Sociality, Hierarchy, Health: Comparative Biodemography: Papers from a Workshop

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Maxine Weinstein and Meredith A. Lane, Editors; Committee on Population; Division of Behavioral and Social Sciences and Education; National Research Council

Sociality, Hierarchy, Health

COMPARATIVE BIODEMOGRAPHY

A COLLECTION OF PAPERS

Maxine Weinstein and Meredith A. Lane, *Editors*

Committee on Population
Division of Behavioral and Social Sciences and Education

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COMMITTEE ON ADVANCES IN BIODEMOGRAPHY: CROSS-SPECIES COMPARISONS OF SOCIAL ENVIRONMENTS, SOCIAL BEHAVIORS, AND THEIR EFFECTS ON HEALTH AND LONGEVITY: A WORKSHOP

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Acknowledgment of Reviewers

The papers in this volume have been reviewed by the audience during the workshop presentations, and in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published volume as sound as possible and to ensure that the papers meet institutional standards for clarity and scientific rigor.

Review comments and draft manuscripts remain confidential to protect the integrity of the process. However, we wish to thank the following individuals for their review of papers in this volume: Elizabeth Barrett-Connor, Division of Epidemiology, Department of Family & Preventive Medicine, University of California, San Diego; Cynthia M. Beall, Department of Anthropology, Case Western Reserve University; Dan G. Blazer, Duke University Medical Center; Christopher L. Coe, Institute on Aging and Department of Psychology, University of Wisconsin; Lee T. Gettler, Department of Anthropology and Hormones, Health, and Human Behavior Lab, University of Notre Dame; Daniel Levitis, Department of Biology and Max-Planck Odense Center on the Biodemography of Aging, University of Southern Denmark; Charles Nunn, Department of Evolutionary Anthropology and Duke Global Health Institute, Duke University; Daniel Promislow, Department of Pathology and Department of Biology, University of Washington; Jacob Raber, Division of Neuroscience, Oregon Health and Sciences University; Gene E. Robinson, Institute for Genomic

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final drafts of the collection of papers before its release. The review of this collection of papers was overseen by Mark D. Hayward, Population Research Center, University of Texas at Austin. Appointed by the National Research Council, he was responsible for making certain that an independent examination of each paper was carried out in accordance with institutional procedures, and that all review comments were carefully considered. Responsibility for the final content of the papers in this volume rests entirely with the authors and the institution.

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Sociality, Hierarchy, Health: Comparative Biodemography

Maxine Weinstein, Hillard Kaplan, and Meredith A. Lane

INTRODUCTION

In the nearly 20 years since the first meetings that resulted in the publication of *Between Zeus and the Salmon* (National Research Council, 1997), biodemography as a discipline has flourished, generally proceeding in three complementary directions. Along one line, biosocial surveys have proliferated. Initiatives as diverse as the Health and Retirement Study[1] and its offshoots; Midlife in the United States;[2] the National Social Life, Health, and Aging Project;[3] and the Taiwan biomarker study, Social Environment and Biomarkers of Aging Study[4] have been providing social and demographic data that also incorporate a wide range of biomarkers. This line of research is explored in three National Research Council (NRC) volumes: *Cells and Surveys* (2001), *Biosocial Surveys* (2007), and *Conducting Biosocial Surveys* (2010).

In a second line of research, diverse studies of the biodemography of longevity have been thriving, with much of the work led by contributors to the 1997—as well as to this—volume: Steven Austad, James Carey, Caleb Finch, Hillard Kaplan, Ron Lee, James Vaupel, and Ken Wachter. The first paper in this volume, by Kenneth Wachter, is particularly helpful in looking

[1]See http://hrsonline.isr.umich.edu/ [June 2014].

[2]See http://www.midus.wisc.edu/ [June 2014].

[3]See http://www.norc.org/Research/Projects/Pages/national-social-life-health-and-aging-project.aspx [June 2014].

[4]See http://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/3792 [June 2014].

back at a condensed history of biodemographic research on longevity and forward to much of the workshop. A third direction, on the biodemography of reproduction, was followed in *Offspring,* which was published by the National Academies Press in 2003 (National Research Council, 2003).

Development of this volume was prompted by the sense that it would be a good time to revisit both the theoretical underpinnings of biodemography and the empirical findings that have emerged over the past two decades. This introduction does not pretend to be a comprehensive summary of the contents of this volume; rather, it is an admittedly idiosyncratic tour through some of the key areas of inquiry, important workshop discussions, and intellectual foci of the individual papers.

The steering committee for the workshop that led to this volume was charged with commissioning papers that would examine cross-species comparisons of social environments with a focus on social behaviors along with social hierarchies and connections, to examine their effects on health, longevity, and life histories.

A large charge! The result is far ranging, covering a broad spectrum of human and nonhuman animals, exploring a variety of measures of position in social hierarchies and social networks, and drawing links among these factors to health outcomes and trajectories. The scope of biodemography—with apologies to T.S. Eliot[5]— has been substantially expanded beyond the mere birth, copulation, and death of a cannibal isle. Clearly, no single workshop or volume can cover everything related to comparative biodemography. This workshop did not address, for example, the kinds of genetic and social changes that have occurred over the last ten thousand years or so since people began living in settled communities, the effects on health of sedentary group life, or the genesis and increase in hierarchy in human societies.

Notably missing from among the papers in this volume is consideration of migration. Surely, migration is linked to social connection, given the large remittances that migrants often send to their natal home, and to hierarchy, given the variable social and economic niches that migrants occupy. The workshop touched on it indirectly in discussions of the movement of young male baboons away from their maternal groups, and in comments about swarming bees, but there was no thorough consideration of it.

Also missing is consideration of ape social systems, especially those of chimpanzees and bonobos, and their implications for health and longevity, a topic that is receiving increasing attention. Among chimpanzees, females migrate and males remain in natal territory, cortisol is positively correlated with rank in males but negatively correlated among females (Muller

[5]Elliott, T.S. (1932). *Sweeney Agonistes: Fragments of an Aristophanic Melodrama. Fragment of an Agon.* London, England: Faber and Faber.

and Wrangham, 2004; Emery Thompson et al., 2010), and females mate with all or most adult males in their community during estrus (Emery Thompson, 2013). All of these characteristics unfold in ways that affect profiles of stress over the lifecourse, and sex and rank differences in morbidity and mortality. More generally, the workshop papers and discussions addressed only a limited number of species; it must be considered a *start* on comparative biodemography.

In addition to members of the original cast of *Zeus* mentioned above, the workshop was enriched by the contributions of biologists and anthropologists—as well as a few new demographers and epidemiologists—who brought new perspectives, data, and analysis to the fore: Chris Kuzawa and Dan T.A. Eisenberg, Anne Bronikowski and her colleagues, Steve Suomi, Michael Marmot and Robert Sapolsky, Paul Hooper and his colleagues, John Wingfield, Karen Ryan, Jenny Tung, Kenneth Weiss, Jonathan Stieglitz and his colleagues, Brian Johnson, Peter Ellison and Mary Ann Ottinger, Joan Silk, Susan Alberts and her colleagues, Janet Mann, John Haaga, David Miller, and Jeffrey Kahn. Papers from most of the presenters at the workshop are included in this volume, and video-recordings of the workshop talks by those authors and discussants who have agreed are available at UCTV Seminars.[6]

LIFE HISTORIES AND INTERGENERATIONAL TRANSFERS

Intergenerational transfers were a recurring theme in the presentations, papers, and discussions (see, for example, papers in this volume by Hooper, Gurven, and Kaplan, by Lee, by Stieglitz and co-authors, and by Wachter). Mostly, intergenerational transfers are from older to younger generations. Genetic material is a fundamental form of downward intergenerational transfer; transfers of wealth taking the form of food or other resources figure prominently in life histories. A particularly interesting form of intergenerational transfer is position in social hierarchy—an inheritance that has a strong effect on health. As noted in presentations by Alberts and her coauthors, by Suomi and his collaborator, and by Silk, among both baboons and rhesus macaques, infants inherit their mothers' position in the social hierarchy. Generally speaking, as discussed in the presentation of Michael Marmot, among humans in industrialized settings, higher position in hierarchy is associated with better health and lower mortality. And, while less documented than in humans (see Finch and Singer), position in hierarchies among nonhuman primates is also directly related to health. If position in hierarchies is determined by parents' status, then changes in opportunities for upward mobility will affect the health of the inheritors. The extent to

[6]See http://seminars.uctv.tv/ [June 2014].

which social mobility has declined, or whether indeed it has declined, in industrialized nations has become a matter that is much discussed in the popular press, although the scholarly evidence appears to be mixed. But, if it is true that social mobility is declining, it has important consequences for improving the health of future generations and addressing social disparities in health.

The so-called "grandmother hypothesis" is part of an ongoing discussion about life history theory—the tradeoffs and relationships among reproduction, longevity, and senescence. Humans typically enjoy a long post-reproductive life, although this is rare among other species. The question is, why do women live past menopause? An important aspect of this post-reproductive life is the contribution made to their descendants by post-reproductive humans, mothers in particular. The grandmother hypotheses—there are various formulations—seek to attribute this post-reproductive period to improved survival of those descendants. The paper by Hooper and colleagues suggests an amendment to the grandmother hypothesis, with evidence of large flows of resources from older men to their adult children and to their grandchildren. The importance of grandfathers, and the role of men in general, has been underappreciated in models of human life history evolution, and in the health and well-being of three generations of individuals.

The paper by Ellison and Ottinger puts forward important insights drawn from comparative data. They argue that an incremental approach, as proposed, for example, by Chu and Lee (2013), is central to the explanation, but make an interesting case for an alternative evolutionary pathway. These authors suggest that post-reproductive survival has been lengthened rather than reproduction ending early; their conclusion is that "post-reproductive life selects for 'grandmotherly' behavior, not the other way around." This issue was further discussed at the workshop. Given that there is significant intra-population variability in ages of last reproduction, menopause, and death, and in rates of aging, it is clear that natural selection is continually acting on aging in both reproductive and other organ systems. Thus, a fundamental question is why natural selection has favored similar rates of reproductive aging among humans and apes, but a much longer lifespan in humans. Another question is whether reproductive aging differs between chimpanzees and humans in the extent to which physical condition determines age of last reproduction, with, as suggested by Emery Thompson et al. (2010), the effect of physical condition being much stronger in chimpanzees.

Not all intergenerational transfers are downward, and as noted by Ellison and Ottinger, their proposed pathway allows for upward contributions from individuals who have not yet reached reproductive maturity, an opening for what they term "indirect reproductive effort." Such upward

transfers should be familiar, at least to demographers, from explanations of fertility transitions that posit that changes in the direction of intergenerational transfers contribute to declines in fertility. Even when *net* flows are downward across generations, day-to-day flows tend to go in both directions in small-scale human economies, revealing the importance of social integration to individual health and survival.

The paper by Lee focuses on his work on the role of intergenerational transfers in life history theory. Underlying his work is how consideration of intergenerational tradeoffs enhances the classical, typically *intra-individual,* understanding of allocations among growth, maintenance, survival, and reproduction. Using both simulation and analytic techniques, he develops a set of six hypotheses that form the basis of an ambitious empirical research agenda. One hypothesis—that the parent that is more involved in care or transfers to the child will live longer—is well supported by evidence among humans and baboons (see, for example, the paper by Alberts and her colleagues and discussion of it below). Another hypothesis, addressed by Ellison and Ottinger, is that post-reproductive life is associated with longer dependency of offspring. As noted below, documentation of extended post-reproductive life in the wild is sparse, but it will be enlightening to start looking at data that address this hypothesis and the others Lee proposes.

Like Lee, the paper by Hooper and his colleagues explores human life histories, providing a framework for understanding how links among ecology, sociality, and demographic characteristics provide insight into human evolutionary history. They propose three underlying social relationships that respond, and have responded to, human ecology and which have important effects on health: kin-based altruism, cooperative pair bonds, and reciprocal cooperation. They draw on data from ethnographic research to examine interdependencies among the kinds of factors explored by Lee (longevity, post-reproductive survival, and intergenerational transfers), parental coupling and investment, and cooperative social insurance. It was especially refreshing to see a discussion of the pros and cons of using data from currently existing hunter-gatherers or forager-horticulturalists to infer information about humans' evolutionary past. All too often, it seems, the assumption is made that such populations reflect our history: ". . . contemporary populations," they remind us, "are not frozen relics of the past."

Psychological well-being and mood disorders, a dimension of health that has not been widely considered by biodemographers, is examined in light of life histories by Stieglitz and his colleagues using data from adult Tsimane forager-farmers of Bolivia. They explore whether mood disorders have an adaptive value that is linked to the ability to produce and transfer resources that improve survival of oneself or one's kin. They propose that productivity has both a direct effect on well-being and an indirect effect that is mediated by transfers of resources.

SOCIAL HIERARCHIES

The social gradient in health, that is, that expectation of life is directly associated with position in social hierarchies as measured, for example, by education or income, is widely observed in both contemporary societies, and—as far as the data will help determine—in historical populations (Marmot and Sapolsky, Finch and Singer), but individual health conditions show more variable relationships that depend on context. Using data from baboons, ". . . who don't smoke, eat fast foods, or have differential access to health care depending on ability to pay," Marmot and Sapolsky speculate that low rank itself may not be the causal agent, rather, it may be that low rank is associated with lack of control over life circumstances, which in turn lead to stress and ultimately poor health. That is, what is observed as low rank may be a proxy for psychosocial stressors that are beyond the control of the person, or baboon, who experiences them.

There may be cross-species similarities among primates (including humans) in the role of stress in mediating the relationship between low status and poor health and mortality outcomes. At the same time, it is likely that the relationships among resources, social status, and health will vary across human societies depending upon numerous factors. Whether access to food energy is a constraint on health is one example: the relationship between socioeconomic status and obesity varies by sex, ethnicity, race, and country, and those factors interact in complex ways.

The understanding that mind and body are intimately linked has a venerable history: "The body's mischiefs, as Plato proves, proceed from the soul: and if the mind be not first satisfied, the body can never be cured."[7] The paper by Karen Ryan focuses, in particular, on mechanisms that link chronic exposure to stress with metabolic disease and health. One such mechanism is stress-induced chronic activation of the immune system, which appears to play an important role in the development of metabolic diseases such as obesity, cardiovascular disease, and Type-2 diabetes. As described by Ryan, a recent area of research elaborates the relationships among inflammation, the microbiome, and health. One hypothesis of interest is that psychosocial stress causes changes in gut microbiota, which in turn stimulates the immune system, ultimately leading to chronic metabolic disease.

Evidence from biosocial surveys is mixed. Links between self-reported stress (both perceived stress and stressors) and measures of overall physiological dysregulation were weak in work reported by Glei, Goldman, and their colleagues (Glei et al., 2007). In support of Ryan's hypothesis, however, there is some evidence of an association between exposure to stressors

[7]Burton, R. (1631). *The Anatomy of Melancholy*. [Reprinted 1924.] New York: Empire State Book Company (p 358).

and inflammation (Glei et al., 2013a). Comparative work also suggests that perceived stress is associated with cardiovascular and metabolic markers and inflammation, at least in some populations (Glei et al., 2013b).

SOCIAL CONNECTION

E.M. Forster exhorts, "Only connect!"[8] For both human and nonhuman animals, connection matters. The importance of social connections reverberated throughout the workshop and appears throughout this volume. The paper by Joan Silk provides an excellent example of the effects of social relationships. The work of Silk and her colleagues, first among the Amboseli baboons and later elaborated observing the Moremi baboons, shows strong evidence of stable social bonds, with grooming partners generally drawn from close kin, but existing even among females that had no close relatives. The connections had important consequences for health: females with strong social connections had greater longevity and better infant survival than those with weaker connections. Position in hierarchy had no effect on infant survival although higher position was associated with greater longevity.

A comparison of the chapters that focus on social relationships among baboons with those on humans reveals an important difference. Social support is critical in the lives of both species, but among baboons, most support is utilized in competitive relationships with other group members; that is, social support in baboons appears to be largely a zero sum game with clear winners and losers. It has been proposed (e.g., Alexander 1974) that predation risk motivates grouping in primates, and the complex social relationships that result help manage the competition generated by group life. In contrast, among humans, social support and transfers of resources generate positive surpluses by buffering risk, providing help in times of illness, increasing resource production through cooperation, accruing gains from a division of labor by age and sex, and creating intergenerational assistance in human capital formation. Of course, competition and status striving is a feature of human social relationships that parallel those of baboons.

The importance of social connection for human health was dramatically illustrated by Finch and Singer. They presented work by Singer and Ryff (1999) and Ryff et al. (2001), who used data from the Wisconsin Longitudinal Study.[9] Both men and women who had positive relationship pathways, that is, who had at least one very caring parent when they were growing up and who had a good relationship during adulthood, had lower health risk profiles than those on negative pathways. What is especially

[8]Forster, E.M. (1910). *Howard's End*. London, England: Edward Arnold.
[9]See http://www.ssc.wisc.edu/wlsresearch/ [June 2014].

striking about the relationship pathways is how much they moderate the effects of disadvantageous economic conditions. Among people who had negative economic pathways (either persistently poor or declining), those who also had negative relationships were two or three times as likely to have high health risk indexes as those with positive relationships. More generally, variability in a health risk index was lower among study participants who had positive relationships than among the participants who had negative relationships. Finch and Singer conclude that "with positive relationships across life, health is less dependent on money." Perhaps this finding offers some hope if indeed society is facing dwindling levels of social mobility: "Only connect!"

GENES: WHAT'S BRED IN THE BONE WILL OUT IN THE FLESH

A central challenge for biodemographers is elegantly stated in the paper by Tung: "Biodemographers are fundamentally interested in real populations—in which individual genetic effects will generally be modest, and individual study subjects will be genetically diverse." As noted by Wachter, "the scientific returns from biodemographers doing the same kinds of studies that biomedical and genetic researchers are already doing seem modest." What then, can biodemographers contribute? There was considerable debate on this question during the workshop. One promising area is the kind of work being done by Wachter in stochastic vitality models and in non-linear mutation accumulation. The extent to which model calibration can be achieved using the kinds of genome-wide data that are becoming increasingly available remains to be seen. Wachter appears to be cautiously optimistic.

The mathematical work by Wachter and his colleagues relaxes some of the more restrictive assumptions of earlier models, and imagines genetic variants with effects throughout life. The effects of different mutants on mortality are allowed to change non-linearly with age. These more recent models can be integrated more easily with physiological processes and are more realistic than earlier formulations, yet they still predict that specific kinds of mutants will be selected out of the population more slowly than others (those whose effects increase with age, such as one that might increase LDL cholesterol, for an example not used by Wachter). Given rates of entry of new mutants and rates of exit through selection, there will be a tendency toward age-based genetic load that can account for Gomperz-like aging.

Discussion and exchanges that followed Wachter's presentation point to the direction for the future. Wachter acknowledges that the genetic load explained by mutation accumulation theory is just a tiny part of the genome, and that optimizing selection on genes with pleiotropic effects is a major driver in genetic architecture. The question of what the aging process

and mortality curve would look like in the absence of genetic load remains unanswered. So, there is now some clarity of purpose for future research to (1) integrate optimality and mutation accumulation approaches into more adequate theories of genetic architecture and phenotypic changes with age; (2) understand why there is so much persistent heritability of what appear to be important traits that presumably should have been fixed by selection; and (3) discover what genetic architecture underlies both heritability and plastic responses to different environments.

The paper by Weiss is far more cautious about the potential contributions of genetics research; indeed, the apt word might be "pessimistic." While agreeing in principle that genetics can be used to understand causal mechanisms that underlie age patterns of mortality and morbidity and ultimately life histories, he is not sanguine about "when, where, or even whether a genomic approach is justified." He identifies a number of core constraints for such an enterprise, including: (1) Identification of causal variants of interesting phenotypes is limited by somatic mutation combining with genetic mutation that combine to create imprecise mappings. (2) Most genes regulate or process other genes, therefore DNA sequences operate only in the context of multi-way interactions that may not occur in the locations where the interacting factors are produced. Thus, local gene function cannot be understood from local mapping "hits" alone. (3) Epigenetic effects that affect gene action can mimic familial correlations and can also involve enzymes that are coded by genes located elsewhere in the genome. In short, it's complicated. And, as noted above, the effects of genes cannot be separated from the context in which they operate.

Context, context, context. It was a recurring theme throughout the workshop, and recurs throughout the papers in this volume. Here, we present a few examples. Weiss talks not only about the context of multi-way interactions at the micro level, but also the context of the genomic background and environmental experience of each individual. Kuzawa and Eisenberg provide additional examples of how context plays into intergenerational transmission of environmental effects in their paper. Substantial notice has been given to the effects of early environmental experience on adult outcomes both in humans and nonhuman animals, but their paper and presentation highlight the pathways through which environmental effects can be transmitted to descendants: phenotype-to-phenotype transmission via placenta, breast milk, or parental behavior; direct germline epigenetic inheritance; and possibly, plasticity in telomere length as a potential transgenerational influence on lifespan. These pathways can affect such characteristics as obesity and diabetes, metabolism, stress physiology, memory, affect regulation, and even mortality.

Weiss proposed one potential direction for further research to be drawn from synthesizing these papers. He suggested that, at least for the time

being, genetic work should be focused on the few diseases for which large effects of single nucleotide variants can be detected. Another possibility is that attention should be directed to understanding the sources of missing heritability by taking advantage of what is now known about regulation of gene expression, and by building more adequate functional models of interactions among genes. Models of the functional design underlying important biological traits, such as energy management, inflammation, and social interactions, should help guide the search for organizational principles underlying gene regulation, gene-gene interactions, and gene-by-environment interactions. Such models may help identify the processes underlying the heritability of complex phenotypes.

Tung's paper proposes a second potential direction for future research, one that also emphasizes the importance of functional analysis. She argues that studying the functional organization of the genome, particularly its role in gene regulation, is a fruitful approach to understanding the comparative biodemography of aging. The core idea is that measures that get at variation in gene regulation, especially when viewed across the genome, can provide insight into how variation in environmental factors, including social experience, affect aging. Her paper lays out an ambitious agenda for integrating studies of population health and aging on the demographic side with, on the genetics side, functional genomic strategies for understanding the effects of the social environment.

Context matters for genes. It matters for individuals. It matters for societies. It matters for frogs and baboons, for turtles and humans, for macaques and snakes and birds. Very simply, it matters.

HUMAN AND NONHUMAN ANIMAL SUBJECTS

When *Between Zeus and the Salmon* was published in 1997, the application of ethics to biodemography *seemed* simpler—although maybe it wasn't. *Drosophila* and nematodes are not warm and cuddly, and their use in experiments on longevity did not immediately raise the kinds of questions that come up when primates and other vertebrate animals are subjects of study, when anthropology and biology are integrated into biodemography. Even in the 1990s, there was discussion of the results of the experimental manipulation of rodents and monkeys; it's just that not much time was spent in consideration of the ethics of "animal models." This workshop highlighted the increase in cross-disciplinary integration, and also threw a spotlight on lack of sophistication regarding the ethics of nonhuman animal research and on human research in the age of "big"—no, make that "massive"—data. The workshop presentations stimulated discussion about the scientific necessity for and ethical considerations in captive-animal research.

One concern that arose in discussion is the inherent tension between the overwhelming scientific imperative of making data available for all researchers and the equally compelling need—indeed, it's usually a promise—to protect the confidentiality and privacy of those who provide cheek swabs or other specimens to researchers. These competing goals are not new, but they have taken on new and increased urgency: The greater expense of studies leads to greater pressures to make data publicly available, and the need for greater statistical power encourages pooling data across studies, while increasing internet access to data makes individual privacy and the confidentiality of data ever-receding targets. *Conducting Biosocial Surveys* (National Research Council, 2010) made a start on considering these issues—at least with respect to the proliferating number of demographic surveys that incorporate the collection of biospecimens. A strong recommendation in that volume was that data sharing plans be carefully designed and vetted; a corollary was that the National Institutes of Health (NIH) prepare and publish guidelines for acceptable plans. The conclusions regarding protecting confidentiality are particularly instructive. Other recommendations (pp. 76-79) included the following: explicit informed consent for any uniquely identifying data (including genetic data); encryption of such uniquely identifying data on institutional or personal computers; sharing data that change little over time only under restricted conditions; the development by the NIH of standards and procedures for sharing confidential data; periodic expert audits of confidentiality and computer security. To date, few of these recommendations have been implemented, but perhaps the proposed changes to the Common Rule[10] on human subjects, if they are adopted, will address many of these concerns.

Studies of nonhuman animals were a more prominent part of this workshop than those related to previous NRC biodemography publications. In his commentary, Jeffrey Kahn suggested that the criteria the NIH now applies to the use of chimpanzees in research could serve as a starting point for developing guidelines for the use of other nonhuman primates and other animals. He put forward three (minimal) criteria proposed for the use of chimpanzees in research: (1) that the research be critical to human health, not just "interesting"; (2) that no other acceptable model is available; and (3) that it would be unethical to perform the research on human subjects. *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity* (National Research Council, 2011) also mandated that the animals be maintained in ethologically appropriate environments and that the animals "acquiesce" (i.e., do not object) to the research.

These guidelines themselves raise additional questions, for example, how "acquiescence" to invasive experimentation can be a meaningful in-

[10]See http://www.hhs.gov/ohrp/humansubjects/anprm2011page.html [April 2014].

dication of "agreement," or how such acquiescence—assuming it could be obtained—could be separated from a response to positive (or negative) reinforcement. How necessary is experimental research on nonhuman animals? As reported in the *NIH Record*,[11] former NIH Director Elias Zerhouni has argued that "we need to refocus and adapt new methodologies for use in humans to understand disease biology in humans" because it is becoming clear that animal research on human diseases is not producing the results that are needed.

Since its original publication, the chimpanzee report has been modified to permit non-invasive behavioral observation on chimpanzees in their natural environments. The papers in this volume attest to the methodological advances that have been made in measuring stress, health, and social relationships among nonhuman primates in that context.

THE CONTRIBUTIONS OF COMPARATIVE BIODEMOGRAPHY

Humans are complex, nonhuman animals are complex, and all exist within different contexts. But, despite the differences between mice and men—as Marmot and Sapolsky note, humans are not "simply baboons in clothes"—perhaps we can learn from studies of nonhuman animals. The contribution by Alberts and her colleagues takes a fresh look at the male-female mortality paradox by comparing data on baboons and humans. Briefly, the "paradox" is the observation that while women live longer than men in virtually all modern societies, they also suffer from poorer health. The Alberts et al. wide-ranging review of the available historical data suggests that for humans, with some exceptions, both the female advantage in mortality and the health-survival disjunction is evident. Among baboons, however, while females experience lower mortality, there is little evidence to suggest that females have worse health. They conclude that the delayed mortality advantage has a long evolutionary history, but the male health advantage does not. They propose explanations: (1) that the rapid changes in sex steroid concentrations observed in women over age 50 are not seen in baboons, and (2) that the measures of health that are typically used for women are impossible to collect among wild baboons. These proposals themselves lay out an agenda for future research. One might speculate about how their results link back to the evolutionary pathway proposed by Ellison and Ottinger regarding post-reproductive survival. What would be seen if post-reproductive baboons were commonly observed? Or what could be learned about the paradox if it were possible to measure health in the few other species (some toothed whales for example, see Ellison and Ottinger in this volume) that have long periods of post-reproductive life?

[11]See http://nihrecord.od.nih.gov/newsletters/2013/06_21_2013/story1.htm [April 2014].

Papers by Johnson and Carey and by Miller and Bronikowski and their colleagues take us farther afield, into the realms, respectively, of social insects (particularly honeybees) and ectothermic vertebrates (specifically painted turtles, garter snakes, and yellow-legged frogs). What are the commonalities? Like many of the papers discussed here, the work by Johnson and Carey points to the importance of considering multiple levels of investigation, from molecular and individual to colony (or society) and the role of intergenerational transfers in survival, growth, and reproductive success. Miller, Bronikowski et al. report that environmental factors, including stress, affected mortality of the animals they studied, and like humans and the rhesus macaques discussed by Suomi at the workshop, the quality of early life experience and subsequent resilience were related: among the long-lived ecotype garter snakes, inferior early life conditions provided inadequate preparation for substandard subsequent environmental circumstances. Evidently, even among garter snakes, the arm of childhood reaches long and strong into later life.

A FEW CLOSING THOUGHTS

All aspects of people's lives, from birth to death, are affected by their social relationships and their larger social context. In this, there is continuity with many nonhuman primate relatives. Interdependence is deeper in the human case, however, because a division of labor in the production of resources, and the redistribution of those resources, are universal features of human societies.

Scientists are now getting a glimpse of the mechanisms through which social conditions can affect gene activity, both within the lives of individual organisms and across generations. Still missing, though, is a functional understanding of those mechanisms. It is not known, for example, whether patterns of methylation during development and aging represent adaptive responses to phenotypic conditions. Still, in light of what appears to be a long evolutionary history of social interdependence in our species and in our ancestral primate line, it seems likely that natural selection has acted on how gene activity—and cellular machinery more generally—change in response to changes in social environments and phenotypic conditions. Development of theory that considers functional relationships may help organize the complexity of those mechanisms.

Initial attempts to explain significant variation in health through the identification of single nucleotide polymorphisms may be faltering, and more of the same may produce diminishing returns. However, scientists are coming to a deeper understanding of the nature and nurture duality. These insights have come about not simply through blurring the distinctions between the two, but through a more nuanced grasp of their interplay over

diverse time scales during the life course of organisms and over evolutionary time. There is no map for how to explore this new territory, but a greater integration of bench science with research into the life histories of whole organisms in their social contexts and natural habitats is a path forward.

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Alleles, Mortality Schedules, and the Evolutionary Theory of Senescence

Kenneth W. Wachter

EVOLUTIONARY SENESCENCE IN THE DAYS OF ZEUS AND THE SALMON

The publication of the collection *Between Zeus and the Salmon* edited by Wachter and Finch (National Research Council, 1997) marked a moment of consolidation for the field of biodemography. Regularities in the shapes of demographic schedules as functions of age across a small set of highly diverse species had been established and confirmed. Demographers were learning about classical evolutionary theory of senescence. They were becoming familiar with Medawar's ideas about the process called mutation accumulation, with Williams' ideas about the phenomenon called antagonistic pleiotropy, and with the need to understand commonalities in demographic outcomes across species within evolutionary frameworks.

In 1997, on the other hand, quantitative models for evolutionary processes affecting senescence were short on demographic structure. Overall scientific knowledge of the character of genetic variation across the genome was limited. Demographic thinking stood in need of greater clarity about the distinct roles of genetic variation maintained in equilibrium and erstwhile genetic variants, now omnipresent or gone to "fixation."

"Allele" in the title is a word for a genetic variant. In this paper, I generally refer to the most common kind of alleles, found in Single Nucleotide Polymorphisms (SNPs) and Single Nucleotide Variants (SNVs). An individual's genetic code can be pictured as a string of letters; at most positions or "sites," all members of a species have the same letter, but at some mil-

lions of sites, a majority has one letter and a minority a different letter. Any minority, no matter how small, counts as an SNV. Substantial minorities, say 1 percent or more, count as SNPs. Alleles with multiple effects, for instance, effects on both fertility and mortality, are called pleiotropic; when some are beneficial and some detrimental, they are called antagonistic. These words have become important to demography, because biodemographic theory is generating hypotheses about the statistical properties of alleles and their relationship to demographic schedules while genetic sequencing technology is making it possible to confront hypotheses with observations.

Demographers turn to evolutionary theory for two purposes: to understand commonalities and to understand differences. In this paper, I concentrate on commonalities. I consider research aimed at understanding general patterns shared across very different kinds of organisms in very different environments. The genetic process of mutation accumulation introduced by Medawar offers some of the best material for this purpose, for finding what flies, worms, elephants, and humans have in common. Other papers in this volume concentrate on differences. They scrutinize research aimed at making sense of specific contrasts, the differences in adaptive strategies and body plans that separate flies, worms, elephants, and humans. A rich literature drawing on a long tradition of fieldwork in biology employs the tools of optimal life history theory. Demographers have been extending this direction of inquiry with studies of the implications of sociality and intergroup and intergenerational transfers in social species. This part of evolutionary demography is described in this volume in the papers by Ronald Lee and by Paul Hooper, Michael Gurven, and Hillard Kaplan. Broader implications of biodemography are described by James W. Vaupel (2010).

A word is in order about fixation versus persisting genetic variation. Consider the treatment in Kaplan and Robson (2002) of symbiotic relationships between investment in brain size, intelligence, and longevity, described further in papers in this volume. The legacy of evolutionary tradeoffs is presumably encoded into alleles that have long since progressed to fixation. An association between brain size and intelligence driven by genetic variation is not to be expected across a present-day class of undergraduates. By the same token, age-specific demographic outcomes may easily reflect optimal tradeoffs across the lifespan without being driven by genes that differ from person to person. Within social species like humans, transfers within groups and across generations may be seen as shifting the optimal balance of investments in growth, reproduction, survival, and repair under hypothetical physiological constraints (Chu and Lee, 2006; Baudisch, 2008) without a mandate for genetic specification. Tradeoffs may be realized in strategies pursued by individuals within environments during their lives in accordance with evolved norms of reaction. Allelic variation is not required for optimal life history theory to make sense.

Successor volumes to *Between Zeus and the Salmon*, entitled *Cells and Surveys*, *Offspring*, and *Biosocial Surveys*, edited respectively by Finch, Vaupel, and Kinsella (National Research Council, 2001), Wachter and Bulatao (National Research Council, 2003), and Weinstein, Vaupel, and Wachter (National Research Council, 2007), emphasized the need for collection of genetic markers in conjunction with longitudinal social science surveys rich in demographic and behavioral information. The hurdles standing in the way of these enterprises were surmounted, and we are starting to reap the benefits of the new data. Analysis of genome-wide data is a huge enterprise pursued by giant research teams all over the world. The scientific returns from biodemographers doing the same kinds of studies that biomedical researchers are already doing seem modest. Many groups are looking for "silver bullets" or immediately valuable needles in haystacks, small numbers of candidate genes where different alleles entail big effects. They are, in other words, looking for cases where allelic variation in a population is strongly associated with medical and behavioral outcomes. Big effects mean "bingo."

Biodemographers, on the other hand, while sometimes sharing such ambitions, also bring a different perspective. We are interested in small effects, in haystacks rather than needles. It is the accumulation of large numbers of somewhat independent small age-specific effects, whose distribution has been shaped over long stretches of time by natural selection, that seems most plausibly responsible for shared regularities in age-specific demographic schedules. The obvious comparison is with the heights of members of a population, going back to Francis Galton, where the observation of Gaussian distributions among adult members of populations is not ascribed to the detailed action of a few alleles but to the Central Limit Theorem applying to a large collection of small statistically independent contributions. It is generally a disappointment to biomedical and behavioral researchers when few, if any, effects on some trait from a large suite of genetic polymorphisms prove statistically significant. But for the program of evolutionary demography, when analysis pertains to traits that are known from twin studies to be heritable, bounds that show that genetic effects are individually small, but numerous and various, have payoff. They underwrite the relevance of statistical sources for regularity. Small effects mean "bingo."

Ideas presented here are developed with more formal structure in Wachter et al. (2014), based on the January 2014 Sackler Colloquium of the National Academy of Sciences. Our discussion is restricted to adult, senescent mortality, where most progress has been made so far. Extensions to the analysis of regularities in infant and child mortality and in age-specific fertility should be possible, but the requirements and concomitants of growth and development and of mating practices make for complexities that are prudent to postpone.

Different kinds of heterogeneity are at stake in different segments of biodemographic modeling. The next section begins with a context familiar to many demographers, proportional hazards, and shows how new models can be seen as attempts to overcome limitations of fixed-frailty specifications in hazard analysis. Succeeding sections take up in turn three parts of the modeling repertoire: stochastic vitality, Genome-Wide Association Studies, and mutation accumulation. The final section draws back from details to survey some big questions and answers that evolutionary demography is offering. It concludes with a glance at early results from genome sequencing and the promise they hold for connecting some biodemographic models with empirical genetic data.

HETEROGENEITY: LIFELUCK, RISK, AND FRAILTY

Natural selection operates on phenotypic variability correlated with genetic variation. The underpinnings of evolutionary demography are therefore found in demographic treatments of population heterogeneity. For demographers the familiar treatment of heterogeneity is the fixed frailty formulation of Vaupel, Manton, and Stallard within the framework of proportional hazard models (Vaupel et al., 1979). The advantages and limitations of fixed frailty models serve as a convenient point of departure.

The appeal of proportional hazard modeling, on top of its empirical success, is the separation it allows between the characterization of differentials and the characterization of age patterns. Sir David Cox launched the subject with partial likelihood methods by separating estimation of age-independent effects of covariates from estimation of an age-dependent baseline hazard function. More generally, who dies early and who dies late can be studied on a percentile basis separately from studying the ages to which percentiles correspond. In one modern formulation (Wachter, 2014b), distinctions are drawn among three sources of heterogeneity called "lifeluck," "risk," and "frailty."

Lifeluck is represented by a unit exponential random variable denoting on a logarithmic scale the relative position of an individual's duration till death among people entirely alike in observed and unobserved covariates. It is the quantity in use for simulating an age at death, once the survival curve is completely specified. Risk encapsulates effects of an individual's observed covariates, familiar from the hazard multiplier in any Cox model. Frailty is the lifelong fixed multiplier of Vaupel et al. (1979), a random statistical effect meant to capture unobserved heterogeneity, generally assumed to be drawn from a Gamma probability distribution. These three components of heterogeneity within the context of proportional hazards adumbrate the processes described in the following sections on stochastic vitality, effects in Genome-Wide Association Studies, and mutation accumulation.

The mechanics of hazard modeling via lifeluck, risk, and frailty may be followed in the textbook treatment in Chapter 8 of *Essential Demographic Methods* (Wachter, 2014a). For this paper's purposes, what matters is the metric provided by the quotient of lifeluck divided by the product of risk and frailty. In this metric, for studying frailty distributions, populations with different baseline hazard functions can be pooled.

Variance in frailty manifests itself in a tendency for aggregate population hazard functions to taper off into plateaus at extreme ages. As population members age and die, demographic selection is culling high-frailty individuals early, leaving a set of survivors with lower frailties. The observation of plateaus in survival data for a number of model organisms and for humans, findings that did much to launch the field of biodemography, is a chief empirical phenomenon whose explanation is at stake in evolutionary models. It is well understood, however, that most kinds of heterogeneity, and not solely fixed frailty, tend to promote plateaus.

The fixed frailty framework has advantages and limitations, advantages notable in early studies of the heritability of longevity and limitations coming to the fore as data and modeling progress. In Yashin et al. (1995), frailties for a pair of related individuals are treated as the sum of a gamma variate shared between them and gamma variates unique to each of them, with the same rate parameter and differing shape parameters estimable from twin data. The sum of shape parameters, estimated at 4.1 in that study, is often rounded up to 5 to fit observations of plateaus among cohorts now reaching old age. Twin-study estimates of the heritability of adult lifespan at around 25 percent are described on page 537 of Vaupel (2010). Parameters can be chosen so that demographic selection with fixed Gamma frailty and Gompertz baseline hazards can fit observed survival curves and so in a formal sense could fully account for observed plateaus, but in a substantive sense such an explanation for plateaus is unsatisfactory.

In particular, if frailty is taken as a quantity fixed across the lifespan, the extent of heterogeneity required to promote plateaus at old ages implies some individuals with such low frailties as to have implausibly low death rates at early adult ages. Thanks to the pooling property already mentioned, it is reasonable to think about samples of a million or even a billion individuals. The least-frail member in a sample of a million with Gamma frailty with shape parameter 5 has average frailty 1/33. Such factors are many times smaller than those for the most potent observed risk factors and they entail the presence of a few individuals with superhuman low mortality at early adult ages.

A second substantive limitation of the fixed frailty formulation is the implication that heterogeneity among survivors always decreases with age. It is hard to maintain that the physiological condition of 90-year-olds is more homogeneous than the condition of 25-year-olds, even bearing in

mind that the proportional effect of higher old-age hazards amplifies whatever heterogeneity is there.

These two limitations of the fixed frailty perspective point the way toward two main refinements of the treatment of heterogeneity in mortality. The first limitation can be avoided by viewing a baseline hazard as a sum of cause-specific components, each with its own profile of age-specific effects within a competing risk framework. If separate random components of frailty multiply each age-specific component of baseline, heterogeneity driving plateaus at older ages is partially decoupled from heterogeneity at young adult ages, relieving the sense of implausibility. For components associated with genetic influences, this generalization of frailty points forward toward models of mutation accumulation.

The second limitation of the fixed frailty perspective is the enforced decline of heterogeneity among survivors. That can be avoided by replacing fixed frailty with a form of frailty changing over time. Initial randomness in physiological condition can be supplemented by incremental randomness across the lifecourse from the "thousand natural shocks that flesh is heir to." This generalization of frailty points forward toward models of stochastic vitality.

STOCHASTIC VITALITY

In stochastic vitality models of survival through the lifecourse, heterogeneity present at birth is supplemented age by age by systematic trends and random shocks, usually modeled with a Markov process. Vitality may be modeled as a high-dimensional vector including physiological indices whose transitions can be estimated from longitudinal surveys, as in the sophisticated stochastic risk factors models of Kenneth Manton, Anatoli Yashin, and their collaborators. Generic properties are readily examined with stylized unidimensional models building on the pioneering work of Le Bras (1976). For purposes of visualization, variations on Brownian motion processes along the lines of Weitz and Fraser (2001) supply easy examples. A Brownian motion is a continuous counterpart of a random walk. Picture a variable called "vitality" summarizing a person's state of physical robustness and vulnerability to death. At birth, for each person, it has some initial value, whose unobserved distribution across people is somewhat akin to the frailty in Vaupel et al. (1979). Vitality, however, does not stay fixed across life but heads up and down in haphazard little random steps superimposed on a long-term trend. The accumulation of many kinds of illnesses, physiological insults, treatments, nutrition, stress, and the like can be imagined as driving a person's trajectory of vitality.

In such models, unobserved heterogeneity among individuals is being augmented across the lifecourse by new variation even as it is being

diminished by demographic selection. The observable outcome, death, is determined to occur when the trajectory or "sample path" of vitality hits some lower boundary or hovers below it for a lethal amount of time. The boundary may be some fixed minimal level or some curve varying with age. In sophisticated versions, probabilities of death may vary smoothly with distance from the boundary rather than impinging only when the boundary is crossed.

