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James R. Carey: Longevity

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Introduction

1.1. The Problem

Some of the most profound questions in biology are those concerned with the nature and origin of both life span and aging—equal in stature to those involving the genesis of life, of sex, and of human consciousness. One of the most important reasons for studying aging is because it is basic to life and its endpoints—morbidity and death. As Gavrilov and Gavrilova (1991) note, it will never be possible fully to understand the nature and origin of life without understanding the nature and origin of both its constraints and its limits. Another reason for exploring the large mystery of aging is that slowing the aging process in humans could yield powers to retard senescence, to preserve youthfulness, and to prolong life greatly (Kass 1983). This would have vast and far-reaching affects on all of our important social institutions and fundamental beliefs and practices inasmuch as it is not possible to change one segment of society without affecting the entire network of relations.

Despite the intense interest in human aging, virtually nothing is known about why some individuals live to middle age and others live to extreme ages. Indeed in humans, the life-style recommendations that follow from biomedical and social studies of the elderly are unremarkable—do not smoke, use alcohol in moderation, exercise, avoid fatty diets, shed excessive weight, and minimize risk of accidents (Christensen and Vaupel 1996). Although this strategy of identifying individual factors associated with extended longevity in humans may eventually provide valuable insights for improving quality of life and reducing mortality risks, most gerontologists believe that the evolutionary and biological determinants of longevity can only be understood through the use of comparative demography and of model experimental systems such as yeast, nematodes, fruit flies, and laboratory rodents. This book is about studies using both of these approaches: (1) a large-scale Mediterranean fruit fly experimental system used to construct life tables, which, in turn, are brought to bear on questions concerning the nature of aging and longevity; and (2) comparative demography of life span using large-scale databases containing information on both vertebrates and invertebrates.

My broad goal is to collate, integrate, and synthesize the results of over a decade of research on both actuarial aging in the medfly and the comparative

demography of life span and to interpret these findings in the context of human aging. Specific goals for the book are (1) to present the major conceptual, empirical, and analytical results from medfly studies on longevity and mortality using graphical arguments and actuarial techniques; (2) to integrate concepts related to the science of aging at the level of the whole organism from demography, gerontology, and insect biology; (3) to identify general biodemographic principles including those concerned with senescence, mortality, and longevity as well as conceptual aspects of life span and maximal ages; and (4) to situate the biodemographic findings in the context of human aging and to use these fundamental principles both as a foundation for the emerging field of biodemography and as a framework for considering the future of human life span.

1.2. The Epistemological Framework

1.2.1. *Mortality and Aging as Fundamental Processes*

The results of studies on the biology of death, mortality, longevity, and life span using animal models such as the medfly are as relevant to humans as are those on basic aspects of inheritance in *Drosophila* flies (Ashburner 1989; Jazwinski 1996) and on development in nematode worms (Hengartner 1995; Thomas 1994). In these cases emphasis is placed on studying the basic process rather than on studying the specific outcome (Carey 1997). For example, eye color in *Drosophila* has little to do with eye color in humans; but geneticists and evolutionary biologists have made major advances in understanding genetic aspects of populations such as drift, dominance, sex linkage, mutation rates, and selection by studying the changes in the frequency and inheritance patterns of these traits in experimental fly populations. Similarly, studies of fly mortality provide important insights into the nature of many fundamental actuarial processes important to demography: whether differential rates of aging underlie the gender differences in longevity; whether Gompertz mortality rates are manifestations of universal senescence “laws”; whether animals possess definitive life-span limits; and whether physiological changes at the individual level influence both local (short age periods) and lifetime patterns of cohort mortality.

I believe that answers to these basic actuarial questions are important to biodemography for several reasons: (1) they provide a frame of reference for interpreting actuarial data for both human and nonhuman species; (2) they serve as a stimulus for new approaches to studying aspects of human mortality such as the gender gap or the existence of life-span limits; (3) they provide a biological context for predicting possible changes in mortality trajectories in situations where human data are sparse or less reliable such as for

mortality trajectories at the most advanced ages; and (4) mortality studies on nonhuman species can provide “proof of principle” for alternative hypotheses concerning the underlying causes of changes in the age trajectory of mortality, such as demographic heterogeneity versus physiological changes at the individual level.

