KEYNOTE ADDRESS:
GENETICS AND AGING; THE WERNER SYNDROME AS A SEGMENTAL PROGEROID SYNDROME

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ABSTRACT

The maximum lifespan potential is a constitutional feature of speciation and must be subject to polygenic controls acting both in the domain of development and in the domain of the maintenance of macromolecular integrity. The enormous genetic hererogeneity that characterizes our own species, the complexities of numerous nature-nurture interactions, and the quantitative and qualitative variations of the senescent phenotype that are observed suggest that precise patterns of aging in each of us may be unique. Patterns of aging may also differ sharply among species (for example, semelparous vs. multiparous mammals).

Some potential common denominators, however, allow one to identify progeroid syndromes in man that could lead to the elucidation of important pathways of gene action. (The suffix "-oid" means "like"; it does not mean identity.) Unimodal progeroid syndromes (eg., familial dementia of the Alzheimer type, an autosomal dominant) can help us understand the pathogenesis of a particular aspect of the senescent phenotype of man. Segmental progeroid syndromes (eg. the Werner syndrome, an autosomal recessive) may be relevant to multiple aspects of the senescent phenotype.

Some results of research on the Werner syndrome may be interpreted as support for "peripheral" as opposed to "central" theories of aging; they are consistent with the view that gene action in the domain of development (adolescence, in this instance)
can set the stage for patterns of aging in the adult; they point to the importance of mesenchymal cell populations in the pathogenesis of age-related disorders; finally, they underscore the role of chromosomal instability, especially in the pathogenesis of neoplasia.

INTRODUCTION

All phenotypes result from an interaction of nature with nurture, but all of us participating in this conference have the conviction, I'm sure, that the most productive route to understanding the biology and pathobiology of aging (including the major age-related diseases of human beings) will come from a dissection of the genetical aspects.

In this review, I shall briefly summarize the rationale behind this belief, some genetic approaches to the problem, and how the so-called progeroid syndromes of man, and especially the Werner Syndrome, can help in these endeavors.

The Maximum Lifespan Potential is a Constitutional Feature of Speciation

The principal rationale for the genetic approach to the study of aging is the well-established species-specific variation in maximum lifespan potential (MLSP) (Comfort, 1979). Among mammals, the range of MLSP is about 40-50 fold (Altman and Dittmer, 1962). Thus, when genetic variations are such as to lead to the evolution of a new species, a characteristic lifespan is typically among the new constitutional features of its phenotype.

Lifespan Must be Subject to Highly Polygenic Controls

A corollary of the above conclusion is that it is almost certainly the case that comparatively large numbers of genes are involved in modulating the rates at which aging (and, presumably, of age-related diseases) develop, since it is reasonable to assume that changes in the expression of numerous genes are involved in speciation.

Three attempts have been made to estimate the numbers of genes that might be involved in the aging of Homo sapiens. All of them, including my own attempt (Martin, 1978) are based upon questionable assumptions, however, so that a sound quantitative answer to that important question is still not available.

The first such attempts, carried out independently by the late George Sacher (1975) and by Richard Cutler (1975), involved an