For demographers, the most noteworthy property shared by models of this kind is a generic prediction of plateaus in hazard rates at extreme ages. Mathematical proofs for a wide class of models have been offered by Aalen and Gjessing (2001), Gjessing et al. (2003), and Steinsaltz and Evans (2004). As heterogeneity in vitality accumulates, deaths progressively cull individuals with lower vitality, and under a broad range of specifications the distribution of vitality converges to what is called a "quasi-stationary" state. In the true stationary state, everyone is dead. At any particular advanced age, the vitalities of those still surviving come to have a distribution that persists. Vitalities at the low end of the distribution are removed by death but replenished by the random arrival of individuals whose state of health is going downhill.

The move from fixed frailty to stochastic vitality avoids the drawback I have discussed from implausibly low mortality rates at early ages from individuals at the extremes of low frailty. In vitality models, heterogeneity accumulates. Individuals with modest survival advantages in middle age may find themselves with palpable advantages in extreme old age, but only a rare few of them for whom the luck of the draw has happened to come out in their favor over and over. This picture accords with common sense. Some inborn advantages are erased over the lifecourse, others bolstered. It is only reasonable to think that a lifetime of ups and downs increases the power of demographic selection at extreme ages and reinforces the formation of plateaus. The demographic relevance of stochastic vitality models is enhanced by another property described in the following section. They are particularly amenable for combination with models of mutation accumulation, potentially allowing informative connections with genomic observations.

EFFECTS IN GENOME-WIDE ASSOCIATION STUDIES

In public consciousness, the subject of alleles and mortality calls up a picture of the gene for X, the gene for Y, of a handful of "genes for longevity." Some individual alleles with palpable effects on longevity have been discovered in model organisms and a few have been detected for humans. A careful account is given by Vaupel (2010). Substantial effects from specific genetic variants can be treated as statistical fixed effects, that

is to say, observable covariates in stochastic risk factor models. They are the counterpart of risk in the trio of lifeluck, risk, and frailty. The techniques of Genome-Wide Association Studies (GWAS) are devoted to ferreting out such effects from data on millions of SNPs for thousands of survey respondents.

The APO-E polymorphism is the most famous example for demographers. From the point of view of evolutionary demography, however, such alleles are not very informative about the origin of common regularities in demographic schedules across species with widely different body plans and environmental niches. Each specific causal effect presumably has its own specific age pattern and presumably depends heavily on environmental context, affecting the hazard rates of nematode worms in different ways than, say, Icelanders. Understanding such effects is important for health and welfare, but it is not the big part of evolutionary demography. First, alleles with large detectable effects on outcomes studied by demographers and social scientists appear to be very rare. Second, for explaining statistical regularities, it seems natural to examine statistical properties, in this case properties characterizing the accumulation of small, somewhat independent effects in large numbers, in the tradition of explaining Gaussian distributions for human heights via the Central Limit Theorem.

In most social science GWAS studies, few or no alleles have effects whose statistical significance exceeds the stringent cutoffs imposed by statistical adjustments for multiple comparisons. However, from the demographic point of view, these are not "null" results per se. They allow detectability bounds to be calculated, bounding the number of alleles that can be having effects exceeding some given size. A case is made in the final section of this paper that large numbers of small effects, rather than small numbers of large effects, are more promising sources for regularities in demographic schedules, so bounds on numbers of large effects offer encouragement to the biodemographic agenda.

These approaches are being tested on outcome variables other than longevity. Some early results pertaining to longevity have been published from applications of GWAS studies to genetic markers from the first wave of the Framingham Heart Study, including Yashin et al. (2010). However, these remain controversial for technical reasons and are awaiting confirmation.

The most clear-cut bounds on effect sizes to date come from a GWAS by Rietveld et al. (2013) combining samples from many previous studies to obtain a total of 126,559 respondents. The trait under study is educational attainment, one of the few traits measured in somewhat consistent ways across many surveys. Only three SNPs were found to achieve genome-wide statistical significance with this sample size, and estimated effects of those polymorphisms were small. Most of the alleles accounting for the moderate heritability of educational attainment as assessed from twin studies must be below thresholds of detectability and thus very small.

Mutation accumulation theory makes assumptions not only about the dominant role of small effect sizes, but also about the prominence of effects with age-specific signatures. Small physiological differences originating from small differences in protein coding or regulation play out through different causal pathways. It is reasonable to expect that different pathways are important for viability at different stages and ages, making ultimate effects on demographic schedule age-specific. As far as it goes, there is also a little direct empirical evidence for the age-specificity of genetic effects, in this case from one of the few alleles with sufficiently large effects on survival to be individually detectable. In unpublished work, I have examined tabulations published by Flachsbart et al. (2009) of the frequency of a particular SNP in the Human Forkhead Box 03A Gene "FOX03A" among respondents in four age groups from 60- to 75-year-olds up to 105- to 110-year-olds. The gene is involved in insulin-signaling pathways. The increase with age in the frequency of the minor allele for this polymorphism is consistent with small early age effects on survival and rapidly increasing effects at later ages.

MUTATION ACCUMULATION WITH DEMOGRAPHIC COSTS

The route from the days of *Between Zeus and the Salmon* to the second decade of the 21st century goes from an impressionistic application of evolutionary theories in demography to quantitative theories with predictive content capable of calibration with emerging data. A critical early step was taken by Brian Charlesworth (2001), who put forward a stylized model connecting mutation accumulation to Gompertzian exponential increases in age-specific hazards and to possible plateaus. The basic idea is to consider a setting dominated by heavy exogenous mortality from predation and mishaps affecting mature individuals largely without regard to age. A hazard function constant over age implies an exponentially decreasing proportion of survivors by age. If fertility rates are more or less constant over ages with significant numbers of survivors, then a burst of mortality at a single age implies a loss in net reproduction that is an exponentially decreasing function of age.

In the tradition of the Oxford geneticist W.D. Hamilton (see Baudisch, 2008; Charlesworth, 2001), a linear approximation to a quantity called the "age-specific force of natural selection" can be computed. Its reciprocal is meant to be proportional to the number of mildly deleterious mutant alleles that will be found in "mutation-selection equilibrium," among alleles whose effect is to impose a burst in probabilities of dying at the given age. The equilibrium is established when new mutations are appearing in the genomes of population members generation by generation at a rate that balances the disappearance of mutant alleles as they are weeded out of the population by natural selection. The assumption that alleles act by impos-

ing bursts of mortality can be relaxed. What is critical to Charlesworth's idea is that age-specific effects of each of the relevant alleles are restricted to ages beyond some cutoff depending on the allele, and that every cutoff has at least some minimal rate of corresponding mutations.

The fascination of Charlesworth's model is that it predicts exponentially rising Gompertz hazards at adult ages. Of course, there are numberless other ways proposed by biologists and demographers to explain Gompertz hazards. However, Charlesworth's idea has two special advantages. First, it is highly generic. It is the kind of process that could pertain across a wide range of body plans and evolutionary environments. Second, it does not require putting some exponential function in somewhere in the model in order to get an exponential function out.

Charlesworth went on to observe that one could optionally posit a small fixed selective cost to every allele on top of the age-specific costs, and the result would be hazard functions whose exponential increases tapered into plateaus at extreme ages as observed. Later parts of this section describe results that put these ideas in a new light. A huge literature on mutation-selection balance is surveyed by Buerger (2000); most of it is rich in genetic detail but limited in demographic detail. Stimulated by Charlesworth's idea, David Steinsaltz, Steve Evans, and I have worked to develop and analyze a model originally formulated by David Steinsaltz that incorporates age-specific demographic structure, population heterogeneity, and non-linear interactions into a general treatment of mutation, selection, and recombination.

The important word here is "non-linear." The approaches of Hamilton and Charlesworth employ a linear approximation. The loss in net reproduction from the effects of two mutant alleles acting together is set equal to the sum of their effects acting alone. But mutation accumulation is inherently non-linear. Reduction in survival at one reproductive age reduces the remaining reproductive potential that can be lost by a reduction in survival at later reproductive ages. In other words, effects of alleles interact with each other. In this setting, linear approximations cannot be justified in the usual way by claims that total effects are small, because the predictions of the formulas are for large total effects cumulating out of small individual effects, whenever rates of mutation are not negligible. The linear theory is inconsistent and a non-linear theory is required.

Non-linear theory for mutation accumulation raises many mathematical challenges. Over the decade from 2000 to 2010, the challenges were eventually overcome. The theory developed most fully in Evans et al. (2013) now allows predictions of age-specific mortality schedules generated from assumptions about mutation rates and the profiles of mutational effects in the presence of recombination. Specifically, a demographer can specify a family of curves to serve as profiles of age-specific action. Many sites in the genome are assumed to share the same action profile, so that the

alleles found in SNVs come, as it were, in teams, each team with its own characteristic pattern of deleterious demographic impacts. The relationship between assumptions about profiles and empirical evidence is discussed in the next section. Each individual in a population is assumed to carry some random batch of mutant alleles drawn from each of the teams of alleles. The cumulative hazard function applying to the individual is formed by adding up the profiles for the alleles that the individual carries along with a baseline exogenous hazard. Decrements from alleles that affect age-specific fertility can also be included, but the present exposition focuses on hazard functions. Once mutation rates and baseline fertility and mortality are specified, the mathematical formulas predict the aggregate population hazard function to be found over time as mutations accumulate. They also predict the aggregate population survivorship at equilibrium, if a mutation-selection equilibrium occurs.

This framework describes a heterogeneous population. Different individuals carry different random batches of alleles. These batches turn out to be realizations of a Poisson process, a consequence of an assumption that genetic recombination operates more rapidly (in a specified sense) than mutation and selection and that the pool of SNVs corresponding to each action profile is large. The description is reasonable, inasmuch as mildly deleterious alleles with age-specific effects, however numerous in total, are expected to be fairly sparse and well-separated on chromosomes, avoiding any strong role for the correlations called linkage disequilibrium. The linear approximate theory deployed by Charlesworth assumed a similar kind of Poisson variability and seemed likely to provide a reasonable rough guide to the non-linear case.

Results from new modeling, as mentioned above, turn out to transform this picture. Predictions from the full non-linear theory overturn these predictions from linear theory. Mathematical proofs are found in Wachter et al. (2013) and Wachter et al. (2014). When it is the case that for any adult age there are mutant alleles whose effects are entirely restricted to later ages, as envisioned by Charlesworth, then the non-linear interactions among effects erode the selective pressure that holds in check the representation of late-acting alleles. In turn, interactions erode the selective pressure for earlier-acting alleles, and mutation-selection equilibrium is destroyed. The destruction of the equilibrium is predicted no matter how low are the rates of new mutations, so long as they are bounded below.

This finding explains that a far-reaching demographic difference emerges from what has seemed to be a minor difference for phenotypes, namely whether there are non-negligible deleterious effects at young ages for most alleles whose primary action is to raise hazard rates at old ages. Small early-age consequences of deleterious alleles can, in principle, exert small but sufficient selective pressure to keep the representation of these alleles in check

and rescue mutation-selection equilibrium. Effects at young ages may be undetectable, but through natural selection their role is expressed in the shape of hazards at late ages: They produce plateaus in hazard rates.

It follows that the logic of mutation accumulation argues for the existence of plateaus at extreme ages as a typical concomitant of mortality acceleration at middle ages. What was an optional feature in Charlesworth's linear account comes out appearing to be a feature plausibly promoted by natural selection. It may have been a reasonable expectation that anything that pushes deleterious genetic effects back to later and later ages would be advantageous. But the results on mutation accumulation indicate that such processes, carried too far, have undesirable consequences. They also indicate that some part of an observable constant term in hazard functions might be attributable to genetic load, reflecting the accumulation of minimal effects at all ages.

In a paper in *PLOS One*, Danko et al. (2012) take issue with the approach described here, claiming that "mutation accumulation may be a minor force in shaping life history traits." However, their model supports the opposite conclusion. For their simulations they impose an arbitrary bound of 10 on the maximal number of alleles and thus severely restrict the maximal allelic contribution, moving from a model for mutation accumulation—allowing large numbers of small effects—to a model for mutation nonaccumulation—allowing only small numbers of small effects. In their model with the bound removed, mutations do accumulate and reshape the survival schedule. Life history optimization has modest effects. However, in other models, it could have more importance.

In no sense does mutation accumulation operate alone. It has to operate within a framework determined by the portfolio of physiologically feasible adaptations. A better understanding of how genetic load interacts with optimal life history allocations and strategies in the presence of environmental variation across time and space is a high priority. By the same token, combination of mutation accumulation with stochastic vitality models likely holds a key to understanding the present-day post-reproductive signatures of deleterious alleles whose equilibrium frequencies were established over evolutionary time when their lethal consequences were often felt at prime reproductive and nurturing ages.

The selective pressure that holds deleterious alleles in check has to operate over evolutionary time at ages that matter for procreation, parenting, and grandparenting, that is, that matter to the bequeathing of genes to descendant generations. Ages of nurturing extend beyond ages of reproduction. However, it is clear that the extreme ages at which regularities in mortality schedules continue to be observed in humans are too late to have been directly subject to selective pressure over evolutionary time. Some account is therefore required for processes that have transferred the imprint of

natural selection operating at younger ages in bygone epochs into regularities now observed in schedules at old ages after enormous environmental changes and reductions in the level of mortality.

For natural selection to do its work, deleterious effects of mutant alleles have to be ultimately expressed in fertility and survival. But it makes sense to think of the effects of alleles operating through a number of intermediate causal pathways that might be reflected in the transition rates for a stochastic vitality model. What is gained from this point of view is the possibility of modeling changes in mortality concomitant with the advantages of civilization through changes in the boundary curve representing lethality. In such models, one would expect the imprint of natural selection over evolutionary time to be expressed at later ages in recent times, as the trajectory of vitality takes more time to reach a more distant boundary. The enterprise of constructing and analyzing such combined models is just beginning and may lead to new insights in the coming years.

EVOLUTIONARY DEMOGRAPHY: TENETS AND HYPOTHESES

The demographic relevance of evolutionary demography does not go without saying. It is easy to imagine that humans might have so drastically reshaped the environment and their physiological capacities as to make the general genetic legacy from the distant past irrelevant. On the other hand, it is also easy to imagine the contrary, that regularities in age-specific patterns shared to some extent with utterly different species have deep origins that partly override the vicissitudes of modern human life.

Biodemographic models are appealing, but they are technical, continually developing, and full of detail. In this final section, before surveying empirical evidence from genome sequencing, it may be helpful to pull back and venture a brash sketch of the big picture. Why do demographers want to know the things that genome sequencing may help explain? My sketch takes the form of a list of questions and the answers to these questions that evolutionary demography proposes:

Question: Why are adult human mortality rates generally quite regular functions of age, relatively free of waves and bounces and squiggles in the curves?
Answer: Human mortality still bears marks of long shaping in the challenging environments of human prehistory.
Question: How do messages from human prehistory come down to the present?
Answer: Alleles with small age-specific effects originating in deleterious mutations of long ago are still being inherited in large numbers by each person.

Question: Why small?
Answer: Alleles with big bad effects are rapidly removed by natural selection.
Question: Why would it be harder to explain regularities in terms of alleles with big effects?
Answer: All outcomes as we see them come out of interaction between genetic potential and environmental opportunity. Bigger big effects bespeak big potential plus big opportunity, and big opportunity means a large role for special features of the contemporary environment.
Question: Why would it be easier to explain regularities in terms of alleles with small effects?
Answer: Alleles with small effects entering the population long ago, long buffeted by natural selection, are expected to have frequencies that compensate for specific environmental opportunities of long ago.
Question: Why compensation?
Answer: Something in the environment that reduces the bad effect of a set of alleles also reduces the rate at which they vanish out of the population generation after generation through natural selection. Frequencies of such alleles rise until outflow balances the inflow of new mutations and an equilibrium balance between mutation and selection is restored.

Making this picture concrete requires confronting theory with data. Each main tenet of mutation accumulation theory constitutes a hypothesis about what is to be found in genome sequence data from samples of living individuals. This area of science is in rapid development and definitive results are still in the future. What can be done now is to sketch out how different pieces of a jigsaw puzzle look as if they might be able to be joined together.

Which hypotheses, suggested by demographic theory, are on the table?

1. Mutation accumulation theory proposes that each individual carries a personal sample from a large pool of mildly deleterious alleles, leading to the hypothesis that such a pool exists.
2. The theory proposes small effects allele by allele for alleles whose cumulative impact shapes age-specific adult human mortality, leading to the hypothesis that fitness costs for many deleterious alleles are individually small.
3. The theory proposes that most relevant alleles arose from mutations fairly far in the past, well before dramatic reductions in human mortality and likely before many of the transformations accompanying sustained population growth, leading to the hypothesis that age estimates for relevant alleles should often come out at more than several hundreds of generations.

What are genome studies published so far telling us with respect to these hypotheses? For the first hypothesis, concerning the existence of a large pool of mildly deleterious alleles, there is some striking confirmation. It comes from genetic sequencing of the roughly 2 percent of the genome that directly codes for proteins. A quest for low-frequency alleles by Tennessen et al. (2012) in the coding regions in the genomes of 2,044 individuals of European and African descent turned up a pool of 503,481 Single Nucleotide Variants (SNVs, as described at the outset). Individuals in the study were found to carry 13,959 SNVs on average. The overwhelming majority of these SNVs were deemed to be neutral or nearly neutral, with no selective cost or with negligible selective cost in comparison to the force of genetic drift. But an important minority of SNVs were classified as functional and deleterious. The classification depends on whether an SNV implies no change or some change in a protein product, whether it occurs in certain kinds of positions, and whether it meets various other criteria. The average number of SNVs per individual classified as functional and deleterious in protein-coding regions of the genome was estimated conservatively at around 318 and less conservatively at around 580. The proportion of rare SNVs among these functional SNVs was found to be higher than the proportion of rare SNVs among all SNVs, implying that the pool from which the functional SNVs are drawn is substantial. Thus, the first hypothesis is borne out by these early data.

The study by Tennessen et al. (2012) does not provide estimates of selective costs for putative deleterious alleles. What makes alleles deleterious are effects on the net reproduction of those who carry them, either on adult survival, on infant and child survival, on fertility and mating success, or on some combination. The term "MA-alleles" denotes the subset of deleterious alleles that affect adult hazard functions and, under equilibrium conditions, are held in equilibrium by mutation-selection balance. From the estimated numbers in the Tennessen paper, it seems reasonable to expect that numbers of MA-alleles should be in the hundreds or more. Only some fraction of deleterious alleles in coding regions belong to the subset of MA-alleles, but it is also likely that MA-alleles are found outside coding regions, interfering in small ways with the efficiency of transcription and the regulation of gene expression. The model of mutation accumulation motivates some informed guesses about a relationship between numbers of MA-alleles and average sizes of effects, as will shortly be described. These guesses come out consistent with the second hypothesis, that effects are small.

The third hypothesis concerns typical numbers of generations elapsing from the events of mutation which introduced each allele into the population. Alleles that descend from a given mutant are "derived alleles" and the number of generations is the "age" of the derived allele. Relationships between age, present-day frequency, past population size, and selective

cost are complicated by many factors, but arguments are described here that suggest that MA-alleles with average selective costs have average ages of more than several hundred generations, consistent with the third hypothesis.

A review of methods of age estimation for alleles is found in Slatkin and Rannala (2000). The complications of the subject emphasized in recent literature include expansion in effective population size since the beginnings of agriculture about 400 generations ago. These relationships are current subjects for genetic research. For demographers, the interpretation of results is further complicated by the uncertain translation between "effective population size," a quantity entering genetic models that assume random mating among all population members, and "census population size," half the number of feet on the ground that a prehistoric demographer would have found if he or she had completed an actual enumeration. The last 20 generations or so of very rapid world population growth are too few to have much bearing on the genetic results, but growth over the last 400 generations or so has implications that will shortly be discussed.

Mediation between results from the genetic literature and interpretations of demographic processes is aided by the model of Evans et al. (2013). One new tool for calibration is supplied by a generalization of Haldane's Principle. In its older, classical form, Haldane's Principle for deleterious alleles held mutation-selection balance equates the total mutation rate to the total loss in fitness. This equality fails in the presence of non-linear interactions. However, a generalized form for the non-linear setting has been proved in Wachter et al. (2013) equating the relevant total mutation rate to a quantity related to lifetable entropy.

This generalized Haldane's Principle allows for inference of a total mutation rate for relevant deleterious alleles from a combination of theory and data. The rate is independent of the size and age-specific profile of allelic effects. The application of the principle proceeds from a comparison of a hypothetical baseline survival schedule dominated by exogenous mortality in the absence of MA-alleles with a hypothetical observable mortality schedule for populations over evolutionary time when mutation-selection equilibria could have prevailed. Guesses at the hypothetical observable schedule can be informed by anthropological lifetable estimates for present-day hunter-gatherers summarized, for example, by Gurven and Kaplan (2007).

For application of the generalized Haldane's Principle, assumptions about the effective age-specific shape of contributions to net reproduction also have to be made. Such contributions reasonably include allowances for the protective effects of care from surviving parents and grandparents. Conceptually, an "effective Net Reproduction Ratio" might be defined to equal the cube root of the average number of daughters of daughters of

daughters born per newborn prospective great-grandmother, or in some other comparable way. It is the age-specific shape of contributions, not the level of fertility, that is important, because over long time periods, homeostatic mechanisms may be assumed to adjust population growth to near stationarity.

This paper is too brief to develop detailed estimates from Haldane's Principle. However, a simple version of the calculation, coming out with an estimated rate of 0.20, may serve as a rough guide to an order of magnitude. The rate in question is the rate of new mutations per generation per individual for MA-alleles held in mutation-selection balance. The simple version takes as its starting point the average mortality schedule for hunter-gatherers in Gurven and Kaplan (2007). The version attributes half of the Makeham constant term to exogenous mortality and half to MA-alleles and adds moderate allowances for nurturing on top of a Coale-Trussell schedule for natural fertility. Implied reductions in effective net reproduction around 0.13 from genetic load are multiplied by an adjustment for non-linearity of around 1.5 for a mutation rate of $0.13 * 1.5 \approx 0.20$. Inasmuch as optimal life history models positing substantial costs to repair often imply increasing hazards due to factors other than genetic load, it could be argued that this estimate should be even lower. None of the more extreme population lifetables in Gurven and Kaplan (2007) would justify a much higher estimate, beyond, say 0.50.

An estimate of MA-alleles carried per individual is also needed. The estimate around 300 given conservatively by Tennessen et al. (2012) has to be adjusted upward for MA-alleles outside of coding regions and adjusted downward for deleterious alleles that are not MA-alleles. A simple version proposes that the two adjustments may roughly offset each other. Then the dynamic equation in Evans et al. (2013) gives an average selective cost equal to the quotient $0.20/300 \approx 1/1500$. More formally, this quantity is an estimate for the average over all MA-alleles of the generalized age-specific force of natural selection at equilibrium in the model.

The model of Evans et al. (2013) is a model for mean values, not for the random fluctuations in allele frequencies arising from genetic drift in populations with finite, moderate effective sizes. The age distribution of alleles is shaped by drift and by effective population size over time as well as by selective cost. However, the quantities of demographic interest are not frequencies of alleles at single genetic sites but aggregated counts of sets or "teams" of alleles sharing a single age-specific effect profile. Furthermore, the model assumes that recombination operates on a faster timescale than selection and mutation, a reasonable assumption when hundreds of generations are at issue. An effect of recombination is to make the distributions (across the population) of alleles at single sites appear statistically independent. The upshot is that a sum over all the alleles in a team of substantial

size is plausibly described by the model for mean values. No theorem is yet in hand, but simulations support this expectation.

An implication of this picture is an estimate for average age measured in generations for a set of deleterious alleles sharing an age-specific profile that comes out to be on the order of the reciprocal of the age-specific force of natural selection. This calculation presumes a stationary population and the establishment of mutation-selection equilibrium. Population growth since the beginnings of agriculture some 400 generations ago alters the calculation as it disturbs any equilibrium. Impacts of such growth have been assessed with simulation studies by Gazave et al. (2013) in the context of European populations. As compared to an imaginary population that remained stationary, they find population growth over 400 generations to entail much larger total numbers of mutant alleles present in the much larger total population at the end. However, they find only modestly larger numbers of alleles carried per person resulting from the growth. Most alleles are neutral. For functional deleterious alleles, they find only small changes in distributions. Their results are tailored to the case of European population growth as reconstructed by Gazave et al. (2014).

Taken together, all these results combine to suggest an average age for MA-alleles with average selective costs on the order of 1,500 generations or about 37,500 years. Variations around this average are bound to be large, both because of the variations in selective costs between alleles whose actions on hazard rates are concentrated at different ages and because of the intrinsic randomness of natural selection. However, it does appear that a substantial portion of genetic load affecting adult hazard rates is a legacy from long before the transformations of modern times.

In summary, then, data from studies of variation in human genome sequences are beginning to permit confrontation between predictions from evolutionary demographic models and empirical findings. Results from the first large sample study with high resolution on variants in coding regions of the genome, Tennessen et al. (2012), appear consistent with the main tenets of the existing demographic model for mutation accumulation. A large pool of variants of the kind posited by the model appears to exist. The number of functional deleterious alleles estimated to be carried per individual appears consistent with the smallness, on average, of the effects posited by the model. Rough early estimates of ages for such alleles are consistent with the idea of a legacy of genetic variation structured by natural selection long before the advent of modern mortality decline.

Opportunities are coming on the scene for more detailed confrontations between theory and data. Specific implementations of the mutation accumulation model make predictions about plausible distributions of selective cost across alleles from sets with similar age-specific profiles. Genetic sequencing studies can provide data on frequency distributions for alleles deemed to be

functional and deleterious, which should in due course allow more specific estimates of ages of alleles.

The 17 years since the volume *Between Zeus and the Salmon* have brought advances in theory and advances in genetic information that put the concept of an evolutionary origin for demographic regularities on a concrete footing. There is now a refined predictive model for mutation accumulation. Biodemographers have an agenda for combining mutation accumulation theory with stochastic vitality models to relate present-day patterns of post-reproductive survival to earlier patterns of reproductive-age survival over evolutionary time. We have an account that links the ubiquity of Gompertzian increases in hazard rates at medium-old ages to the plateaus at older ages. We have empirical evidence from genomic analyses that the kinds of genetic variants posited by mutation accumulation are indeed a predominant kind observed. Along with progress in understanding fundamental relationships between alleles and regularities in demographic schedules, surveyed in this paper, biodemographers are breaking new ground in understanding the fine-grained implications of sociality and adaptive strategies for the biodemography of health and lifecourse. This new ground is explored in this volume.

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3

Genes Revisited: The Biodemography of Social Environmental Variation Through a Functional Genomics Lens

Jenny Tung

INTRODUCTION

Like all biological processes, genes play an important role in aging. Within humans and other species, variation both in susceptibility to individual diseases of aging and in overall longevity has a heritable component (Finch and Tanzi, 1997). Across species, overall lifespan can vary by many orders of magnitude, and the shape of the relationship between mortality risk and age is similarly diverse (Jones et al., 2014). Such differences are indicative of a long history of evolutionary change in the aging process, which requires underlying genetic variation on which to act. Finally, targeted manipulations of individual genes in laboratory model organisms have pinpointed specific mutations that have strong effects on longevity. Mutations in the insulin-like growth factor receptor gene *daf-2* in the worm *Caenorhabditis elegans*, for example, result in a more than 2-fold increase in lifespan (Kenyon et al., 1993). Effects of a similar magnitude have been identified in studies of fruitfly (*Drosophila melanogaster*) and mouse (*Mus musculus*) mutants (reviewed in Kenyon, 2010). Together, the cumulative evidence from quantitative genetic analysis, cross-species comparisons, and model systems research argues that understanding aging will necessarily involve, at some level, understanding the role played by genes.

How can a gene-centered perspective be integrated into aging biodemography? Unlike studies of the genetics of aging in lab models, which take advantage of large effect mutations, genetic clonality, and environmental homogeneity to isolate aging-related genes and pathways, biodemographers

are fundamentally interested in aging in natural populations—in which individual genetic effects on aging will generally be modest, and individual study subjects will be genetically diverse. In addition, biodemographers are often explicitly interested in the consequences of natural environmental heterogeneity, much of which cannot be replicated in the lab. For example, social environmental effects are risk factors of substantial demographic importance in humans and other socially complex animals, because social adversity both occurs at high frequency and confers high relative risk for mortality and many of the major diseases of aging (Berkman and Syme, 1979; House et al., 1988; Sapolsky, 2004; Sapolsky, 2005; Marmot, 2006; Holt-Lunstad et al., 2010). Thus, gene-focused approaches will be most relevant to biodemographers of aging not when they exclude environmental variance, but when they contribute to a mechanistic or predictive understanding of how environmental risk factors act to influence aging-related phenotypes.

Recently, the field of genomics has shifted from a primary emphasis on the static sequence composition of the genome to an emphasis on its functional organization and potential (e.g., Dunham et al., 2012, for an impactful recent example of this shift). This "functional genomic" perspective suggests how studying genes—and particularly gene regulation—could yield valuable insight into the comparative biodemography of aging. The functional genomic perspective treats gene regulation as a dynamic process influenced by a combination of intrinsic genetic effects, extrinsic factors, and demographic variables like age and sex. Hence, functional genomic data promise to shed new light onto the mechanistic basis of biodemographically important environmental effects, including the enduring puzzle of how adverse social environments "get under the skin" to influence health (Taylor et al., 1997; Adler and Ostrove, 1999; Hyman, 2009). For example, such approaches can be used to investigate which genes are mutually affected by social adversity and age, how gene regulation contributes to social environmental effects on health, and whether gene regulatory responses to social stressors vary across species in a predictable manner.

Functional genomic approaches have already been embraced for aging research in laboratory model systems (Vijg and Suh, 2003; Partridge and Gems, 2006; de Magalhães et al., 2012). They have been less explored in human population studies or in nonmodel systems, which include many of the species in which social environmental effects on health most closely parallel those in humans. However, recent studies have established a strong link between social conditions and gene regulation in both of these contexts (reviewed in Slavich and Cole, 2013; Tung and Gilad, 2013). Using social environmental variation as a focal point, this paper considers the potential for a closer integration of functional genomics and biodemography in studies of populations outside the lab. To do so, I first review the evidence that the functional genomics of gene regulation is important for understand-

ing aging, and I outline the arguments in favor of collecting genome-scale data. I then consider how functional genomic studies and biodemography could inform one another and, jointly, an understanding of social environmental influences on aging. Finally, I close by suggesting future directions and discussing the potential prospects for this approach.

THE RATIONALE FOR ADOPTING A FUNCTIONAL GENOMIC PERSPECTIVE

Gene Regulation in Aging

Functional genomics focuses on the biochemical potential and activity of the genome, including the molecular changes that influence gene activation, the determinants of RNA and protein synthesis and decay, and the factors that affect the binding and conformation of nucleic acids and proteins. Hence, functional genomics is closely tied to the study of gene regulation, and adopting a functional genomic strategy to study aging relies on the assumption that changes in gene regulation are an important component of the aging process.

Support for this assumption comes from several independent sources. First, shared pathways are involved in aging in a broad set of species, yet produce widely variable life history outcomes. For example, although *C. elegans* can live for days, fruitflies for weeks, and mice for years, genes involved in the stress response and nutrient sensing are linked to control of aging in all three species (Partridge and Gems, 2002; Kenyon, 2010; López-Otín et al., 2013). This remarkable conservation suggests that evolutionary shifts in expected lifespan are not due to changes in the identity of the genes involved, but instead stem from changes in the regulation of these genes—in other words, when and to what degree the molecular species that mediate aging are employed, as opposed to which molecules are used. This argument echoes well-established arguments made for the evolution of development, in which striking differences in body plan can arise from regulatory changes in genes that are otherwise highly conserved at the protein-coding sequence level (Carroll, 2005). Indeed, in support of a parallel pattern for aging, cross-species comparisons have revealed that the protein-coding regions of genes linked to aging tend to be evolutionarily conserved (de Magalhães and Church, 2007).

Changes in gene regulation also account for dramatic changes in aging and longevity that can arise within a single species in response to environmental cues. This pattern is most clearly demonstrated in taxa that are capable of adopting discrete, alternative life histories, such as eusocial insects. For example, honey bees are capable of developing into either nonreproductive worker bees, with an expected lifespan of several months, or

reproductively active queen bees, which can live up to five years (Amdam, 2011). They do so based on nutritional cues provided in early life, which activate distinct gene regulatory programs without requiring changes in the DNA sequence itself (Evans and Wheeler, 1999; Kucharski et al., 2008; Elango et al., 2009). Similarly, isogenic (i.e., genetically clonal) lines of the nematode *Strongyloides ratti* can develop into either a short-lived, free-living form or a long-lived parasitic form, which are differentiated by an over 80-fold difference in expected lifespan (Gardner et al., 2006). Less dramatic shifts can be induced in species without distinct alternative life histories. In lab model systems, environmental manipulation of temperature or diet can substantially change how long animals live: For example, *C. elegans* subjected to dietary restriction can live up to 150 percent longer than those fed ad libitum (Greer and Brunet, 2009). Such shifts clearly involve variation in gene regulation as opposed to variation in DNA sequence, as no genetic variation is present in the sample. Together, they have given rise to the observation that animals in general likely have "the latent potential to live much longer than they normally do" (Kenyon, 2010).

Finally, direct empirical evidence ties gene regulation to aging. Environmental interventions that influence aging and longevity often do so via their effects on gene regulation (e.g., Pletcher et al., 2002; Fok et al., 2014), and longevity-associated mutations are often components of gene regulatory pathways. For example, the *C. elegans* gene *daf-16* (as well as its fruitfly and mammalian homologues) is a transcription factor that regulates hundreds of downstream genes (Murphy et al., 2003). Age is also closely tied to variation in gene expression levels in unmanipulated populations. For example, chronological age explains variation in the expression levels of approximately half the genes expressed in the human prefrontal cortex, a pattern that is qualitatively recapitulated in other tissues and species (Lund et al., 2002; Lu et al., 2004; Fraser et al., 2005; Göring et al., 2007; Berchtold et al., 2008; Hong et al., 2008; Cao et al., 2010; Somel et al., 2010; Yuan et al., 2012). While other gene regulatory phenotypes have been less well studied in relation to age, where data are available, they show similar patterns (Christensen et al., 2009; Fraga, 2009; Han et al., 2012). In particular, epigenetic marks—chemical modifications to the genome that can influence transcription rates and gene expression levels—are closely associated with the aging process (Fraga, 2009). DNA methylation, histone acetylation, and histone methylation marks all have been shown to either covary with age or modify aging-related phenotypes (reviewed in Fraga, 2009; López-Otín et al., 2013). Indeed, epigenetic patterning is so consistently altered during aging that it is now widely considered to be one of the major molecular hallmarks of aging (López-Otín et al., 2013).

Genomic Approaches to Gene Regulatory Studies of Aging

Taken together, the cumulative evidence strongly supports the importance of gene regulation in aging. However, variation in gene regulation also reflects the effects of important environmental variables, and for humans and other socially complex species, social status, social support, and social competition are central components of the environment. Gene regulatory phenotypes—measurements that capture variation in gene regulation, including gene expression levels and epigenetic marks—can thus provide a useful common currency for studying how social experiences influence aging-related genes. While studies of single genes or small sets of genes can take advantage of this approach as well, it can be particularly valuable when applied to genome-scale datasets (see Box 3-1) for two key reasons (see also Robinson et al., 2005, 2008; Boyce et al., 2012).

First, genome-wide datasets allow the generality of relationships between the social environment and aging to be assessed. For example, social stressors have been hypothesized to influence biological targets that are also affected by age, potentially accelerating the aging process (Bauer, 2008). This idea predicts that physiological changes associated with social stress should also be associated with age, and that the direction of these effects should be positively correlated. Studies of a few individual biomarkers, such as IL-6 cytokine levels and telomere length, have lent support to this argument (Epel et al., 2004; Cherkas et al., 2006; Juster et al., 2010; but see Dowd and Goldman, 2006, who report few consistent relationships between social adversity and biomarkers of chronic stress, challenging a major assumption of the argument). However, these individual cases are not sufficient to reveal a general pattern, especially given that age is associated with a large set of biological pathways (identification of an overlap for a single biomarker could thus be attributable to chance alone). Because

BOX 3-1
Genome-Wide Measures of Gene Regulation in Population Studies

In recent decades, population studies have pioneered collection of physiological and molecular biomarkers of health, and such data are now a routine component of many population-based analyses of aging. This paper outlines how genome-wide measures of gene regulation might serve to further advance such a synthesis; here, I address several practical considerations linked to this possibility.

continued

BOX 3-1 Continued

What is "genome-wide?"
"Genome-wide" is a flexible term and depends in part on the aspect of gene regulation under study. For example, a human genome-wide gene expression profile might involve ~ 10,000–20,000 genes, but a complete survey of DNA CpG methylation could involve ~ 450,000 sites (the number measurable using current off-the-shelf methods) or > 25 million sites (all sites in the genome). Regardless of numbers, genome-wide studies of gene regulation are unified by the attempt to generate enough measurements to capture the true distribution of trait values across the genome. This approach allows investigators to test whether a given association is unusual or widespread in comparison to the rest of the genome (as opposed to whether it is unusual in comparison only to a theoretical null). Genome-wide approaches thus can provide valuable biological insight unavailable from smaller-scale studies and help to identify potential systematic sources of bias.

How are genome-wide gene regulatory phenotypes measured?
Genome-wide assays of gene regulatory phenotypes vary depending on the phenotype of interest. However, most genome-wide assays now converge on one of two strategies: array-based methods or high-throughput sequencing methods. The basic difference between these methods depends on whether measurements are made based on matches to a pre-specified set of sequences (on arrays) or based on the counts of *de novo*-generated sequences associated with a regulatory feature of interest (sequencing-based approaches). The choice of one approach versus the other depends on cost (often favoring arrays), sensitivity (favoring sequencing), and feasibility (commercial arrays are not available for most non-model species). See Marioni et al., 2008; Mortazavi et al., 2008; Wang et al., 2009; Hawkins et al., 2010; and Metzker, 2010, for recent comparisons and reviews.

Are genome-wide approaches realistic for population studies?
Three major considerations are at play here: (1) *Sample quantity.* Many approaches for measuring genome-wide gene regulatory phenotypes are able to utilize very small amounts of sample (e.g., < 50 uL of blood). For some types of analyses, studies that already collect biological samples are therefore well positioned to either modify existing protocols or utilize previously collected samples. (2) *Cost.* Generating genome-wide data, especially using sequencing-based approaches, remains prohibitively expensive for large sample sets (i.e., in the hundreds to thousands of individuals). Investigators will therefore often have to choose informative subsets of individuals, rather than the full sample, to interrogate (potentially banking additional samples for later analysis). Notably, sample sizes in functional genomic studies are often small by population survey standards. (3) *Cell/tissue type.* Biological samples that can be obtained using minimally invasive approaches (e.g., blood draws) will be the most feasible to study in population surveys. While other tissues, such as the brain, are clearly also of interest, changes in the periphery, including in blood, have consistently proven to be important in the response to social adversity, suggesting that this sample type will provide important first insights into social environmental effects on aging. Over time, opportunistic sampling may make it possible to eventually investigate other tissues as well (e.g., McGowan et al., 2009).

genomic approaches generate data for many gene regulatory traits simultaneously, they facilitate more comprehensive tests of parallels between social environmental variation and aging. At the same time, genomic datasets provide important information about whether the effects of a particular social environmental variable are concentrated in a handful of pathways versus broadly distributed across the genome.

Second, genome-wide datasets facilitate the use of analysis tools targeted above the level of individual genes. For example, gene set enrichment approaches help test whether genes that share a particular property (e.g., involvement in a specific biological function or known association with a disease trait) appear more often than expected by chance among a group of genes identified in the focal analysis (e.g., among genes for which gene expression covaries with age). Such tools allow researchers to utilize prior knowledge about gene function, pathway membership, or other associations to investigate whether genes linked to a particular environmental effect are biologically coherent in other ways (Subramanian et al., 2005; Backes et al., 2007; Huang et al., 2008). Gene set approaches have been useful, for instance, in revealing that genes that are differentially expressed in response to social adversity are often related to inflammation and glucocorticoid signaling (reviewed in Slavich and Cole, 2013). Importantly for comparative studies, because the units of analysis are collections of genes, enrichment analyses do not require exactly the same loci to be measured in different datasets. Especially when individual studies are low powered, similarities between different populations, species, or environmental conditions may be more detectable at the level of gene categories than at the level of individual genes. However, pathway-level, rather than gene-level, similarities may also reflect real biological patterns.

Research on aging in model systems supports the latter explanation. Pathway-level effects on aging are remarkably conserved across species: Changes in the insulin/insulin-like growth factor signaling pathway, for example, affect the aging process in species from *C. elegans* to humans—taxa that have been independently evolving for hundreds of millions of years (Partridge and Gems, 2006; Kenyon, 2010). In contrast, changes in gene expression levels associated with chronological age, longevity-enhancing mutations, or longevity-enhancing environmental treatments are rarely replicable at the individual gene level (McElwee et al., 2007; de Magalhães et al., 2009). Instead, similarities are primarily observable at the level of functionally related gene sets: advanced age is consistently associated with downregulation of genes involved in energy metabolism and upregulation of genes involved in the immune response, apoptosis, and insulin-like growth factor binding (de Magalhães et al., 2009). Focusing on one or a handful of genes is likely to miss these similarities, as well as the opportunity to assess where differences truly lie.

FUNCTIONAL GENOMICS AND THE BIODEMOGRAPHY OF SOCIAL ENVIRONMENTAL VARIATION

Functional genomic studies of aging and studies of social environmental effects on health and senescence have largely proceeded along parallel lines. They are bridged, however, by recent evidence that social environmental variation also impacts gene regulation. In humans, self-perceived loneliness, early and adult socioeconomic status, and provision and receipt of social support have each been linked to variation in the expression levels of hundreds of gene transcripts (Cole et al., 2007; Miller et al., 2008; Chen et al., 2009; Lutgendorf et al., 2009; Miller et al., 2009). The causal nature of at least some of these relationships is supported by work in animal models. For example, social status (i.e., dominance rank) and early rearing environments can be experimentally manipulated in captive rhesus macaques, which, like humans, have evolved to navigate complex social group environments (Cole et al., 2012; Tung et al., 2012). These manipulations lead to extensive changes in gene expression patterns in the blood, as well as accompanying changes in DNA methylation (Provencal et al., 2012; Tung et al., 2012). Further, in rodent models, targeted changes in epigenetic gene regulatory mechanisms have been successfully demonstrated to reverse some of the negative behavioral consequences of social adversity (Weaver et al., 2004; Tsankova et al., 2006). For example, chemical repression of *HDAC5*, a gene involved in epigenetic patterning, restored social interaction rates in socially defeated mice to normal (higher) levels (Tsankova et al., 2006).