1.2.2. Model Systems and Actuarial Patterns

One of the main stumbling blocks to the serious use of model systems in studying actuarial aging has been the mistaken belief that, because causes of death in humans are unrelated to causes of death in invertebrates (e.g., nematodes, fruit flies), little can be learned from detailed knowledge of age-specific mortality in these model species. This perspective is based on the “theory of the underlying cause” in public health and medicine—if the starting point of a train of events leading to death is known (e.g., cancer), death can be averted by preventing the initiating cause from operating (Moriyama 1956). For aging research the problem with this perspective is that death is seen as a single force—the skeleton with the scythe. A more apt characterization that applies to deaths in all species is given by Kannisto (1991), who notes that deaths are better viewed as the outcome of a crowd of “little devils”; individual potential or probabilistic causes of death, sometimes hunting in packs and reinforcing each other’s efforts, at other times independent. Inasmuch as underlying causes of death are frequently context-specific and are difficult to distinguish from immediate causes, and given that their post-mortem identification in humans is often arbitrary (and in invertebrates virtually impossible), we find that studying the causes of death often provides little insight into the nature of aging. If aging is considered as a varying pattern of vulnerability to genetic and environmental insults, then the most important use of model species in aging research is to interpret their age patterns of mortality as proxy indicators of frailty.

1.3. Importance of Scale

1.3.1. Historical Background

One of the most important conclusions of the National Institute of Aging’s workshop on “Upper Limits to Human Life Spans,” held at UC Berkeley in 1987, was that data on mortality at advanced ages on nonhuman species was lacking. For example, a review of the literature on life tables on several hundred species of arthropod revealed that the vast majority of studies were based on less than fifty individuals. While these small numbers provide reasonable estimates of life expectancy at birth for cohorts, it is not possible to

estimate mortality rates from data derived from small cohorts because so few individuals remain alive at the older ages. Even the widely cited classic life-table studies suffer from this problem, including those by Pearl and Parker (1924) on *Drosophila*, Leslie and Ransom (1940) on voles, Leslie and Park (1949) on flour beetles, Evans and Smith (1952) on the human louse, Pearl and Miner (1935) on several “lower” organisms, Deevey (1947) on a wide range of invertebrates and vertebrates in the field, and Birch (1948) on insects. In general, the biological, ecological, and gerontological literature contains perhaps several thousand life tables on a wide variety of species but collectively these life tables contribute very little to knowledge of age-specific mortality rates. In particular, they contribute virtually nothing to knowledge of age-specific mortality at the most advanced ages.

1.3.2. Large-scale Medfly Life Tables

A universal assumption made by most biologists and gerontologists is that mortality rates increase with age at the same exponential rate over all mature age classes (Gompertz 1825). Because no one seriously challenged this assumption, constructing mortality schedules required only that researchers monitor mortality in a relatively small cohort at younger ages, fit a straight line to the logarithm of these rates, and extrapolate to the older ages. That the logarithm of these rates did not increase linearly with age was simply not open to question.

Perhaps the main reason that no one previously challenged the gerontological canon that mortality rates increase exponentially at older ages in most species was a practical one—large numbers of individuals of any species are both expensive and difficult to rear. Enormous amounts of time, money, and effort are required to construct the mortality schedule for a cohort of even a few thousand laboratory rodents. For example, it is estimated that the maintenance costs for a single mouse is \$1/day. Thus monitoring a cohort of 1,000 mice throughout their life times would cost nearly \$1 million. But even these studies would provide little information on mortality rates at the oldest ages since only 100 mice would be alive when 90% of the original cohort was dead, and there would only be 10 individuals alive when 99% of the cohort was dead. Moreover, the numbers are halved when questions about mortality sex differentials are addressed. Insects are less expensive to rear than rodents but are still relatively costly. This is because a considerable amount of space is needed for rearing and a full-time staff must be hired that is dedicated exclusively to rearing.

Gaining access to essentially unlimited numbers of medflies at the medfly rearing facility in Mexico removed the main logistical obstacle to gathering mortality data on a large scale. Even if an insect rearing program would have

been developed exclusively for the studies discussed in this book, the scale could not possibly have matched the industrial scale of the Moscamed medfly rearing program. Consequently the mortality studies would have consisted of perhaps a 1,000 insects reared from each of 1,000 different batches of diet rather than over 100,000 flies reared from 8 to 10 different batches, as was the case with access to the factory flies. A large amount of variation in mortality rates between cages and trials is eliminated by having essentially unlimited numbers of same-aged flies at any time.

