THERAPEUTICS IN THE ELDERLY

Scientific Foundations and Clinical Practice

Editors:
K. O'Malley
J. L. Waddington

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Editors:

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Preface

The proportion of Western populations living to old age is gradually increasing. Not alone is the percentage of persons reaching the age of 65 becoming greater; a dramatic change is also forecast for the distribution by age of those over 65. By the turn of the century more than 10% of those who are over 65 will, in fact, be over 85 years of age. The elderly, by dint of their burden of disease, make disproportionately large demands on the Health Care system, not least in the area of drugs and therapeutics. As physiology and the pattern of pathology change with age it is apparent that the 'substrate' for drug treatment is altered. We know relatively little of these changes and furthermore have little quantitative feel for the implications they may have for drug responses, both wanted and unwanted.

There is a growing commitment on the part of those concerned with health care, and here we include politicians, civil servants and those involved in funding research, to encourage research in the field. The contributions in the first part of this volume represent some of the fruits of research into the biology and pharmacology of ageing. The applicability of much of this information to the clinical situation is currently being evaluated. It constitutes essential building blocks towards our understanding, and therefore contributes to the scientific foundations of therapeutics in the elderly.

A symposium such as this would be incomplete without considering broader aspects of drug evaluation and use in the elderly. This is an area of concern both to prescribing physicians and the drug regulatory agencies. Finally, we have up-to-date statements on clinical management in selected conditions. The data base for much of this is incomplete, and very often we must extrapolate rather blindly from younger populations both in relation to pathophysiology and treatment.

It is our hope that getting basic scientists and clinical investigators together will have enriched both groups and provide insights that can form the basis for new approaches to research in many aspects of drug treatment in the elderly.

We wish to thank most sincerely those who have made this symposium possible. In particular we thank the President of the Royal College of Surgeons in Ireland, Mr. Victor Lane, and the Council for supporting this publication. Finally it is a pleasure to record our gratitude to Rosemary Donohoe for her invaluable help in organising this symposium and in the preparation of this volume.

Kevin O'Malley.
John Waddington.
Dublin, May 1985.

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THE AGING PHENOMENON

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INTRODUCTION

The phenomenon of biological aging is generally believed to be a manifestation of the sum of a multitude of physiological decrements that occur after sexual maturation. Yet this concept, although widely believed, cannot be accepted without qualification.

There are animals in which aging is rare or has never been demonstrated. Some fish and amphibians that have an indeterminate size may also have an indeterminate lifespan (1). Thus, the universality of aging, even in vertebrates, remains unproven. These animals are not immortal. They will die eventually of disease, predation or accidents at an actuarily determined annual rate which is not true aging.

In fact, the occurrence of aging arguably is restricted to humans and the domestic and zoo animals that we choose to protect. The extreme manifestations of old age that are found to occur in humans simply do not occur in feral animals. If aging occurs at all in wild animals its expression is brief because the physiological decrements of aging quickly make these animals vulnerable to disease and predation. They simply do not live long enough to get really old.

In developed countries humans have been so successful in resolving these causes of death that their aging is expressed to an extreme unattainable by wild animals. Civilization has produced life expectations that were unknown in prehistoric times, revealing a plethora of physiological decrements that perhaps, teleologically, should never have been revealed. Aging may be an artifact of civilization or domestication because that "unnatural" circumstance has permitted the expression of aging that otherwise would not have occurred.

AGING AND DISEASE

Phenomena of aging must be distinguished from phenomena of disease. Biological changes attributable to aging are frequently referred to as "normal age changes," as if there was a category of "abnormal age changes." Age changes are not diseases, they are natural losses of function. Loss and greying of the hair, reduced exercise capacity and stamina, wrinkled skin, the menopause, presbyopia, loss of short term memory and hundreds of other similar decrements of old age are not regarded as diseases. They do not increase our vulnerability to death. Other "normal" decrements in vital organs do produce increased vul-

nerability to pathological change. For example, normal age related decrements in immune system functions increase vulnerability to diseases that in youth would be easily resolved. Or, although antigens might be recognized as self in youth, when they are recognized by an aging immune system as non-self, they produce many of the chronic autoimmune diseases of old age.