Combined, these findings suggest that gene regulatory phenotypes (including, but not limited to, gene expression levels) may act as useful biomarkers for tracking the association between social environmental variation, health, and aging. In addition, they suggest potential research avenues aimed at understanding the mechanistic basis of this relationship. To do so will require forging stronger links between population studies of health and aging on one hand, and functional genomic approaches for studying the social environment on the other. Below, I outline two broadly defined strategies for pursuing this research agenda. The first involves using biodemographic observations as a motivation for functional genomic studies, with the aim of understanding how, and in what contexts, gene regulatory changes with age intersect with gene regulatory effects of the social environment. The second involves development of a tighter integration between functional genomics and biodemography, in which demographic concepts of mortality rates and senescence can be leveraged to investigate the role of gene regulation in aging.

Biodemographically Motivated Studies

In biodemographically motivated studies, social environmental variables of known biodemographic importance can be tested for their effects on gene regulation using standard functional genomic methods, without explicit reference to demographic parameters or theory. Current research on the relationship between gene regulation and social adversity implicitly uses this approach (Cole et al., 2007; Miller et al., 2008; Chen et al., 2009; Lutgendorf et al., 2009; Miller et al., 2009; Cole et al., 2012; Tung et al., 2012): The rationale for studying the effects of social status and social integration in this work derives in large part from population-based research highlighting their importance as predictors of disease susceptibility and mortality risk (Berkman and Syme, 1979; House et al., 1988; Holt-Lunstad et al., 2010). Jointly, these studies have established that social environmental variation influences both health and longevity and the molecular control of gene regulation. The next steps forward for biodemographically motivated studies will involve, first, establishing the degree to which these observations reflect a shared phenomenon, and second, investigating how the type and timing of social adversity affects its downstream consequences.

Does the Social Environment Affect Aging-Related Pathways?

Circumstantially, it makes sense that gene regulatory changes in response to social adversity are related to aging. Aging-related genes and pathways are often involved in the response to environmental stressors. Altering the levels of environmental stress by manipulating ambient temperature or caloric intake represent some of the most robust ways to alter life expectancy in lab model systems (Kenyon, 2010; López-Otín et al., 2013), and dietary restriction also may confer health and life-extending benefits in primates (Colman et al., 2009; Mattison et al., 2012). Importantly, for highly social species like humans, the social environment acts as one of the most potent sources of environmental stress. Consequently, the effects of social adversity on gene regulation may also mediate aspects of the aging process. In general, however, the effects of socially mediated stress on aging have not been evaluated in the lab environment. This is probably in part because the types of social adversity important in humans often have no direct parallels in the major lab models for aging (e.g., *C. elegans*, yeast, and *Drosophila*, although mouse and rat models represent a partial exception). Hence, the degree to which social adversity affects the regulation of genes that are also affected by aging remains unclear. It thus remains conceptually possible that social environmental effects on gene regulation and social environmental effects on aging in fact tap into independent pathways.

Genome-wide datasets on both age-associated and social environment-associated gene expression patterns provide one approach for differentiating between these two alternatives. Specifically, they facilitate an exploration of whether, and for what genes, socially induced changes in gene expression match shifts in gene expression linked with aging. While such overlaps provide only indirect evidence for a mechanistic relationship, they can at least exclude the possibility that changes with age and changes with the social environment are broadly independent. They also have the potential to greatly enrich the small set of existing biomarkers known to be influenced by both effects. As illustrated by telomere length in blood cells (Epel et al., 2004; Cherkas et al., 2006; Boonekamp et al., 2013), which both decays faster in chronically stressed women and is a predictor of mortality risk (Epel et al., 2004), such markers can serve as useful measures for capturing aspects of biological "age" that do not map well onto chronological age (but see Boonekamp et al., 2013, who argue that telomere length is a better marker of somatic redundancy than biological age).

Two analyses suggest that gene regulatory responses to the social environment are indeed similar to those observed during aging. As part of a study of sex differences in aging in the prefrontal cortex, Yuan and colleagues observed a pattern of accelerated age-related change in gene expression levels in human women relative to men (Berchtold et al., 2008; Yuan et al., 2012). They hypothesized that this pattern might reflect greater vulnerability to social stressors in women. Suggestively, genes that exhibited the female-biased pattern were significantly more likely to be altered in the same direction by social isolation stress, based on data from the prefrontal cortex of spider monkeys (Karssen et al., 2007). Likewise, blood expressed genes for which gene expression levels were associated with both age (in humans: Göring et al., 2007) and social status (in rhesus macaques: Tung et al., 2012) were significantly more likely to be changed in the same direction (Snyder-Mackler et al., 2014). Genes that were more highly expressed in low social status macaques tended to be more highly expressed in older humans, and vice-versa. Consistent with comparisons between disparate aging datasets, similarities between gene expression changes with age and the gene expression effects of social status were stronger for functionally coherent gene sets than for single loci. For example, genes involved in insulin growth factor I signaling and genes involved in inflammation—two processes tightly associated with aging—were identified in both the human age-associated (Göring et al., 2007) and rhesus macaque social status-associated (Tung et al., 2012) datasets. Overall, the number of these overlapping pathways was substantially greater than expected by chance (Snyder-Mackler et al., 2014). Such findings thus provide initial support for the argument that social environment-induced changes in gene regulation may also explain something interesting about aging. Additional datasets

would greatly improve the resolution of these comparisons, however, and studies in which the effects of age and the social environment are studied in the same population will be particularly important.

Does the Social Environment Impact Known Hallmarks of Aging?

A second way to investigate whether social environmental effects on gene regulation are involved with aging is to test whether they impact biological phenomena believed to be fundamental to the aging process. Recently, López-Otín and colleagues identified nine basic hallmarks of aging that have received broad support in aging research on nonmodel organisms and humans (López-Otín et al., 2013). Several of these hallmarks, particularly changes in epigenetic patterning and altered intercellular communication, provide natural bridges between aging and social environment-associated changes in gene regulation.

The first, epigenetic patterning, plays a fundamental role in determining the three-dimensional configuration of DNA and hence its accessibility to the cell's transcriptional machinery. Epigenetic marks, including DNA methylation, histone methylation, and histone acetylation levels, show marked patterns of age-related change, and targeted manipulation of some epigenetic regulatory mechanisms affects longevity in model organisms (reviewed in Fraga, 2009; López-Otín et al., 2013). Changes in the epigenome also arise as a consequence of social environment-mediated life experiences. Early rearing environment is associated with differential DNA methylation levels in rodent models, nonhuman primates, and human populations (Champagne et al., 2003; Weaver et al., 2004; Champagne et al., 2006; McGowan et al., 2009; Murgatroyd et al., 2009; Roth et al., 2009; Bagot et al., 2012; Borghol et al., 2012; Provencal et al., 2012). Further, experimental manipulation of social status in rhesus macaques is linked to a large, broadly distributed set of differentially methylated regions across the genome (Hansen et al., 2012; Tung et al., 2012). The degree to which these changes overlap with those involved in aging remains unknown. However, in the macaque prefrontal cortex, age-associated changes in histone H3K4me2 (histone 3, lysine 4, dimethylation) methylation levels, which are markers of transcriptional activation, are preferentially observed near inflammation and environmental stress-related genes (Han et al., 2012). This observation suggests that social adversity may influence at least some aging-related epigenetic pathways.

Similarly, studies of the gene regulatory response to social adversity frequently identify genes involved in intercellular communication, a second major hallmark of aging. These genes include the cellular targets of steroid hormone and sympathetic nervous system signaling and, most consistently, genes involved in the inflammatory response. For example,

multiple studies of social adversity-linked gene expression have highlighted genes that are likely regulated by the inflammation-related transcription factor NFκB (e.g., Cole et al., 2007; Chen et al., 2009; Miller et al., 2009). NFκB-regulated genes tend to be upregulated in poor quality social environments, suggesting that social adversity produces a chronic condition of low-grade inflammation—a state also associated with aging (Larbi et al., 2008; López-Otín et al., 2013). Strikingly, targeted repression of NFκB in mouse skin has been shown to reduce markers of cellular senescence, increase cell proliferative potential, and change genome-wide gene expression profiles to match characteristics of young mice (Adler et al., 2007; see also Tilstra et al., 2012). NFκB signaling is thus a promising pathway for investigating shared mechanistic links between social adversity and aging. Indeed, NFκB is repressed by hypothalamic-pituitary-adrenal axis-mediated glucocorticoid (GC) signaling, another pathway associated with social adversity. Although chronically stressed individuals may exhibit elevated GC levels, they also can become insensitive to GC signaling at the cellular level, perhaps in part due to downregulation of glucocorticoid receptor transcript levels (Tung et al., 2012).

A focus on the regulation of specific aging-related pathways therefore promises to improve the understanding of how social environmental effects influence the aging process. In natural populations, the kinds of invasive manipulations possible in lab model systems, or even captive primates, will generally be impossible. However, assays of the gene regulatory response to experimental stimuli in primary (i.e., not immortalized) cells outside the body can be a useful way to investigate how environments experienced by the whole organism impact the function of individual cells. For example, white blood cells collected from study subjects who were low socioeconomic status early in life present a more pro-inflammatory phenotype following experimental stimulation than individuals who were high socioeconomic status in early life (Miller et al., 2009). These observations suggest potentially powerful approaches to directly test, using experimentally controlled conditions, whether aging-related signaling pathways can be differentially activated in low social adversity versus high social adversity individuals (including in a cross-species comparative context: see Barreiro et al., 2010 for an example investigating species differences in the innate immune response). Such assays facilitate a number of downstream gene regulatory trait assays. For example, in addition to measuring changes in gene expression levels, NFκB and glucocorticoid receptor protein-DNA binding can be directly measured using chromatin immunoprecipitation techniques to compare stimulated versus unstimulated cells (e.g., Reddy et al., 2009; Wang et al., 2012; Luca et al., 2013).

The Types and Timing of Social Environmental Effects

Work on the genomic response to social environmental variation is still in its early days. Consequently, the tendency is to emphasize similarities across studies, which reinforce their reproducibility and generalizability. Indeed, studies of social environmental effects on gene expression do tend to identify more overlapping genes than expected by chance (Tung and Gilad, 2013). These commonalities suggest that different studies may be pointing to a set of shared gene regulatory pathways, which some investigators have termed a "conserved transcriptional response to adversity" (Slavich and Cole, 2013). However, even in highly controlled lab settings, the consequences of aging-related environmental treatments are highly dependent on the nature of the intervention. For example, at least nine different dietary restriction protocols have been studied in the context of aging in *C. elegans*, and their effects range widely from about a 25 percent to a 150 percent increase in expected lifespan (Greer and Brunet, 2009). The timing and magnitude of environmental and molecular manipulations also matter. Mild heat shock, which is lifespan extending in *C. elegans*, is more protective if applied intermittently throughout life than during a single event early in life (Wu et al., 2009). In contrast, the protective benefits of lowering cellular respiration rates seem to be specific to larval development (Rea et al., 2007).

It seems reasonable to expect that any effects of social environmental variation on aging in natural populations will be at least as nuanced. In addition to investigating conserved social environmental signatures (either between studies or with signatures of age), functional genomic studies can also be used to dissect context-specific effects. Several types of context-dependency are already suggested in the literature. For example, both monocytes (Cole et al., 2011, 2012), which primarily function as part of the innate immune system, and cytotoxic T cells (Tung et al., 2012), which function in adaptive immunity, have been implicated as important in the response to social adversity. Similarly, observations that gene expression changes with age seem to be accelerated in human women compared to men, potentially due to differences in exposure or susceptibility to stress, suggest the potential importance of sex differences (Yuan et al., 2012). Finally, timing-dependent effects are indicated by the observation that early life social adversity can lead to long-term, stable changes in gene regulation. These changes may often be mediated by epigenetic patterning, as in the case of the long-term effects of maternal rearing environment on the regulation of brain- and blood-expressed genes. Interestingly, sites responsive to maternal rearing environment in the rat arginine vasopressin promoter appear to be protected from a general pattern of aging-related hypomethylation elsewhere in the region (Murgatroyd et al., 2010). Under-

standing timing-dependency will thus be key for understanding plasticity in, and the reversibility of, social environmental effects (including, as some have argued, whether differing levels of plasticity are adaptive: Boyce and Ellis, 2005; Ellis et al., 2011). Importantly, some studies indicate that social environment-associated epigenetic marks do not irreversibly crystallize in early life. For example, changes in social status in adulthood alter genome-wide DNA methylation levels in rhesus macaques, and perceived stress in adult humans is associated with a similar number of changes in DNA methylation levels as childhood socioeconomic status (Lam et al., 2012; Tung et al., 2012).

Finally, functional genomic analyses can contribute to a better understanding of how multiple types of social adversity, or social conditions acting at different periods in the lifecourse, jointly act to influence health. The degree to which social environmental effects act independently has important ramifications for understanding whether they act through independent molecular mechanisms. Other environmental effects linked to aging sometimes do affect discrete pathways. In *C. elegans*, for instance, dietary restriction and lowered temperature act additively to produce more dramatic effects on lifespan extension than either alone (Yen and Mobbs, 2010). It will be interesting to learn whether different social environmental factors also act additively. A good place to start would be in discriminating the gene regulatory consequences of social status versus social isolation—two distinct sources of social adversity that are often discussed together, but that need not be correlated. Functional genomic data would help resolve whether, and to what degree, social status and social integration act additively or nonadditively, as well as whether additive effects arise because they affect different molecular mechanisms.

Biodemographically Integrated Studies

Functional genomic studies have primarily defined aging-related gene regulatory phenotypes as those that change linearly with chronological age. This approach has been very useful for demonstrating the pervasiveness of associations between age and gene regulation. However, it leaves a great deal unanswered about how, exactly, a given regulatory phenotype is linked to the aging process—that is, the pace at which health declines and mortality rates increase over time. In demographic terms, aging is not described by the clocklike passage of time, but instead by a progressive loss of physiological function that results in an increase in age-specific mortality rates across the lifecourse. Biodemographic approaches allow the shape of this relationship to be quantitatively parameterized, and differences in these parameters across environmental conditions, populations, and species are of fundamental interest to the field. Integrating a biodemographic perspec-

tive on aging with functional genomic approaches therefore promises to provide novel insights into how social environmental variation affects the aging process. In this section, I detail potential avenues through which this integration could progress, recognizing that, at this early stage, these possibilities remain speculative.

Using Biodemographic Concepts to Identify Biomarkers of Social Environmental Effects on Aging

In humans, as well as in the animal species generally used as models for social adversity, the relationship between mortality rate and age tends to have a characteristic "bathtub" shape (see, for example, Figure 1 in Bronikowski et al., 2011, and Figure 1 in Jones et al., 2014, for the period following maturity). This relationship reflects a high risk of mortality in the post-natal period that reduces to a period of low risk during development and adolescence. Senescence begins after reproductive maturity and is characteristically marked by an exponential increase in mortality rate over time. In this last stage, mortality rate can be modeled as a function of age using one of a family of generalized logistic functions, most commonly the Gompertz function.

This relationship states that mortality rate at any given age is a consequence of both the initial mortality rate—a constant offset—and the pace at which mortality rates increase with age. When age-specific mortality rates are log-transformed, these two parameters become, respectively, the intercept and slope of a linear model. The Gompertz model provides a convenient way of expressing the relationship between the linear progression of chronological age and the non-linear increase in mortality rate (or physiological decline) associated with getting older. Genetic variation or environmental conditions that affect lifespan can do so by changing the Gompertz intercept, slope, or both. Importantly, though, because the intercept affects individuals of all ages equally, only the slope captures age-dependent changes in mortality risk. Thus, some investigators have emphasized that environmental conditions that alter the Gompertz intercept may be unrelated to aging, because they do not change the rate of senescence over time (Jacobson et al., 2010). Perhaps counterintuitively, though, they actually can reverse an individual's risk of death to the level associated with being chronologically younger. Dietary restriction in fruitflies, for example, seems to operate in this manner (Mair et al., 2003; Jacobson et al., 2010).

Defining whether a given social environmental variable influences the Gompertz intercept or the Gompertz slope can therefore provide a useful framework for testing the relationship between social adversity, aging, and putative functional genomic biomarkers of both processes. In model systems, genetic and environmental effects on the Gompertz intercept are

often independent of effects on the Gompertz slope, implying that these two components of mortality rate are affected by discrete molecular mechanisms (Mair et al., 2003; de Magalhães et al., 2005; Wu et al., 2009; Yen and Mobbs, 2010; Sarup et al., 2011; Kelly et al., 2013). Several investigators have formalized this prediction with respect to biomarkers of aging (Jacobson et al., 2010; Kelly et al., 2013). According to this logic, aging is an irreversible process, as no interventions have successfully produced a decrease in mortality rates with age in senescing organisms (although this phenomenon, termed "negative senescence," does seem to occur in some species in nature: Jones et al., 2014). Hence, biomarkers of aging, which reflect the Gompertz slope, should themselves be irreversible even if the environment improves: change in these biomarkers reflects uncorrectable, accumulated molecular damage. In contrast, biomarkers that reflect the Gompertz intercept should be capable of reverting to the state associated with younger individuals, but should continue to change with age at the same rate.

These predictions have been used to identify advance glycation end products (AGEs) as a biomarker of the rate of aging in fruitflies (Jacobson et al., 2010). Uniquely among a set of putative biomarkers, the rate of AGE accumulation slowed, but AGE levels did not reverse, in concert with temperature shifts known to influence the Gompertz slope. However, AGE accumulation did not change in association with the imposition of dietary restriction, which only influenced initial mortality rate. As the number of putative gene regulatory biomarkers of both the social environment and aging accumulates, it should be possible to perform similar kinds of analyses to support or refute the likelihood that individual markers of social adversity are mechanistically connected to aging. Unlike in fruitflies, experimental approaches that alter social context will often be practically and ethically unfeasible (although interventions in captive social primates could in principle be conducted). However, studies in both human and animal populations often document cases in which an individual's social environment changes over time. Indeed, some of these studies have been highly influential in making the case for the long-term effects of early social adversity. For example, even among highly educated, socioeconomically privileged adults, early-life socioeconomic status can still predict rates of cardiovascular disease later in life (Kittleson et al., 2006).

Understanding whether social environmental conditions influence the Gompertz slope or the Gompertz intercept may also motivate the types of gene regulatory phenotypes investigators wish to investigate. Epigenetic marks, in particular, have been associated with the kind of long-term "memory" of past insults that might suggest a closer relationship with the rate of aging than with initial mortality rate. Importantly, studies in model systems have demonstrated that variation in both Gompertz parameters is

clearly reflected in functional genomic data (Pletcher et al., 2002; Sarup et al., 2011; Fok et al., 2014). For instance, artificial selection for increased longevity in *Drosophila* resulted in a marked change in expected lifespan primarily accounted for by a change in the Gompertz intercept. This change was mirrored by shifts in gene expression levels for genes known to be correlated with age, in which old flies from long-lived lines exhibited gene expression patterns that clustered with control flies at a younger age (Sarup et al., 2011).

Functional Senescence in Gene Regulation

While senescence often refers specifically to the pace at which mortality rates change with age, physiological function also declines with age. Understanding the properties of this decline, which can be usefully distinguished as functional (as opposed to demographic) senescence (Grotewiel et al., 2005), may also shed light onto how social environmental effects on gene regulation impact aging. For example, Bronikowski and Promislow (2005) suggested that mechanistic links between a given trait and the aging process could be indicated when the shape of the relationship between age and that trait mirrored the shape of the relationship between age and mortality rate.

To investigate this possibility will require moving away from testing simple linear relationships between age and gene regulatory traits towards investigating whether they, too, can be modeled using non-linear functions like the Gompertz. This seems likely, as exponential decay is a general property of many physical and biological systems, including protein decay and the regulation of RNA decay within cells (Levinthal et al., 1962). If so, then it will be particularly interesting to examine cases in which functional senescence in gene regulation recapitulates the parameters describing demographic senescence in mortality rates in the same population. A mechanistic link between the social environment and aging would then be supported if variation in social conditions (e.g., for low versus high social status individuals) produced parallel changes in both functions.

To my knowledge, analyses of this type have not been conducted. However, several studies have investigated non-linear relationships between gene expression levels and age. For example, Somel et al. (2010) showed that age-gene expression relationships in the brains of humans and rhesus macaques can be described by a relatively small set of clusters of discrete non-linear shapes. These clusters appear to be biologically meaningful, as genes within clusters tend to be functionally related. Genes involved in DNA repair, for instance, were enriched in a cluster that exhibited progressive stages of downregulation from birth through early life, stability during adolescence, and then upregulation after adolescence and into old age; metabolism-related genes tended to show the inverse pattern. Interest-

ingly, the two transition points for these curves fell around ages 4 and 25 in humans, suggestively close to the demographic transition points that mark the fall in mortality rate after the early high-risk period and the onset of senescence.

In a second analysis, Yuan and colleagues examined the age trajectories of genes that were significantly differentially expressed with both age and sex (Yuan et al., 2012). They were able to identify distinct sets of genes for which sex predicted differences in log-transformed gene expression for either the onset of aging-related change or the rate of that change. These two patterns are again suggestively similar to the biodemographic concepts captured by the Gompertz intercept and slope parameters. In both studies, age-gene expression relationships were modeled using somewhat arbitrary, but highly flexible functions (polynomial regression and cubic spline fitting), as opposed to generalized logistic functions with a more interpretable meaning vis-à-vis aging. Nevertheless, they indicate that taking a similar approach for genes that are affected by both the social environment and age would help distinguish between genes that are affected by the social environment in age-dependent versus age-independent manners.

PROSPECTS

The ability to investigate the functional genomic correlates of both age and the social environment in natural populations, outside of the lab, is very recent. Nevertheless, research in the last 10 years has clearly established that (1) both chronological age and demographically defined senescence are associated with variation in genome-wide gene regulatory phenotypes; (2) key aspects of the social environment associated with health and longevity also impact gene regulation, particularly gene expression and DNA methylation levels; and (3) gene regulatory signatures of age and the social environment reflect functionally coherent, and probably intersecting, biological pathways and processes, some of which are related to the known hallmarks of aging.

These findings are important from the perspective of understanding the biodemographic impact of social adversity. However, they are also very broad-brush and do not yet address many basic questions important to identifying which individuals in a population are most vulnerable, or the possibilities for ameliorating the effects of past adversity. For example, while sex differences in the relationship between social adversity and gene regulation probably exist, studies to date have focused either on a single sex, have been too small to investigate differences by sex, or simply have not asked the question. Reanalysis of existing datasets may contribute to a better understanding of these differences (e.g., Yuan et al., 2012). More likely, though, is that a synthetic treatment of differences by sex will

require the accrual of additional studies in more systems, and targeted investigations of both sex and social environmental effects within the same population. Basic differences in vulnerability to social stressors in men and women (Rohleder et al., 2001; Kudielka and Kirschbaum, 2005), as well as sex differences in the relationship between social status and age in many animal models (e.g., in baboons: Altmann et al., 2010), suggest that such studies will be illuminating.

Similarly, comparative studies across species and environmental contexts are sorely needed. To date, there are no published studies of social environmental effects on genome-wide gene regulation in a natural population of any nonhuman species. While captive populations and lab models have thus provided important proof of principle that social environmental variation can impact gene regulation, they explain little about its effects in naturally aging populations. What social status and social integration mean to wild animals may differ from their meaning to captive animals; indeed, some types of social adversity tested in captivity, such as extended maternal separation or peer-rearing conditions, have no analogue in natural populations. Further, gene expression patterns can themselves reflect a signature of captivity, particularly at stress response and inflammation-related genes (Kennerly et al., 2008). Finally, initial mortality rates (the Gompertz intercept) and potentially the rate of aging as well (the Gompertz slope) have been shown to differ between captive and wild primates of the same species (Bronikowski et al., 2002). Thus, all three dimensions of the relationship between social adversity, gene regulation, and aging could differ between captive and wild animal populations. Similar variability may affect studies in humans as well, in which subjects have been recruited from clinical and patient populations as well as from population-representative samples.

Future work targeting an expanded set of systems will thus be important for understanding the generality of proposed links between social environmental variation and gene regulation. For example, they will help reveal whether, as in aging, pathways involved in this relationship are conserved across species, and highlight the contexts in which specific types of social environmental variables matter. Comparative research on the relationship between glucocorticoid levels and social status provides a useful model here. Such comparisons have helped to replace the concept of an invariable relationship between low status and elevated glucocorticoid levels with a model in which this association is expected primarily in species with strictly enforced hierarchies, and for classes of individuals who have few sources of social support (Abbott et al., 2003).

Similar patterns may hold in the case of social environmental effects on gene regulation, and it will be interesting to learn if genes associated with social conditions are therefore more closely linked to aging for some species than others. Because genomic data are becoming increasingly easy

to collect, high-quality phenotypic data will ultimately be the limiting factor in expanding research on social effects on gene regulation to new systems. Populations for which high quality sociobehavioral and demographic data already exist, including large-scale population studies of humans and long-term field studies of social mammals, should therefore be prioritized. Notably, some of these populations provide the opportunity to track social environment-related longitudinal changes in gene regulation as well, something that is yet to be accomplished except at very limited (e.g., single gene) scales (Murphy et al., 2013).

CONCLUSIONS

In humans, genotype explains approximately one-third of variation in longevity, with much of the remaining variance accounted for by environmental effects. Variation in the social environment clearly accounts for some of these effects, and probably exerts its influence in part through altering the regulation of genes. Functional genomic approaches suggest strategies for investigating this relationship through either biodemographically motivated or biodemographically integrated approaches. Further, they provide a path forward that can take advantage of the rich phenotypic and demographic data already available in human population studies and field studies of wild social mammals.

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4

The Long Reach of History: Intergenerational and Transgenerational Pathways to Plasticity in Human Longevity

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INTRODUCTION

In humans, evolution has produced a species with a lifespan several decades longer than expected for a mammal or primate of its size. Evolutionary principles provide helpful clues to what likely facilitated this outcome (Hawkes et al., 1998; Kaplan et al., 2000). First, human ancestors must have found ways to limit extrinsic mortality sufficient to make it less risky to spread reproductive effort across a long adult life, thus favoring intensive investment in lifespan-extending maintenance effort (Kirkwood and Rose, 1991; Stearns, 1992; Ricklefs, 2008). Second, humans' social units are unusual in the extent of the reliance upon intergenerational transfers of energy and knowledge from older to younger generations, which selected for increased longevity (Hawkes et al., 1998; Lee, 2003). Reduced mortality relative to other great apes, and the increased reproductive value of later human life stages, are among the forces that worked to favor a strategy of maintaining relatively healthy, functional bodies several decades beyond the ages of direct reproduction.

Although an unusually long lifespan is a defining characteristic of *Homo sapiens*, prehistoric and historic evidence for trends in human life expectancy, along with contemporary disparities in relation to ethnicity, class, and race (Keppel et al., 2002), demonstrate the enormous impact of environments as influences on heterogeneity in potential longevity among members of the species. Large historical improvements in life expectancy in Europe and elsewhere were due primarily to the control of common in-

fectious diseases, which greatly reduced infant and child survival (Omran, 1971). As one example, increases in life expectancy occurred in the United States as the germ theory of disease gained in acceptance and led to new public health measures like boiling bottles and milk, hand washing, and isolating sick children (Preston, 1996).

As early life infections are controlled in a population and individuals begin living to advanced ages, chronic degenerative processes come to predominate as determinants of mortality and life expectancy. Although it was traditionally believed that such post-demographic and epidemiologic-transition populations would eventually reach a ceiling in life expectancy, long-term demographic data suggest that high-income human populations are not yet approaching this ceiling, if in fact it exists (Oeppen and Vaupel, 2002). This is reflected in the fact that, despite pervasive disparities within societies (Keppel et al., 2002), lifespan in many industrialized nations has been consistently increasing, at a remarkably steady rate, for more than a century (Oeppen and Vaupel, 2002; Tuljapurkar et al., 2000; Vaupel, 2010). These ongoing secular trends in population life expectancy have generated much attention, and there is great interest in understanding their underlying causes. Particularly because the most pronounced changes have come about in a scant four generations, genetic change is an unlikely explanation for them (Burger et al., 2012).

Recent years have witnessed growing interest in a new potential explanation for some of these trends. An extensive literature now supports the hypothesis that part of what determines late-life function and mortality are experiences early in life, starting in utero, and potentially even tracing to the experiences and behaviors of recent generations of ancestors (Gluckman and Hanson, 2006; Kuzawa and Quinn, 2009). Early observational work in humans reported an inverse relationship between birth weight (BW) and future risk of cardiovascular and other chronic diseases, pointing to a likely role of prenatal nutrition in risk for diseases associated with late-life aging and mortality. Importantly, the elevation in cardiovascular disease (CVD) risk is not limited to abnormally low birth weight individuals, but is found in relation to increases in BW across the full BW spectrum, suggesting that the overall quantity of nutrition that a fetus receives may be important. In parallel, an extensive nonhuman literature has replicated many of these findings in model species using experimental designs, demonstrating that early environments, per se, are likely important drivers of many of these effects.

Inspired by this work, research by economists and demographers has been instrumental in demonstrating the likely causality of such relationships in humans (e.g., Almond, 2006; van den Berg et al., 2009). As a result of this work, the idea that long-term health traces in part to early-life experiences is increasingly accepted by researchers across many fields.

While this work has clearly been important, basic scientific understanding of the effects of early environments is rapidly expanding and now routinely demonstrates effects that linger not only into later life, but also that are transmitted to two, three, or even more generations of offspring, operating through several distinct biological inheritance pathways. For biodemography, this work implies that a full understanding of the determinants of human life expectancy, including the vast heterogeneity across and within societies, may require investigating not only the role of early rearing environments, but also historical environments experienced by ancestors, potentially extending back multiple generations.

In this paper, we begin by briefly tracing the history of scientific interest in the early-life determinants of late-life health. Then we review some of the mechanisms now understood to contribute to these relationships. This serves as a backdrop for the second section, in which we explore newer evidence that the effects of early environments can linger beyond adulthood to impact offspring, operating not only through several distinct maternal-offspring pathways, but also through direct parent-offspring epigenetic transfers. These emerging findings add new complexity to understanding of the determinants of aging and life expectancy and inspire a new generation of hypotheses. Our goal is to review the state of evidence for such effects in humans and other species and to outline testable hypotheses for the determinants of human health and life expectancy that emerge from this literature. As we will argue, we believe that demography and related population research fields are well situated to help refine understandings of the pathways for intergenerational transmission of environmental influences on health, which are coming to light through animal model research but have thus far proven challenging to evaluate in human populations.

DEVELOPMENTAL AND INTERGENERATIONAL PLASTICITY

History and Summary of Research Linking Gestational or Infancy Conditions to Adult Health

The hypothesis that undernutrition or early deprivation could compromise adult health was proposed in the early work of Kermack, McKendrick, and McKinlay (1934) documenting birth cohort effects on mortality in England, Sweden, and Wales (see Doblhammer, 2004). In a 1934 *Lancet* article, they noted that secular trends in mortality were predicted by year of birth and concluded (Kermack et al., 1934, p. 700) that "the expectation of life was determined by the conditions which existed during the child's earlier years." Forsdahl (1977, 1978) later provided additional support for this hypothesis from analyses of Norwegian demographic data.

Subsequently, researchers in the United Kingdom observed that the risk of dying from CVD, or of suffering from conditions that precede CVD like hypertension or diabetes, is highest among individuals who were light as newborns, thus linking these late-life outcomes with an early life proxy of nutrition (Barker et al., 1989; Barker, 1994). Human studies have since replicated similar findings relating lower BW to CVD risk factors and CVD mortality in populations across the globe (Leon et al., 1998; Adair et al., 2001; Law et al., 2001; Kuzawa et al., 2003; Yajnik, 2004; Tian et al., 2006; Gupta et al., 2007; Huxley et al., 2007).

Although BW is a complex phenotype, there is considerable evidence that the relationship between birth outcomes and adult chronic disease are not simply due to genetic influences or the result of BW indexing environmental status, which also has persistent effects on chronic disease risk later in life. For instance, among monozygotic twins, the twin born lighter has been shown to have elevated risk for obesity, diabetes, and hypertension later in life (Bo et al., 2000; Iliadou et al., 2004; but see Oberg et al., 2011, for an alternate view), showing that differences in birth size predict adult CVD risk among genetically identical siblings occupying the same post-natal environment. Animal model work provides true experimental tests of the hypothesis that early-life experiences shape future adult health. Such studies have replicated many of the disease outcomes found in relation to lower BW in human populations (Symonds et al., 2003). For instance, restricting the nutritional intake of pregnant rats, mice, or sheep, or directly restricting blood flow to the fetus, increases post-natal blood pressure, cholesterol, abdominal fat deposition, stress reactivity, and diabetes risk in offspring (Kind et al., 2003; Langley-Evans et al., 2003; McMillen and Robinson, 2005; De Blasio et al., 2007).

Developmental and Epigenetic Pathways Linking Early Environments with Adult Health

Several types of biological adjustment are made by the developing fetus in response to prenatal stimuli that contribute to these long-term changes in disease risk. All are examples of developmental plasticity, or the capacity of the developing body to modify its structure and function in response to environmental or behavioral experiences. The most straightforward mechanism of plasticity involves changes in growth of a tissue or organ as reflected in size or cell number. For instance, the kidneys of prenatally undernourished individuals tend to be smaller and have fewer nephrons, a trait that increases risk of hypertension and renal failure in adulthood (Lampl et al., 2002; Luyckx and Brenner, 2005). Similarly, changing the number or type of muscle cells can modify the body's ability to clear glucose

from the blood stream, leading to changes in insulin sensitivity and diabetes risk (Jensen et al., 2007).

One increasingly well-studied set of mechanisms linking early environments with adult health involves epigenetic changes, defined as chemical modifications that alter gene expression in a specific tissue or organ without changing the nucleotide sequences of the DNA (Jenuwein and Allis, 2001; Waterland and Michels, 2007). Several epigenetic mechanisms have received attention for their likely role as links between early environments and adult health. Chemical modification of histone proteins that the DNA strands are wound around in the cell nucleus can lead to tighter or looser DNA packing in the region of specific genes, reducing or enhancing gene expression respectively. A second molecular mechanism of epigenetic marking involves noncoding RNA (e.g., microRNA or miRNA). These DNA transcripts do not code for proteins, but can influence biology and health by regulating gene expression at other protein-coding genes (Fabian et al., 2010). To date, most attention in human epidemiological studies has focused on a third mechanism, methylation, in which methyl groups are attached to DNA in regions adjacent to specific gene promoters. Although there are exceptions, increased methylation in the vicinity of a gene impedes binding by transcription factors and thereby silences gene expression in that cell (Berger, 2007). All three mechanisms of epigenetic marking are potentially responsive to environmental stimuli and stable for varying timeframes, thereby potentially helping link experiences across the lifecourse with altered biology and health.

Experimental animal model studies confirm that modifying nutritional or other characteristics of early environments can lead to durable epigenetic changes that persist into later life to influence biology and underlying disease processes (Gluckman et al., 2007; Waterland and Michels, 2007). Maternal experiences during or prior to pregnancy have similarly been shown to predict altered epigenetic markings in human offspring, supporting a role for such effects on human biology and disease (Heijmans et al., 2008; Waterland et al., 2010).

In summary, there is solid evidence that the widely documented relationships between early life measures such as BW and later CVD partly reflect the effects of the gestational and infancy environments on the development of biological systems, including effects on how the body manages glucose and lipids, deposits fat, regulates blood pressure, and responds to stress. Each of these is an important determinant of the pace of chronic disease development and thus life expectancy. These effects typically reflect changes in the growth and development of specific organs and tissues or modifications in the regulation of hormones, metabolism, or physiology. They are increasingly being traced to durable, environmentally induced epigenetic changes in the chromosomes that modify gene expression without modifying the DNA sequence.

Pathways for the Intergenerational Transmission of Environmental Effects

There is mounting evidence that environmental effects may be transmitted to future generations operating through several pathways (Drake and Liu, 2010; Daxinger and Whitelaw, 2012; Guerrero-Bosagna and Skinner, 2012; Benyshek, 2013). To date, these intergenerational effects have received little research attention among demographers, despite their potentially large impacts on patterns of health and life expectancy within and between societies.

There are two primary biological pathways by which environmental experiences or behaviors in one generation may impact health and lifespan in future generations. The first involves phenotype-to-phenotype transmission in which the lingering biological effects of early experiences (e.g., fetal programming leading to altered adult metabolism or physiology) impact the next generation by altering the gestational environment or milk composition experienced by offspring (Benyshek et al., 2001; Kuzawa and Sweet, 2009; Drake and Liu, 2010).

As a second pathway, there is now a compelling body of research documenting direct transmission of environmental influence across one or more offspring generations transmitted by epigenetic factors packaged in sperm or egg (Daxinger and Whitelaw, 2012; Guerrero-Bosagna and Skinner, 2012). These studies show that environments can have biological effects that linger across two, three, or more generations of offspring, while also showing that such effects reflect not only maternal but also paternal experience. Taken together, these intergenerational pathways greatly extend the "reach" of past environments as influences on health and aging, and provide new challenges and opportunities for researchers interested in explaining this heterogeneity.

Intergenerational Pathway #1: Phenotypic-to-Phenotype Transmission

Perhaps the most straightforward phenotypic pathways for intergenerational effects involve biological systems that, when modified, directly alter the gestational or lactational environments experienced by the developing fetus or infant. The long-term effects of an adverse gestational environment on traits like insulin resistance, high blood pressure, inflammation, or stress reactivity can all negatively impact the gestational environment experienced by the next generation. There are many such examples of mutually reinforcing early-life and adult biological change. For instance, not only does fetal growth restriction or low BW predict higher adult blood pressure (Adair et al., 2001), but also prepregnancy hypertension in turn leads to fetal growth restriction and lower BW (Kramer et al., 1999). Similarly, inflammation has been shown to be higher among individuals born with a lower BW

(McDade et al., 2010), while adult inflammation is associated with more adverse birth outcomes (Kuzawa et al., 2012).

One well-understood pathway for human phenotype-to-phenotype transmission involves the intergenerational effects of maternal obesity and metabolic dysfunction, which are increasingly important in societies faced with rising obesity rates (see Benyshek, 2013). Fetal growth and fat deposition are under control of hormones that are driven by insulin (Gluckman and Pinal, 2003). Because insulin is stimulated by circulating glucose and other nutrients, maternal circulating glucose levels during pregnancy are strong predictors of offspring BW and adiposity (Metzger et al., 2008). Longitudinal studies have shown that maternal glucose during pregnancy continues to be a strong predictor of adiposity and insulin sensitivity measured in childhood (Chandler-Laney et al., 2011), while adult obesity and diabetes have been linked back to prenatal exposure to gestational diabetes (Benyshek, 2013).

Evidence that maternal overweight can directly impact offspring adiposity and metabolic disease risk is seen in the excess estimated heritability for body mass index observed through mother-offspring pairs compared to father-offspring pairs (Murrin et al., 2012). Although a range of genetic (e.g., mitrochondrial DNA) or environmental explanations for such an effect are possible (Kuzawa and Eisenberg, 2012), among obese mothers electing for gastric bypass surgery to lose weight, offspring born after the surgery have been shown to have dramatically reduced body fat and normalized metabolic parameters when compared to their siblings born prior to the surgery (Smith et al., 2009). This suggests that the metabolic characteristics of the gestational environment associated with an obese mother, per se, are important influences on offspring metabolism and metabolic disease risk. These findings show how any change in glucose metabolism triggered by the prenatal or early post-natal environments that a woman experienced as a fetus or infant may also alter disease risk in her future offspring (Drake and Liu, 2010; Benyshek, 2013).

The effects of the adult phenotype on offspring are by no means limited to physiology and metabolism, and indeed, there are abundant opportunities for parental behavior (itself reflecting a lifetime of experience and development) to influence offspring epigenetic state and development, particularly during early periods of dependence and attachment. As a well-studied example, stress physiology is responsive to social interaction and stress, which can link early experiences with lasting changes in the stress response and downstream traits, including metabolism, memory, and affect regulation (Entringer et al., 2009; Flinn et al., 2011). In humans, maternal exposure to stress during pregnancy predicts changes in stress hormone regulation in early infancy (Lee et al., 2014) and adulthood (Entringer et al., 2009).

Experimental work in rats illustrates how epigenetic changes can contribute to the intergenerational perpetuation of the effects of stress on offspring biology and behavior. In a well-known study, Meaney and colleagues reported that highly attentive rat mothers who exhibit a nurturing grooming style raise pups that, as adults, exhibit changes in gene promoter methylation and histone acetylation that modify hypothalamic–pituitary–adrenal (HPA)-axis function (Weaver et al., 2004). These modifications include heightened negative feedback sensitivity of the stress hormone axis, lower stress hormone levels, and reduced anxiety. Intriguingly, in part as a result of these epigenetic modifications, female offspring are biased towards exhibiting the same style of maternal care that they experienced as pups, thereby contributing to the intergenerational transmission of an environmentally induced behavioral phenotype.

Intergenerational Pathway #2: Direct Germ Line Epigenetic Inheritance

In a second class of nongenetic inheritance, a variety of epigenetic factors capable of directly regulating gene expression are modified in the parent in response to their experiences and then transferred via sperm or egg to offspring (and potentially, grand and great-grandoffspring), among whom they can have lasting impacts on biology and health. In these examples, ancestral environmental experiences may be viewed as having direct access to, and influence over, gene expression in future generations of offspring.

During early development, most epigenetic markings are erased during the formation of gametes (sperm and egg) and again in the embryo prior to implantation (Reik et al., 2001). This epigenetic resetting is believed to be necessary to remove parent-of-origin imprinting at imprinted loci (in which genes are only expressed in offspring if inherited from one or the other parent) along with any accumulated epigenetic modifications or errors (Reik et al., 2001). Early epigenetic reprogramming events are crucial to establishing the cellular totipotency that allows the cells in the early embryo to differentiate into any of the body's hundreds of cell types. Nonetheless, a growing body of work demonstrates that some environmentally induced epigenetic markings are not erased, but may be maintained in the germ line. This work links exposure to toxins, stressors, nutrients, or other factors to altered epigenetic marking, gene regulation, and phenotypic state across one or more generations of offspring (Daxinger and Whitelaw, 2012; Guerrero-Bosagna and Skinner, 2012).