1.3.3. Experimental Principles

Studies were initiated according to three operational principles. *First*, focus on only a small number of basic questions. For example, the initial project focused on two straightforward questions: “What is the trajectory of mortality at the most advanced ages?” and “What are the sex-mortality differentials?” *Second*, conduct studies on a large scale. The scale of the database from each study provided a rich source database for subsequent analyses. This proved to be extremely important because of the nature of mortality measurement—large initial cohorts become small at older ages due to attrition. Thus extraordinarily large initial cohorts provide enough survivors to measure mortality at the most advanced ages. *Third*, keep both the data and the data-gathering simple. We required technicians to record only two pieces of information on each fly—sex and age of death. This simplicity minimized the likelihood of error. However, the simplicity of the original question helped to reinforce the main goal, foster a clear sense of purpose at all research levels, and promote simplicity and a sense of purpose in design and execution of the project.

1.3.4. Overview of the Medfly Mortality Database

Inasmuch as a substantial part of this book is based on the results of large-scale life table studies of the medfly, it will be useful to review briefly the database that serves as its empirical foundation. A summary of the main experiments, species used, and number of individuals is presented in table 1.1. Three aspects of this table merit comment. The first and most obvious characteristic of the database is experimental scale—the majority of studies used anywhere from 100,000 to 1.2 million individuals. This scale provided considerable statistical power with respect to differences within and between treatments, between sexes, and over many age classes including the most advanced ages. A second characteristic of this database is the range of conditions under which adult mortality and longevity were measured, including

TABLE 1.1

Large-scale Mortality Studies on Mediterranean Fruit Fly and Other Tephritid Fruit Flies or Parasitoid

<i>Species/Study Description</i>	<i>n</i>	<i>Reference(s)</i>
Mediterranean fruit fly (<i>Ceratitidis capitata</i>)		
1. Large-scale life table study (groups)	1,200,000	Carey, Liedo, Orozco, Tatar, and Vaupel 1995; Carey, Liedo, Orozco, Tatar, and Vaupel 1992
2. Large-scale life table study (solitary)	50,000	Carey et al. 1995; Carey et al. 1992
3. Effects of initial density	215,000	Carey et al. 1995; Carey et al. 1992
4. Effects of sterilizing irradiation	425,000	Carey et al. 1995; Carey et al. 1992
5. Old vs. new medfly strain	200,000	Liedo and Carey 2000
6. Sugar vs. full (protein) diets	416,000	Müller et al. 1997b
7. Larval density effects on adults	232,000	Liedo and Carey (unpublished)
8. Periodic starvation	400,000	Carey, Liedo, Müller, Wang, and Chiou 1999
9. Irradiation-by-diet effects	536,000	Carey, Liedo, Müller, Wang, Love, Harshman, and Partridge 2000
10. Catastrophic starvation	200,000	Liedo and Carey (unpublished)
11. Sexes reared separately (virgins)	120,000	Carey, Liedo, Harshman, Zhang, Müller, Partridge, and Wang 2002b
12. Reproductive history of individuals	1,000	Carey, Liedo, Müller, Wang, and Chiou 1998a; Carey, Liedo, Müller, Wang, and Vaupel 1998b
13. Dual modes of aging	500	Carey, Liedo, Müller, Wang, and Vaupel 1998c
14. Periodic alteration of diet (sugar-full)	<u>800</u>	Carey, Liedo, Harshman, Liu, Müller, Partridge and Wang 2002a
Subtotal (medfly)	3,996,300	
Life table studies of other fruit fly species and a parasitoid		
15. <i>Anastrepha ludens</i> (Mexican fruit fly)	1,100,000	Vaupel et al. 1998

TABLE 1.1 (continued)

<i>Species/Study Description</i>	<i>n</i>	<i>Reference(s)</i>
16. <i>A. obliqua</i> (West Indian fruit fly)	300,000	Vaupel et al. 1998
17. <i>A. serpentina</i> (Sapote fruit fly)	340,000	Vaupel et al. 1998
18. <i>D. longicaudatis</i> (parasitoid wasp)	<u>28,000</u>	Vaupel et al. 1998
Subtotal (other species)	1,768,000	
GRAND TOTAL	5,764,300	

Note: See cited reference(s) for technical details and study objectives. Number of individuals denoted by *n*.

cage densities, cage types (group vs. solitary), medfly strains, larval rearing density, diet types, diet periodicity, starvation conditions, mate availability, irradiation effects, reproductive timing, and male behavior. These manipulations provided important insights into the plasticity of mortality, the determinants of longevity, and sex-mortality differentials. A third characteristic of the database is that it includes the results of large-scale life table studies, not only on the medfly but also on 3 different tephritid fruit flies and a parasitoid wasp. This is important in the context of comparative biodemography and enabled us to answer the general question “How robust are the findings from the medfly studies?”