CAUSES OF AGING

What is the cause of the aging phenomenon? This question, regarded to be a fundamental goal in the science of gerontology, might well be analagous to asking: "What is the cause of development?" Similarly, the frequently asked question: "How can aging be stopped or slowed?" is equivalent to asking: "How can development be stopped or slowed?"

There is no good reason why aging has to happen. August Weismann believed that aging occurs to benefit the species by removing less fit animals from an environment where limited space and other resources should be conserved for the young (2). This is an illogical argument because if chronologically older animals continued to remain fit, their deaths would not benefit younger members. Thus, there would be no basis for an aging process to evolve in the first place. Weismann's notion can also be discredited on the basis that there is little possibility that evolution could have selected for the aging process.

As discussed earlier, few feral animals live long enough after sexual maturation to experience old age. As soon as they incur even slight decrements in, say, running speed or jumping ability, they are culled by predators. Similarly, as soon as their immune system becomes less capable, they may die of disease. Or, what is more likely, they will also be culled by predators when the disease has reduced their ability to escape. As a result, the likelihood is remote that evolution could have selected for the aging process. There are simply too few feral animals on which selective pressure could have applied. Thus, aging cannot be viewed as an adaptation.

Furthermore, there is no selective advantage for a species to have its members live much beyond the age of sexual maturity and child rearing. For example, from the standpoint of simple survival of the species, there is no advantage for humans to live much beyond the age of, say, thirty. This would permit sufficient time for production of new progeny and rearing of that progeny to sexual maturation. Since life expectation at birth in prehistoric times was about 18 years, it is apparent that the human species has survived for a much longer period of time with an 18 year life expectation than it has with the current 75. Thus, the human species has survived for a much longer period of time with rare, or no, old members than it has with many old members.

Weismann, however, was prescient on one major point. He surmised correctly

that the ability of normal somatic cells to replicate and function was limited (3). Despite the fact that the opposite was believed for decades (4-7), we upset this dogma in 1961 (4,5). Thus, the limited ability for normal human and animal cells to replicate and function may represent a fundamental reason why the lives of individual animals are finite. In fact, many of the multitude of functional decrements reported to occur in cultured normal human cells as they reach the end of their lifespan are identical to the changes that occur in humans as they age (8).

What then are the most likely causes of biological aging? The relative newness of the field of gerontology as a seriously studied science and the consequent lack of an extensive and reliable data base has encouraged speculations on the theoretical underpinnings of the field. An additional cause of the plethora of biogerontological theories is that manifestations of biological changes over time affect virtually all components of living systems from the molecular level up to that of the whole organism. These hierarchical changes have made it possible to construct theories of aging based on events that occur over time at the level of the molecule, organelle, cell, tissue, organ, or whole animal.

Depending more upon the bias of the theorist than actual fact, a selected age-associated change within this hierarchy will often be defended with great vigor and emotion. Nevertheless, most current theories of biological aging suffer from the criticism that they are, or may be, mere expressions of the effect of some more fundamental change. There is common failure to realize that changes more fundamental to the one observed may induce the effect that was chosen for study.

Since all fundamental life processes depend on genomic events, theories of aging that depend on these events have attracted the most attention.

THE GENOME AS THE BASIS FOR AGING

A variety of age-related biological phenomena appear to be orchestrated by events that occur in the genetic apparatus. Many of these phenomena are so profound that, when taken together, they provide the factual underpinning for several genetically based theories of the cause of age-related changes in cell metabolism and function. Some of these phenomena are:

(1) The life spans of animal species are remarkably constant and species-specific. For example, the maximum lifespan for a fruit fly is about one month, a mouse about three years, and a human about 115 years.

(2) In humans, for example, the mean difference in longevity between fraternal twins was found to be twice as great as that in identical twins (9). The ancestors of centenarians and nonagenarians were found

to have significantly greater longevity when compared with a series of ancestors of individuals not selected for great longevity (10).

(3) In many animal species the female is more longevous than the male, but this is by no means true for all animal species (1).