Of particular interest in this literature are examples of "transgenerational inheritance" in which a phenotype is present despite that generation not having been exposed as a fetus or even as a gamete. In pregnant females (F_0), environmental experiences during pregnancy potentially directly affect both the in utero offspring (F_1) and their developing gametic precursor cells,

which will later form the F_2 generation. Thus, clear evidence for transgenerational epigenetic inheritance in females (F_0) requires demonstrating that the phenotype persists to the great-grandoffspring (F_3) of the pregnant female. Because there is no male analogue to maternal-fetal phenotype-to-phenotype inheritance, demonstrating an effect in grandoffspring (F_2) of males (F_0) is evidence for transgenerational inheritance.

Early evidence for such transgenerational epigenetic transmission of environmental effects through the germ line came from animal models involving exposure to toxins and chemical compounds. In rats, exposure to endocrine-disrupting chemicals has been shown to impair the fertility of offspring (F_1), operating through both the matriline and patriline (Anway et al., 2005; Nilsson et al., 2012). In the case of males exposed to the endocrine disrupter vinclozilin, male offspring show evidence for reduced sperm quality, attenuated fertility, and a host of related disorders (e.g., pancreatic cancer) for at least four generations (F_4) (Anway et al., 2005). When female rats were exposed to similar toxicants during the period of gonadal sex determination, offspring (F_1) and great-grandoffspring (the F_4 generation) had impaired fertility and ovarian health as indicated by 35-60 percent reductions in primordial follicle counts along with symptoms of early polycystic ovary syndrome (PCOS; Nilsson et al., 2012). Alterations in methylation and gene transcription were found in ovarian cells in the F_3 animals, pointing to an epigenetic basis to the phenotype. Because the phenotype persisted to the great-grandoffspring (F_3) of the exposed animal in both the male and female experiments above, these studies provide strong evidence of transgenerational epigenetic inheritance, that is, expression of an environmentally induced phenotype in a generation that was entirely unexposed.

In addition to transgenerational effects induced by chemical compounds, a growing list of studies show that "natural" day-to-day exposures, such as psychosocial stress or nutrition, can lead to similar patterns of epigenetic inheritance across one or more generations of offspring. For instance, in an experiment in mice in which maternal separation stress was imposed during the first 2 weeks of post-natal life (Franklin and Mansuy, 2010), methylation was modified in the vicinity of the cannabinoid receptor and corticotrophin-releasing factor receptor in the sperm of the males exposed to stress as newborn pups. A similar pattern of changed methylation and downstream changes in mRNA levels was found in the neurons of female offspring of the stress-exposed males, strongly suggesting direct germ line epigenetic inheritance. Thus, in this example, a stressor experienced by one generation modified the regulation of genes involved in modulating anxiety and stress response in offspring neurons. Another similar study found that chronic (6-week) exposure of male mice to stress either during puberty or in adulthood led to reduced stress hormone (HPA axis) reactivity in offspring (Rodgers et al., 2013), thus suggesting that exposures later in the lifecycle

may also have intergenerational phenotypic effects. In the case of the second mouse experiment, there were large changes in microRNA content in the sperm of the exposed males, pointing to a possible molecular basis for the inherited effect.

Other studies demonstrate epigenetic transmission of the effects of diet on offspring operating through direct germ line inheritance. In one recent experiment (Carone et al., 2010), among male mice fed a low-protein diet, there were large reductions in cholesterol in offspring livers, along with coordinated changes in the expression of genes involved in lipid biosynthesis. The authors found changes in methylation of the PPARα gene, which encodes a transcription factor that regulates expression of multiple genes involved in lipid biosynthesis. This study provides a strong precedent for the concept that diet among males may have intergenerational epigenetic effects on cholesterol and lipid metabolism (and, by extension, cardiometabolic disease risk and longevity) in offspring. As another related example of an intergenerational effect of paternal diet on offspring lipid metabolism, male pigs fed a diet enriched in methyl donors (e.g., folate) had grandoffspring with reduced body fat along with altered gene methylation and gene transcription in the liver (Braunschweig et al., 2012). In a similar study, female offspring of male mice fed a high-fat diet were found to be lighter but more insulin resistant and with reduced beta cell function, contributing to heightened diabetes risk (Ng et al., 2010).

Human Evidence for Germ Line Epigenetic Inheritance of Environmental Effects

Although animal experiments provide important biological precedents illustrating how the environment can impact subsequent generations, the relevance of these findings for understanding human biology and health remains unclear. To date, only a handful of studies provide evidence for possible intergenerational epigenetic environmental inheritance in humans. In a series of well-known studies of a cohort born in 1905 in Överkalix, Northern Sweden (for review, see Pembrey et al., 2013), lifespan was longer when the paternal grandfather experienced poor nutrition during late childhood (9-12 years). Subsequent analyses expanded to three Överkalix birth cohorts and stratified on gender found that paternal grandfather experiences only predicted mortality in grandsons, while paternal grandmother experiences only predicted mortality in granddaughters (Pembrey et al., 2006). They report that findings consistent with this interpretation were present in two of the three cohorts. Specifically, mortality was increased in grandchildren if the corresponding same-sex paternal grandparent was exposed to abundant nutrition during late childhood, compared to individuals exposed to moderate nutrition. In addition, mortality was substantially

reduced in grandoffspring of same-sex paternal grandparents who experienced favorable nutritional conditions from birth to 3 years of age, in this case suggesting an intergenerational benefit of favorable early life nutrition that is passed on to the next generation through sons. This set of findings, which has not been replicated in other populations, provides the strongest human evidence to date for germ-line epigenetic inheritance of nutritional experiences on offspring mortality.

In the same paper (Pembrey et al., 2006), this group used data from the ALSPAC cohort[1] in Britain to demonstrate a possible intergenerational effect of paternal smoking on offspring body mass index (BMI). Offspring BMI showed a modest, but significant, graded relationship with the age when the father first smoked, with earlier ages of smoking (all in late childhood) predicting higher BMI in male, but not female offspring. The authors concluded that these findings, viewed alongside those of Överkalix, provide evidence that the "slow-growth period" of late childhood is a critical period in epigenetic programming in humans.

One additional study suggests an intergenerational effect of paternal diet on offspring health. Studies have shown that chronic betel nut chewing can increase risk for obesity, diabetes, and the metabolic syndrome. In a study of more than 5,000 Taiwanese men, offspring of fathers who chewed betel nut had increased risk of the metabolic syndrome (Chen et al., 2006). The effects were dose-dependent and strong, and consistent with prior findings of hyperglycemia in offspring of male mice fed betel nut (Boucher et al., 1994).

Plasticity in Telomere Length as a Potential Transgenerational Influence on Longevity?

The above examples involve transfer of epigenetic marks that modify gene expression without modifying the DNA sequence itself. Recent findings point to an unusual mechanism of plasticity in which experiences and behaviors in prior generations—in particular, mortality and reproduction—alter the length of telomere DNA that offspring inherit. Telomeres are repeating sequences of DNA found at the ends of chromosomes that shorten as cells divide, leading to a decrease in telomere length (TL) with age. When TL becomes too short, the cell lineage is no longer able to replicate, which is thought to contribute to senescence. Correspondingly, individuals with shorter TL in immune cells show compromised immune function and increased mortality rates (Cawthon et al., 2003; Cohen et al., 2013).

[1]ALSPAC (Avon Longitudinal Study of Parents and Children), see http://www.bristol.ac.uk/alspac/ [June 2014].

Telomere-based constraints on cell proliferation likely contribute to functional decline in cell-proliferation dependent tissues throughout the body.

Contrary to the telomere shortening that occurs with age in somatic cells, older men have longer sperm TL than younger men, and as such offspring of older fathers inherit longer TL (Kimura et al., 2008). This is believed to result from a high level of a telomere-lengthening enzyme (telomerase) in the testes. We recently demonstrated that this paternal age at conception effect persists across at least two generations: the paternal grandfather's age at conception of the father predicts the TL of grandchildren, independent of and additive to the effect of the father's age at his own conception (Eisenberg et al., 2012). These findings raise the intriguing and testable hypothesis that societal trends toward delayed age at male reproduction may themselves lead to the transmission of longer telomeres that contribute to a lengthening of late-life function and life expectancy—and conversely that earlier ages at male reproduction will lead to shorter telomeres (Eisenberg and Kuzawa, 2013).

Evolutionary Significance of Intergenerational Inheritance: Damage or Design?

The above examples show that the biological and health impacts of environments often do not end in adulthood, but may be passed on to offspring generations. These findings thus link the patterns of biology and aging-related chronic disease processes in today's adults to the environments, experiences, and behaviors of their recent ancestors. This leads to two important questions: Why do these effects exist, and do they have a function?

Some of the lingering effects of early experiences on adult health simply reflect a failure of the mother's body, or the placenta, to fully buffer the developing body from nutritional or other forms of stress, which can lead to impaired function (Ellison and Jasienska, 2007). For example, babies born smaller tend to have nephron-deficient kidneys that elevate risk for kidney disease and hypertension in adulthood (Lampl et al., 2002; Luyckx and Brenner, 2005). Fetal life is also marked by rapid brain development, and fetal growth restriction can lead to lasting cognitive impairments as reflected in lower childhood or adolescent school achievement (Low et al., 1992). From the perspective of epigenetic inheritance, the transgenerational disease impacts of exposure to artificial toxicants like vinclozilin in rats suggests an error in epigenetic marking that is passed across multiple offspring generations (Anway et al., 2005), as are human examples of the infertility and immune disorders seen in the children of women who were exposed in utero to the synthetic estrogen agonist diethylstilbesterol (Titus-Ernstoff et al., 2006). Whether scenarios such as these reflect maladaptive responses, a shortage of resources leading to developmental "damage," or adaptive

responses made by the fetus to achieve short-term aims (like surviving gestation), they clearly illustrate that some of the post-natal or adult effects of early environments are nonfunctional by-products that require no adaptive explanation in their own right (Kuzawa and Quinn, 2009).

Other examples are not so straightforward, such as fat deposition, which is a key link between early experience and adult health. Lower BW individuals are more likely to develop CVD, but this is not because they become obese. In fact, they tend to have lower BMIs as adults, but as they gain weight, they preferentially deposit fat in the visceral (abdominal) depot, which is metabolically active as a result of being innervated by sympathetic nerve fibers originating in the brain. When the body experiences stress, these nerves rapidly secrete adrenaline in visceral fat cells, which release fats for use as energy to help the body overcome the stressor. Not only do low-BW individuals deposit more fat in this depot, but also their fat cells mobilize more stored fats when exposed to the same adrenaline dose (Boiko et al., 2005). These changes in fat metabolism are not suggestive of damage. Rather, these findings suggest that the body has a capacity to prioritize depositing fat in a rapidly usable depot in response to early life nutritional stress (Kuzawa, 2010).

Many of the examples of transgenerational epigenetic inheritance discussed above exhibit a level of complexity that is similarly not easily reconciled with a model of simple impairment. Among the findings reviewed was evidence that the diet a male consumes influences how his offspring and grandoffspring metabolize and synthesize nutrients within the body (Carone et al., 2010). Another study showed that the experience of early post-natal separation stress leads to intergenerational epigenetic changes that modify how offspring and grandoffspring respond to similar stressors (Franklin and Mansuy, 2010). Although the specific pathways are only partially understood, such findings are unlikely due to simple impairment or error. In instances such as these, an experience must influence the body and then be communicated in molecular form to the germ line. In cases of transgenerational epigenetic inheritance, any induced changes must survive the normal erasing of germ line epigenetic marks that occurs during gametogenesis and at implantation. In offspring generations, those marks then alter a behavior or biological system that responds to that same environmental stimulus or stressor that initially triggered this cascade several generations prior. The mechanistic basis for such effects is only partially understood in animal models and has scarcely been investigated in humans. But what seems clear is that such examples are improbable and also require a complex multigenerational molecular cascade to sustain. They are unlikely due to chance or damage (Kuzawa and Thayer, 2011).

Because some of the biological changes induced by early-life cues appear to reflect a change in biological regulation, rather than developmental

impairment, it has been speculated that early-life developmental plasticity and epigenetic sensitivity could help the fetus prepare for conditions likely to be experienced after birth (Bateson et al., 2004; Gluckman and Hanson, 2005; Kuzawa, 2005). Some of the adjustments made by the nutritionally stressed fetus in utero, such as a tendency to deposit more abdominal body fat and the glucose-sparing effect of muscle insulin resistance, could help save scarce glucose for use in more essential functions like brain metabolism and immunity (while also heightening risk for diabetes and CVD; Kuzawa, 2010). In addition, other systems that change biological settings in response to early environments, such as stress reactivity (Weaver et al., 2004), immunity (McDade et al., 2010), and reproductive biology (Kuzawa et al., 2010), also hint at capacities to use early-life cues to "fine-tune" how systems function and are regulated. By this reasoning, nutrition, hormones, and other gestational stimuli experienced by the developing fetus might convey information about local ecological conditions, thereby allowing the fetus to adjust priorities in anticipation of these future experiences.

Intergenerational Phenotypic Inertia

One challenge to the hypothesis of long-term anticipatory adaptation comes from the long duration of the human lifespan. Because humans typically live many decades, the ecological conditions experienced during a few months of early development, such as gestation or early infancy, may not serve as reliable cues of environments likely to be experienced in adult life (Kuzawa, 2005). We have argued that it is precisely the brief and early timing of many of the body's periods of heightened developmental sensitivity that paradoxically helps the developing organism reliably predict its future (Kuzawa and Quinn, 2009). Here the idea is that the mother's biology buffers the fetus against the vagaries of day-to-day, month-to-month, or seasonal environmental fluctuations, while passing along integrative information about local conditions that is more stable and reliable. Because the mother's biology and behavior have been modified by her lifetime of experiences, the nutrients and hormones that she transfers to the fetus in utero, or to her infant via breast milk, could correlate with her average experiences more than what she is experiencing during any week or month of gestation itself (Kuzawa, 2005; Wells, 2003).

Evidence for this capacity to convey average, rather than transient, ecological information comes from studies of the effects of a mother's nutrition on offspring BW (Kuzawa, 2005). While BWs tend to be lighter in populations in which nutrition has been marginal for multiple generations, supplementing the dietary intake of pregnant women often has minimal effects on offspring BW (Kramer and Kakuma, 2003). In contrast, the mother's body composition and weight prior to conception, reflecting her energy balance in

the years in the run-up to pregnancy, tends to be an important predictor of BW (Institute of Medicine, 1990). Other studies show that the mother's leg length is among the strongest of predictors of her offspring's BW (Lawlor et al., 2003; Martin et al., 2004; Chung and Kuzawa, 2014). Because leg growth is more sensitive than other stature components to infancy and childhood nutrition (Frisancho, 2007), this finding is evidence for an intergenerational effect of the mother's cumulative nutrition during the early years of her own development on the nutrients transferred in utero to her future offspring.

Thus, it appears that long-term nutritional history in an environment may be an important influence on the resources transferred in utero in support of offspring growth, but that fluctuations in intake during pregnancy itself—reflected, for instance, in dietary supplementation—have comparably modest effects. This "phenotypic inertia"—reflecting the lingering biological but nongenetic effects of the mother's average experiences in the past—could allow the fetus to track those dynamic features of environments that are relatively stable on the timescale of decades or several generations (see Figure 4-1; see Kuzawa, 2005).

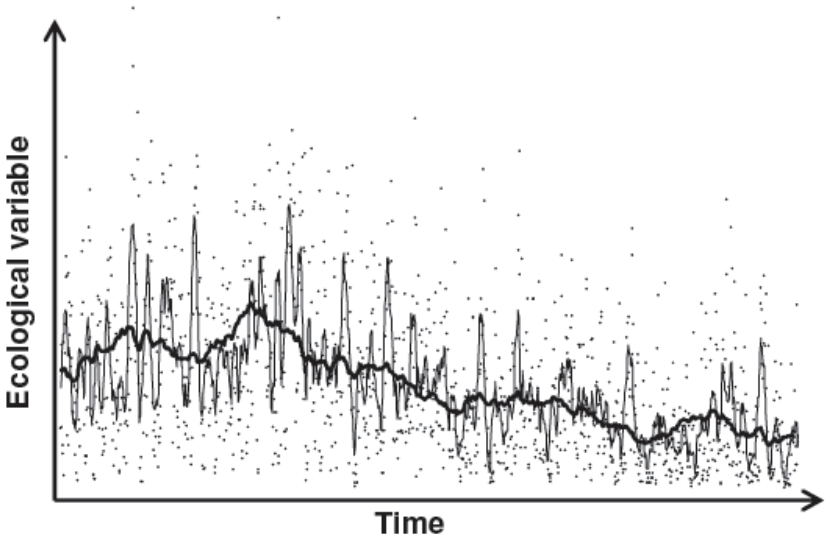

FIGURE 4-1 The intergenerational phenotypic inertia hypothesis.
NOTE: Dots represent the fluctuating availability of a hypothetical ecological resource (e.g., nutrition). The two lines are running averages calculated across 10 time units (thin line) and 100 time units (dark line). As the window of averaging increases, an underlying long-term trend is uncovered. It has been hypothesized that the intergenerational influences of maternal and grandmaternal nutritional history on fetal nutrition help achieve a similar feat.
SOURCE: Kuzawa and Quinn (2009), used with permission.

Above, we reviewed evidence for direct germ line epigenetic inheritance reflecting experiences across multiple generations and through both the matriline and patriline. Although their role in human populations is far less understood, these findings hint at additional means by which the developing body takes multiple samples or assays of local ecological conditions over time, when setting developmental trajectories and biological settings. Because maternal physiology buffers the effects of transient, short-term nutritional fluctuations, these deeper signals may serve as reliable bases for adjusting characteristics such as growth rate, body composition, or nutritional requirements as environmental conditions gradually shift across decades or several generations (Kuzawa and Quinn, 2009). From an applied perspective, the phenotype inertia model underscores the need to envision the goal of interventions as not simply alleviating stress temporarily, but finding creative ways to mimic cues of sustained environmental improvement in the recent past (Kuzawa and Thayer, 2011).

INTERGENERATIONAL PLASTICITY: HYPOTHESES FOR BIODEMOGRAPHY

The pathways for phenotypic and epigenetic inheritance that we reviewed could have substantial impacts on individual and population heterogeneity in morbidity and mortality, including ongoing secular trends in life expectancy documented in high-income populations. Specifically, they suggest that improvements in living conditions, reflecting factors like nutrition, control of infections, or reduced psychosocial stress, will have complex relationships with patterns of health and disease in offspring generations. These pathways should be testable with demographic and cohort databases in which phenotypes are available across two or more generations. To date, the majority of biodemographic research investigating these effects has focused on the late-life effects of stressors experienced during infancy or early childhood, or the role of maternal experience, particularly during pregnancy, on offspring adult outcomes (e.g., Doblhammer and Vaupel, 2001; Almond, 2006; van den Berg et al., 2009; Gagnon, 2012; Gagnon and Bohnert, 2012). The evidence that we reviewed shows that focusing on these lifecourse pathways alone underestimates the potential impact of developmental and epigenetic contributions to health and aging, many of which may have intergenerational and transgenerational components. Building on our review, we next outline testable hypotheses for biodemography inspired by the literature on intergenerational and transgenerational inheritance.

Hypotheses: Phenotype-to-Phenotype Transmission Across Two Generations

In some ways the most straightforward tests of intergenerational effects include examples in which early environments influence adult characteristics that have similar downstream effects on fetal or infant development in the next generation, which alters the gestational environment of offspring and thereby increases risk of these same phenotypes in grandchildren. In such cases, early-life and adult female phenotypes may reinforce each other across generations (Drake and Liu, 2010). Environmental or lifestyle change could thus drive not only phenotypic transmission, but also cumulative intergenerational phenotypic change (Benyshek, 2013). Although there are other possible interpretations (see Kuzawa and Eisenberg, 2012), excess estimated heritability of the phenotype through the matriline than through the patriline would be evidence consistent with matrilineal phenotype-to-phenotype transmission. In contrast to a conventional gene X environment interaction model, in which each generation only inherits its genotype from the prior generation, this model assumes that the phenotype is partly heritable as well, and, thus, a different pattern of phenotypic development within and across generations can be expected (see Figure 4-2).

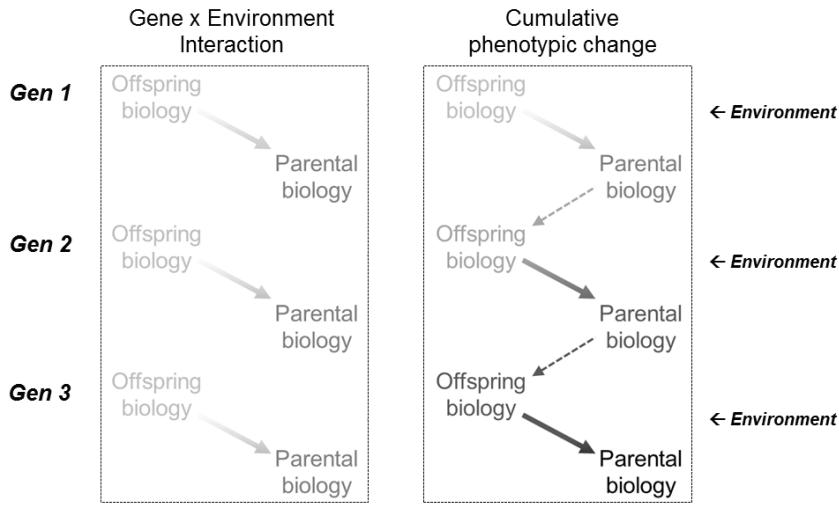

FIGURE 4-2 Conventional gene x environment model of phenotype and a cumulative phenotypic change model.

Hypotheses: Direct Germ Line Epigenetic Inheritance

Examples of germ line epigenetic inheritance do not involve a direct effect of an altered phenotype on offspring and thus can be transmitted through both the matriline and patriline. It is important to note that the relative abundance of animal model studies reporting patrilineal inheritance speaks more to the simplicity of demonstrating transgenerational epigenetic inheritance in males (among whom gestational, lactational, and other direct phenotype-to-phenotype pathways are not present) than to any inherently stronger effects through the patriline.

As we reviewed above, there is now evidence for epigenetic inheritance of phenotypes through both the matriline and patriline that is truly transgenerational, meaning that the phenotype is present in a generation that was never exposed (even as germ cells in their in utero parents). Animal model studies are providing some clues about the likely timing of critical periods. In male and female rats, true transgenerational inheritance has been demonstrated when the environmental factor is experienced during gametogenesis (soon after conception), which is a critical period in the establishment of epigenetic marks in both sexes. In contrast, exposures during spermatogenesis (adulthood) have been shown to only have effects on the next generation (intergenerational inheritance). It is presently not clear whether similar critical periods apply to humans, but these findings represent the best starting points for hypothesis testing with human databases. These findings lead to the prediction that exposures or stressors around the time of conception will have the potential to influence multiple generations of offspring. If a pregnant woman experiences a stressor at this time, her fetus and the fetus's gametes (future grandoffspring) may also be exposed. Thus, demonstrating the induced phenotype in great-grandoffspring of the originally exposed pregnancy generation would be necessary to demonstrate transgenerational epigenetic inheritance of the phenotype with more confidence. On the other hand, if a male is exposed in utero or after birth and the phenotype persists to grandoffspring, this would be strong evidence for transgenerational epigenetic inheritance.

Hypotheses: Replicating and Extending the Överkalix Findings

The Swedish Överkalix findings provide among the best evidence for transgenerational epigenetic inheritance in humans. Despite this, this pattern of findings is limited to a single population, and we are aware of no attempts to replicate them. The Överkalix findings lead to the prediction that favorable nutrition during the prepubertal "slow-growth period" of late childhood will increase risk for chronic disease, and reduce life expectancy, among same-sexed grandoffspring. In addition, if the paternal grand-

mother (PGM) experienced favorable early life nutrition (birth ~3 years) granddaughters had improved health and survival, pointing to possible epigenetic transmission of early grandmaternal experience that is relayed through her son to her granddaughter (i.e., is not phenotype-to-phenotype transmission).

The sex-specificity of the Överkalix findings, wherein the childhood experience of PGM only shows an association with granddaughters' (GDs) disease risk and paternal grandfathers' (PGFs) late childhood experience only show an association with grandsons' (GSs) disease risk, is puzzling. Extending the adaptive logic of intergenerational inertia (see above), it is possible (although speculative) that same-sex ancestors' environmental experience is more predictive of the environment a descendant will experience than those of opposite-sex ancestors. This adaptationist perspective leads to the prediction that maternal grandparents experience should similarly influence same-sex offspring but not opposite-sex offspring. To the extent that this is true, the pattern might be more extreme in highly sexually dimorphic species among whom each sex occupies more discrete ecological niches and/or in which reproductive strategies differ more.

Pembrey and colleagues however suggest an alternative explanation for the same-sex ancestors finding—mainly that they are mediated by X- and Y-chromosome[2] linked epigenetic mechanisms (Grossniklaus et al., 2013). The unusual inheritance of the sex chromosomes (males are XY and inherit one X chromosome from their mother and one Y chromosome from their father, whereas girls are XX and inherit one X from each of their parents) leads to some specific, testable hypotheses about the nature and strength of transgenerational effects in humans. PGMs pass on ~50 percent of their two X chromosomes (equivalent to one X chromosome) to their GDs and none to their GSs. In contrast, PGFs do not pass on their X chromosomes to their sons, GDs, or GSs at all, but do have a 100 percent certainty of passing on their Y chromosome to their sons and GSs and 0 percent certainty of passing their Y chromosome along to their GDs.

On the matrilineal side, maternal grandmothers (MGM) pass on ~25 percent of their two X chromosomes (equivalent to half an X chromosome) to their GS or GD, and maternal grandfathers (MGF) pass on 0 percent of their Y chromosomes to GS or GD but ~50 percent of their one X chromosome to their GS or GD (see Figure 1 in Fox, 2009, for an illustration). These mechanistic peculiarities of the mammalian sex inheritance/determination patterns, together with Pembrey and colleagues' hypothesis, lead to a very particular set of predictions about the magnitude of effects if additively mediated via X-chromosomes: (1) MGM and MGF effects on

[2]When we refer to Y-chromosome here, we are only referring to the nonrecombining portion of the physical Y-chromosome (which makes up ~ 95 percent of the physical Y-chromosome).

grandchildren should be equal and (2) effect GS and GD equally; however, (3) MGM/MGF effects on grandchildren will be half that of PGM effects on GD, (4) PGM will have no effect on GSs, and (5) PGF will have no effect on GSs or GDs.

We note that there is also some evidence that grandmothers provide care to grandoffspring in a fashion predicted by their degree of sex-chromosome relatedness (Fox et al., 2010). It is thus possible that differential grandparental care is a mediator of the Överkalix findings. One test for this hypothesis would involve an examination of whether the grandparent was alive and living nearby the grandchild (e.g., same village or household) as a marker of the potential provisioning of care. Care-mediated effects will only be evident with grandparents who live nearby grandchildren, while epigenetic effects should be invariant to this.[3]

Hypotheses: Intergenerational Phenotypic Inertia

The phenotypic inertia model, discussed above, leads to several testable hypotheses. This model proposes that fetal development is buffered against transient ecological fluctuations, allowing transfer of cues reflecting more stable average trends. Focusing on the determinants of fetal nutrition and growth, the model leads to the hypothesis that offspring birth outcomes will be relatively refractory to the mother's macronutrient nutrition during pregnancy, but will relate to chronic nutrition as experienced across several matrilineal generations.

Because what is "transient" or "stable" for individual organisms is inherently relative, the model also leads to the prediction that species will vary in the magnitude of response to similar maternal pregnancy stimuli depending on generation time or lifespan. Because humans typically live decades rather than months or years, this implies that the types and magnitudes of environmental change that are relevant when orienting an individual human life will be different than for a member of a short-lived species. Consistent with this prediction, we recently showed that offspring of longer-lived species tend to experience comparably small changes in BW and adult disease risk in response to maternal diet restriction in pregnancy compared to offspring of smaller and shorter-lived species (see Kuzawa and Thayer, 2011).

Hypotheses: Paternal Age at Conception Effect on Telomere Length

The finding of cumulative, multigenerational increases in offspring telomere length in relation to delayed paternal and paternal grandfather ages

[3]Future studies should also consider possible bias from nonpaternity or paternal/grandparental uncertainty.

at conception leads to relatively straightforward and testable hypotheses (Eisenberg et al., 2012): that telomere length and thus late-life function will be positively and cumulatively related to age at conception of direct patrilineal ancestors. At present there is evidence from one small study that these effects are cumulative across two generations (Eisenberg et al., 2012), but no study has looked for effects beyond this. Historical databases would provide an ideal means of testing these effects across multiple generations. Because telomeres are believed to influence health primarily by limiting cell division, it will be important to test this model using an appropriate endpoint that is plausibly downstream of shortened telomeres, such as infectious disease or cancer secondary to impaired immunity (Eisenberg, 2011).

Hypotheses: How Important Is Selection?

As we have emphasized in this review, there is compelling evidence that a variety of nongenetic mechanisms can link early-life environments with adult phenotype and the phenotypes of successive generations. However, to date, few studies have considered the potential role of early-life mortality/selection effects, which may contribute to some of these findings. The probability of human conception under ideal circumstances is estimated at only 33 percent (Wilcox et al., 1995). After conception, pregnancy loss rates (many silent) are estimated to be 55 percent for 20-year-old women and to increase progressively with age to 84 percent at age 30 and 96 percent at age 40 (Holman and Wood, 2001). Many of these fetal losses are believed to arise from chromosomal abnormalities, which are unlikely to account for the types of phenotypic variation seen in studies of early origins or intergenerational effects. However, environmental chemicals, endocrine factors including stress hormone levels, infections, and other immunological causes are also implicated in fetal loss (Holman and Wood, 2001; Nepomnaschy et al., 2006). If there are genotypes that, under some environmental conditions, have a higher likelihood of being conceived and/or not aborted and have pleiotropic effects on later-life health, this would be difficult to distinguish from some of the postulated nongenetic inheritance patterns.

Evolutionary models point to the likelihood of selective fetal loss based on the phenotype of the conceptus and maternal environment (reviewed in Haig, 2008). Empirical evidence for conception/prenatal selection in humans comes, for instance, from evidence that some genotypes vary depending upon season and photoperiod at birth (Lucock et al., 2010; Gonda et al., 2012) and evidence for increased fetal loss of male conceptuses in poor environmental conditions (Bruckner and Catalano, 2007). An expanding list of genes that pleiotropically influence early- and late-life phenotypes and could lead to selection of this sort are being discovered. For instance, alleles in the *IGF1* and *ADCY5* genes have been associated with both low

BW and type 2 diabetes risk (Vaessen et al., 2002; Horikoshi et al., 2013). Thus, selective mortality and survival as an influence on fetal loss should be considered as a potential explanation in studies linking early environments with adult health outcomes. This is a potential issue not only in observational research, but also in quasi-experiments and laboratory based experiments. If such selection effects are found to mediate some of the associations between parental experiences and offspring health, it will be important to consider whether this reflects evolved adaptive mechanisms to improve the reproductive success of the parent or nonadaptive constraints.

CONCLUDING POINTS

Among early biologists, including Darwin, there was a prominent and uncritical assumption that environmental experience led to biological changes that were transmitted to offspring (now widely referred to as "Lamarckian inheritance"). In response to these unsubstantiated assumptions, and in the wake of subsequent insights into the genetic basis of heredity, mainstream biology adopted a firm view that environments do not meaningfully influence the phenotype of descendants except via conventional genetic inheritance. The research that we review is posing important challenges to these assumptions, for it illustrates a range of molecular pathways by which environments in one generation can impact the biology of one or more generations of offspring (Jablonka and Lamb, 2005). There is a long research tradition demonstrating the importance of phenotypic and developmental plasticity to human adaptation (Lasker, 1969). Recent findings of inter- and transgenerational epigenetic inheritance are revealing new levels of complexity in the nature of human developmental and epigenetic adaptations to environmental change (Kuzawa and Bragg, 2012).

Despite these recent advances, much more is known about the nature and health effects of these responses in animal model species than in humans, and indeed, there is only minimal evidence for transgenerational epigenetic inheritance in human populations. As we emphasize in our review, the likely pathways of environmental inheritance are not limited to the better-studied effects linking early or gestational environments to adult health, but can also include patrilineal and matrilineal effects that linger across one or more offspring generations. These are inherently challenging to study in a long-lived species such as humans, for they require information on environments and experiences across multiple generations, with extreme care taken to minimize confounding and other factors that constrain causal inference.

Given these challenges, biodemographic research, and population research more generally, is well situated to advance an understanding of the basic biology of nongenetic inheritance and its impacts on human longevity.

Strengths of this field, including access to historical databases and multi-generation cohorts, a focus on exogenous shocks and quasi-experimental designs, and careful attention to issues of selection and endogeneity, will be critical to better understand how current health reflects not only one's own experiences, but those recent ancestors. We hope that this review, and the hypotheses that we outline, will help inspire new studies focused on exploring these fascinating effects and their impacts on human aging and longevity.

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5

Genomic and Evolutionary Challenges for Biodemography

Kenneth M. Weiss

The world is experiencing a flood of new knowledge about the evolution and nature of genomic causation. New technologies and data have, in general, supported prior clearly predictable and expectations from the best of 20th century biology (Weiss, 1992; Weiss and Terwilliger, 2000). Inherited factors with strong effect on biodemographic traits promise opportunities for major clinical application (e.g., Gordon et al., 2014). However, relevant causation is more often so subtle and complex as to defy simple solutions and, instead, to raise serious epistemological challenges.

The challenges go beyond increased data collection. What is needed is better theoretical understanding of genomic causation. This applies particularly to behavior traits that are hard to define and affected by experience. Improved ability to relate genetic effects to age patterns, and hence life history, reflects causal mechanisms and could be a fruitful area of research. However, an important question is when, where, or even whether a genomic approach is justified. In what follows, I will try to provide a picture of the state of the science, briefly highlighting some of the many issues, of which I have described my views elsewhere in more detail (Buchanan et al., 2009; Weiss and Buchanan, 2009a, 2009b, 2011; Weiss, 2010; Weiss et al., 2011).

EVOLUTION AND DEVELOPMENT: NESTED GENOMIC SYMMETRIES

Each person is the product of development, constrained by the products of evolution. Evolution among populations and development among

cells both generate trees of nested local descent, as shown schematically in Figure 5-1. Both processes depend on differential proliferation among cells that inherit their progenitors' genomes.

In a descent lineage among individuals or from a fertilized egg during the lifetime of one individual, the DNA sequence will experience mutational changes. These arise randomly and are essentially irreversible. But in addition to a tree of sequence variation, each individual is a tree of DNA *usage* variation that is altered during development and life history by controlled, context-dependent mechanisms that are reversed by similar context-dependent mechanisms.

The phenotype in an individual is the net result of its inherited constitutive (germ line) genotype and the distribution of somatically generated cellular phenotypes. The trait distribution in a population jointly reflects these two independent sources of variation.

These biodemographic phenomena generate life history-based nested descent trees, but DNA sequence samples from the population may not be a very reliable indicator of the integrated genome of each individual. The effect of somatic mutation, overlaid on inherited genotype, results in a net

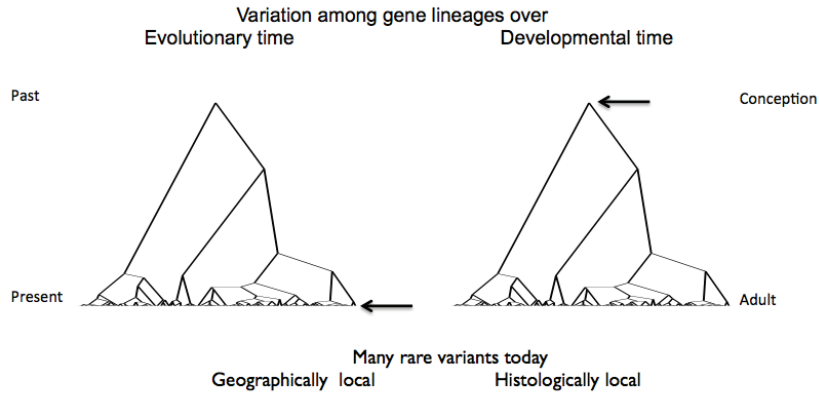

FIGURE 5-1 Symmetry between evolutionary and somatic genomic variation trees. NOTE: Population (left) and embryological growth yield many localized variants. In the case of populations, recent variants are newly arisen mutations that have not had time to rise in frequency or spread spatially. In the case of somatic mutations, recent ones have arisen later in development and are localized to more specific tissues, based on the trees of related tissues as they arise embryologically. The arrows identify the sequences that are sampled in typical genomic studies—individuals from populations sampled for their inherited genotype (but each individual (right) is not typically sampled for his/her tree of somatically arisen genotypes). SOURCE: Modification of a base drawing courtesy of A.G. Clark.

phenotype that includes hidden somatic variation, presenting a precision problem for genome-wide trait mapping aimed at finding causal variants of traits of interest. In a similar way, the inherited genomes as a set vary among populations. Both in evolution and development, variants that arise early in a descent tree, whether it be that within an individual, among individuals in a population, or among populations, are generally more common and widely dispersed than more recent arrivals, and the same may be generally said about the effects they may have on phenotypes.

What are typically sampled in mapping studies are collections of individual constitutive genotypes in different individuals (arrow in left panel, Figure 5-1), which correspond to the single genotype of each individual (arrow on right). Unfortunately, no real theory exists about the degree to which this multiply-nested variation matters. Instead of explicit theoretical modeling, genomic causal inference typically has rested on inductive, exhaustively reductionist, retrospective data fitting, rather than rigorous prediction. The approaches rest essentially on generic statistical association and regression models, which are mechanism-free approaches that, in the presence of the kinds of complex causation I will try to outline, can lead to conclusions so indirect as to provide weak predictive power and hamper understanding of causal mechanisms at the genetic or evolutionary level. This matters because a major public promise has been personalized prediction. There are subtleties here that some in the profession understand: This may be possible in some situations, but the drive for individual prediction and the belief in strong genomic causation are persistent and quite widespread. Many newly documented genomic phenomena are clearly not well treated by these approaches.

THE DISSOLVING IDENTITY OF "GENES" AND THEIR FUNCTION

Genomes achieve complex functions of many kinds beyond protein coding, many of which are not yet understood. These functions are differently active within each cell's context and concealed from other cells except through intercellular communication. The scientific community has very incomplete knowledge of these mechanisms, especially from quantitative (dose-response or age-related) predictive perspectives.

Context Is Everything

DNA is basically an inert molecule that functions only by its interactions with other factors in a cell. Remarkably, despite enormous amounts of data and knowledge, there is still heated controversy over how much of the genome is "functional" at all. As a reductio ad absurdum shows, ATG is the DNA code for the amino acid methionine, but not all ATGs

are involved in coding (roughly 1/64 of all adjacent nucleotide triplets are ATGs but only a tiny percent are protein-coding). So what are they doing and why are they there?

DNA sequences function only in the context of overlapping sequence-based multiway interactions (often modeled as "networks") of factors. In fact, most genes are primarily used to regulate or process other genes. In this sense, life is a "Boolean" (combinatorial) phenomenon that functions via the context-specific arrangement and spatiotemporal combination of factors, which, as Figure 5-2 suggests, occurs not necessarily in the location where the interacting factors are produced. A gene activated in one cell that leads it to secret a signal may have its effect in distant cells that monitor their external environment for signals. Though generated in diverse other locations, combinations of such signals in the latter location may be responsible for the local effect. This is rather abstract, again nested, causation relative to the usual linear model of DNA as a long necklace of discrete causal elements.

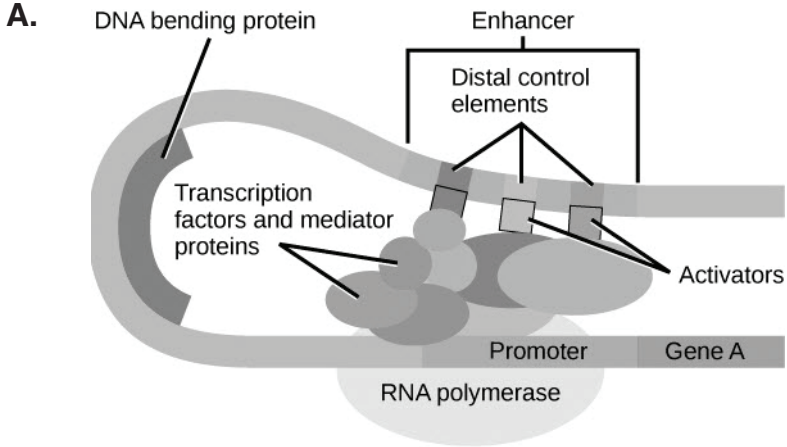

FIGURE 5-2 The Boolean nature of genomic function.
Panel A. Combinations of regulatory factors are needed to express a given gene. Many short DNA sequences near a gene are bound by proteins (themselves coded for by genes elsewhere in the genome, with their own comparable structure). The combination of these proteins binding the regulatory sequences and with each other affects the amount of transcription of the gene.
SOURCE: Mahr (2014).

B.

