reduce the sensitivity of brain to these insults may reduce the incidence of or forestall the development of AD. Our research suggests that nutritional intervention might be important in this effort.

8. Evolutionary aspects of aging (**Perry**)

Passage of time couples life with death for the individual and change for the species. A central aspect of biology – adaptability to all challenges – is inviolate. Over the past billion years, of all organisms living on earth, none has evaded death, nor species remained unchanged by evolution, implicating a process governed by laws as precise as those we know in the physical world.

Our personal experiences of maturation and aging are those of development and increased robustness until reproductive competence. After the reproductive period there is decline and increased chance of death. While advances in sanitation and modern medicine have increased lifespan, they have done so by making the average closer to the maximum so that, instead of dying of infection or other causes early in life, death results from degeneration of the aged, the major cause of morbidity and mortality in the developed world. Incidence of death is dependent on the generation time ($\sim$24 years) in man and is marked by decline after reproductive senescence. Forces that maintain organisms past reproduction have often been considered stochastic and not selected for regardless of whether they increase risk of death. The forces that shape reproduction and work to maintain parents and some grandparents as caregivers leave few great-grandparents. Parental loss puts children at greater risk of death whereas surviving ancestors are close competitors. If our ancestors lived for 15 generations we would have to survive in the midst of 32,000 competitors with essentially the same genetic information. This makes death an inherent function of survival.

9. Summary

A fundamental discussion in this session addressed the definition of aging, since the definition used to describe a process will determine how one attempts to

understand or provide an explanation for that process. The onset of the "aging process" was discussed. Aging is a phenomenon that occurs not just in later parts of an individual's life, but something that begins at the onset of life itself. However, there was discussion about the distinction between the processes of development and aging, especially as these two processes have common components (e.g., cell death, cancer). Aging can be understood as a multi-system process that affects all living organisms. It is important to consider what factors regulate the aging process. Within an organism, there is a balance between the evolutionary energy devoted to the development of robust systems and the accumulation of environment-related deleterious impediments in each system over time. A central pressure is reproduction, the most important function of an individual in terms of survival of the species. Removal of individuals from the ecological niche of the species once they are no longer reproductive may also be an active process that allows younger animals of the species more resources in which to mature and reproduce, so that the species can survive and evolve in an ever-changing environment. There remained a conflict about whether one system plays a dominant role in the aging process and about how pressures related to maturation and reproduction are related to the aging of the many systems of the body of the organism and the overall aging agenda for the species.

In the discussion of which single body system could be most relevant to the determination of the aging mechanism associated with AD, considered issues ranged across the full gamut of theories related to AD, including oxidative stress, neural plasticity, sex hormones, lipid metabolism, inflammation, and aberrant cell-cycle signaling. Of particular concern was whether the age-related mechanism leading to AD was a direct factor, such as a post-reproductive trigger, or a passive process, such as progressive loss of integrity in complex mnemonic systems in the brain. With age and stress, injurious changes in brain memory mechanisms accumulate, initiating the course of AD. These injuries lead to the loss of neuron processes culminating in neuron death. The progressive loss of neural plasticity eventually exceeds the brain's capacity to maintain sufficient information management for adequate function, and, at this point, dementia appears. This process occurs at an earlier age in genetically predisposed individuals and with certain types of familial mutations. There is also evidence that suggests that environmental stress (e.g., head injury) and lack of support systems (e.g., less education) may decrease the age of AD onset.

The dominant question in the discussion concerned the roles of genes and hormones that apply to AD. At the species level genes determine the overall aging pattern of the species and are the major factors contributing to the population incidence of AD. However, the 2:1 gender prevalence for women developing more AD could be related to hormonal mechanisms or only to factors which favor greater longevity for women, since women successfully age into the risk-age for AD more frequently than men. At the individual level genes provide the attribute of longevity and are the principal elements leading to the catastrophe of Alzheimer's disease.

There are two different ways to conceptualize the relationship between aging and AD. First, AD may be an integral part of the aging process. Alternatively, the AD-specific biochemical and neuropathological changes may be triggered, when vulnerable conditions develop, by an age-related mechanism. The development of AD may be dependent upon the individual's unique genetic profile, specific environmental exposures, or, more likely, both. The role of Medicine is then to understand how Nature exerts its devastating influence on the brain to cause the AD stigmata and to seek to protect individuals from this increasing adverse consequence of aging.

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