(4) In the past decade, it has become apparent that some single gene changes result in accelerated aging in humans, as in the case of progeria and Werner's Syndrome. On the other hand, Down's Syndrome is characterized by trisomy. In each of these conditions several age-related phenomena appear to be accelerated. Polygenic changes are also thought to influence the rate and characteristics of age changes in normal individuals.

(5) Genotoxic effects, that is, the effect of mutagens (e.g. radiation) on longevity, are thought to result from effects on the cell genome.

(6) A direct correlation has been reported to occur between the efficiency of certain kinds of DNA repair processes and species longevity. More long-lived species are found to have more efficient DNA repair capabilities. However, DNA ligation is also associated with normal development (11).

(7) Heterosis, or hybrid vigor, occurs when members of two different inbred strains are themselves mated. They produce F_1 hybrids having greater longevity than either parental strain. A phenomenon known as the Lansing effect suggests that in some animals, including humans, the progeny of older mothers have a shorter life expectation and that this effect may extend through several generations (1,12).

(8) In a study of inbred mouse strains, Goodrick (13) estimated that half of the variance associated with longevity was due to genetic factors.

These observations have persuaded many biogerontologists to believe that the genetic apparatus plays the central role in causing age changes. It is important, however, to emphasize that contrary opinions prevail. Some of the non-genetic factors that may produce age changes include passive stochastic processes such as the accumulation of damage or errors in important macromolecules (14).

GENOME-BASED THEORIES OF BIOLOGICAL AGING

The Somatic Mutation Theory

The somatic mutation theory of aging enjoyed its greatest popularity in the late 1950's and early 1960's as a derivative of burgeoning developments in the field of radiobiology. The central concept is that the accumulation of a sufficient level of mutations in somatic cells will produce physiological decrements characteristic of aging. If mutations are the fundamental cause of age changes, they must occur randomly in time and location (15). Early champions of this idea

were Szilard (16) and Failla (17,18). Failla postulated dominant mutations as causes of aging. Szilard argued that aging was due to genes ("targets") being "hit" or "struck" by a mutational event which, unlike Failla, he regarded as recessive. Thus, a pair of homologous genes must be hit at a particular rate and in a sufficient number of cells in order to achieve phenotypic expression.

Maynard-Smith (15) pointed out that if Szilard was correct, inbred animals, homologous at most gene loci, would display the maximum species lifespan since homozygous faults would be lethal and heterozygous faults would be few or non-existent. Yet, in mice and Drosophila, inbreeding reduces life span. Furthermore, Szilard's hypothesis would predict that diploid organisms would live longer than their haploid counterparts who contain only one chromosome set. In the hymenopteran wasp, Habrobracon, haploid and diploid males have identical life spans. Haploid males are more sensitive to ionizing radiation than are diploid male wasps, yet irradiation shortens the lifespan of diploids far more than that of haploids. These observations are inconsistent with the mutation theory. Although reduced lifespans do occur in irradiated animals, extended lifespans have also been observed (19,20). Also, irradiated old animals should show accelerated age changes, as should animals treated with mutagenic agents, but they do not (21).

Curtis (22), the last major advocate of the somatic mutation theory, based his conclusions on the frequency of abnormalities observed in the chromosomes of dividing cells in the livers of old mice. He found a higher frequency of abnormalities in the cells of a short-lived strain when compared with those found in long-lived strains. Curtis made similar findings in guinea pigs and dogs. Nevertheless, other comparisons between short- and long-lived strains were inconsistent with these findings, and hybrids between short- and long-lived strains did not yield the expected results. Neutron irradiation of dividing cells was found by Curtis to yield aberrations in up to 90 percent of the cells, yet lifespan was unaffected.

In the past decade, few significant studies have been conducted on the role of somatic mutations in aging. In spite of the contrary evidence, there is an expectation that the critical experiments should be redesigned using the technology of modern molecular biology.

The Error Theory

This theory, to some extent derivative of the somatic mutation theory, was first postulated by Medvedev (23), elaborated by Orgel (24), and received experimental support principally from Holliday and Tarrant (25).

It has been suggested that the repeated DNA nucleotide sequences in the genome of eukaryotic organisms may be (1) a reserve of information for evolu-