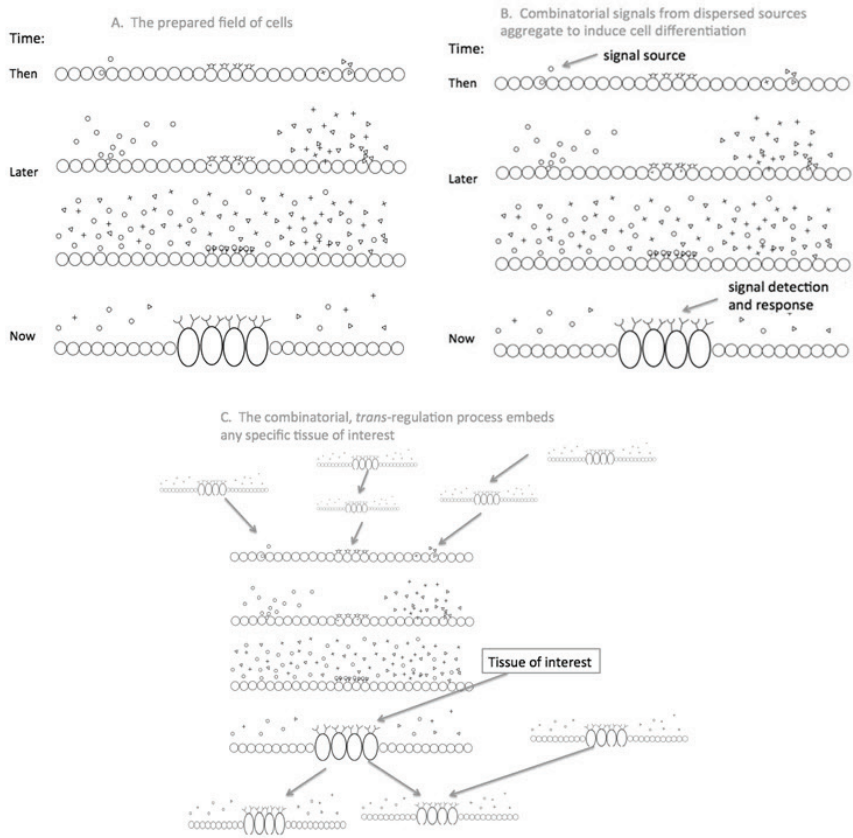

FIGURE 5-2 The Boolean nature of genomic function.
Panel B. Stages in tissue differentiation: Left to right, a bed of cells shown, in which some cells produce signal molecules and others (at the center here) have receptors for specific signals; next, local cell differentiation activated over time by the receipt of appropriate combinations of signals and receptors, coded from various genes in various cellular sources elsewhere. The lower panel shows that this is a multiple step, hierarchical phenomenon without a beginning or end: a trait is studied by measuring some chosen set of cells at some time (or by ignoring all of this and assuming causation can be inferred from the inherited genome alone).

Genomic Functions Are Not Easy to Define

Many parts of the genome are transcribed into RNA. But while there are hundreds of thousands of these RNA transcription sites (Mattick et al., 2010; Kells et al., 2014), only a fraction of the resulting RNA has known function. But what is known already is enough that the very definition of biological "function" is contentious (Doolittle, 2013; Eddy, 2013; Graur et al., 2013).

Humans are the collective product of the population processes of evolution, and if one holds the strong adaptationist view that almost everything that is functional has been made so by natural selection, then an obvious criterion for function is DNA sequence *conservation*: Functional sequence should not vary much compared to parts of DNA with no or little apparent function. The nominal Darwinian explanation is that over billions of years, what works has been favored and thence kept in place by "purifying" selection against new mutations, which in the face of this adaptive history are likely harmful if they have any effect. Even variants that are strongly adaptive are rather quickly fixed in the population and thereafter maintained by purifying selection. By contrast, mutational variation that arises in a functionless sequence element will therefore not be screened for fitness and will accumulate among individuals in the population or among species.

However, sequence conservation can also arise from other processes. Close phylogenetic relationship means general sequence conservation, since divergence is largely due to the slow, stochastic, clock-like accumulation of mutational differences. Your and your parents' sequences are very nearly identical. And about *half* of humans' DNA is comprised of short "repeat" sequence elements that disseminate from place to place and time to time within the genome by inserting copies of their sequence elsewhere in the genome. The resulting dispersed elements retain a sequence identity even though gradually diverging because of mutations that arise slowly over the generations.

Thus, sequence conservation itself is not a definitive criterion for locating evolutionary function in the genome and generally must be assessed by means such as calibration in comparative context. That is, sequence differences that are "important" must be statistically judged relative to what would be expected based on differences accumulated by phylogenetic relationships alone. Even though a newly documented DNA sequence can be annotated to identify many likely functions by recognizing conserved canonical sequence structures, even this can be problematic, and much or most of the sequence at present remains unannotatable. For example, function may reside in the length of a sequence element, serving as a spacer, rather than its exact sequence. Such facts reduce the a priori utility of con-

servation for extrapolating genomic function from one species to another, as in comparative biodemographic analysis.

Even more problematic is that, though not generally recognized even by evolutionary geneticists, there are reasons to think that conservation is *not* a necessary prerequisite for biological function. The reasons relate to complex, or "polygenic," control, and will be discussed below. But first, I wish to identify a few rather strange phenomena that frustrate attempts to identify function even when mapping has statistically implicated a specific location in the genome.

STRANGE ENCOUNTERS OF THE *N*-DIMENSIONAL KIND

The general theory of "the" gene has not changed much for many decades. It is basically a linear-regression theory of point-causation by *cis*-coding: that is, by discrete elements located along a string of nucleotides. With the discovery of sequence used for local gene regulation (binding by transcription factors) and transcribed RNAs of various directly functional types other than protein-coding, research has only gone slightly beyond this classical linear-causation view. That in part explains why the basic methodologies for finding genomic causality have not fundamentally changed.

Trans Functionality

It has long been known that the usage (expression) of "gene" X is regulated by the binding of multiple proteins to DNA recognition sites chromosomally near to the regulated gene (shown earlier in Figure 5-2). Typically tens of such regulatory proteins form a local complex by interacting with the local DNA and with each other. This local control phenomenon is known as *cis*-regulation. But the binding of *cis*-regulatory sites by proteins coded elsewhere in the genome clearly shows that local gene function is also a *trans* phenomenon that depends on the context of things elsewhere in the genome, and cannot be inferred just from local mapping hits.

The idea has been that *cis*-regulation involves the regulatory proteins finding chemically attractive DNA binding sites. But far more subtle *trans* effects are being identified. There appears, in fact, to be 4-dimensional arrangement of genomes in cell nuclei that are 3-dimensional in space but also time-dependent as cells change their gene usage depending on their contextual circumstances (Dekker et al., 2013). Specific areas within and between chromosomes juxtapose in the nucleus in clustered subregions in which active transcription—for a given cell's given context—is taking place. There is at least some stochastic cell-specific variation (Nagano et al., 2013). This is at least to some extent DNA-DNA rather than DNA-protein

affiliation, and at this early stage, no theory exists for this aggregation and how it occurs.

Given this, gene mapping may identify a region whose variation has a statistical association with a trait. However, the reason for the effect may be elusive, because it is not clear a priori how such hits reflect the 4D genomic usage phenomenon: A local map hit may relate to effect(s) elsewhere—but why, where, and how? If the result of mapping is strong and consistent, it may possible to follow the networks involved (e.g., Chen et al., 2008; Emilsson et al., 2008; Keller et al., 2008), but, to date, results are weak and not highly transferrable across species.

Dynamic Feedback

Lamarckian inheritance has a bad name. Jean Lamarck held that inherited factors were themselves changed by an organism's behavior in ways that directly (and adaptively) reflected that behavior. The famously comical example (only mentioned in passing by Lamarck himself) is that a giraffe successfully stretching its neck to reach high leaves and hence to survive will produce long-neck-causing elements and transmit them to its offspring.

As far as DNA sequence changes go, such ideas of the inheritance of acquired traits seem totally incorrect. But it has been shown that context-specific "epigenetic" chemical changes do modify DNA molecules in ways that affects gene *usage*, without changing their nucleotide sequence. Epigenetic changes can be inherited and thus mimic Mendelian familial correlations (Flanagan et al., 2006; Petronis, 2010). There is a long history, going back to early 20th century genetics, of study of variation in genetically identical (inbred) organisms showing no evidence of inherited nonclassically genetic variation. However, more direct evidence for at least short-term inheritance of epigenetic variation is being found in at least some instances, as documented elsewhere in this volume, so the degree to which this is a current technologically driven fashion or an important source of heritable variation is as yet unclear.

In any case, epigenetic DNA modification is driven by context-specific, genome-encoded processes that respond to various conditions in the cell. But variation in epigenetic patterns can be affected not just by environmental conditions, but also by either *cis* or *trans* genomic sequence variation. This is because an epigenetic modification involves both the modified sequence and the modifying enzymes, coded by genes located elsewhere. Understanding epigenetics is challenging, because the effects are tissue- and context-specific, not directly assessable from constitutive DNA sequence alone. There are some sequence-based methods for identifying potential epigenetic sites in mapped genome regions, but showing that epigenetic change is actually responsible for a studied phenotype may require directly testing the right cells at the right time.

Monoallelic Expression

Another manifestation of sophisticated genome-wide *trans* communication within the nucleus of a cell is *monoallelic* expression. Mendelian theory for diploids is that the two alleles carried at any gene location are both expressed, in their appropriate cellular context. The phenotype of the individual is the net result. That is the basis of classical (and I think persistent but rather dated) Mendelian concepts like "dominant" and "recessive" causation. But there are thousands of instances already known in which only one allele is used. Given these known cases, it seems inevitable that there are others (Chess, 2012).

The first-known example was X-inactivation. Most X-linked genes are inactivated in one of the two X chromosomes in a female. Several genes in the immune system undergo local rearrangement on one copy and inactivation of the other. Genes are differentially modified epigenetically in sperm and egg, so the early embryo is using only one of them. Olfactory reception is a most extreme instance. There are about 1,000 olfactory receptor (OR) genes (2,000 in humans' diploid set) that code for cell-membrane proteins that bind odorant molecules leading to a signal pulse to the brain. These genes are located in multigene clusters found among most of the chromosomes. But in each olfactory neuron, only one OR gene from one cluster, and not its homolog, is chosen for expression. The rest are inactivated: even if there turns out to be some "leaky" multi-OR expression, this pattern reflects genome-wide regulatory interactions.

These and other well-documented monoallelic phenomena occur at appropriate developmental stages but are thence inherited in the cell's somatic lineage. They produce mosaic tissue organization, unique in each individual. The known examples are ancient (have been around for millions of years) and produced by active genome-encoded mechanisms. Precedent would suggest that many more are to be discovered; indeed, some enticing new evidence suggests monoallelic expression may be stochastically ubiquitous. At the very least, such effects can be expected to reduce statistical signal strength in mapping studies.

To Thine Own Self Be . . . What?

The vertical transmission of somatic mutations generates a hierarchical descent tree of variation among the tissues as part of each person's life history. This has long been recognized and most clearly documented in regard to cancer, where there has been some clinical progress but where the picture is clearly complex (Vogelstein et al., 2013). However, there is also horizontal transmission. Viruses can sometimes be incorporated into the genome and join the somatic tree in any branch and at any point. More recently

documented is the potential importance of parallel hierarchies of infecting microbes, collectively called the *microbiome*, which introduces a complex ecosystem of tissue- and context-related colonization. Though typically transferred horizontally from the environment, its elements interact with each other and with the genomes, evolving unique descent patterns with each individual. Genome mapping alone may generate hits whose effects are not to be seen within the genome itself. There are clear pathological interactions, and the microbiome may have major contributor to aging patterns (Gordon et al., 2014). However, at present, little more than very generic theory for these phenomena has been developed.

THE HUMAN GENOME DOESN'T EXIST, AND NEITHER DOES YOURS!

"The" human genome sequence available online in GenBank is often treated as a Platonic ideal. But though the sequence is real, it is not that of any individual. It is a wholly arbitrary composite *reference* sequence. People neither carry two imperfect instances of "the" human genome nor "copies" of it. Each person carries instances of human genomes, landmarked against an arbitrarily chosen referent. That is all!

The reference sequence is from person(s) unaffected by identified diseases at the time. This does not make it "normal," and abnormal genetic traits are not reliably to be found by differences from this reference. Indeed, as discussed above, individuals don't carry even two instances, because their billions of cells each have unique sequences, closely related but not identical to what was inherited. From this perspective, it is a little like science fiction to attempt to map genomic causation from single (or pairs of) constitutive sequences, sometimes assessing function by comparison with an arbitrary reference. This is a strange definition of "normal" since the donors of "the" sequence will eventually incur a variety of age-related disorders that may be affected by their particular genotype.

Implications for Comparative Strategies

The picture is comparably dicey in relation to comparative analysis. There is no such thing as "the" mouse or dog genome. There are different inbred strains, which can be ordered off the shelf from various suppliers or obtained from the kennel club. But none of these are "normal"! Most have been bred under controlled, protective conditions, often for some prespecified trait, whether a healthy or pathogenic one.

The purpose of inbreeding is to have identical, replicable genomes to work with on the assumption that the resulting genome causes the desired trait. There is indeed much variation among inbred animals, but I think

it is generally assumed to be of environmental, epigenomic, or stochastic origin (Martin, 2009, 2012; Smith, 2011). But even forgetting (or, rather, choosing to ignore) somatic mutation in each individual, inbred mice are genomically variable, if less so than people (or real mice). There are not many in-depth tests of this that I am aware of, but a simple computer simulation of genomes of strains, and crosses between strains, generates considerable allelic variation comparable to what is empirically seen (work not shown).

The arbitrary reference nature of species-specific genome sequences may seem obvious, but is subtly ignored every day in many ways. For example, researchers routinely engage in this sort of Platonism when inserting a single transgene to demonstrate its effect in "the" mouse. That this is a kind of Platonic fiction is clearly shown by the high fraction of phenotypic effects among strains into which the same transgene is engineered. This clearly shows that genomic "background" is not just incidental noise. The literature is rife with careless claims or reports from animal experiments (Couzin-Frankel, 2013). These facts have important implications for comparative studies, between natural and even inbred animals, especially for complex biodemographic traits whose genomic basis one wishes to understand. But these well-known facts of unkown, because usually untested, importance are typically and conveniently ignored.

Genomic Causation Is Typically Polygenic

From a genomic point of view, many traits important in behavior and aging are clearly polygenic: The traits are each affected by "genes" often numbering in the tens or even hundreds. The term is in quotes because it can involve protein-coding genes as well as regions serving regulatory or other functions. Variation among genomic sites contributes (along with environmental factors) to the trait's variation. Even in lucky situations, it is often clear that major easily found variants in individual genes are responsible for only a small subset of the total trait variation. Most sites identified by genome-wide mapping methods, such as comparing variation in cases with controls, contribute only trivially small individual effects, such that sample structure and arbitrary significance criteria are more important than biology in whether they are identified. A long-standing argument, or I would say defense of (or excuse for) continued mapping in the face of this reality is that it can identify important "druggable" pathways. But the history to date does not provide sufficient reason to persist in that hope.

The sequence variants at each of the contributing sites have some frequency in a sample or population. Each person represents a sampling from the "pool" of these variants in the population. The result is that to a good approximation, each individual's relevant genotype is unique.

One thing learned from genome sequences of randomly sampled individuals is the importance of context, involving the genomic background and environmental experience of each individual. People are walking happily around with numerous mutationally defunct genes. Even studies of genes known to be associated with given conditions are mutated in damaging ways in unaffected people. This might be attributed to environmental exposure differences and the clearly genetic strain-specific transgenic results in animals raised in identical conditions, but models in which there are very different responses to the same transgenic manipulation show that genomic context is important.

The major implication of polygenic causation is, first, *phenogenetic equivalence*: Many different genotypes can generate the same trait value (here, even ignoring environmental interactions). Secondly, every individual has a different genotype for the implicated set of variants, even ignoring somatic variation. The upshot is that the *Detectance*, the Pr[Genotype | phenotype], is often quite small: that is, the genotype from the trait cannot be reliably inferred. Perhaps worse is that the *Predictance*, the Pr [Phenotype | Genotype], is also small and unreliable. Thus even retrospective model-fitting may not yield high Predictance in new samples. This is a widely known fact, though, in my view, persistent hope often overrides facing up to the reality.

If the relevant genotype of each person in a population is unique, the frequencies and even presence of given variants will vary from sample to sample. Over time, as individual variants change frequency or are lost by failure to be transmitted, or new variants arise by random mutation, isolated populations will evolve increasing differences in both the identity and frequency of relevant variants. This makes the tactic of meta-analysis to increase sample size problematic. For common variants—those that preceded human expansion into the several groups included in a meta-analysis—replication can be found, and there are cases in which this has been the case (Hindorff et al., 2009). But this is to me a somewhat selective optimism rather than the rule, in particular because it is difficult to interpret that lack of confirmation that is commonly found. For the same reason cross-species comparative analysis presents fundamental challenges. The challenge is greater if genomic action is interactive with lifestyles and yields gradual effects on age-related life history functions.

Genomic Effects Are Often Essentially Age-Specific

Age is an ultimate rate-dependent measure, so that genetics is at the heart of much biodemography in long-lived species. Complex traits not obvious at birth depend on the amount, timing, and quantitative level of interacting genetic and environmental effects. They can affect the amount

and tempo of responses to environmental changes, and hence the rate at which they accumulate with age. Despite their fundamental importance, age-specific effects are usually tested only very generally, such as by contrasting "early" vs. "late" onset. An obvious problem is that age-matched unaffected controls can later become cases. It is difficult to do better with a reliance on statistical sampling in the absence of solid predictive theory. Compounding the problem is that life history events vary greatly even among closely related species—including preferred comparative model animals. Age effects seem highly stochastic within species, with high variance in onset among related individuals, usually raised in an essentially arbitrary controlled, standardized environment. Yet there are major characteristic species differences in hazard functions. A long-standing question is why mice, with biology very similar to humans and fewer at-risk cells, have cancer hazards that increase over 30 months compared to humans' 80 years. But cancer is a "mechanical" disease at the cell level, largely due to genomic mutations, and one must expect much greater hazard-function related questions regarding species-specific behaviors that involve learning, if inferring genomic causation is the objective.

There are two other factors to be considered. Model animals have been bred for specific traits, including behavior, and hence the genomic results may not accurately reflect the more complex mechanisms in naturally evolved populations. The selection is generally strong and teleological, fundamentally different from natural selection. So the genomic consequences in a model may not be easily transferrable to wild animals . . . like humans. In addition, while model species' behavior is often context-dependent, humans *respond* to environments culturally in confounding ways, such as changing exposures *because* of knowledge of their effects. When I read that eating eggs is good for you, I eat them . . . until I read that they're bad. There is no good theory for this!

SOME RELEVANT EPISTEMOLOGICAL ISSUES

As I noted at the outset, most models of genomic causation are essentially sample-based, theory-free internal statistical comparisons, such as cases vs. controls, rather than tests of a formal theory. Or "theory" is nothing more than the assumption that with "appropriate" samples, contrasts between the comparison groups will be detectable by some inherently subjective "significance" or other criterion. Without adequate formal theory for what to expect to find, this means finding strong effects will perforce ignore smaller ones that may be present. Significance cutoffs are important and have been explicitly used to avoid having to follow up a sea of false positives, but they force the apparent fact that many or even the bulk of causal effects are too small to detect with chosen cutoff criteria.

Individually this may make little practical difference; in aggregate, perhaps not so.

When there is strong point-like causation, experimental confirmation and understanding is achieved, which can be followed up experimentally. Examples abound. This is how, by careful choice of traits, Mendel opened the door to the discovery of genetics in the first place. Indeed, such a result in one species can sometimes be applied to others, which is why mouse models are often useful. But no formal evolutionary or genomic theory predicts that "sometimes."

High-penetrance "Mendelian" variants are an addictive lure, relative to the more general pattern. What is now known about genomes and causal complexity stretches the ability of current explanations and methods to account adequately for is seen, with implications for both experimental and comparative research. Indeed, what is known affects basic epistemological criteria. These implications are easy to see, but it's far more difficult to understand how to respond.

Life in a Nonclocklike Universe

If life were a purely Newtonian clockwork phenomenon, then with complete information the entire future could be predicted and the entire past retrodicted. "Extrapolation" might not even be a word in the lexicon. But this is not the reality of the world. Time's arrow in this cosmos does have a direction. It is due to the probably inherent probabilistic nature of fundamental causation.

As a result, a *fundamental* challenge is that genomic risks are necessarily estimated retrospectively. The past is over and to some extent can be measured, but the future is yet to come. The past can be retrofitted if the right things are measured, but that isn't the same as retrodiction and certainly not prediction. It's often a huge and sometimes inescapable problem that the relevant risk factors were unknown, much less measured.

But what about the future? Genetic risk factors are typically treated as inherent, present at conception. Based on this is the widespread promise to predict future outcomes. However, although environmental factors predominate even in strongly "genomic" traits (where heritability is still usually far less than 1.0), future environmental exposures cannot *even in principle* be predicted. This also applies to stochastic effects, especially without an accurate determination about what is environmental and what is stochastic. In general, these considerations make genome-based prediction epistemically inaccurate to an unknown degree.

Time's cosmic arrow is based on the accumulation of entropy. The corresponding biodemographic arrow is of the accumulation of irreversible effects of age and the one-way tree of population history. The degree

of probabilism in genomic causation is unclear. Genome mapping suggests that countless small contributions are responsible for complex traits. Each contributes so small an amount that any given element's long-term survival cannot be predicted; they will often be lost to drift, especially since most are rare in the population (of people, or of cells). Thus, among populations and species, and over time, a fluid flow of causal contributors is to be expected.

This relates to sequence conservation, which I mentioned earlier is a commonly invoked criterion for biological function. If polygenic contributors have only weak individual effects, these effects may be ephemeral even in the presence of natural selection. In turn, their sequence will not be highly conserved relative to expectations of drift alone. This applies both between and even within populations, even within species.

Yet, perplexingly, in sequence conservation patterns, known functional elements of the genome are relatively highly conserved. Likewise, experimental evidence, in animals and other model species, and in the evolution of domestication in plants and animals, suggests an expectation to find a much higher level of determinism. Inbred animals are approximate replicates of a same genome, with generally specifiable traits (e.g., body size, susceptibility to a given type of cancer), yet despite this increased genomic determinism, even in standardized environments there is variation (Gartner, 1990). In any case, it is clear that environmental context is an important part of variation in traits, but phenogenetic equivalence is also fundamental.

Replication

Modern life science is derived based on Enlightenment-era principles of replicable cause and effect. That is essentially the basis of statistical inference. But if everyone is unique, then epistemic limitations are rarely taken seriously if even recognized. Lifetime or age-specific risk effects are based on statistical sampling designs and are probabilistic, usually in unclear ways. Often huge numbers of measured genetic and other factors are included in survey samples, inference depending on the user's choice of sample, which is affected by facts already known, what is practicable, and other factors, which are difficult to account for or even to be aware of in study design or analysis. The issue here is individual vs. group predictability. This might be said to be the difference between medicine and public health. Probabilistic causation can mean that individual prediction is weak but group prediction stronger, but the issues of unknowable future factors that I mentioned above can vitiate even that to an unknown extent. And I think it is true that currently there is a pressure to extrapolate group mean values to individuals (e.g., in policy or "personalized" medicine).

Because of the essential nature of variation in evolution, which is, after all, a population process, no two individual organisms are alike. Indeed,

a key aspect of polygenic traits is phenogenetic equivalence. There is no specific theory for *how* or, except generically, *how much* two individuals vary relative to the genomic causal basis of a trait. As a result, the bedrock criterion of replicability is not a reliable one for genomic studies. As noted above, people are all walking around with many entirely defunct genes, which should affect health but don't, and the same will surely be extended to the other functional elements of the genome.

There are legitimate reasons for this kind of approximate approach, and statistical sampling is a core element of the research toolbox. But in important ways, inferences are based on the methods rather than the biology. There are often major multiple-testing problems that are hard to correct for accurately, despite extensive and very sophisticated statistical corrections that are routinely applied, because so many issues are being examined by so many investigators in so many studies. Still, the issue is taken seriously and carefully (Yang et al., 2012; Hemani et al., 2014). But to me, most importantly is that such corrections explicitly trade conservative inference, to escape masses of false positives as noted earlier, for dismissal of small effects even if they are numerous and large in aggregate.

Also as noted earlier, over time evolution generates genomic divergence both within and between populations. For this reason, meta-analysis relies on detecting older variants still found in populations descendant from a common founding population. The variant's effects must not depend too heavily on the genomic background, which will have diverged, and must have similar effects in the diverse environments. They are older if they are shared among populations and that makes them relatively more common than the typical genomic variant. Replicable results may occasionally follow, but they will typically be for strong-effect alleles that do not really require replication studies. But because humans are a very large population with a recent history of rapid expansion, most genetic variants are new or recently arisen in some place in the world. This same property must apply to those variants that contribute to traits of interest, normal or otherwise. Rare variants may be discoverable in families if they have very strong effects, but not in statistical association studies.

Replication has its central place in science and is useful, of course, and there are clear examples where it works as expected. But because of evolution, it is not a guaranteed criterion. Even when the same factor, perhaps a given locus genotype, is present and relevant to an outcome of interest, the strength of effect may not be replicated, and a serious level general theory about the extent of these issues is lacking.

Falsification

If replication is not a reliable criterion because failure to replicate may mean simply that samples have different characteristics for reasons including evolutionary divergence, what about the oft-invoked Popperian criterion of falsification? For many reasons, that is not a very useful criterion. Superficially, failure to replicate may be due to measurement or laboratory error. But the *evolutionary* reason is that two samples are not necessarily expected to have replicate causal distributions. The alleles and genes involved may depend on variation that affects their frequency (and hence detectability) or even their actual relevance to a trait.

A gene may contribute, even fundamentally, to a trait but simply not *vary* in a given sample. Methods based on sampling variation cannot detect the presence of such effects. The problem may apply especially to inbred crosses, but variation in a given natural population may simply be low or only have weak effects. The latter could be because the gene is too important for the studied trait to withstand serious mutations. Not finding a mapping hit in the gene is nonreplication but is not falsification of the idea that the gene is involved. It is to be expected with many or even most nonobvious genomic contributions to traits. To the contrary, falsification is in a sense reinforcement of the correctness of an understanding of evolution.

Parsimony

Physical theory is often taken to imply that nature follows the simplest path between two points and that the simplest explanation of a phenomenon is the "most likely" (or, said in a more neutral way, to be preferred). But if one accepts the many-paths view of physics, not even light rays travel in the simplest direct path.

Evolution is a local, highly stochastic process. There is no reason to think that the simplest way to evolve a causal regime is taken, nor is it required to be similar in different lineages. There are tens of different paths to vision and many other traits for which there are data. Polygenic control shows that there are *countless* ways to the same height, body mass index, psychopathology, or blood pressure. Even if some elements are conserved, there is no "simplest" way.

While it can be an occasional general guide, Occam's famous razor can cut in many directions. It is simply a weak guide to choosing among hypotheses. One might say that, for statistical data, a likelihood or Bayesian approach addresses this issue. But I (though no statistician) am not convinced: These methods only optimize among a prespecified range of options.

Descriptive statistical modeling is in a sense an invocation of parsimony, in that it detects strongest effects and dismisses lesser ones. The

results of multiple studies may not generate a specific mechanistic theory, but can provide general guides about pattern. There are many quasiregular patterns found in various aspects of genomes and their usage (Koonin, 2011a, 2011b). Figure 5-3 provides a generic description of the way things look (in my view).

Rather than a Darwinism-Mendelian duality in which individual genetic variants are the causally deterministic units of life, fixed by an equally deterministic force like Darwinian natural selection, life has evolved to be a multidimensional web, with at least a *generic* statistical spectral structure of effects. The "shape" shown is schematic and the details case-specific, but

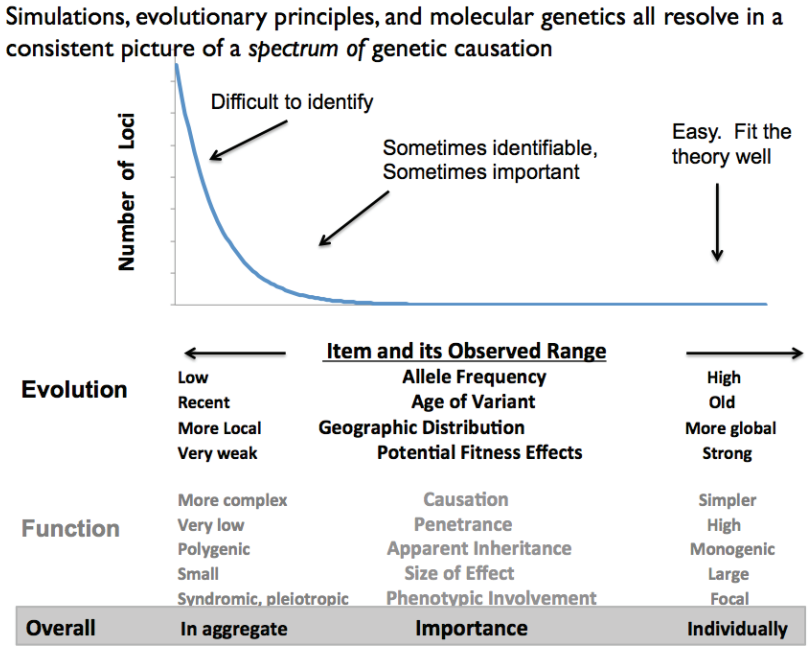

FIGURE 5-3 The causal and inferential spectrum of life.
NOTE: The relative distribution of effect strengths, and their manifestation, are generally found as suggested here. Evolutionarily, most effects are rare, recent, and hence geographically localized. Common variants are older and geographically widespread, but are rarer. Corresponding to this, functionally most variants have weak effect are of low frequency in the population and have their effects jointly. Strong individual effects are relatively rare, but they are the ones easy to detect. The bottom line suggests that the numerous, local, weak effects generally have their effects in aggregate while strong effects more clearly act individually on their own. However, this is schematic and empirical, because there is no formal theory for the shape of the distribution.

what can be said is that a minority of cases follow simple classical ideas, perhaps seducing researchers to think that everything else will, if only they have adequate samples and enumeration. The middle ground presents with some predictive power, but much—often the bulk—of instances are of many-to-many, essentially unenumerable causal factors. It is they that present the challenge, and, of course, when dealing with age effects the causation and requisite study scope are much more problematic. Between species, knowledge is still largely in never-never land a priori understanding is sought.

SOME STRATEGIC THOUGHTS

The aspects of genomic causation that I have outlined are substantial and relevant to biodemography. While they do not present problems with "solutions," they can affect research strategies. Here are some thoughts about what that might involve.

Where Is Genetics Really Relevant?

I am a geneticist, but to me the first strategy might be to understand whether a question of importance really requires a genetic answer. If relevant genetic causation is complex and polygenic, perhaps one should concentrate on the empirical trait itself, rather than attempting to enumerate its genomic causation. This would be especially apt if the trait is common in humans or is a reflection of cultural attributes, or is clearly shared between species and their ecology. When I look at the roster of biodemographic topics considered in this volume, most seem to be sufficiently tractable (or challenging!) at the trait level itself. At least, given the nature of genomic causal complexity, one should be clear what serious biodemographic information would justify the time and cost of attempting to reduce to genomic terms.

Isolating Age Effects and Developing Useful Theory

Where it seems appropriate, even for basic knowledge, there is still much to be learned about the basic mechanisms by which genomic variation affects age-specific risk or outcomes. An obvious tactic would be to take a more carefully designed rather than incidental age-stratified approach to data, to increase contrasts such as comparing very early to very late onset of traits. Comparison of age-stratified results among *different* populations (rather than pooling them in meta-analysis), or animal strains, searching for correlates of signal strength, without relying on significance cutoffs, could provide clues.

I must add, however, that tail-based mapping comparisons have not found very much, either within the normal or pathogenic range, in part because the tails are affected by sets of rare, strong-effect variants. Indeed, while there are important exceptions, long, focused, large, and very costly attempts to understand traits like cancer or cardiovascular disease have generated only rather generic ideas like the gradual accumulation of various sorts of cell or tissue damage whose implicated genetic basis remains unstable and largely elusive.

Still, mapping studies have rarely made serious attempts to fit hazard functions to genomic effects, site-by-site or in aggregate. One might adjust current regression approaches to do that. I don't think it is just nostalgia to suggest that resuscitating serious hazard and competing-cause modeling of these effects, in light of what is known about genomes, especially where these can be based on at least an approximation to relevant mechanism.

But what causal model would one use, if one really wished to reflect the nested population and somatic processes of age-related change? One might try modifying current aggregate genome-wide risk estimation methods. But since relevant phenotypes are affected by so many genes that each person is unique, innovative methods would have to be devised. It is possible that plant or even animal breeders using mapping methods have relevant experience.

The Value of Controlled Crosses

Mapping in strain crosses as in dogs, mice, and perhaps some other husbanded species could reveal aspects of mechanism. Crosses between strains or breeds with widely differing biodemographically relevant traits could be particularly revealing, and here I would suggest that dogs are a good model because they have been bred to have specific traits that vary widely among breeds. Much good work is actively being done on dog genomic causation. But dogs are large animals, slow growing with long generations, and expensive to study and often problematic to interpret in human terms. Some relevant mouse social or behavioral traits could be substituted if the traits are carefully chosen.

Identifying Noncoding Functional Processes

Mapping generally results in hits in many areas of the genome, even where no known, or known-relevant, functional elements are there. Expedient whole-exome mapping is not suitable for this. However, comparative mapping in different species or strains for clearly homologous traits could at least confirm that mapped function-unknown elements really are involved.

Facing the Somatic-Mutation Realities

Somatic variation is vitally important in some traits, and there is no reason why this should not also affect behavior, even within a "normal" (nonpathological) range. There may be value in sampling different embryological tissue lineages (on separate developmental branches, or left vs. right side) to identify somatic allelic differences and then see if they have phenotype correlates (probably not useful for behavioral traits).

Small Data Rather Than Big Data?

Even when mapping is felt to be important, I personally think one should stick to smallish samples, which will at least detect major effects with less statistical noise and greater useful replicability than huge (and hugely expensive) samples.

Somewhat more positively, as major "Big Data" databases come online, if multiple *trustworthy* measures of relevant traits at different ages are included, the data can be retrospectively mined, at low additional cost, to identify genomic (or environmental) contributing factors, in ways I have suggested above. It should be kept in mind that there can only be analysis on what has been measured, and how, at the time.

Overall

Overall, I believe that what is most needed is better mechanistic theory for biodemographic processes if they are to be understood in genomic (including evolutionary) terms. To me, that means moving away from the very indirect linear models that assume replicable phenomena *or* at least coming to better terms with their ephemeral nature in the face of the great amount already known about genomic variation and the evolutionary processes that generate it—rather than the relentless pursuit of ever more data of the same kind.

CONCLUSIONS: CAN THE CAUSAL WEB BE UNWOVEN?

Evolution involves a complex local, ad hoc web of natural selection, migration, and chance. The sieving of genomic effects, slowly over eons of time and space, is responsible for the causal complexity found. In essence, causal effects that natural selection cannot "detect" (directly screen) will be as hard to detect as causal factors in contemporary mapping studies. Slow evolution generates, or at least tolerates, complex variation. This is what is found even for abnormal or unusual traits, or indeed even in relatively low variation model systems like mice or even flies—or yeast (Bloom et al., 2013).

Obviously, when it comes to genetic explanation, I am less sanguine about the current state of the science than are most, including other authors here. To me, the allure of known simple Mendelian answers engenders a simplistic Darwinian-Mendelian way of thinking. The perplexing complexity of genomic causation being revealed is thus often treated as surprising or even disappointing. But it's actually a positive reinforcement of theoretical expectations present (but often not recognized) for nearly a century. This shows an understanding of important *general* aspects of genomic causation.

An important difference in perspectives is that between individual "personalized" and group-based patterns, risks, and predictability. Most papers and most authors recognize the difficulties, but too often, in my view, in caveats or small print, and too often persist in the same costly studies knowing the landscape. Individual prediction works when there are strong enumerable factors that are relatively unaffected by environments. But from common diseases and patterns related to aging, these seem to be the exception. A population perspective, in which interventions can be applied without knowing the specific genotypes that might be most affected, seems most promising. Nonetheless, I believe that researchers should by now know, given the rather massive secular changes in the most common disorders (and traits like stature), that even population prediction based on genotypes can be problematic. Without a better formal theory, I think that the extent this is so is not known, and, of course, it will differ with each trait of interest.

Perhaps there is no new theory to be found that will reduce this generic complexity to a desired kind of Mendelian predictability except in those instances, many already known, where it does happen to work. If so, it is correct that evolution is an ad hoc, largely stochastic process of divergence and diversity. Researchers will just have to soldier on enumerating variation and using subjective statistical criteria for assessing causation.

Alternatively, the current reliance on readily available and essentially standard statistical survey approaches may impede fully acknowledging the lack of a better way of understanding. Whatever the answer, this is a time of discovery by enumerative induction, enamored with mass data collection for various venal, bureaucratic, as well as scientifically legitimate reasons, but which has, to date, yielded only limited ability to generalize or extrapolate.

In my view, there should be major investment in innovative attempts to develop better theory for well-posed questions, rather than mega-projects of standard types, essentially to refine statistical evidence or association that may not point very directly to genomically causal elements of importance. And perhaps more effort should be expended on understanding what is "normal"—or even the meaning of a "norm" in considering both evolution and contemporary causation.

Both during evolution and today, competing causes, population distribution, and age-specific effects are core topics that are given rather scant attention. They present sampling and analytic challenges, even in the limited experimental settings available. Cross-species comparisons are interesting and potentially informative, but their limitations in the current theoretical environment need to be recognized.

Such a focus raises societal challenges of its own, given the politics and economics of modern science, the competition for resources, and, it must be said, the appeal and immediacy of technology and "Big Data" in which thinking is, often explicitly, deferred. Yet there is the accompanying promise of biomedical miracles.

Insightful creative genius cannot be ordered up just because there are serious problems with the current "paradigm." But this exculpation only can legitimately go so far. Incremental success, technology, and scale provide convenient excuses for not having to slow down and think about a problem. Known challenges exist, and they should be taken seriously.

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I maintain a blog that regularly deals with these sorts of topics: *The Mermaid's Tale* (a blog: ecodevoevo.blogspot.com)

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6

Evolutionary Perspectives on the Links Between Close Social Bonds, Health, and Fitness

Joan B. Silk

INTRODUCTION

The goal of this paper is to assess the impact of close social bonds on the health, longevity, and reproductive success of individuals in animal groups. Much of the work I discuss has been conducted on nonhuman primates. This taxonomic bias primarily reflects the fact that primatologists have a long history of interest in the complex dynamics of social relationships and commonly collect detailed information about the form, frequency, and sequence of interactions among individually identified animals with known reproductive histories. These kinds of data are not commonly available for other taxa. However, there are indications that similar processes operate in a range of species and may be part of a broader mammalian pattern. These data suggest that there may be important parallels between humans and other species in the association between relationship quality, health, and fitness outcomes.

I approach this problem as a behavioral ecologist, which means that I am motivated to understand how evolution shapes phenotypic traits to enhance the fitness of individuals. Phenotypic traits include physical characteristics, such as body size, strength, and running speed; physiological factors, such as stress response systems and immune function; and behavioral traits, such as vigilance, foraging strategies, and parental care. Behavioral traits take on added complexity in group-living species because individuals have opportunities to interact with conspecifics on a regular basis, and social interactions create opportunities for individuals to help or harm one another.

Sociality evolves when the net benefits of aggregation (e.g., higher vigilance rates, pooling information, and collective resource defense) exceed the costs that come from living in close proximity to conspecifics (e.g., resource competition, disease risk, and conflicts of interest). However, for individuals that live in social groups, the costs and benefits of group life are often distributed unequally. Members of particular age-sex classes may be systematically disadvantaged in competition over resources or exposed to greater predation risks. Moreover, within age-sex classes, there may be consistent variation in benefits and costs of group life, and these disparities may generate individual variation in lifetime fitness. Natural selection is expected to favor behavioral and social strategies that enhance the benefit/cost ratio for individuals.

In some cases, the adaptive logic of these kinds of strategies is relatively straightforward. For example, animals require resources to survive and reproduce successfully, and they often compete for these resources when they are in short supply. In many group-living species, the outcomes of competitive encounters within dyads are stable from day to day, and individuals can be assigned ranks within a dominance hierarchy. If high-ranking animals have priority of access to resources, and access to resources is an important component of survival and reproductive success, then a positive correlation between dominance rank and reproductive success and for selection to favor traits that enhance success in competitive encounters would be expected. Both these predictions are widely supported, although there are some interesting exceptions to the general patterns (Ellis, 1995; Clutton-Brock, 2009; Majolo et al., 2012).

In other cases, the link between behavioral strategies and fitness outcomes is less clear. For example, animals in many taxa devote considerable amounts of time to affiliative social interactions, such as social grooming. Grooming has hygienic functions and may therefore confer direct benefits on recipients (Akinyi et al., 2013). It has also been hypothesized that animals use grooming (and other forms of affiliation) to strengthen relationships with favored partners (Dunbar, 1991) and selectively invest in social relationships that enhance their fitness (Kummer, 1978). For example, in spotted hyenas (*Crocuta crocuta*), bottlenosed dolphins (*Tursiop aduncus*), and chimpanzees (*Pan trogloydytes*), reproductive success depends, in part, on the ability to recruit coalitionary support. Allies may be cultivated and alliances may be reinforced by affiliative interactions, such as greetings (Smith et al, 2011), displays (Connor, 2007), or grooming (Mitani, 2006). However, until recently, there was little evidence that investments in social relationships produced fitness payoffs. This is now beginning to change as researchers explore the links between relationship quality and important components of fitness, such as infant survival and longevity.

This new work builds on two separate developments in primate behavioral ecology. First, there has been a shift in the unit of analysis in behavioral studies. Behavioral ecologists tend to construct analyses in which the individual is the unit of analysis, not the dyad, and to examine correlations between individual traits and fitness outcomes. However, for animals that live in social groups, the fitness of individuals depends at least in part on the outcome of their interactions with other group members. This has prompted a shift from a strict focus on individual behavior to a broader view that includes the behavior of individuals and the nature of the relationships that they form with others (Silk et al., 2013).

The second important development is that behavioral ecologists have begun to explore the physiological mechanisms that mediate the relationship between social behavior and fitness outcomes. For many years, there was a tacit division of labor among researchers working at different levels of analysis. Behavioral ecologists focused mainly on questions about how natural selection shaped behavior to enhance genetic fitness and did not evaluate the underlying mechanisms that regulate behavior. Studies of the mechanisms that influence behavior were mainly conducted by psychologists working in the laboratory where fitness effects could not be evaluated. However, the development of noninvasive methods for assessing stress physiology (Beehner and Lu, 2013) has altered the status quo. These methods allow fieldworkers to assess the impact of social factors on health and disease, a potentially important cost of living in social groups (Nunn and Altizer, 2006). They also provide insight about how animals perceive the events that they experience and how social strategies influence their ability to cope with chronic and acute sources of stress.