1.4. Overarching Themes

Three broad themes emerged from the medfly research that cut across many aspects of aging research and that we use as conceptual anchors for the book. One overarching theme derived from the research project is *absence of species-specific life span limits*. As will be shown in subsequent chapters, evidence for the veracity of this concept is found in the results of virtually every large-scale life table study on the medfly and related species. The slowing of mortality rates at advanced ages in all studies suggested that it is not possible to specify a specific life-span limit to the medfly and, by implication, to that of any species.

The second overarching theme of the book is that *the mortality response of males and females is context-specific*. Although this concept seems both intuitive and obvious due to behavioral and physiological differences between the sexes, there are surprisingly few experimental studies that include not simply measures of the sex-specific mortality response but also in-depth analyses of sex-specific differences. Reasons for the paucity of information

and analyses on sex differences are, in large part, related to the particulars of the model systems used in aging research. For example, sex differentials are not measured in the yeast model because reproduction in yeast is primarily asexual, nor in the nematode model because *C. elegans* is hermaphroditic, nor in the *Drosophila* model because fruit fly researchers are primarily concerned with genetic rather than demographic differences, nor in the rodent models because the primary research area in rodents is dietary restriction and males are used mainly in this research because many mouse and rat researchers believe that the more complicated response of females to dietary restriction would be difficult to interpret.

The third major theme that became apparent from the results of the medfly research is the “*biodemographic linkages between longevity and reproduction.*” Reproduction is the cardinal function of all living organisms and, therefore, it is not surprising that reproduction and the length of life are related. However, this relationship is often not straightforward since what constitutes a “reproductive unit” is not necessarily the single offspring. For example, in mammals there is a physiological cost of gestation but there is also a cost in the depletion of primordial follicles (i.e., atresia).

1.5. Organization of the Book

The book unfolds in a hierarchical sequence consisting of three clusters of chapters. I introduce the book in the first cluster: chapter 1 (“Introduction”) describes the conceptual, empirical, and analytical details, and chapter 2 (“Operational Framework”) provides a brief survey of experimental and analytical concepts and methods. These chapters contain a quick overview of the main themes in aging and biodemography research, background information on the medfly, a description of the facility where the NIA-funded research was conducted and the basic experimental protocols, and a review of demographic techniques and concepts. The second cluster of chapters (3–7) contains experimental and/or theoretical results of the medfly studies. In chapters 3 (“Mortality Deceleration”) and 4 (“Reproduction and Behavior”) I present the results of descriptive studies on mortality, longevity, reproduction, and what my colleagues and I have termed “supine behavior” in the medfly. These baseline studies include the results from the original large-scale life table study on 1.2 million medflies and reproductive patterns obtained from studies of the reproductive history of 1,000 individual females. The results from research described in these chapters provided the foundational work for posing hypotheses about underlying mechanisms that framed the research on mortality and longevity that is described in chapters 5 (“Mortality Dynamics of Density”), 6 (“Dietary Effects”), and 7 (“Linkages between Reproduction and Longevity”). The results of research contained in

these chapters all involved different types of environmental manipulations. The last cluster of chapters is concerned with syntheses, identification of general biodemographic principles, and theory. In chapter 8 (“General Biodemographic Principles”) I outline a total of seventeen fundamental principles derived from either the results of medfly research presented in previous chapters or from the general literature. I then build on the concept of principles but focus on those pertaining to “humans as primates” as well as those pertaining to humans in contemporary societies. Chapter 9 (*A General Theory of Longevity*) consists of a theoretical paper that my colleague Debra Judge and I wrote arguing that life span extension in humans and other social species is self-reinforcing. In chapter 10 (“Epilogue: A Conceptual Overview of Life Span”) I provide a synopsis of the main abstract and conceptual elements concerned with research on aging and longevity including hypotheses on the future of human longevity.