I begin by establishing the empirical foundation for the claim that sociality influences fitness outcomes. Much of this evidence comes from two long-term studies of baboons. I describe how social relationships in other primates are assessed, then present results drawn from this body of data. I also describe what is known about the fitness effects of sociality in other animal taxa. I then consider the mechanisms that underlie relationships between sociality and fitness outcomes, discussing both the direct benefits that animals may gain from their social partners (e.g., protection from predators) and the indirect benefits that they may derive from social ties (e.g., reduced stress levels). Finally, I consider what is known about negative impacts that sociality may have on health and fitness via its impact on the prevalence, persistence, and virulence of pathogens.

SOCIAL BONDS AND FITNESS OUTCOMES: INITIAL EVIDENCE

In the late 1990s, Susan Alberts, Jeanne Altmann, and I began a collaboration to investigate the structure and function of social bonds among

female baboons. Alberts and Altmann are co-directors of the Amboseli Baboon Research Project (ABRP), which has been monitoring baboons in the Amboseli basin of Kenya since the early 1970s. Systematic observations of two social groups were initiated in 1971 and 1980, respectively (Altmann and Alberts, 2003). These two study groups subsequently fissioned, and the project continues to monitor several of the daughter groups from the original study groups. The reproductive histories, dominance ranks, and maternal kinship relationships of all females in the study groups are known. Research assistants regularly conduct 10-minute focal samples on all adult females in the study groups. During these samples, the activity and nearest neighbors of focal subjects are recorded on 60-second intervals.

We developed a measure of social integration that was based on the frequency with which females groomed or were groomed by other adults and were in proximity to other adults during focal observations. We used these values to create a composite index of sociality for each female (Silk et al., 2003). Females that have high values of the index spend more time grooming and associating than the average female, and females that have low values of the index spend less time grooming and associating than the average female. To assess female reproductive success, we tabulated the proportion of infants that survived to 1 year of age. We chose this measure because infant survival is an important source of variation in lifetime fitness among females in the Amboseli population (Altmann and Alberts, 2003).

We found that females that were more socially integrated into their groups had higher reproductive success than females that were less socially integrated (Silk et al., 2003). These effects were independent of variation in female dominance rank and ecological conditions that affected both females' activity budgets and their reproductive performance. These results attracted considerable interest because they provided the first systematic evidence that social relationships are linked to reproductive success, and they suggest that investment in close social bonds has an adaptive payoff. However, the Amboseli analyses were vulnerable to several potential questions and criticisms:

1. The analyses included interactions and association with adult males, and it is possible that females gained fitness benefits from their associations with males, not their associations with other females. Our analyses do not tell us whether relationships among females have fitness consequences.
2. The relationship between social integration and infant survival might reflect elevated levels of sociality for mothers of surviving infants rather than benefits derived from sociality (Henzi and Barrett, 2007) because female baboons in Amboseli are strongly attracted to other females' infants (Altmann, 1980).

3. The measure of social integration that we used did not fully characterize the nature of social bonds. Thus, it is not clear whether our results reflect differences in the quantity of social contacts of the quality of social bonds that females form.
4. Our findings were based on several groups in a single population, and the results might not hold for other populations of baboons or for other taxa. Clearly, the findings warrant more attention if they turn out to be robust.

In the next section, I will discuss how my colleagues and I have addressed these problems. I begin by discussing the methods we have developed for characterizing dyadic social bonds, and then discuss the structure of social bonds among female baboons in Amboseli and in a second population of baboons.

DEFINING AND DOCUMENTING THE STRUCTURE OF SOCIAL RELATIONSHIPS

Primatologists must take a different approach to studying social relationships than psychologists or sociologists because we cannot interview our subjects about their relationships with others, and we cannot rely on introspection for an understanding of what these relationships mean to them. Instead, we have been forced to take a bottom-up approach, looking for patterns in behavior to characterize relationships.

Hinde (1983) described social relationships as abstractions that represent the history of interactions between two individuals. As empiricists, we need methods of operationalizing this concept. It may be useful to think about social relationships (or social bonds) as a multidimensional space, and the empirical task is to map the contours of that space (Silk et al., 2013). There are a number of dimensions along which relationships might vary. For example, some pairs of monkeys might interact often, while others do so rarely. Some individuals might interact in a restricted set of contexts (e.g., sexual or agonistic), while others interact in a broader range of situations. Directional interactions, like grooming or approaches, may be highly one-sided or evenly balanced. The tenor of interactions within dyads may range from mostly hostile to mainly friendly. Some pairs of individuals may interact at high rates for short periods of time, while others may consistently interact at high rates over long periods of time. Finally, some pairs may be relaxed when they are together or tense. This scheme can be expanded as other dimensions are defined.

This way of thinking about social relationships has several useful features. First, it allows for the exploration of "relationship space" in a systematic way. Second, this way of characterizing social relationships does not

rely on preconceived notions about how social relationships are structured. While it might be predicted that animals that frequently groom and affiliate would be very relaxed when they are together and rarely fight, it might be that these dimensions are not aligned as expected. For example, among baboons in Moremi, maternal sisters have both high rates of affiliation and high rates of aggression (Silk et al., 2010a). Third, although we initially developed this scheme to describe social relationships among baboons, it may be adapted for other taxa with different behavioral repertoires.

The Structure and Function of Social Bonds Among Female Baboons in Amboseli

We used the approach described above to assess the nature of social relationships among females. For each pair of females, we tabulated the proportion of observation time that they were nearest neighbors or grooming one another, and used these values to create a dyad-specific composite sociality index (DSI, Silk et al., 2006a). As before, high values of the dyadic index represent dyads that spent more grooming and associating than the average pair of females.

We found that most pairs of females had very low DSI values, but a small number of dyads had quite high values. As in many other primate species, females showed strong preferences for close maternal kin, particularly their mothers, daughters, and sisters. Females also distinguished between paternal half-siblings and unrelated females. In a separate analysis, we also found that females selectively supported close kin more than they supported distant kin or non-kin (Silk et al., 2004). Although the availability of close kin had strong effects on the number of close social bonds that females formed, virtually all females in the population formed at least one close social bond even if they had no close maternal relatives in the group.

There was considerable variability in the distribution of grooming within dyads. That is, in some dyads, grooming was well-balanced, but in other dyads one female groomed her partner much more than she was groomed in return. Pairs that formed strong social bonds groomed more equitably than pairs that formed weaker social bonds (Silk et al., 2006b). This result could be an artifact of maternal kinship because related partners groomed more equitably than unrelated partners and related partners also formed stronger social bonds than unrelated partners. However, the relationship between grooming balance and the strength of social bonds held when the analysis was limited to unrelated females, so the connection between the strength of social bonds and the degree of grooming balance seems to be at least partly independent of kinship.

We also examined the stability of females' relationships with their favored partners. For each female, we identified her top three partners in

each year, and then we tabulated the number of consecutive years in which particular partners appeared among the focal females' three top partners. We found that females had consistent preferences for their most favored partners (Silk et al., 2006b). For example, mothers and daughters were quite likely to remain top partners for as long as they lived together in the group. At the same time, relationships with most unrelated partners were ephemeral, with strong relationships existing in one year, but not lasting until the next. Females' relationships with their top three partners are more likely to be sustained from year to year than would be expected by chance, while relationships with lower-ranking partners have little stability from year to year (Silk et al., 2012).

In summary, our findings indicate that female baboons in Amboseli form strong, supportive, well-balanced, and enduring relationships with selected partners. Preferred partners are typically close kin, but nearly all females seem to form a few close relationships even if no close kin are available.

Replication: The Structure and Function of Social Bonds Among Female Baboons in Moremi

After the Amboseli data were published, Dorothy Cheney and Robert Seyfarth invited me to collaborate on analyses of social relationships among female baboons in the Moremi Reserve of the Okavango Delta of Botswana. We were able to capitalize on the fact that a number of researchers who worked at the site from 2000-2007 (Jacinta Beehner, Thore Bergman, Catherine Crockford, Anne Engh, Liza Moscovice, and Roman Widdig) conducted focal observations on adult females using the same protocol that Cheney, Seyfarth, and I had used in the early 1990s.

Our analyses were designed to avoid two of the possible problems with previous analyses of the Amboseli data. That is, we limited our attention to interactions and associations among adult females and excluded observations that were conducted when females had young infants. Our goal was to draw comparisons across populations, so we mirrored the structure of the Amboseli analyses as closely as we could.

The social relationships of the Moremi females were strikingly similar to the social relationships of females in Amboseli. The Moremi females formed strong, well-balanced, supportive, and enduring relationships with selected partners (Silk, 2010a). Like the Amboseli females, the Moremi females showed strong preferences for close maternal kin and for peers. And females formed enduring relationships with preferred partners, particularly their mothers, daughters, and sisters, and only close social bonds are more likely to be sustained from year to year than would be expected by chance (Silk et al., 2012).

We were not able to assess the effects of paternal kinship on the strength of social bonds, but there is good reason to believe that peers will often be paternal half-sisters. Top-ranking males monopolize access to receptive females in Moremi (Bulger, 1993) and sire the majority of infants (Cheney and Seyfarth, unpublished data), but average tenure length for top-ranking males is fairly short (Palombit et al., 2000). This means that animals that are close in age are likely to have the same father.

We also evaluated the tenor of social bonds, by assessing the proportion of dyadic interactions that were friendly. Kinship did not preclude aggression, but the proportion of all interactions that were friendly was positively related to the degree of relatedness among females. Females were more tolerant of their most preferred partners than they were of others (Silk et al., 2010a).

Finally, we investigated the adaptive consequences of close social bonds among the Moremi females using survivorship analysis methods. The infants of mothers with strong social bonds lived longer than the infants of mothers with weaker social bonds (Silk et al., 2009). In contrast, female dominance rank had no consistent effect of infant survival. We also found that females that formed the strongest social bonds with their top partners lived longer than females with weaker social bonds (Silk et al., 2010b). In addition, high-ranking females lived longer than other females.

Evidence from Other Taxa

There is a gap between what is known about the form and function of social bonds in baboons and what is known about other primate taxa and in species outside the primate order. Kin are preferred partners in a wide variety of taxa, and the presence of kin has positive effects on fitness for females in a number of species (reviewed in Silk, 2007). A number of species form "fission-fusion groups," which means that group members frequently subdivide to form temporary subgroups. Studies of a number of species that live in fission-fusion groups show that females form preferences for particular same-sex partners, and these preferences are not always based on kinship (bottle-nosed dolphins: Möller et al., 2006; giraffes, *Giraffe camelopardalis*: Carter et al., 2013; eastern grey kangaroos, *Macropus giganteus*: Best et al., 2013; Carter et al., 2009; chimpanzees, *Pan troglodytes*: Langergraber et al., 2009; Lehmann and Boesch, 2009). However, few details about the form or function of these relationships are available. Below I briefly describe studies in which researchers have investigated links between the some aspects of the quality of social bonds and fitness outcomes.

Schülke et al. (2010) evaluated the form and function of social bonds among male Assamese macaques, *Macaca assamensis*. Males in this species disperse from their natal groups at puberty and join groups in which they

have few close relatives. Like female baboons and male chimpanzees, the male Assamese macaques spent more time grooming and associating with some male partners than others. Schülke and his colleagues discovered that males that formed the strongest bonds were more likely to support one another in aggressive interactions. The strength of males' social bonds was directly related to the number of infants that they sired in the subsequent breeding season.

Wild horses form stable groups that typically contain one male, a number of unrelated females, and their offspring (Linklater, 2000). Using information about time that females spent in close association with one another and their participation in grooming interactions with other females, Cameron et al. (2009) computed a composite index of social integration for each female like the one that we used for the Amboseli baboons. They found considerable variation among females in the extent of social integration, but females that were most fully integrated into their groups had higher foaling success than other females.

Bottlenosed dolphins live in fission-fusion groups, and the size and composition of parties changes frequently. Analyses of long-term party association data from Sharks Bay, Australia, indicate that females associate at higher rates with some females than others. The structure of females' social networks are associated with the production of surviving offspring (Frére et al., 2010). Females that spend much of their time together tend to have similar reproductive success as well.

Male bottlenosed dolphins form close ties with one or two other males, often relatives, and these associations may last for many years. Close associates engage in friendly contact, and perform highly synchronized displays as they leap from the water (Connor et al., 2006). These close associations are labeled "alliances" because males team up with their associates to mate guard receptive females. In Sharks Bay, members of different alliances sometimes team up to take receptive females away from other males or to prevent disruption of their own consortships. Males with more stable alliances consort with females at higher rates (Connor et al., 2001), and the great majority of paternities are assigned to males that belong to alliances (Krützen et al., 2004). These data suggest that strong and stable bonds among male dolphins may enhance their reproductive success.

In the wild, house mice form mixed sex groups that include one adult male, several adult females, and their litters. Females that give birth about the same time usually pool their litters and nurse them communally (König et al., 1994a, 1994b; Hayes, 2000). In an experimental study of house mice, Weidt et al. (2008) evaluated the social preferences of females in groups composed of unrelated individuals and then paired females with either their most preferred partners or their least preferred partners. Females that were paired with preferred partners were significantly more

likely to produce litters and weaned more pups than females paired with non-preferred partners.

PROXIMATE MECHANISMS THAT MEDIATE THE RELATIONSHIP BETWEEN CLOSE SOCIAL BONDS AND FITNESS OUTCOMES

The correlation between close social bonds and fitness outcomes may arise because animals gain direct or indirect benefits from their relationships with others. Direct benefits might include things like coalitionary support, protection from harassment, greater access to resources, or reduced vulnerability to predators. Indirect benefits would include positive effects on stress response systems, immune function, and health.

Direct Benefits Derived from Close Social Bonds

There is not yet enough information to generate a comprehensive analysis of the direct benefits that animals gain from close social bonds. Instead, case studies illustrate a range of direct benefits that animals may gain that enhance their fitness.

Coalitionary Support

Male Assamese macaques that formed close social bonds also supported one another in coalitions. Males that participated in coalitions most often were most likely to rise in rank, and high-ranking males had priority of access to receptive females and achieved higher reproductive success than lower ranking males. Social bonds may enhance the likelihood of gaining coalitionary support in chimpanzees as well. In the Ngogo chimpanzee community, males spend the most time grooming the males that they most often support in agonistic coalitions (Mitani, 2006). At Gombe, chimpanzee males that participate in coalitions most often are more likely to rise in rank and sire more offspring than males that participate in coalitions less often (Gilby et al., 2013). Thus, for both male Assamese macaques and male chimpanzees, social bonds may provide a route to achieving high rank and more mating opportunities.

Predator Deterrence

Michelleta et al. (2012) examined the relationship between the strength of social bonds among females and the effectiveness of predator responses in crested macaques, *Macaca nigra*. Crested macaques give alarm calls when they detect the presence of pythons, and their alarm calls attract other group members who may subsequently mob the predator, often

leading to its retreat. Mobbing is potentially dangerous, and the success of mobbing efforts depends on the effective coordination and cooperation of participants. In experiments that simulated a python encounter, experimenters played previously tape-recorded alarm calls back to other group members. The monkeys responded more strongly to alarm calls given by close affiliates than other group members. If effective predator responses enhance survival, then the individuals that form close social bonds may gain important fitness benefits.

Eastern grey kangaroos form groups, but frequently divide up into subgroups with fluid membership. Females associate with some females more often than expected based on chance, while there are others that they spend less time with than expected by chance (Best et al., 2013; Carter et al., 2009). The strength of a female's relationship with the female nearest to her predicted the amount of time that she spent grazing. The authors suggest that females are less vigilant when they are near preferred partners, and this enables them to devote more time to foraging.

Access to Resources

King et al. (2012) investigated the impact of close social bonds on the frequency with which female chacma baboons in semi-arid habitats in Namibia fed together in a single food patch. Their measure of relationship quality was based on the frequency of dyadic grooming. They found that females with close social bonds were more likely to feed together than females with weaker social bonds. These effects were not due to the effects of maternal kinship or dominance rank. These findings complement previous evidence that showed that females were more likely to follow preferred partners into experimental food patches (King et al., 2008) and fed at higher rates when they co-fed with preferred partners (Covas, 2005, cited in King et al., 2011).

Protection from Infanticide/Harassment

In some species, close associations among males and females may provide females and their offspring protection against harassment by conspecifics. Infanticide, in which adults direct lethal attacks on immatures, is the most severe form of harassment. As noted earlier, mothers of newborn infant baboons often form "friendships." Male friends are often, but not always, the fathers of their friends' infants (Nguyen et al., 2009; Moscovice et al., 2009, 2010). Mothers are primarily responsible for maintaining proximity to their male friends, and groom them more than they are groomed in return (Palombit et al., 1997). Playback experiments conducted on baboons in Moremi, where infanticide is common, show that males are

sensitive to their female friends' distress (Palombit et al., 1997). And, as infants mature, males selectively support the offspring of their former associates (Moscovice et al., 2009). In Amboseli, where infanticide is not observed, male-female friendships are also common. Females' infants receive less rough handling and exhibit less distress when their male associates are nearby (Nguyen et al., 2009).

Similarly, among wild horses, females that are more socially integrated receive less harassment from stallions (Cameron et al., 2009). This may be an important benefit because male harassment has a negative impact on female reproductive success (Linklater et al., 1999).

Indirect Benefits of Close Social Bonds

When animals experience events that threaten their well-being, such as predator attacks or aggression from conspecifics, stress response systems are activated. This enables individuals to mobilize energy reserves for critical activities, such as flight, and divert energy from other less immediately essential metabolic processes, such as growth and maintenance (Sapolsky, 2005). Stress responses are also activated in anticipation of danger, and animals react most strongly to events that they cannot control or predict. Prolonged activation of the stress systems has deleterious long-term effects on health and reproductive function (Wingfield and Sapolsky, 2003). If social bonds enhance animals' sense of predictability and control, or reduce the need to remain vigilant against threats from predators or conspecifics, then they may reduce stress levels and have indirect effects on health and reproductive success. In this section, I review evidence that suggests that social ties help animals cope with several major stressors, social isolation, social instability, and subordinate status. I also describe results from several studies that suggest that the structure of individuals' social networks is linked to stress levels.

Social Isolation

If sociality is favored by natural selection because it reduces vulnerability to predation, then animals are expected to be safer and feel more secure when they are in groups than when they are alone. Social isolation may activate stress responses that enhance vigilance and responsiveness to danger. Female Norway rats, *Rattus norvegicus*, are gregarious, share their burrows with conspecifics, and rear offspring communally. In a series of experimental studies, McClintock and her colleagues explored the impact of social isolation on females' ovarian function and vulnerability to mammary tumors. Isolated individuals are hypervigilant and neophobic, and they display higher cortisol levels, develop mammary tumors earlier,

and their tumors are more likely to be malignant (McClintock et al., 2005; Hermes et al., 2009).

Social ties can help animals cope with the stress of isolation. In mixed-sex captive groups, guinea pigs (*Cavia aperea*) form strong bonds with a single individual of the opposite sex. These bonds are characterized by high levels of friendly contact and sexual behavior. When males or females are removed from their social group and placed alone in an unfamiliar cage, their cortisol levels rise significantly. For both sexes, this response is reduced by the presence of their preferred partner (Sachser et al., 1998; Kaiser et al., 2003). Siberian hamster females form strong ties to their sisters, and social isolation delays wound healing (Detillion et al., 2004).

Social Instability

Social instability is a major source of stress for animals (Mendoza et al., 2000; de Vries et al., 2003). This is likely due to the fact that social relationships are altered by the presence of new group members or the absence of familiar partners. For example, when new individuals enter a group, levels of aggression often rise, new dominance relationships are formed, and the existing dominance hierarchy may be altered. And when familiar animals are removed from the group, social ties may be disrupted, important allies may be lost, and the dominance hierarchy may be disrupted.

Capitanio et al. (1998) assessed the impact of social stability on the survivorship of juvenile male rhesus macaques, *Macaca mulatta*, after inoculation with SIV. Monkeys that interacted regularly with the same individuals (stable associations) spent more time in proximity and more time grooming than males that regularly interacted with unfamiliar individuals (unstable associations). Levels of aggression were also higher in the unstable associations than in the stable associations. Monkeys in the stable associations survived significantly longer after exposure to SIV than monkeys in the unstable associations.

Gust et al. (1996) studied the physiological impact of group formation on juvenile rhesus macaques. They compared the cortisol levels of juveniles who were placed in a new group with a familiar peer, juveniles that were placed in a new group on their own, and juveniles that remained in their natal groups. Juveniles tended to stay close to familiar peers during their first weeks in their new groups. Those that entered new groups on their own had substantially higher cortisol levels after one week than those that were accompanied by a familiar peer.

Instability in the male dominance hierarchy has direct effects on females in some species. For example, in the Moremi baboon population, after a new male immigrates into the group and achieves top rank, he often kills unweaned infants. When mothers lose their infants, they rapidly resume

cycling, and the infanticidal male is then likely to be able to mate with the mother. Similar events are seen in a wide range of mammalian species, and are believed to be a product of sexual selection acting on males (Palombit, 2012). The fecal glucocorticoid (fGC) levels of females rise in the days that follow the arrival of new males, and the fGC levels of lactating females, whose infants are vulnerable to infanticide, rise more than fGC levels of females in other reproductive states (Beehner et al., 2005; Engh et al., 2006a).

Social ties can buffer the effects of social instability. Lactating females that have established friendships with adult males have significantly lower fGC levels than females without close male associates (Engh et al., 2006b). This is likely due to the fact that male friends help protect females and their infants from infanticidal aggression (Palombit et al., 1997). Moreover, during a period of instability in the male dominance hierarchy, females initially reduced the number of different females that they groomed (lower grooming diversity). Females that reduced their grooming diversity the most reduced their fGC levels the most as well (Wittig et al., 2008). Those females that had more focused grooming networks before the period of instability began experienced smaller increases in fGC than females with more diffuse grooming networks.

The disruption of close social bonds appears to be an important source of stress for female baboons. Engh et al. (2006a) monitored responses to predation events among the Moremi baboons. They found that fGC levels generally rose in the days that followed predation events. This makes sense, because the stress response system is designed to cope with imminent threats. However, females that lost a close relative experienced greater increases in fGC levels than individuals that were present in the group, but did not suffer a personal loss.

Subordinate Status

There is considerable discussion about the effects of dominance rank on stress levels, with some studies showing that high-ranking individuals have lower cortisol levels than low-ranking individuals, and others showing the opposite effect (Sapolsky, 2005). However, the effects of rank seem to be at least partially affected by the social context. Comparative analyses indicate that subordinates have high glucocorticoid (GC) levels in relation to dominants in species with high levels of harassment by dominants and low levels of social support (primates: Abbott et al., 2003; vertebrates: Goymann and Wingfield, 2004). Abbott and his colleagues also found that social support and access to kin mediate the effects of low rank on subordinates across species. Sapolsky and his colleagues showed that high-ranking male baboons in the Masai Mara of Kenya have lower GC levels than low ranking males, but high-ranking males that rarely groom females or inter-

act with infants have elevated GC levels (Ray and Sapolsky, 1992; Virgin and Sapolsky, 1997). In Amboseli, male baboons that are more socially integrated into their groups have significantly lower GC levels than males that are more isolated (Sapolsky et al., 1997). Ostner et al. (2008) found that high-ranking male Assamese macaques have lower cortisol levels than lower-ranking males, and they suggest that close social bonds among males (see above) may mitigate the costs of maintaining high rank.

Reciprocity

There is also some evidence that the structure of interactions may influence how individuals cope with stress. Yee et al. (2008) evaluated the behavior of young female Norway rats housed in groups of three sisters while they experienced a brief stressor. Females that had more well-balanced affiliative interactions with their sisters during these events exhibited lower corticosterone responses to an acute stress in late adulthood, developed mammary tumors later, and lived longer than females with less well-balanced relationships. It is not clear why reciprocity has this effect or whether reciprocity has similar effects in other taxa.

Social Networks

Two studies have examined the impact of an individual's social networks on cortisol levels in primates. During a period of stability in the male dominance hierarchy, female baboons in Moremi had lower fGC months during months in which they concentrated their grooming on a small number of partners than in months in which they distributed their grooming more evenly among potential partners (Crockford et al., 2008). The structure of females' grooming networks had a bigger impact on their fGC levels than the overall frequency that females groomed or were groomed by others.

It is not yet clear why the size of females' social networks is linked to their cortisol levels. If grooming is exchanged for coalitionary support (Seyfarth, 1977; Schino, 2007), then females that spend more time grooming a small number of partners may be more successful in recruiting coalitionary support than females that spread their grooming over a larger number of partners. However, this hypothesis has not been tested directly

Brent et al. (2011) use social network methods to assess the impact of the distribution of grooming, affiliative vocal exchanges, and proximity on monthly fGC levels of female rhesus macaques. They evaluated a number of network metrics for each of these behaviors and found that high-ranking females had significantly lower GC levels in months in which their proximity networks were smaller and more focused. However, this was not true of

lower-ranking females, and the structure of grooming networks and vocal exchange networks did not have consistent effects on fGC levels of high- or low-ranking females.

Costs of Close Social Bonds

The primary costs of sociality are likely to be increased competition over access to resources, particularly food, and increased vulnerability to disease. The data reviewed above suggest that some animals use social bonds to mediate the costs of competition. Now, I turn to the relationship between sociality and disease.

There is a growing literature about the impact of sociality on the prevalence, persistence, and virulence of pathogens (Loehle, 1995; Nunn and Altizer, 2006). Much of this work has focused on the effects of group size and social structure (the patterning of social interactions within groups) on parasite loads using comparative methods (e.g., bats: Langwig et al., 2012; carnivores: Nunn et al., 2003a; rodents: Bordes et al., 2007; primates: Vitone et al., 2004; mammals: Altizer et al., 2003; mammals, birds, lizards, fish, insects, spiders: Rifkin et al., 2012.) While there is generally a positive relationship between group size and various measures of disease risk, there is considerable variation in the pattern. This variation may be related to a number of factors, including the mode of parasite transmission, the measure of pathogen risk considered, and the details of social structure. For example, there seems to be an inconsistent relationship between group size and levels of parasitism across the primate order (Nunn et al., 2003b). This may be linked to how associations are patterned in large and small groups. In a subset of 19 primate species, it was found that larger groups tend to have a more modular structure of interactions than smaller groups, and groups with more modular structure have a lower richness of socially transmitted parasites (Griffin and Nunn, 2012).

There have also been efforts to examine the effects of individual characteristics, such as age, sex, and dominance rank on disease in a broad range of species (reviewed by Benavides et al., 2012). The effects of individual characteristics such as age and dominance rank on parasitism might be due to differences in physical condition or immune function among individuals of different age or rank, but they may also be due to differences in their pathogen exposure. Griffin and Nunn's (2012) results suggest that the structure of individuals' social networks might matter, and several studies provide evidence that supports this idea. In free-ranging Japanese macaques, high-ranking females have higher parasite richness than lower-ranking females (Macintosh et al., 2010, 2012). High-ranking females did not have higher cortisol levels than lower-ranking females, but they did occupy more central roles in the group grooming network. Thus, the structure of females'

social contacts may influence their exposure to parasitic infections. Among meerkats, *Suricata suricatta*, those that groomed others the most were more likely to be infected with tuberculosis than those that groomed others less. At the same time, those that received the most aggression were more likely to be infected than those who received less aggression (Drewe et al., 2010). Among brush-tailed possums, *Trichosurus vulpecula*, the likelihood of contracting tuberculosis was higher for individuals that had frequent contacts with a small number of others than for individuals that had equal numbers of contacts spread over a larger number of partners (Porphyre et al., 2011). In a study of wild giraffes, VanderWaal et al. (2013) examined the relationship between patterns of associations, space use, and genetic similarity of a common pathogen (*E. coli*). They found that individuals who spent more time together shared more genetically similar subtypes of *E. coli* than those who spent less time together. In contrast, patterns of shared space use had little effect on parasite transmission networks.

These studies suggest that the structure of social contacts can influence pathogen transmission in group-living species. There might be tradeoffs between the stress-reducing effects of social support and close social bonds and the disease-enhancing consequences of high levels of social contact. However, the relative magnitude of these effects cannot yet be weighed because no studies have yet assessed the relationship between relationship quality, levels of parasitic infection, mortality, and fitness outcomes.

CONCLUSIONS

The data reviewed here suggest that the structure of social networks and the quality of social relationships may influence animals' ability to enhance the benefits and reduce the costs of social life. For group-living animals, including other primates, the ability to form and maintain close social bonds may create multiple direct benefits, including reduced vulnerability to predators, greater access to food resources, and protection from harassment. Moreover, social ties seem to help animals cope with various sources of social stress, perhaps because their relationships provide a greater sense of predictability and control, and this in turn affects health outcomes.

It is not yet clear whether there are differences in the impact of well-differentiated relationships across taxa. Primatologists are typically attuned to the nuances of social relationships and record detailed information about dyadic interactions. Researchers working on other animals do not often obtain the same kind of information about their animals, and this makes it difficult to draw clear comparisons about the quality of social relationships across taxa.

Going forward, it may be useful to design studies to assess and compare the impacts of different elements of relationship quality. For example,

my colleagues and I have examined the impact of relationship strength on the fitness of female baboons, but we have not compared the effects of relationship strength and the extent of grooming balance. Similarly, Yee et al. (2008) documented the effects of reciprocity on female rats' response to stress, but did not assess other elements of females' relationships with one another. To conduct these kinds of analyses, there is a need to expand current methods for describing relationship quality and to learn more about the natural history of social bonds in a diverse range of species. Efforts to match detailed behavioral studies with analyses of stress, health markers, and mortality must be extended. And finally, these data must be linked to reproductive outcomes over the lifecourse.

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7

Pathways of Survival and Social Structure During Human Transitions from the Darwinian World

Caleb Finch and Burton Singer

Pathways of survival within and between social structures have undergone remarkable change in recent centuries, largely through minimization of infection as the main cause of morbidity and mortality at all ages. Within the past two centuries, the human life expectancy (LE) has doubled, whether measured at birth (Oeppen and Vaupel, 2002) or at age 70 (Finch and Crimmins, 2005). As lifespans lengthened, vascular disease and cancer became dominant causes of morbidity and mortality at later ages. Social status and gender continued to be, as in centuries past (Benedictow, 2004), major influences on morbidity and mortality that in the United States separate socioeconomic status (SES) and gender groups by up to 20 years of LE (Crimmins et al., 2009).

Since the early 1800s, the increasingly rigorous demographic data show inverse relationships between SES and rates of overall mortality, age-specific mortality, and a variety of measures of disease morbidity. These mortality-morbidity relationships to SES hierarchies can be characterized in various ways (Humphreys, 1887; Sorokin, 1959). There is an analogous, but more limited, literature for nonhuman primates. Eusocial insects also have hierarchical communities—e.g., bees (Al-Khafaji et al., 2009; Seeley, 2010) and ants (Hölldobler and Wilson, 2009)—but their structure and modes of operation differ qualitatively from primates and humans (Fewell, 2003).

The recently identified and pervasive inverse association between SES to mortality and morbidity in human populations raises a major question: Has inequality among human groups always been present? A minimal answer at least requires some understanding of the origin and character of social

inequality in humans. We ask the same question for wild animal populations that have well-defined hierarchies, but with evolutionary pathways that differ importantly from social and cultural evolution in humans.

We also move beyond associations in human populations to seek understanding of individual-specific pathways from position in a hierarchy to disease and mortality outcomes. Of necessity, this topic requires longitudinal data on different time scales—daily, weekly, monthly, and over multiple years. For example, a person's relative position in a wealth or household income hierarchy can be fixed over most of his/her adult life, whereas on a daily or weekly basis the same individual may spend time in different hierarchies—for example, church groups or voluntary organizations, the workplace, military reserve—where the negative impact of low position on income in the workplace may have strong positive countervailing effects from high position and influence in a local church group. The study of the psychological consequences for individuals of having distinct positions in multiple hierarchies simultaneously and in moving among hierarchies on both short and long time scales is a topic in its infancy. The reality of this dynamic, however, indicates the need to move from perception to signatures in the brain to physiological impact and feedback to break new ground on mechanisms that underlie the quite coarse-level associations that occupy most of the contemporary literature on inequality and disease, mortality, and health. Over the long sweep of history, few have had the opportunity to occupy multiple hierarchies. However, contemporary technological advances, particularly in communications, are adding considerable complexity to relationships between hierarchical positions and disease, mortality, and positive health outcomes.

Associations between position in a single social hierarchy and LE have points of commonality and differentiation when comparing humans and animals. The change from primarily infectious disease causes of death to noncommunicable chronic diseases in humans leads to different mechanisms associated with pathways to death and a major deviation from the Darwinian background where mortality from predation and infection was dominant. Extending the current focus in studies of LE from single hierarchies to the more nuanced consideration of multiple hierarchies and movement of individuals among them will require longitudinal data collection on human populations with this particular kind of emphasis. A particularly valuable shift of emphasis would be the collection of information on dyadic (network) relationships among individuals in diverse communities. This would facilitate consideration of more subtle, and important, notions of hierarchy than heretofore. Apicella et al. (2012) describe an interesting example from hunter-gatherers in Tanzania.

A central point about hierarchy that social network data would illuminate is that the word "hierarchy" itself has multiple meanings, only one

of which is encapsulated in the vast literature on SES and its association with morbidity and mortality. As discussed above, a hierarchy means a set of ordered categories into which individuals are classified. If dyadic relationships among individuals were assessed, then an idealized notion of hierarchy is a tree-structure (directed graph) in which the vertices (nodes) represent individuals, with the directed arrows signifying an ordering, or dominance, based on criteria such as wealth, power, position in an organization, control, and others. Few real-world communities that we will consider have a structure of this type. A common theme is that at intermediate levels in a tree structure, a subgroup of the community that are essentially unorderable among themselves may be encountered, but as a group, they dominate individuals or other subgroups lower down in a tree-like structure.

For example, a pair of individuals at the top of a hierarchy may dominate the overall community, but cannot be ranked between themselves. Lower down in the tree-like structure, there may be other unorderable groups that, as collectivities, dominate individuals or other unorderable groups lower down. The combination of individual vertices and subsets of unorderable individuals constitute a tree-like structure that is a cruder approximation of the idealized tree structure, the more subgroups there are containing unorderable individuals. In contrast to the branching from the top description just provided, a community may be top-heavy with many individuals dominating fewer and fewer individuals as one moves down a tree that narrows and appears as a cone with apex at the bottom. With no intermediate unorderable groups in such a top-heavy tree, an idealized reverse shape of the idealized tree with single vertex at the bottom can be envisioned. Scoring these extreme trees as +1 for the standard idealized tree and –1 for the inverted idealized tree would score approximations to each of these according to a degree of treeness taking values between –1 and +1. The standard hierarchies in the SES–morbidity mortality literature have no branching structure at all, and thus score 0 in terms of degree of treeness. For a rigorous discussion of measures of treeness, see Corominas-Mutra et al. (2011).

In addition to treeness, it is useful to bring in the notion of feedforwardness, meaning the extent to which there is a flow of order relations from the top of a structure to the bottom. An idealized tree structure as described above would have full feedforwardness. However, if there are intermediate groups in a graph that are unorderable, but as a collectivity if each forms a subgraph of a larger graph that is orderable, degrees of feedforwardness in a community can be represented as a directed graph. A score of 0 corresponds to a cyclic graph—no orderability—and a score of 1 corresponds to a full-ordered structure with no intermediate unorderable subgroups. Feedforwardness and degree of orderability (with scores ranging between 0 and 1) are also fully developed quantitatively in the insightful papers of Corominas-Mutra et al. (2011, 2013).

Assuming dyadic data corresponding to relationships between individuals in a community, the community can be scored as a point in a 3-dimensional morphospace with coordinates T (= treeness, taking values between –1 and +1), F (= feedforwardness, taking values between 0 and +1), and O (= orderability, taking values between 0 and +1). This kind of representation adds considerable nuance to the notion of hierarchy. A substantial research agenda for the future concerns investigation of the dynamics of communities of diverse types and their trajectories in the morphospace with coordinates (T,F,O).

With this background at hand, the purposes of this paper are to (1) review and compare hierarchy–morbidity/mortality associations in animals and humans and identify their place in a more rigorous quantitative formulation of "hierarchy"; (2) embed current evidential bases about the origin of inequality in humans in a quantitative caricature of the changing structure of hierarchies; (3) indicate the shift from a Darwinian view of human lifespan to present and future complex settings where survival extends well beyond reproductive ages; and (4) specify a research agenda focused on a quantification of hierarchy involving multiple kinds of ties simultaneously. The latter topic is a critical missing link in the current studies of associations between membership in stratification systems and morbidity–mortality outcomes.

SOCIAL HIERARCHIES, PAST AND PRESENT

On the Origin of Hierarchies in Human Populations

Hunting and gathering societies that possessed no grouping larger than the extended family were, as seen from archaeological evidence (Flannery and Marcus, 2012), to be nonhierarchical. The networks of extended families approximated the location (0,0,0) in the morphospace. They tended to be small, almost completely connected networks governed by reciprocal friendship and work relationships. Cooperation was the order of the day. At the most basic level, neither individual nor family units were orderable on the basis of ties involving interpersonal interactions. Furthermore, in the arctic and in prehistoric communities residing in current Colorado, there is considerable archaeological evidence for wide networks of nonrelatives cooperating in hunting on a scale not achievable with extended families alone (Flannery, 1972; Flannery and Marcus, 2012). These are also unorderable networks located at (0,0,0), or close to it, in the morphospace.

The formation of clans in a distant Paleolithic horizon ushered in hierarchy in human communities. Despite a seeming lack of power differential, clans have an "us vs. them" mentality, and violence between clans became commonplace. The simplest version of a two-clan society, one of which

dominates the other, with extended family structure within a clan would have location approximately (1,0.5,0.5). The two clans are unorderable within themselves, but the dominance of one clan over another provides a feedforward structure and partial ordering, with the overall community described by two large collapsed nodes—the clans—and a directed arrow pointing from the dominant to the subordinate clan.

With the onset of agriculture, stable communities had village chiefs, thereby building a small power hierarchy within the village. With the household as the unit of analysis, such communities consisted of an unorderable set of households dominated by the household of the chief. Such a village was located at (1,1,1) for a two-node network consisting of the chief's household and a collapsed network comprising all other households. The farming communities comprising the Jewish Pale of Settlement in Eastern Europe (Poland, Lithuania, parts of Russia, and other areas), had a two-tiered system ordered by wealth. The majority in these communities was quite poor, with minimal ordering by wealth. Among the rich, there was also limited ordering by wealth, but this group totally dominated the lower class, with rabbis playing a central role in maintaining hierarchies (Wienryb, 1972; Risch et al., 1995). In the morphospace, with the wealthy and the poor collapsed into distinct classes, the overall structure was located at (1,1,1).

The onset of the Industrial Revolution introduced greater within-population differentiation based on wealth. In the language of the morphospace, this meant that populations were tree-like, but that there were multiple tiers on the tree corresponding to essentially unorderable wealth groups, and with a strict hierarchy from one tier to the next moving down from the wealthiest to the poorest groups. The wealth groups reflected an ordering of persons by occupational skills with accompanying wage differentials in the occupational hierarchy. Basically, the organization of production induced the hierarchies, and they have persisted to the present time. Company towns were located at (1,1,1) in the morphospace. This structure broke down and became somewhat more complex when industrial cities grew up with diverse types of companies within them. If individuals are the unit of analysis, select subgroups of a population can be unorderable by wealth but nevertheless fit into a hierarchy with location (1,0.5,0).

Hierarchies and Disease, Illness, and Death

Simple Hierarchies

An early example of a hierarchy–mortality association is available from 19th-century England and Ireland, with ordering based on occupational categories (Humphreys, 1887). The ordering of mortality rates as deaths

per 1,000 under age 5 is consistent across five different attributed causes of under-age-5 mortality. In the language of the morphospace, the nodes of a graph based on these data would be the occupational categories for one or both parents, and the arrows moving downward from "Professional" at the top to "General Service" at the bottom would have the interpretation "is a riskier environment than." The vertical graph has morphospace coordinates (T,F,O) = (0,1,1), as it is not at all tree-like but is nonetheless orderable and has feedforward structure.

For a more contemporary example of occupational hierarchy, we consider the all-cause 10-year (1969-1979) mortality experience of British Civil Service workers in the Whitehall I study (Marmot et al., 1984) (see Table 7-1).

The key point is that the top three levels in the British Civil Service would qualify as "Professional" in the classification scheme used above for 19th-century England and Ireland. Thus a refinement in the broad category "Professional" into the top three Civil Service Grades produces an ordering of mortality rates within the broad category, as well as an ordering relative to a subset of "Middle Class," represented by "Other" in Table 7-1. A more nuanced analysis of the Whitehall II population is given in Case and Paxson (2011). For a more comprehensive discussion of hierarchy in work environments, see Spilerman (2000).

Hierarchies of Trajectories

Using longitudinal data from the Wisconsin Longitudinal Study ([WLS]; University of Wisconsin–Madison, 2013), Singer and Ryff (1999) constructed coarse-grained economic status histories and personal relationship pathways and investigated their association with a biomarker risk index. The *Economic Pathways* are based on classification of individuals according to (1) whether or not the household income of the family in which the person grew up was in the upper (+) or lower (–) half of the income distri-

TABLE 7-1 Mortality in Age Group by Civil Service Grade

Age	Administrators	Professional and Executive	Clerical	Other
10-Year Mortality: % Died Within 10 Years Beyond Baseline (# of deaths)				
40-49 years	2.1 (10)	3.7 (211)	3.6 (29)	9.6 (27)
50-59 years	6.4 (27)	9.3 (493)	16.0 (216)	19.3 (155)
60-64 years	5.6 (4)	17.2 (188)	23.9 (148)	26.7 (144)

NOTE: Hierarchy rank order: Administrators > Professional and Executive > Clerical > Other.
SOURCE: From Marmot et al. (1984).

bution for the state of Wisconsin when he/she was age 18; and (2) whether or not the individual's household income at age 59 was in the upper (+) or lower (–) half of the income distribution for the state of Wisconsin at that time. The *Economic Pathways* were defined as Early life category and Later life, with the inclusive four possibilities: (–, –), persistently negative; (+,–) = downwardly mobile; (–,+) = upwardly mobile; (+,+) = persistently positive. The *Relationship Pathways* are (1) Negative [N] if the person had an uncaring/abusive parent when growing up or a poor relationship with a significant other in adulthood, or both; and (2) Positive [P] if at least one parent was very caring when the person was growing up, and in adulthood there was a good relationship with a significant other.

Besides the economic and relationship measures, a set of 10 biomarkers for morbidity were assessed on the same individuals at age 59 (see Table 7-2). An individual was classified as having elevated morbidity risk for a given

TABLE 7-2 Economic-Relationship Pathways[a] X Risk Index in the Wisconsin Longitudinal Study

A. Economic-Relationship Pathway	Fraction with Biomarker Risk Index[b] ≥ 3
(–,–); N	0.69(13)[c]
(+,–): N	0.65 (8)
(–,+); N	0.55 (9)
(+,+); N	0.36 (11)
(–,–); P	0.22 (9)
(+,–); P	0.31 (13)
(–,+); P	0.20 (10)
(+,+) P	0.36 (11)

B. Aggreged Pathways	Fraction with Biomarker Risk Index ≥ 3
At least one economic (–), N	0.63 (30)
(+,+)	0.36 (22)

[a]*Economic pathways* are defined as Early life and Later life, with four possibilities: (–,–) persistently negative; (+,–) downwardly mobile; (–,+) upwardly mobile; (+,+) persistently positive. *Relationship pathways* are (1) Negative [N] if the person had an uncaring/abusive parent when growing up or a poor relationship with a significant other in adulthood, or both; (2) Positive [P] if at least one parent was very caring when the person was growing up and there were good relationships with a significant other in adulthood. For detailed specification of the scales and their scoring, see Singer and Ryff (1999).

[b]The biomarkers and thresholds defining elevated risk zones are systolic blood pressure (> 147 mm Hg); diastolic blood pressure (> 82 mm Hg); Waist-hip ratio (> 0.93); Ratio of total cholesterol/HDL (5.9); glycosylated hemoglobin (> 7.0%); urinary cortisol (> 25.6 ug/g creatinine); urinary norepinephrine (> 47 ug/g creatinine); urinary epinephrine (> 5 ug/g creatinine); HDL cholesterol (< 38 mg/dl); DHEA-S (< 351 ng/ml).

[c]Number of persons on the designated pathway.

biomarker if he/she was in the upper (or, in some cases, lower) quartile of values for that measure in the WLS population. The risk index simply counts for each individual the total of biomarker scores with elevated morbidity risk. A threshold of risk index ≥ 3 was interpreted as "elevated risk" based on prior studies that showed that such levels were predictive of earlier mortality, incident cardiovascular disease, and decline in physical functioning (Seeman et al., 2001). For those on a negative relationship pathway, there is a basis for an ordering of economic pathways from persistently positive at the top to persistently negative at the bottom. An alternative order would put the relationship pathways from P at the top to N at the bottom. Table 7-2 shows the associations between socioeconomic pathway structure and the morbidity risk index on a pilot sample from WLS.

Among the more interesting results in Panel A is the fact that if an individual is persistently positive on the economic measures, then the relationship history does not matter to morbidity risk. However, if economic measures are persistently negative, then being on a positive relationship (+,+) pathway tends to maintain lower risk index. Further, the lowest morbidity risk index is for persons who are both upwardly mobile economically and on the positive relationship pathway. The WLS thus reveals a richness of possible findings if two or more types of SES measures are considered simultaneously. This analysis also challenges a large literature that discusses biomarkers, disease, or mortality in association with but one socioeconomic measure.

A useful hierarchy based on an aggregation of the pathways in panel A is shown in panel B with larger sample sizes. This hierarchy implies that persistent economic advantage is protective against physiological wear and tear, regardless of the relationship history. In contrast, at least one period of economic disadvantage combined with negative relational experience lead to elevated morbidity risk.

The above pair of hierarchies is very coarse-grained in time and limited in context. However, this unique dataset (University of Wisconsin–Madison, 2013) also contains information about membership in voluntary organizations, church groups, military experience, and other alternatives to the workplace where hierarchies are salient and where possibly negative disease and disability influences of low position in a work environment can be compensated by positive experience at high rank in other hierarchies. Exploring this kind of question in WLS, which has longitudinal follow-up data on individuals from age 18 to age 74, as well as a current wealth of biomarker data, should be an important sequel to the discussion herein.

We note that the hierarchies discussed here for WLS are not interesting in the context of the morphospace introduced above. Little can be done about this because WLS does not have the requisite network data that would allow us to capture the full impact of social connections on health. For example, Berkman et al. (2000) give a nice theoretical treatment of

the cascade of factors involved in translating social ties of various types to health outcomes. This analysis gives a useful template for network-based surveys that would allow a population, such as in WLS, to be situated in the morphospace with interesting dynamics as the people age.

Having indicated this data analytic opportunity, we caution that person-centered strategies using the full individual history as the unit of analysis should be employed if the nuances of movement between distinct hierarchies at several time scales and the health consequences of this dynamic are to be identified. Such an analysis with a dataset like WLS requires that the information for a single individual with survey responses on over 1,000 variables be distilled into a life history narrative. Then, narratives from a small subsample of the population must be compared and contrasted via text analysis, and sets of composite variables focused on different life domains and varieties of experience need specification for quantitative analysis of the full population for ascertainment of multiple hierarchies.

Details of such a person-centered analysis on WLS data are presented with a focus on mental health outcomes in Singer et al. (1998) and Singer and Ryff (2001), but without the multiple hierarchy focus we are advertising here. An especially informative example of person-centered analysis is given by Zhao et al. (1999), who focused on resilience in young children ascertained in the Child Supplement of the National Longitudinal Study of Youth (NLSY-CS).

Social Hierarchy and Life Expectancy

The Evolution of Lifespans

In current evolutionary theory, the LE is an indirect outcome of natural selection to balance mortality against fecundity. This balance, which must be steady-state neutral or positive for species survival, can be achieved via a vast range of reproductive strategies. At one extreme are mayflies and Pacific salmon with short adult lifespans and death soon after laying thousands of eggs (Finch, 1990; National Research Council, 1997). Species with single event "big-bang" reproduction have negligible parental investment in feeding or protection from predation. Humans, at another extreme, have singleton births, prolonged maturation, and lifespans of many decades.

Relative to the great apes, human reproductive schedules are uniquely evolved in three synergizing features: faster weaning, greater maternal support from fathers and others in the community, and a definitive post-menopausal life phase. Great apes typically are not weaned before age 4 to 5, and may still be suckling until puberty, whereas humans under conditions of natural fertility usually wean by age 2 to 3. Consequently, human pregnancies can occur twice or more frequently than in great apes. The young

child requires considerable support for feeding and care, which is uniquely provided by the father and other members of the social group. Rarely do great ape fathers give any direct child care. Humans are also unique in multigenerational social support that reduces mortality of mothers and their children (Hooper et al., this volume). The grandmother hypothesis proposes that the uniquely human post-menopausal phase was important to the evolution of humans' long lifespans by enabling maternal support (Hawkes and Coxworth, 2013). More broadly, resource transfer and alloparenting are known to involve many individuals in a community besides grandmothers (Hooper et al., this volume).

Social Hierarchy in Darwinian Outcomes

Social status is also a major factor in morbidity, mortality, and lifespan across the animal kingdom. By morbidity, we mean organ damage, infections, and chronic disease. We present selected examples of the character of social hierarchies in social insects and primates to help calibrate the even greater complexities of human social status, disease, disability, and lifespan.

Honey Bees. The honey bee (*Apis mellifera*) is an archetypal example of genomic programming for social classes with major differences of mortality and lifespan. Alternate life histories of honey bees include short-lived workers with lifespans of weeks to months and queens that live several years (Rueppell et al., 2007; Finch, 1990; Flatt et al., 2013). Worker bees maintain the queen by providing housekeeping for hygiene, caregiving, and nest repair. As hive bees, their mortality is low. However, in their foraging phase as field bees, worker bee mortality increases rapidly with lifespans of only days (Omholt, 1988; Omholt and Amdam, 2004; Rueppell et al., 2007). The timing of foraging flights varies widely. If born in the late summer, worker bees over-winter and delay foraging until the following spring. If born in the later spring, foraging begins much sooner. Mortality of field bees is attributed to external risk factors of predation and "wear-and-tear" on irreplaceable brittle wing parts and nutrient reserves. Resistance to oxidative stress, starvation, and heat also decline (Remolina et al., 2007), while aging pigment also rapidly increases in brain neurons (Flatt et al., 2013). The relationship of foraging flights to mortality was shown by experimental manipulation (Rueppell et al., 2007; Münch et al., 2013).

The plasticity of honey bee life histories joins numerous examples of polyphenisms, or phenotypes with different lengths of developmental and adult stages that are adaptive for particular environments, as discussed in a recent synthesis by Flatt et al. (2013). The broader role of social class in life history polyphenisms, however, merits further inquiry. In the case of social insects, the social castes are determined from genetically identical eggs by

micronutrients in royal jelly fed during development. However, even within these developmentally defined castes, workers with identical genes show individual variations in their preferences for tending larvae destined to be workers or queens (Robinson et al., 1994). Thus even the most rigidly defined castes show some degree of developmental plasticity (Finch and Kirkwood, 2000).

When considering caste systems in the context of the morphospace, it is natural to think of the castes as being in an order relationship, somewhat like human occupational hierarchies. However, this is decidedly not the case, as communication within and between castes, differing according to a particular task being executed, is a fundamental feature of honey bee and other social insect communities. To illustrate, imagine a network with five tasks (pollen dancing, pollen foraging, pollen storage, feeding pollen, and brood care) as nodes and directed arrows representing types of workers (Forager, Recruit, Nurse, Brood) transmitting information. Four of the tasks (pollen foraging, pollen storage, feeding pollen, and brood care) are not orderable. However, they can be collapsed into a single large node, giving a condensed graph with pollen dancing as the top task with recruits signaling to foragers in the condensed set of nodes via the task, pollen foraging. The condensed graph would be T = 0, F = 0, and O = 1 in morphospace. If individual bees were used as nodes rather than tasks, the result would be a very complex set of interconnections (i.e., communication paths) whose overall position in the morphospace is unclear due to the current unavailability of a technology to measure such a network in detail.

Ants. The caste system in ants is specialized to tasks, and the activities of all individuals are in service of the needs of the entire colony. There is no chain of command, and any ant can communicate with any other ant. Most importantly, ants in worker castes communicate in a feedback fashion with a queen, who also sends direct messages to them. In a word, an ant community is replete with multiple channels of communication in the form of a heterarchy, in which each type of individual can communicate with every other type of individual. This is a vast oversimplification of the caste structure and modes of communication in ant colonies. However, a heterarchical structure with dense communication interconnections between ants is generic (Wilson and Hölldobler, 1988). The communication system for diverse ant species at the individual and community levels is discussed by Hölldobler and Wilson (2009).

Baboons and Chimpanzees. Primate social status is strongly associated with morbidity and mortality in field studies of baboons and chimpanzees. Because of ecological variation, we note the location of each population. Female chacma baboons from Moremi have a range of lifespans that differ

based on the stability of social bonds (Silk et al., 2010). High-ranking females live about 35 percent longer than the bottom third, mainly due to social bond stability. Comparisons with human populations are not appropriate because field studies offer small samples and because field mortality rates are much above modern humans (Hill et al., 2001; Bronikowski et al., 2011).

The very coarse description of female chacma baboons needs to be supplemented by network data over time to show bond formation and dissolution at the level of individual animals. This would facilitate an analysis of interaction structure over time where, for example, detection of block model representations (White et al., 1976) of the full troop would allow placement of baboons in a more behaviorally driven set of positions in the morphospace, and over time. This would give a more nuanced association between mortality and troop hierarchy than is possible with current data.

Female high-ranking chimpanzees from Gombe also tend to live longer (Pusey et al., 1997) and also show robust associations of maternal rank with their offspring. High maternal rank increased survival of offspring ages over a 2-fold range; their daughters also grow faster, mature earlier, and have more offspring (Pusey et al., 1997). High rank also shortened intervals between births (Jones et al., 2010). These reproductive advantages are attributed to better access to food or protection from aggression by the higher ranking. Most deaths at Gombe and elsewhere are attributed to infectious disease (Lonsdorf et al., 2006). Infanticide is another cause: several infants of the lower ranked mothers were killed by higher rank females and their daughters (Pusey et al., 1997).

Higher social status was associated with the parasite load in several populations, based on fecal counts of protozoans and eggs of parasitic worms. In Amboseli baboons, worm egg numbers varied inversely with rank in both sexes, with a greater load in females (Hausfater and Watson, 1976). However, infections in males showed the opposite relationship: As indicated by coughing and diarrhea, infections were more common in lower-ranking males, including older individuals that tend to be low ranking (Archie et al., 2012). While female baboons from the Namib Desert also had more worms and protozoans than males, neither sex showed association of parasite load with social status (Benavides et al., 2012). The Kibale alpha male chimpanzees had more worms, ranging 2-fold across rank and positively associated with cortisol (Muehlenbein, 2006; Muelhenbein and Watts, 2010). Alpha males may receive more grooming than other males (Newton-Fisher, 2002), thus acquiring health benefits through removal of ectoparasites and stress reduction (Sapolsky, 2005).

These associations of rank and parasite load suggest rank-differences in immunity. A large literature documents that resistance to infections and the capacity for wound-healing are influenced by steroids, particularly cortisol,

which can be immunosuppressive. Cortisol has been shown to be elevated in high-ranking baboon males (Muller and Wrangham, 2004a, 2004b). However, within the complex social hierarchy, cortisol varies in relation to degrees of social challenge and stress (Sapolsky, 2005; Gesquiere et al., 2011), a topic that would be better investigated by monitoring dyadic interactions among members of a troop over time. Further analyses of baboon female associations with rank and disability and mortality are forthcoming (Archie and Altmann, personal communication).

Intriguingly, skin wound healing was 25 percent faster in high-ranking male baboons than in lower ranks (Archie et al., 2012). Within the highest ranks, the alpha and beta males did not differ in healing rates, which was unexpected because alphas have lower cortisol than betas. Evolutionary flexibility in hormones and immune function may arise through genetic variation in steroid influences on specific immune functions that include pathogen clearance and tissue regeneration. Evidence for these pathways is the association of allele-specific differences of gene expression in white blood cells with social connectedness (Runcie et al., 2013).

Humans. Despite the huge advances in public health and social services, social status remains a strong influence on morbidity and mortality (Crimmins et al., 2009; Marmot and Sapolsky, this volume). SES effects are strongly shown for both genders in age-related morbidities and survival. Analysis of the multiethnic U.S.-wide National Health and Nutrition Examination Survey, III (NHANES III) Sample (Crimmins et al., 2009) showed that poverty is consistently associated with shorter lifespan, mean and maximum, across a range of vascular disease risk factors. Similar social rank differences are present across the world, from the least to the most developed countries (Marmot and Sapolsky, this volume). The same phenomenon was also shown in the 19th-century study of Humphreys (1887) noted above. Despite the stark differences in operationalization of SES, the basic qualitative findings are quite robust. The dichotomy of poor versus non-poor in Crimmins et al. (2009) was not intended to fully represent the gradations of LE across the complex continuum of hierarchies of human societies.

Social and behavioral factors are the major focus in analyzing these associations with morbidity and mortality. Figure 7-1 outlines some of the pathways by which sociobehavioral traits are transduced into outcomes of morbidity and mortality (Crimmins and Finch, 2006).

Boxes labeled “Infection(s)” and “Diet” also include variable exposure within an SES hierarchy. The subsidiary boxes are associated with consequences of infection(s) and dietary quantity/quality, and drugs and medications. Before antibiotics became generally available after 1950, exposure to infections and co-infections was greater in the lower classes. Moreover, concurrent malnutrition exacerbated the cross-class differences, with associated

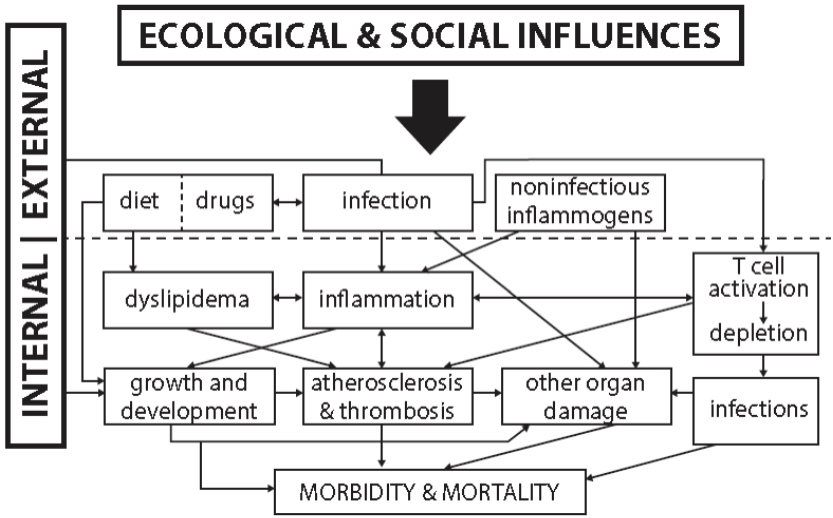

FIGURE 7-1 External and internal pathways to morbidity and mortality.
SOURCE: Expanded from Crimmins and Finch (2006) to include ecological and social influences.

morbidity and mortality via the pathways shown in the figure. Indeed, increased inflammation, dyslipidemia, atherosclerosis and thrombosis, and other organ damage, together with retarded growth and development, were a direct consequence of increased mono- and co-infection coupled to increasingly inadequate diets in lower SES.

As a specific example, in the Jewish Pale of Settlement in Eastern Europe from the 1500s into the early 20th century, infant and child mortality were very high in the lower tier of wealth, essentially due to infectious diseases and malnutrition (Weinryb, 1972). An interesting manifestation of this was the rapid increase in gene frequency of a mutation for idiopathic torsion dystonia in the higher wealth tier (Risch et al., 1995, 2003). The origin of the mutation is traceable into the 1600s, and it has been propagated into the present by genetic drift almost entirely via the elites, who had much larger families with greater survival than the lower classes.

When did SES differences in LE, mortality, and morbidity emerge? It is not possible to know, because there were no statistically valid data for mortality of populations before the 17th century (Harlow and Laurence, 2002; Hoppa and Vaupel, 2002; Scheidel, 2007; Woods, 2007; Bengtsson and van Poppell, 2011). Only Sweden has national comprehensive birth and death records from the mid-18th century. Moreover, there are deep

uncertainties in the comprehensiveness and reliability of public and private records, particularly for lower status groups. Skeletal age estimates of adults are arguably limited to +/– 5 years after age 30, while samples are subject to bone loss from acidic soils and by burial and funerary practices, particularly for infants (Finch, 2010, notes 42-45). Records for the poorest are even more elusive, particularly for criminals sentenced to work in mines or row in galleys, and for the urban homeless. The mortality of the dispraised lowest tier could be extremely high. Two millennia ago, Pliny the Younger told of varying mortality, comparing his Tuscany summer estate to pestilent Rome: ". . . My servants are healthier here. . . . I have not lost a single one I brought with me. . . . You can see grandfathers and great-grandfathers of living men and hear stories of the past" (Pliny the Younger, Letter to Domitius Appolinaris, B. Radice trans., 1969). Caveats granted, records of a few special groups before the 17th century suggest that most elites incurred the same high mortality as other groups in the preindustrial era, from rampant infections (Bengtsson and van Poppell, 2011).

The British peerage may have the deepest historical record for a self-defined society, for some families extending back to 740 CE. Two analyses show gradual increase of aristocrats' lifespans after 1700, presaging improvements in the general population (Harris, 2004, based on Hollingsworth, 1964; Westendorp and Kirkwood, 1998).

By the mid-1600s, stable SES differences in mortality were emerging for those of sufficient status to be recognized as permanent residents. A strong case is the city of Geneva, which has kept comprehensive records since the 1550s. By 1625-1644, the upper class LE was about 10 years longer for men and women than the middle and lower classes (Schumacher and Oris, 2011, from Perrenoud, 1975). Even so, these Geneva elites' life expectancies at birth were 37 years (male) to 38 (female), that is, slightly below pre-industrial Sweden and 20th century forager-farmers with limited access to modern medicine (Gurven et al., 2007).

Since the mid-17th century, SES differences in LE have emerged across Europe, with much SES heterogeneity and many fluctuations (Bengtsson and van Poppell 2011; Schumacher and Oris, 2011). Although elites had better diets than the general populace (McKeown, 1976; Fogel, 2004; Harris, 2004), health and good diet may not be sufficiently protective in highly infectious environments. A recent example is the influenza pandemic of 1918, where the healthiest adult group of men and women, ages 20 to 40, had the highest mortality (Morens and Fauci, 2009). We provisionally conclude that SES differences in LE were sporadic in the preindustrial world and did not appear to have stabilized across populations until the 20th century when infectious mortality was greatly reduced.

Since the mid-1800s, the increasing LE began to grow faster for women than men in the most developed countries, from historical baseline of

< 1 year difference, to > 3 years by 1970 (Barford et al., 2006; Thorslund et al., 2013). Although the differences have narrowed in the richer countries, all countries of the world now have excess female LE. The sex differences in lifespan are largely a 20th-century phenomenon and emerged as infectious causes of death fell from > 70 percent of mortality to < 5 percent. Now, cancer and vascular disease are definitively the main morbidities and causes of death in both genders.

In the longitudinal U.S. Health and Retirement Study, for all SES, women had more morbidities at later ages, despite their longer LE (Ailshire and Crimmins, 2013). Low SES was associated with poorer balance, grip strength, and walking speed, and higher blood pressure at later ages, which predicted higher mortality in the following 3 years (Ailshire and Crimmins, 2013). For ages 80 and greater, health-damaging behaviors (alcohol, smoking, low physical activity) accounted for most (68 percent) of the excess mortality with low SES (Nandi et al., 2014).

Besides gender differences in smoking, diet, exercise, and health-promoting behaviors, there may be some underlying biological factors. A growing literature also documents relevant sex differences in animal models studied in vitro, for example, vasoresponses (Zhang et al., 2012), and resistance of cardiomyocytes to hypoxia, which is greater in female-derived primary cultures (Ross and Howlett, 2012). We anticipate a biological substratum in sex differences of chronic disease incidence and progression, in which gene x environment (GxE) effects differ by SES. Invertebrate models show social influences on lifespan through pheromones and sex differences in the p53 gene tumor-suppressor (Finch and Tower, 2014).

FUTURE HUMAN AGING

What lies ahead? How future humans will experience aging may vary widely within populations because of environmental changes and because of access to expansive medical advances. There is also likely to be much greater emphasis on health as defined in the positive sense, and not just as the absence of illness, disease, and disability. We first consider the range of concepts pertaining to "health."

"Health" as the Absence of Illness, Disease, and Disability

Human health is undergoing huge improvements consequential to increased availability of food and the control of infections, entering into a post-Darwinian era with much less selection for maximizing reproduction. These changes began 250 years ago with progressive but sporadic improvements in nutrition and sanitation, followed by medical and hygienic advances in the later 19th century, and lastly by antibiotics after 1950 (Finch

and Crimmins, 2004). In developed nations, most adults expect only the occasional acute infection, while 2 billion people still carry parasitic worms (World Health Organization, 2013).

But! The reproductive success of *Homo sapiens* prior to the industrial age depended on its capacity for enduring chronic infections of microbial and invertebrate parasites, as well as nutritional fluctuations. A contemporary example is the Tsimane, indigenous forager-farmers of the Amazon basin, who until recently lived under minimal hygiene and medicine. Their infant mortality of 10 percent or higher (Gurven et al., 2007) and LE of 42 years are similar to pre-industrial Sweden in 1800. Infections were rampant and white blood cell counts were 3-fold higher than the U.S. average (Vasunilashorn et al., 2010). Tsimane adults have frequent gastrointestinal and respiratory conditions that keep them bed-bound several days per month (Tanner and Rosinger, in press) and additionally carry an everage of 1.3 different species of worms and protozoans (Vasulinashorn et al., 2010). These disease burdens would be considered unhealthy and immediately treated in developed countries, as indeed they are during interviews of the Tsimane by anthropologists. Yet, Tsimane women maintained a very high fertility of an average of 9.1 live births (Gurven et al., 2007). The global growth of human populations during the Neolithic, despite the burden of infections, suggests that the Tsimane were typical in maintaining high fertility under conditions of high infection and fluctuating food availability. Thus, the expectation of life relatively free of infection through old age is a modern concept.

It is useful to compare the absence-of-disease concept of health with the historical usage of this word in the English language. Our word "health" draws from the Old English *hælth*, with positive connotation of well-being and fitness (Oxford English Dictionary). The operationalization of "health" thus leads to the consideration of well-being, a topic with an extensive literature (Ryff and Singer, 1998, 2008; Ryff, 2014). Further, the founding charter of the World Health Organization (WHO) defined health as a "state of complete physical, mental and social well-being and not just the absence of disease or infirmity" (World Health Organization, 1948). However, most "health statistics" during the 20th century have mainly focused on illness, disease, and death (morbidity and mortality). Canada is a leading counter-example, having introduced criteria for positive health and well-being two decades ago in national health statistics (Canadian Population Health Initiative, 2009). Ongoing research is addressing biological substrates of well-being (Ryff et al., 2006; Ryff, 2014).

How can health be conceptualized for a post-Darwinian context wherein reproductive success is no longer a criterion for viability, and when long lives of good health—in the WHO sense of the word—are an increasingly common goal? We suggest that concepts of health at later ages will

require refinement beyond the broad WHO formulation, with particular emphasis on SES and gender, as well as pathways through multiple hierarchies experienced at different time scales. As examples, despite their longer lifespans, older U.S. women are more likely to be obese than men (Wang and Beydoun, 2007) and are 50 percent more likely to survive a heart attack (Lawlor et al., 2001). Because the prevalence of chronic conditions accelerates after age 60, almost no one reaches later ages without some preclinical condition. Among centenarians, > 75 percent have clinical-grade dementia (Perls, 2004). Yet, the majority of centenarians report happiness (Jopp and Rott, 2006). More precise taxonomies of health lie in the future. Meanwhile, definitions of health and well-being are operationalized by vague norms for each age group.

We anticipate that increasing availability of social and economic network data will result in much more nuanced taxonomies of hierarchies that will facilitate classification of communities into the morphospace outlined above, as well as representing community-level dynamics via trajectories in the morphospace. Associating position in these more refined hierarchies with health status and disease/disability condition as a function of age will enable more comprehensive analyses of hierarchy and health and disease outcomes than heretofore.

Aging Futures

Lastly we ponder the future of human lifespans. Humans are entering a post-Darwinian world with minimal natural selection for resistance to acute and chronic infections, and increasing concern about chronic noninfectious conditions. As the 21st century advances, most evidence points to further global reductions of chronic parasitic diseases and of childhood infections. While ongoing efforts seem likely to eliminate most infectious scourges of the past, it is likely that the very poor will remain at greater risk (Hotez, 2008). Family size is shrinking, with negative population growth in many countries. With the increasing proportions of elderly, noninfectious disease is the main concern associated with heart disease, cancer, and mental decline. Later ages are dominated by women whose LE is now greater than men in all countries.

Could there be unexpected consequences from the relaxation of natural selection for resistance to infections? Could the alleles that conferred resistance in early life have delayed adverse consequences to later ages? This possibility extends the "antagonistic pleiotropy hypothesis" of aging. Natural selection tends to favor youth over older ages because evolutionary pressures are greatest on the reproductive ages (Haldane, 1941; Medawar, 1952; Williams, 1957). Thus, pleiotropic gene variants that enhance reproduction in young adults can have delayed adverse consequences at later ages

when natural selection is weaker. Furthermore, with relaxation of natural selection for resistance to infections, previously maladaptive alleles could enter the gene pool with unknown effects. Unfortunately, the earliest population samples available for genetics are a century after the major declines in infectious mortality.

Additionally, environmental changes are occurring. Globally, humanity faces climate change and increasing air pollution from projected global increases in fossil fuels (Finch et al., 2014). Already, the health elite are protected by living and working in buildings with filtered air. Needs for air conditioning will follow warming, adding to increasing fossil fuel use for power, as well as personal vehicles. Access to expensive medical technology will continue to be greater for health elites. The U.N. Intergovernmental Panel on Climate Change (2014) predicts increased poverty throughout the world, even in high-income countries, from rising food prices. Thus we anticipate that the already large SES differentials in health and LE will further expand. Moreover, new Darwinian selection pressures from global environmental challenges may arise, with differential SES reproductive responses. The social network analysis sketched above can be further developed to track emergent trajectories of social support that we believe will remain a key to human health and well-being across the gradients of SES and LE.

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8

Social and Economic Underpinnings of Human Biodemography

Paul L. Hooper, Michael Gurven, and Hillard Kaplan

INTRODUCTION

The human species is an outlier in terms of demographic characteristics including lifespan, the duration of development, and menopause (Bogin and Smith, 1996; Gurven and Kaplan, 2007; Alberts et al., 2013). Human social relationships—including support from extended family, cooperative pair-bonds between men and women, biparental care, and extensive cooperation between non-relatives—are likewise features that set humans apart from many other primates and mammals (Lancaster and Lancaster, 1983; Hill et al., 2009; Hrdy, 2009; Jaeggi and Gurven, 2013). It is increasingly clear that patterns of human demography and sociality are interdependent and mutually reinforcing, making it likely that they co-evolved during humans' evolutionary history. In this paper, we present a framework for investigating the relevant causal links between ecology, social structure, and biodemography that are essential to explaining the unique evolutionary trajectory of the species. This framework aims to explain both humans' unique demographic and social characteristics relative to other taxa, as well as variation in these characteristics within and across human societies.

Our proposal is that three distinctive forms of social relationships evolved and were likely to have been present in most populations prior to the advent of agriculture: (1) kin-based altruism, with net downward transfers of food energy and other forms of assistance across generations; (2) complementary specialization of labor by men and women, and cooperation by couples in reproduction, childcare, household labor, and economic

production; and (3) cooperation and reciprocal assistance among related and unrelated individuals to buffer shortfalls and/or to coordinate efforts in food acquisition (see Figure 8-1). We posit that these social relationships are linked responses to the particular ecological niche to which humans are adapted. We also posit that those three classes of relationships have significant impacts on health and well-being throughout the lifecourse. As a result, they are likely to have played a critical role affecting natural selection on rates of aging and reproduction, and the ability to escape death from economic shortfalls, injury, or illness.

Given that we cannot directly observe the social relationships, demographic characteristics, and behavioral patterns of prehistoric populations during human evolution, we are reliant on data derived from the paleoarcheological record, primatology, and the study of contemporary human populations. The quantitative study of extant human groups engaged in foraging or a mix of foraging and rudimentary horticulture (forager-horticulturalists) in recent decades, in particular, has provided a more detailed understanding of the relationships between social, economic, and demographic variables under pre-modern circumstances than has previously been available. There have been both advantages and disadvantages of this approach.

The disadvantages derive from the fact that contemporary populations are not frozen relics of the past. In fact, it is always the case that by the

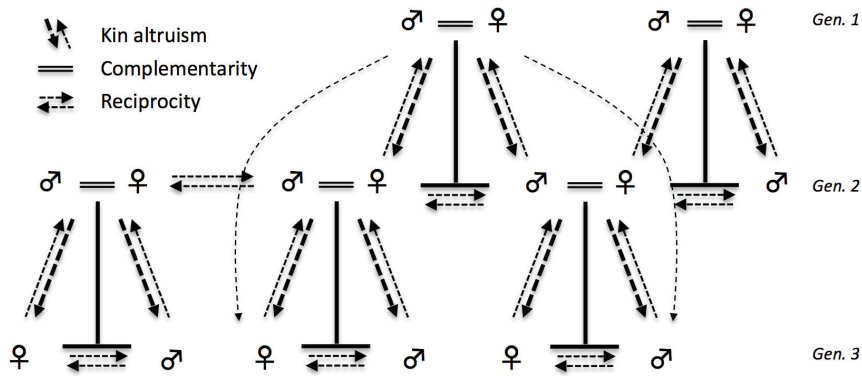

FIGURE 8-1 Evolved modal human social organization.
NOTE: The dominant pattern of relationships based on kin altruism, complementarity, and reciprocity are indicated by the dashed arrows and double solid lines: kinship motivates net downward flows of resources within families (vertical dashed arrows); complementarity promotes cooperative division of labor within pair bonds (double solid lines); and reciprocity supports bidirectional exchange within and between families (horizontal dashed lines).

time foraging populations are studied by scientists, their lifestyle and other cultural characteristics are undergoing change. Moreover, such populations are not randomly distributed in geographical space, but tend to live in remote areas that have had less potential for economic development. Therefore, they represent a nonrandom subset of the lifestyles that existed in places where developed states now dominate the landscape (Headland and Reid, 1991; Kelly, 1995). States and empires have also had the effect of repressing violence between small-scale groups, which has made it difficult to assess the impact of interpersonal and intergroup violence on life histories and behavior under pre-modern conditions (but see Patton, 2000; Wrangham et al. 2006; Hill et al., 2007; Sussman and Cloninger, 2011 for explicit treatments). Global environments have also changed in ways that are likely to have direct effects on the parameters of interest, particularly with respect to the distribution of plant and animal species important in forager diets, and pathogens affecting morbidity and mortality. Finally, all of the groups that have been extensively studied have experienced a unique set of historical forces in recent decades with differential impacts on current conditions and lifestyles (see, for example, Hill and Hurtado, 1996, on the Aché in Paraguay, compared with Headland, 1986, on the Agta in the Philippines).

The advantages derive from the fact it is possible to collect detailed, quantitative data on reproduction, morbidity, mortality, transfers of food and other forms of assistance, conflict, and social status in extant small-scale human communities. Age- and sex-specific patterns of fertility and mortality, work, food production and consumption, food sharing, childcare, and family relationships have been extensively studied in a sample of these populations in Africa, Australia, the Philippines, and South America. Our goal in this paper is to synthesize what appear to be the modal—and sometimes apparently universal—patterns in such groups within a coherent theoretical framework. The common patterns found in populations that have experienced such divergent histories in a variety of ecologies with no recent common cultural ties are likely to be robust features of humans while engaging in foraging-based lifestyles. Such common threads may also indicate their historical depth in human evolution.

In the following sections, we provide a characterization of modal patterns of social organization and demography among human foragers. For each of the key social relationships introduced above—kin-based altruism within families, cooperative pair-bonds, and reciprocal cooperation—we discuss insights derived from evolutionary economic models, and review available evidence from the study of modern human foragers and other small-scale human societies. We follow this with a characterization of variation within and away from modal patterns of social structure and demography among foragers and other preindustrial human groups. We

conclude by discussing the relevance of these patterns for understanding the evolutionary past and present behavior of the human species.

KIN-BASED ALTRUISM, INTERGENERATIONAL TRANSFERS, AND LIFE HISTORY

A crucial aspect of the economic system of human foragers is that production activities are skill-intensive and require a long investment process. Although both humans and chimpanzees (humans' closest primate relative) are both omnivores, the composition of their diets is radically different. Data on diet from chimpanzees in the Gombe reserve in Tanzania indicate that about 95 percent of calories are derived from leaves and fruit. In contrast, for the sample of 10 human foraging societies for which quantitative data are available, fruits constitute an average of only 10 percent of the diet. The remaining 90 percent calories are derived from more difficult-to-acquire hunted and extracted (e.g., nuts, tubers, honey) foods, which are only about 5 percent of the chimpanzee diet (see Kaplan et al., 2000, for data sources).

The nature of the production and processing of foods has implications for how long it takes to become efficient at foraging and for the age at which juveniles become nutritionally independent. Efficiency in activities based on skill development tends to increase with age over a longer period compared with activities requiring less experience. This is pertinent for most traditional forms of hunting, as well as many skill-intensive methods of extraction and processing. The return rates of Aché and Tsimane hunters, for instance, continue to increase across the first three decades of life, and peak remarkably late, in the 30s and 40s, due to the importance of experience and skill development over physical strength alone (Walker et al., 2002; Gurven et al., 2006). The importance of skill-acquisition and learning also tends to reduce productivity early in life, as young invest time and energy in developing the brains, bodies, and skills necessary for later success. Children thus remain nutritionally dependent on parents until approximately 18-20 years of age among the foragers and forager-horticulturalists for which such data exist. Chimpanzee offspring, in contrast, begin to supplement the energy they receive from lactation with their own foraging efforts during their first or second year of life, and are largely energy self-sufficient by age 5 (Kaplan et al., 2000).

Figure 8-2 shows age-specific food production, consumption, and their net (production minus consumption) for Tsimane forager-horticulturalists averaged over males and females (Gurven et al., 2012). During infancy, childhood, and adolescence, individuals run large net deficits in production (more calories consumed than produced each day); during adulthood, however, individuals produce large net surpluses (more calories produced than

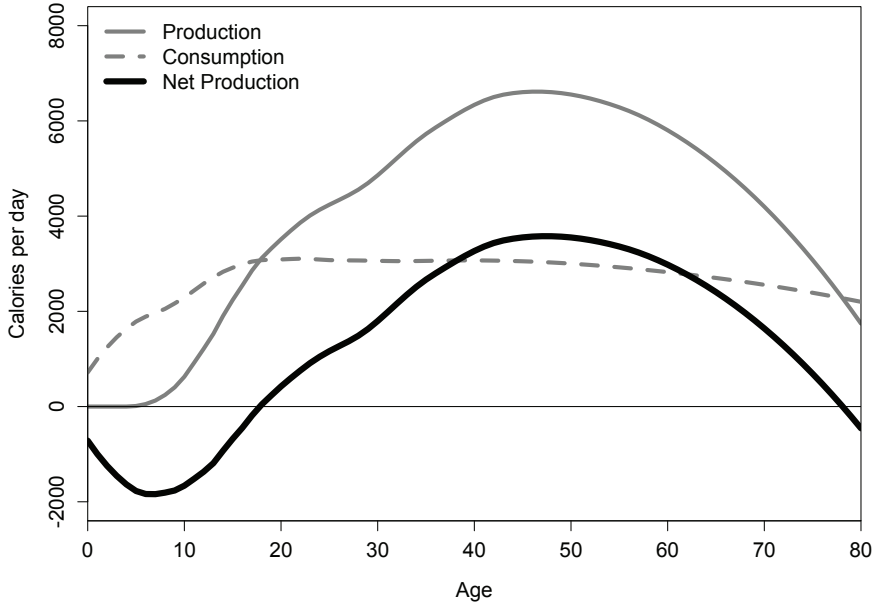

FIGURE 8-2 Mean production, consumption, and net production (production minus consumption) of food per day as a function of age among Tsimane forager-horticulturalists.
SOURCE: Gurven et al. (2012).

consumed), with a peak in net production in the beginning of middle age. Similar curves—with some variation in ages of peak production—have been reported for Aché, Hiwi, !Kung, and Hadza foragers, as well as for Piro and Machiguenga forager-horticulturalists (Gurven and Kaplan, 2006; Hill and Hurtado, 2009; Howell, 2010; Marlowe, 2010).[1] As a result of the slow accumulation of human capital across life (particularly skills, experience, and ability), there are larger differences in productivity between young and old among humans than in other primates or mammals (an exception may be killer whales: Rendell and Whitehead, 2001; Foote, 2008).

Observed life cycles of production among hunter-gatherers are fundamentally interlinked with human biodemographic characteristics, including: (1) longevity; (2) intergenerational transfers; and (3) post-reproductive survival. Analytical models of life history evolution show that exogenous shifts

[1]Because most of these data are cross-sectional, secular trends may confuse age trends. It may be, for instance, that younger cohorts are healthier but less skilled at traditional activities; the former would tend to exaggerate apparent aging, while the latter would exaggerate the importance of lifelong learning.

in economic production to older ages due to learning result in selection for increased investment in survival (Kaplan and Robson, 2002; Robson and Kaplan, 2003). The evidence for the longevity of foragers under pre-modern conditions compared with wild chimpanzees has been reviewed in Gurven and Kaplan (2007). Available data show that conditional on surviving to age 15, a chimpanzee has an expectation of an additional 13 years of life, whereas foragers show an expectation of an additional 40 or so years of life (with an expected age of death in the later 50s). The contrast is even more extreme at age 45, when most women have ceased to reproduce: whereas a chimpanzee can expect to live less than an additional 5 years, a female forager can be expected to live an additional 22 years, to age 67. On average, the modal age of death (i.e., the age with the highest density of deaths) for those surviving to adulthood occurs sometime around age 70 in extant foraging populations.

Second, the age-schedules of productivity, mortality, and reproduction also affect the flow of resources between generations because they determine the distribution of individuals with caloric deficits and surpluses. Inclusive fitness theory provides a specific means of understanding transfers between kin as a function of differential productive ability and need (Hooper et al., 2014). This approach predicts that transfers are determined by the interaction of two factors: (1) the relative gains to the recipient compared with the costs to the donor, which are, in turn, determined by the productivity and consumption needs of individuals and families; and (2) their degree of kinship in terms of the likelihood of sharing genes by recent common descent. Early in life, when individuals are relatively inefficient producers and cannot meet their energy requirements through their own effort, the marginal benefit of receiving calories from others is higher. After efficiency increases at older ages, on the other hand, the marginal cost of giving away calories is reduced due to high productivity and diminishing returns to personal consumption. These effects are expected to interact positively with the degree of relatedness.

This logic provides a basis for understanding variation in parental investment, and net transfers of energy, time, and effort between kin more generally. In humans, asymmetries in productivity combine with the motivation to assist kin to produce systematic and predictable flows of resources from older to younger generations within families. Figure 8-3, adapted from Hooper (2011), illustrates the flow of food across three generations within Tsimane extended families. It plots the expectations of caloric transfers among older individuals (grandparental generation), their adult offspring, and grandchildren. The left-hand panel plots the gross transfers in either direction, while the right-hand panel presents the net transfers (gross transfer from individual *i* to individual *j* minus the gross transfer from *j* to *i*). The right-hand panel shows that net flows tend to be downward. The largest

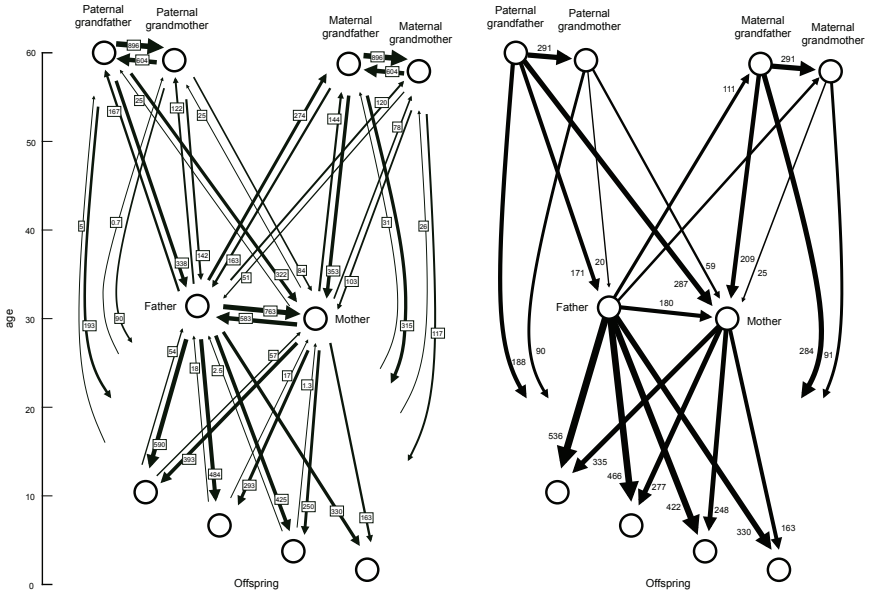

FIGURE 8-3 Mean gross food transfers (left panel) and net food transfers (right panel) within Tsimane extended families.
SOURCE: Hooper (2011).

flows are within nuclear families, from parents to children, but there are also significant flows downward from older individuals to families of adult children and younger siblings. Among the Tsimane, mean transfers are net downward even through the seventh decade of life (Hooper et al., 2014).

While representations of transfers at this level of detail are not available in published data for other groups (but for the Hadza, see Hawkes et al., 1989, 1997; Wood and Marlowe, 2013), evidence suggests that transfers tend to flow among kin (reviewed in Gurven, 2004) and that downward transfers within families appear to be universal in all societies for which transfers have been measured (reviewed in Lee, 2007). In all observed cases, foragers remain net producers after they have ceased to reproduce, implying downward net transfers (Kaplan, 1994; Kaplan et al., 2000; Gurven and Kaplan, 2006; Hill and Hurtado, 2009; Howell, 2010; Marlowe, 2010). While food transfers outside lactation are much more limited in other primate species, sharing is more common for high-quality difficult-to-acquire foods and occurs principally from mothers to offspring (see Silk, 1978; Price and Feistner, 1993; Nishida and Turner, 1996; Jaeggi et al., 2008; Jaeggi and Van Schaik, 2011 for a cross-species analysis). Human foragers have taken this tendency to an outlying extreme.

Third, because transfers from older adults appear to support their adult children's fertility and grandchildren, the life history of production and consumption also sheds light on the evolutionary economics of menopause (Williams, 1957; Lancaster and King, 1985; Hawkes et al., 1998; Kaplan et al., 2010). If all else were held constant but women continued to reproduce until older ages (e.g., age 55), lineages would find themselves in net caloric deficit. Either age-specific production rates or age-specific fertility rates would have to change (Kaplan et al., 2010). "Premature" reproductive cessation can then be thought of as an emphasis on economic contributions to younger generations at the cost of continued production of offspring. Given the similarities between chimpanzees and humans in age of menopause, it has been argued that selection may have favored lengthening of lifespan rather than menopause itself (see, for example, Ellison and Ottinger, this volume). In our view, both menopause and lifespan extension require explanation. Even if human-typical rates of reproductive decline were established prior to selection for lifespan extension in the human lineage, it is still necessary to explain why there would not be selection for continued reproductive function once ancestral people were living longer.

A final striking feature of the caloric transfers illustrated in Figure 8-3 is the economic role that men play, as husbands, fathers, and grandfathers. In general, there are positive net energy transfers from men to their wives, greater transfers to children from fathers than from mothers, and greater transfers to grandchildren from grandfathers than from grandmothers. To shed light on these patterns of investment, and their relationship with mating effort and mate choice, the next section addresses sex roles and mating systems in foraging societies.

COMPLEMENTARITIES, SEX ROLES, AND LIFE HISTORY

The evolution of patterns of mating and parental investment among humans can be understood in light of ecological factors underlying variation in animal mating systems more generally. For females (or males in sex-role reversed species), theory in evolutionary biology emphasizes fitness impacts of choice for male genetic quality versus paternal investment. For males, it focuses on fitness impacts of paternal investment versus investments in mating effort—for example, in displays of genetic quality or contests with other males. We propose that the relative weights of these fitness effects depends on the nature of tradeoffs between acquiring energy (i.e., food) and providing care to offspring in the time budgets of parents. They also depend on the degree of complementarity between investments of care and energy, and between these investments and genetic quality in determining offspring success (for relevant background and evolutionary-economic models, see Becker, 1973; Maynard Smith, 1977; Grafen and Sibly, 1978;

Lazarus, 1990; Clutton Brock, 1991; Kokko and Johnstone, 2002; Kokko and Jennions, 2008; Bowles and Borgerhoff Mulder, 2012).

In this framework, the fitness of offspring (W) can be considered a function of the inputs of genes (G), energy (E), and care (C) provided by female (f) and male (m) parents: $W = w(G_f, G_m, E_f, E_m, C_f, C_m)$. Complementarities in these inputs are reflected in the direction of their cross-partial derivatives. If the cross-partials are positive (i.e., $W''_{GE} > 0$, $W''_{GC} > 0$, or $W''_{EC} > 0$), this reflects positive complementarities between inputs. For example, a positive cross-partial between genetic quality and energy implies that an increase in energy will have a larger fitness impact on an offspring of higher genetic quality, and vice versa. In the case of mammals, who provision their offspring through lactation, or birds, who provision offspring with food, there are likely to be especially strong complementarities between energy and care. A perfectly protected offspring who receives no energy will still likely die, as will a well-fed offspring that is not protected from predators. The problem facing each sex is to optimize these inputs in the face of a time budget constraint, $T = t(t_E,t_C,t_O)$, reflecting the division of time between acquiring energy, providing care, and other activities (such as mating effort).

We hypothesize that patterns of mating and parental investment respond to ecological conditions affecting complementarities and trade-offs between providing care and energy. Figure 8-4 depicts two different kinds of ecological conditions affecting the gains from biparental investment. Figure 8-4a represents what we hypothesize to be the modal mammalian pattern, with a convex budget constraint for individual parents (the solid black line) reflecting a relatively "easy" tradeoff between the production of care and energy. Here, a single parent is capable of providing both goods at a reasonably high level simultaneously, and increased specialization in either care or energy results in diminishing marginal returns.

Most (particularly, female) mammals engage in some strategy that allows for protecting young while foraging. This is accomplished by caching young in hidden burrows (practiced by most rodents), having them accompany on foot (practiced by most herbivores), or by carrying them (practiced by all primates). This means that, compared with the mother that combines care and energy acquisition, the mother who feeds exclusively at the expense of any protection will not get much more food, and the mother who exclusively protects at the expense of energy acquisition will not provide much more protection. These conditions reduce the gains from adding a second parent's investments relative to what can be acheived by a single parent alone (compare points A and C in Figure 8-4a). This would hold especially where the type of foods that are consumed come in small, easy-to-acquire packages (like blades of grass or leaves) that are not efficiently shared. Under these conditions, we predict that the gains to females from choosing males with higher genetic quality will be greater than from choos-

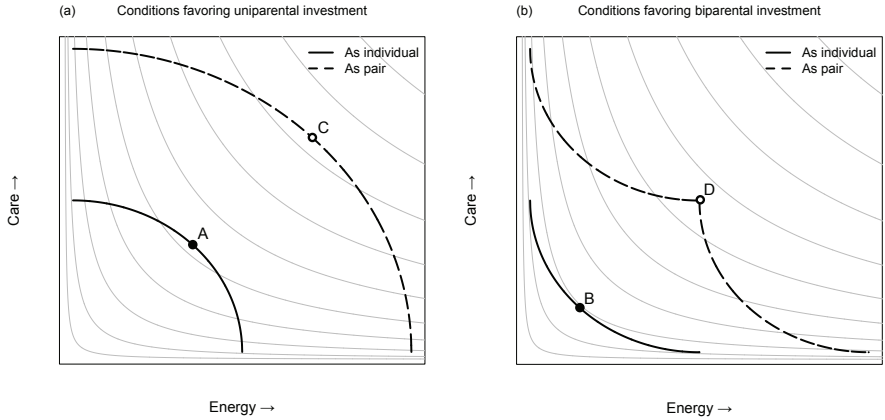

FIGURE 8-4 Hypothetical budget constraints reflecting tradeoffs between the provision of care and energy by parents to offspring.
NOTE: The solid black lines represent the feasible levels of care and energy which a single parent can provide, while the dashed black lines represent the levels of care and energy that two parents can provide together. The thin gray lines represent hypothetical iso-fitness lines for offspring, with increasing offspring fitness from the lower left to upper right of each panel. The solid points A and B represent the optimal allocation of effort for a single parent, while the open points C and D represent the optimal allocation of effort for two parents together. Panel (a) illustrates a convex budget constraint, reflecting diminishing returns to specialization in energy production or care. Under these conditions, because the fitness of offspring with two investing parents (point B) is less than twice that of offspring with a single parent (point A), one sex (usually the male) is likely to benefit from deserting to pursue additional mating opportunities, resulting in an equilibrium of uniparental investment at point A. Panel (b) illustrates a concave budget constraint, reflecting increasing returns to specialization or turn-taking by parents. Under these conditions, because the fitness of offspring with two parents dividing labor (point D) is more than twice that of offspring with a single parent (point C), the gains to biparental investment are likely to outweigh the benefits of desertion, resulting in an equilibrium of biparental investment with a specialized division of labor at point D. The curvature of the offspring fitness surface can also affect the equilibrium outcome, with a greater likelihood of biparental care when there are increasing returns to investment in offspring.

ing males who offer care or energy. This, in turn, affects the tradeoff for males between parental investment versus gaining access to females through competition, favoring the latter. These conditions are expected to foster provisioning of both care and energy by females, and higher mean quality of genes contributed by males than females (i.e., $G_m > G_f$).

Figure 8-4b depicts alternative ecological conditions, which we hypothesize to characterize birds emphasizing aerial locomotion, some species of fish, and humans. These conditions reflect a relatively harsher tradeoff between providing care versus energy and support biparental investment. This would occur, for example, where young are unable to accompany adults while foraging, but face high risks of predation if left unattended; where foraging activites would expose offspring to high levels of risk; or where foraging returns rates would greatly suffer if offspring accompanied adults. In these cases, the budget constraint defining the tradeoff between provisioning of care and energy for an individual parent will be tend to be concave (like the solid black line in Figure 8-4b), reflecting increasing returns to specialization in producing one good or the other at a time, but low returns to producing both at once. These conditions increase the relative gains to biparental over uniparental investment with a cooperative division of labor between parents (compare points B and D in Figure 8-4b). Mate choice under these conditions is expected to emphasize genetic quality relatively less, and parental investment offered and provided relatively more.

In most birds, eggs and nestlings are highly vulnerable to predation. Food supplies are often some distance from nests, not allowing for simultaneous care and energy acquisition. Different solutions to this problem appear to depend on the details of the local ecology, but often involve the help of a second parent (Bennett and Owens, 2002). In birds, a common solution is turn-taking, where one parent stays to protect nestlings while the other forages for food. Parental specialization also sometimes occurs, with one parent caring and the other provisioning. In many fish exhibiting biparental investment, females provide energy to offspring through investment in eggs, while males provide protective care by guarding the eggs from predation (Gross and Sargent, 1985). Males protect eggs and fry in safer places while females forage for energy where food supplies are rich. In other species, biparental mouthbrooding is common, which may allow parents to achieve returns to scale that are unattainable through the investment of one parent alone (Kidd et al., 2012).

The modal pattern among human foragers is characterized by life history specializations in care and gathering by females, and hunting by males. The returns to specialization turn on a number of factors. First, human mothers share with other primates a commitment to carrying infants and providing intensive maternal investment through lactation. Most hunting practices, on the other hand, are incompatible with pregnancy and childcare, given their danger and physicality. Given the skill-intensive nature of hunting and its incompatibility with pregnancy and childcare, women would be unlikely to attain the hunting return rates achieved by men due to the inability to invest sufficient time in practice (Kaplan et al., 2001).

Second, the returns to investment by both sexes are increased by the depth and duration of offspring need during development, as required by the brain- and experience-intensive nature of the human life history. (Similar effects of offspring need are observed in birds: Bennett and Owens, 2002.) Finally, the human pattern of multiple simultaneously dependent offspring further deepens the extent of economic need, drawing the investments of fathers and other close kin (Gurven and Walker, 2006).

The sexual division of labor is a ubiquitous feature of human societies—with the possible exception of some sectors of modern nations—that is well documented in the ethnographic literature (partially represented in the Human Relations Area files: Murdock and Provost, 1973). Among foragers, there is an extensive division of labor with respect to all aspects of household production, including not only direct care and energy production, but also food processing, cooking, collection of firewood, construction of housing, and production of tools (Marlowe, 2007). Compatibility of labor with simultaneous childcare is a strong predictor of women's activities (Minge-Klevana, 1980; Hurtado et al., 1985). It is not that there is no overlap in the activity budgets of men and women, as men do engage in some direct care of infants, for example, among the Aché, Tsimane, !Kung, Aka, and most—perhaps all—other foragers and forager-horticulturalists (Hill and Hurtado, 1996; Winking et al., 2009; Howell, 2010; Hewlett, 1992; Hewlett and Macfarlan, 2010).

Among foragers, the weight of quantitative evidence suggests substantial contributions to familial and offspring well-being from fathers as well as mothers in the context of sex-specific specialization. Among the sample of 10 foraging societies for which quantitative data are available, males produce an average of 68 percent of all food calories and 88 percent of all protein (Kaplan et al., 2001). There is substantial variability across foraging societies in male and female energy inputs, but there are no societies reported for which men are not important providers of meat (with the possible exception of some aboriginal Australian groups for which quantitative data do not exist). The Tsimane show mean net caloric flows from husbands to wives, and net caloric contributions of fathers to offspring are roughly twice those of mothers (Figure 8-3; Hooper et al., 2014).

The behavior of female foragers reflects complementary adjustments to the investments of males, particularly in care and economic activities that are compatible with care. For example, among the Aché who did not maintain permanent camps with safe places for children, women with infants and toddlers under age 3 spent more than 90 percent of daytime hours in tactile contact with those children (Hurtado et al., 1985). Even in safer environments where cleared spaces are maintained, as among the Tsimane, children are actively cared for by their mothers about 30 percent of waking hours (Winking et al., 2009). Consisent with this emphasis on direct

care, female foragers show significant decreases in time spent foraging with the presence of young children. Among the Aché and Hiwi, women who are nursing show reduced time devoted to production and lower production rates than those who are not (Hurtado et al., 1985, 1992). Tsimane women's rate of direct food production—at a mean base of 2,900 calories per day—is estimated to decrease by 900 calories for each child under age 3; it is estimated to increase, on the other hand, by 320 calories for each additional child over 3. On top of a mean base of 5,200 calories produced per day, Tsimane men also increase hunting effort with a greater number of dependents and produce an estimated 240 additional calories of animal fat and protein for each additional dependent offspring (Hooper et al., 2015; see also Marlowe, 2003, for the Hadza).

Complementarities between male and female parental roles affect patterns of marriage and reproduction among foragers in multiple ways. In a cross-cultural sample of 145 foraging groups, the modal percent of marriages that are polygynous is 0-4 percent, and more than 90 percent of marriages are monogamous in the majority of groups (Binford, 2001). Consistent with this pattern, for the foraging societies for which data exist, male and female reproductive schedules tend to be closely linked: Age-specific fertility and expected future fertility for women and men are similar in shape, with the male curves shifted 3-5 years to the right (i.e., to older ages) and having slightly longer tails (see Tuljapurkar et al., 2007, and original data from Howell, 1979; Melancon, 1982; Blurton Jones et al., 1992; Hill and Hurtado, 1996). This pattern differs from what has been characterized as the standard difference between the fertility schedules of male and female mammals. As male parental investment is rare among mammals, male-male competition tends to be high, leading to both later onset of reproduction and earlier termination of reproduction among males, compared with females (because it takes males longer to become competitive than for females to begin reproducing, and the effects of senescencing competitive abilities affects male reproduction more than female; Clutton-Brock, 1991; Clutton-Brock and Isvaran, 2007; see also Alberts et al., this volume).

The demographic linkage between women and men is also manifest in the tendency for male foragers to cease reproducing when their wives reach menopause. In the case of Tsimane, only 10 percent of men reproduce after their wife reaches menopause (Kaplan et al., 2010). Similarly, among the Aché about 17 percent of men reproduced after their wife reached menopause, and only 10 percent reproduced if they had two or more children with that wife (Hill and Hurtado, 1996). As depicted in Figure 8-3, as their wives reach menopause, Tsimane men tend to invest in their children and their grandchildren rather than investing in new reproductive careers. Older men in foraging societies may not be very attractive as mates for young

women. Given that children will be dependent for a long time, men whose productive abilities are on the wane do not offer good long-term prospects. Moreover, ceteris paribus, it is likely that women would prefer to have all their children with one man, since serial fathers would be differentially related to the children (Kaplan et al., 2010).

GAINS TO COOPERATION, RECIPROCITY, AND LIFE HISTORY

In addition to the intensive relationships within nuclear and extended families, cooperation between more distant kin and non-kin is another hallmark of human sociality. This can be defined in terms of both the breadth of relationships, and the volume of goods and services exchanged. Among foragers and forager-horticulturalists, these patterns are most clearly manifest in the cooperative production and sharing of food (Gurven, 2004) and aid during illness and injury (Gurven et al., 2000, 2012; Sugiyama and Chacon, 2000). Hill and colleagues have argued that extensive exchange, facilitated by home-based resource sharing, is a universal pattern among hunter-gatherers (Hill, 2002; Hill et al., 2009). Among the Aché, for example, over 90 percent of the meat that hunters acquire is consumed by members of other nuclear families (Kaplan and Hill, 1985).

Anthropologists, economists, and biologists have not reached consensus regarding why exchange is so pervasive in human groups. Studies from human foragers have suggested that extensive food sharing within and among families relates to the specific feeding niche that foragers occupy. The foods that foragers exploit tend to be large, patchily distributed plant and animal species, whose availability can be clumped either in time or in space. The large package size (i.e., amount of food obtained at one time) and patchiness of foods is associated with large short-term fluctuations in food acquisition, with little or no food being acquired on many days followed by bounties on others. For example, the likelihoods of returning empty handed from a hunting attempt among Aché, Hadza, Hiwi, and Tsimane hunters are 96 percent, 65 percent, 45 percent, and 40 percent, respectively (Hill and Hurtado, 2009; Gurven et al., 2012). Shortfalls of no meat for a week or more would occur frequently for a single hunter and his family under these conditions; at the same time, a single family would be unable to consume a large bounty of meat before it spoiled.

Two different theories have been advanced to explain the extent of food sharing in hunting and gathering societies, both of which emphasize the importance of variability in food supply. According to one view, reciprocity-based risk reduction drives food transfers; according to the other, food transfers are the result of tolerated theft. The "reciprocity and risk reduction" view proposes that where foods are unable to be preserved or stored, the cycle of bounties and shortfalls can be buffered by reciprocal

food sharing (Kaplan and Hill, 1985; Winterhalder, 1986; Hames, 1990; Gurven, 2004). According to the theory, the challenge posed by intertemporal variability in large-package food availability was addressed culturally with an "insurance" mechanism: successful foragers of high-variability resources share food with unsuccessful foragers with the expectation of a reciprocal flow in the other direction when the situation is reversed. By smoothing variability in intake rates, foragers maximized the nutritional benefit from large food packages. The "tolerated theft" hypothesis proposes that large food packages create variation among individuals in their available food, with the "lucky" individuals possessing larger and the unlucky ones smaller quantities or none (Blurton Jones, 1984). Possessors tolerate theft from their supply by individuals with less, because the cost to the possessor of defending the surplus exceeds its value, and the value of the food to the hungry individual makes fighting for it worthwhile. Hence, exchange is not reciprocal, but based on momentary variation in who is hungry and who has abundance.

For reciprocity-based risk reduction to explain food transfers, it is necessary to show that producers can direct food transfers to preferred individuals, and those transfers are directed to those who have given previously. The bi-directionality (or "contingency") of sharing has been evaluated by examining the extent to which the amounts given from one individual or family to another are correlated with amounts received in return, controlling for other factors such as kinship and spatial proximity. Positive contingency has been found in observational studies from the reservation Aché, Aka, Hadza, Hiwi, Meriam, Mikea, Miskito, Shuar, Tsimane, and Yanomamö (see meta-analysis of Jaeggi and Gurven, 2013).

Another way to examine the extent to which food transfers in hunting and gathering groups are governed by individually based social relationships in response to risk, is to examine how much food is given to different food-sharing partners as a function of the size of the food package. Figure 8-5 shows how small and large packages were handled by Aché foragers living at settlement after contact. The figure plots the percent of food items given to other families in rank order based on the total frequency of sharing to each family over time. This plot shows that the likelihood of giving depends on both the size of the game animal and rank order. Most-preferred partners (rank 1) received shares close to 50 percent of the time for both large and small game. However, less-preferred partners received shares less often for small game than for large game. For example, partners of rank 8 received a share only 5 percent of the time for small game, but close to 20 percent of the time for large game. This pattern would make sense if the size of the risk-sharing pool was strategically adjusted to package size, and if transfers were based on individually negotiated relationships (Kaplan and Gurven, 2005).

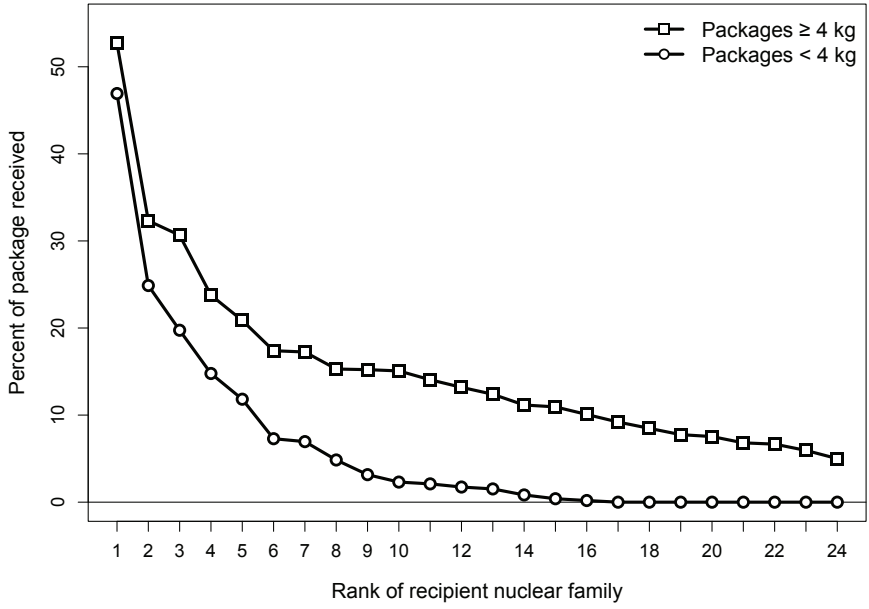

FIGURE 8-5 Aché food sharing by package size.
NOTE: The horizontal axis indicates the rank of recipient nuclear families from highest (rank 1) to lowest (rank 24) amount shared. The vertical axis indicates the mean percent of food items shared with each family. Large foods with more variable return rates are shared with a broader network of social partners than smaller, less variable foods.
SOURCE: Kaplan and Gurven (2005).

Returns to scale in the collective production of food also motivate the formation of reciprocal cooperative relationships and food sharing among human foragers. Many game species are effectively hunted through the cooperation of multiple hunters, which can allow capture of large game—such as giraffes or whales—or achieve multiple kills of animals that move in herds or groups—such as monkeys, coatis, peccaries, or larger ungulates. Among the Aché, approximately 50 percent of all game acquired is derived from cooperatively pursued species, with hunters often signalling each other upon encountering prey in order to recruit help (Hill, 2002). Among many pygmy groups, the majority of game is captured through cooperative game drives; similar drives have been described in western North America. Among the Lamalera in Indonesia, whales are hunted by large, well-organized pursuit groups in boats, and food shares are given to participants and other families according to well-prescribed rules (Alvard and Nolin,

2002). Cooperative whale hunting with concommitant food sharing has also been well-documented among the Inuit (Balikci, 1989; Smith, 1991).

There are two important implications of extensive food sharing and other forms of bilateral cooperation for health and well-being among foragers. First, sharing has important effects in reducing risks of mortality throughout life. Among the Tsimane, for example, food transfers and other forms of assistance are given to orphaned children (who are at risk of increased mortality), to women who have lost a spouse, to sick individuals until they recover, and following loss of food or possessions (Gurven et al., 2012). Sugiyama and Chacon's study of Yora and Shiwiar forager-horticulturalists showed that illnesses and injuries prevented men from foraging on approximately 10 percent of person days. They found that not only would the sick or wounded individual and his family suffer from the reduced protein intake, but so too would others in his sharing network. On the basis of those results, they argued that foragers must maintain large sharing networks to buffer the risks of illness and injury (Sugiyama and Chacon, 2000).

Weissner's analysis of Ju/'hoansi (!Kung) sharing networks came to similar conclusions, but on the basis of environmental risks. She found that Ju/'hoansi maintain sharing partners in a system called *xharo*, in which men and women commit to obligations of mutual aid and gift giving. She found that on average, Ju/'hoansi adults had 16 partners, with a range from 2 to 42 partners. Individual partner sets tended to include individuals of both sexes of varying ages, and with a variety of skills. Approximately 18 percent of partners resided in ego's camp, 24 percent in neighboring camps 1-15 km away, 25 percent in camps 16-50 km away, and 33 percent in camps 51-200 km away. One advantage of maintaining partners in distant camps was that in times of local food or water shortage, *xharo* partners could be visited in distant places where conditions were better. She also found strong associations between foraging efficiency, food transfers, possessions, and reproductive success: Better hunters who transfered more food had 80 percent more *xharo* partners, received more material possessions though *xharo*, and had an average of 50 percent more children (Wiessner, 1982, 2002).

A second potential implication of food sharing, as a response to either risk or the gains from cooperative production, is that it may limit the scope for dominance-based social relationships and the formation of social hierarchies. In many social species, dominance is used to gain exclusive rights to resources. Among female primates, for example, rights to favored territories or foraging locations for themselves and their offspring are often subjects of dominance interactions (Pusey et al., 2008). Among foraging groups, dominance hierarchies and within-group disputes over access to resource patches are not often reported (Boehm, 2009; there are exceptions to be

discussed below). Among foragers, where the gains from cooperation are a major determinant of well-being, overt dominance behavior can bring the risk of losing valuable cooperative partners. It is likely to be difficult to coerce people into working and giving up shares of their food through dominance, particularly when resources are not concentrated and predictable. High mobility between groups, and frequent group fissioning and fusing, are commonly reported for foragers (e.g., Hill and Hurtado, 1996), which may also limit the scope for dominance. In the light of these factors, it appears that "egalitarianism" may emerge in part from the formation of voluntary partnerships, based on mutual support and joint production, but may not imply equal outcomes for all.

One final element may tie these threads together. The greater the importance of male foraging effort to the health and well-being of children, the less will be the gains to men from dominance interactions over mating opportunities. If, at equilibrium, an average man can only support all the children of one woman, the gains from dominance over other men may be small. The gains from risk reduction, cooperative acquisition, and male parental investment may thus combine to generate the relatively egalitarian patterns of interaction that seem to characterize so many foraging groups and that differ markedly from most other primate species.

VARIATION AMONG FORAGERS

To this point, we have discussed general trends in the social relationships of societies that depend on foraging for basic subsistence, and have attempted to describe what we refer to as the modal pattern. In this section, we ask whether the theoretical principles discussed above can explain variation (a) within the modal pattern and (b) away from the modal pattern.

With respect to intergenerational transfers, our discussion emphasized the implications of skills-based foraging for age-specific food production and, in turn, kin-based downward resource transfers. The logic presented above would imply that ecological variation in the skill-demands of the foods exploited, or in age-specific productivity profiles, would be associated with changes in transfers. There are a suite of ethnographic observations suggesting that variations within the modal pattern may be explained by such variation. Seasonal variation in fruit availability among the Aché, for example, is associated with the proportion of children's diet that they can provide for themselves. During fruit seasons, food production for children under age 14 increases 5-fold, allowing them to produce more than half of the calories they consume (Kaplan, 1997). Similarly, intergenerational transfers to Hadza children appear to be smaller than to Ju/'hoansi children, because the former acquire more fruit. Part of this difference in turn has been attributed to the greater safety in Hadza environments for trav-

eling to and from food patches (Blurton Jones et al., 1994). Among the Mikea of Madagascar, many game animals are nocturnal and may be easily captured, even by children, making the children less dependent on parents (Tucker and Young, 2005). In spite of this variation within the modal pattern, we know of no variations away from the modal pattern of downward intergenerational transfers among foragers.

With respect to male parental investment and monogamy, there are fewer quantitative data to assess ecological trends. The expectations derived from the discussion above are that increased polygyny would occur for one of three reasons. One reason would be decreased gains from male parental investment, motivating women to choose males more on the basis of genetic quality, and motivating men to invest more in mating competition. The second reason is that, under conditions of high interpersonal violence, male protection may become a more critical input into wife and offspring success. Where a husband's ability to protect has a direct impact on the well-being of his immediate family, and protection can be provided as an "umbrella" benefit (i.e., a common or nonrival good) to wives and offspring, female choice may shift, with greater preferences for males with greater ability to provide security (and less weight placed on more strictly rival goods, such as time and energy; Bowles and Borgerhoff Mulder, 2012). This could result in greater levels of polygyny because one man might be able to offer protection to several wives and their offspring. The third reason would be increased variaton among males in the parental investment they have to offer, leading "wealthier" (or otherwise higher-quality) males to have multiple wives, and others to have none.

Very high rates of polygyny have been reported for some Australian aboriginal groups and for some native North Americans living on the plains. The causes of high rates of polygyny in aboriginal Australia are not well understood, but Hart et al. (1960) suggested that women in the northern territories could be largely self-sufficient, again because hunting nocturnal animals was relatively easy. In the plains of North America, the adoption of the horse seems to be responsible for major changes in the economy, with large-scale implications for the mating system. Small foraging bands were converted into large raiding parties, stealing herds of horses and women at the same time. Wealthy men with large herds could also obtain additional wives through brideprice. In essence, they became partial pastoralists, with many convergences in social organization (Steward, 1938; Hämäläinen, 2009).

With respect to reciprocity and egalitarianism, there is well-documented variation in patterns of food transfer, both within and among groups. A robust predictor of the amount of food transferred in terms of sharing breadth (the number of partners receiving shares) is the size of food packages and the associated variability in their delivery (see Figure 8-5 and

review in Gurven, 2004). In cases where very large game are customary, such as the Hadza, food transfers often involved members from more than one camp or group (Hawkes et al., 2001). Seasonal variation in resource availability and patchiness can also have dramatic effects on this aspect of social organization. For example, Steward (1938) described that in the great basin of North America, people lived in largely self-sufficient, small nuclear-family clusters during the winter when resources were scarce and congregated in large groups, participating in communal game drives during the summer when resources permitted. Band-wide, fully communistic food sharing has also been observed, as in the case of the Aché and Yora during mobile foraging trips (but not at permanent settlements: Kaplan and Hill, 1985; Hill and Kaplan, 1989). In those cases, producers do not appear to control to whom they give, higher producers give more than they receive, and larger families receive bigger shares (Kaplan and Hill, 1985; Kaplan et al., 1990). Band-wide sharing of meat appears to occur when groups are relatively small, and strategies that maximize group returns through cooperative efforts require some individuals to give up the chance of making a kill.

Movement away from the egalitarian modal pattern has been documented in several places, most notably on the west coast of North America. Large differences in status and restricted access to resource patches based on inheritance have been reported for several groups living in the Pacific Northwest and the coast of California (Ames, 1994). One suggestion for explaining this trend away from egalitarianism toward hierarchy concerns the nature of variability in resource availability. Reciprocity is an effective strategy when variability across individuals is unsynchronized in time. When there is predictable variation in resource availability across space with reasonable intertemporal stability (e.g., salmon runs and acorn groves), there can be gains to investment in dominance in order to gain preferential access to rich resource patches (Dyson-Hudson and Smith, 1978; Kelly, 1995). Such differential access could be converted into inherited differences in wealth, and number of wives (Borgerhoff Mulder et al., 2009; Smith et al., 2010). One can note that the modern distribution of foraging groups is unlikely to encompass the full range of variation in the extent of competition for durable territorial resources possible in the pre-Neolithic past, and that more territorially focused foragers may have clustered in predictably rich areas (e.g., along coasts and rivers), with higher levels of social hierarchy and inequality.

Until now, we have discussed both full-time hunter-gatherers and forager-horticulturalists, who practice shifting cultivation, as conforming largely to the modal pattern. However, the inclusion of cultivation (i.e., farming) in the subsistence regime does seem to have some important downstream effects. For one, farming appears to have complex effects on intergenerational transfers. Among the Tsimane, men shift their effort from

hunting to farming as they age, reportedly because they can no longer hunt effectively (which is consistent with data on age-related decreases in hunting return rates: Hooper, 2011). This may suggest that farming allowed greater contributions of individuals in their 60s and 70s to younger individuals. However, there are farming tasks, such as harvesting, that children can do well, leading to increased productivity of children and an earlier age of nutritional independence (Kramer, 2005). Where farming reduces the importance of hunted foods in the diet, or male labor more generally, it may result in less male parental investment and more polygyny. The largest shifter, however, within farming groups is whether they own and defend territories. It is with territorial ownership that humans shift to forms of social organization outside the scope of this paper. The patterns discussed for "territory owning" hunter-gatherers in North America provide some insights into those transformations.

DISCUSSION AND CONCLUSIONS

The two central messages of this paper are, first, that human demography can only be well understood in light of human social structure, and vice versa; and second, that both of these domains have been conditioned by the ecologies inhabited by hunter-gatherers in the remote evolutionary past. In the preceding sections, we have drawn on a growing body of quantitative ethnographic research to discuss the evolutionary interdependencies among (1) longevity, menopause, and intergenerational transfers; (2) the coupling of male and female reproductive careers, biparental investment, and cooperative pair-bonds; and (3) survival and cooperative social insurance.

This synthesis may afford new insights into both human evolution and contemporary human behavior. Very little is known about the temporal sequence for the evolution of those features of social life that are close to universal among extant foragers. Given the isolation of peoples in the Americas for close to 15,000 years and in Australia for more than 30,000 years, it would appear that such traits are likely to have been present in the first anatomically modern humans. It appears that initial brain expansion and greater emphasis on meat eating occurred with the emergence of the genus Homo some 1.8-2 million years ago. Yet much remains to be learned about the co-evolution of these biosocial traits. Did they slowly ratchet each other, or were some traits in place long before others? The answers to these questions are likely to be found in the future with some combination of paleogenetics, isotype analysis, and other methods yet to be discovered. The theoretical principles discussed above can serve to guide such research.

The insights into modern behavior are likely to derive from two avenues. First, we expect there to be much "carry-over" or inertia from the past. While there is evidence of genetic changes since the advent of agriculture

and animal husbandry—such as with respect to lactose tolerance (Durham, 1991)—there seems to be strong canalization of human development with respect to brain development, growth, maturation, and aging. There are secular trends, but variation is limited: Nowhere are people mature at age 5 or living to age 200. Lee (2007) has argued that downward transfers within families are preserved across societal transitions, and the truly novel development is upward transfers, not within families, but through government institutions, such as Social Security and Medicare.

Monogamous marriage is now prescribed by law in most of the world, but to what extent do those cultural institutions have long evolutionary roots? The endocrinological mechanisms underlying a father's attachment to his children (Gray and Campbell, 2009; Gettler et al., 2011) are likely the product of millenia of selection under past conditions. At the same time, patterns of opportunistic desertion and disinvestment by males indicate subtantial flexibility of strategies and adjustment to local socioecological context (Muller et al., 2009; Stieglitz et al., this volume). Similarly, there is growing evidence that social networks affect virtually every aspect of life and well-being in modern societies. To what extent are those patterns relics of the social past? These are questions that future research can address.

The second avenue of insight into modern human behavior may stem from the theoretical principles that appear to order the data collected among foraging societies. The gains from investments in skill and other factors affecting age profiles of productivity, such as health in old age, may help explain patterns of intergenerational transfers and parental investment that change over time and depend on socioeconomic status. The outcomes associated with biparental care compared with uniparental care—which vary across social, economic, and institutional contexts—may help explain the distribution and duration of marital/cohabiting and nonmarital/noncohabiting unions. Gains from social risk sharing and joint production may also provide insights into the nature of social interactions among non-kin, and into effort put into social dominance both within and among nations. There is still much to be learned regarding the legacy of the past.

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9

Work to Live and Live to Work: Productivity, Transfers, and Psychological Well-Being in Adulthood and Old Age

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INTRODUCTION

This paper considers psychological well-being in adulthood and old age, in light of the economic and social structure of the evolved human life history. Psychological well-being is the subject of significant scientific inquiry in large-scale modern societies (e.g., Easterlin, 2003; Blanchflower and Oswald, 2008; Diener and Chan, 2011), and it is often associated with economic productivity, social status, and network strength. However, very little is known about the evolutionary origins of mood variation or about mood variation during the course of human evolution. In fact, it has been suggested that depression is a maladaptive by-product of modern lifestyles due to inadequate pathogenic exposure in development, low physical activity level, high prevalence of metabolic disorder, or high levels of psychosocial stress from economic inequality, intense social competition, and residential isolation from kin (Raison et al., 2010; Rook et al., 2013).

One way to assess evolutionary implications of mood variation is to focus on small-scale societies. Small-scale societies possess similar socioecological features typical of the vast majority of human evolutionary history, including food insecurity, limited material wealth, and high pathogen burden coupled with little access to health care, but also frequent resource pooling, relative egalitarianism, and minimal social isolation. Research into psychological well-being in small-scale societies can (a) determine whether mood disorders exist, and if so, examine whether risk factors and buffers

are similar to those in modern societies, and (b) provide insight into the role of mood variation during human evolutionary history.

This paper has two goals. The first is to present an evolutionary framework for investigating the role of social relationships in affecting psychological well-being, and how it varies over the lifecourse and in different socioecological contexts. The second is to provide data on the prevalence and correlates of reduced psychological well-being and interpersonal conflict in a small-scale society, the Tsimane of Bolivia, to illustrate an empirical application of the framework. We hope to stimulate further research across populations and social contexts rather than offer a systematic review of the literature on psychological well-being.

Our central thesis is that flows of resources and assistance are critical in every phase of the human lifecourse and that psychological well-being responds to the nature and quantity of those flows. One universal feature of human life histories in small-scale societies is downward intergenerational resource flows (discussed in this volume by Lee, Hooper et al., and by Ellison and Ottinger; for original data, see Kaplan, 1994, and Kaplan et al., 2000, 2010; also see Lee, 2000, for data on the cross-cultural universality of downward flows within families). Children are net receivers of resources and assistance, whereas parents and grandparents are net givers during both reproductive and post-reproductive years. A second universal feature is the formation of marital bonds in which there is a flow of resources and assistance between spouses (see Hooper et al., this volume, and references cited therein). Resource flows from other kin and non-kin can also be important determinants of reproduction, health and mortality (e.g., Hawkes, 2003; Hill and Hurtado, 2009; Hill et al., 2009; Hrdy, 2009; Jaeggi and Gurven, 2013a).

We propose that deviations of those resource flows from expectations affect psychological well-being, both directly and indirectly. Resource flows can be disrupted for various reasons; one principal source of disruptions is the inability to provide support due to disability, illness, or some other permanent or temporary shock. Given that downward resource flows from older to younger individuals are expected in small-scale societies and that illness and disability become increasingly prevalent with age (see Gurven et al., 2012, for data on Tsimane forager-horticulturalists of Bolivia), we expect that the inability to provide expected resources will be a principal driver of reduced psychological well-being among adults, particularly as they age. Another principal source of resource flow disruptions is the intentional withholding of a resource, or resource diversions from expected recipients to other individuals or activities. In such cases, we expect interpersonal conflict to result, with downstream consequences for psychological well-being. Marriage may be particularly susceptible to such conflicts, given the possibility of pursuing reproductive and other interests outside of marriage.

This paper is divided into three parts. In the first part, we focus on psychological well-being in adulthood and old age, and on the direct effects of subsistence productivity on psychological well-being, as well as the indirect effects mediated by food and other resource transfers to kin. We illustrate the model empirically using demographic, epidemiological, and psychological data collected among a representative sample of adult Tsimane. In the second part, we consider conflicts due to resource diversions in marriage. We identify common sources of Tsimane marital conflict, most of which concern household productivity and transfers. In the third part, we compare our conceptual model to previous evolutionary and epidemiological models of depression and outline future research directions.

We conceptualize psychological well-being as a continuum from happiness to sadness, which are cross-culturally recognized emotions (Nesse, 1990). Understanding behavioral and physiological mechanisms underlying regulation of emotions across the continua of valence and arousal is an important goal for basic and clinical research (Holtzheimer and Mayberg, 2011). In this paper, we focus mostly on depression given its large contribution to the global burden of disease and over-representation in psychological well-being research (Whiteford et al., 2013). Although clinical depression in the United States has formal criteria defined by the Diagnostic and Statistical Manual of Mental Disorders, we use the term "depression" to refer to the cluster of symptoms often associated with depression (e.g., sadness, loss of interest). Depression is defined here as persistent sadness that interferes with routine daily functioning. We acknowledge that depressive symptomology may be highly variable across cultures, individuals, and within individuals over time, and that certain symptoms may have a higher sensitivity and specificity for identifying depression (due, for example, to symptoms such as fatigue frequently co-occurring with other morbidities) (Patel, 2001).

PART I. AN EXPLANATORY FRAMEWORK FOR PSYCHOLOGICAL WELL-BEING IN ADULTHOOD AND OLD AGE

Psychological Well-Being Varies with Determinants of Productivity

Our general hypothesis is that the ability to produce and transfer resources that have fitness value for self and kin is a primary determinant of psychological well-being in adulthood and old age (the "productive value" hypothesis). Food obtained from subsistence activities is necessary for growth, reproduction, and survival, and food production and transfer to descendants is a fundamental determinant of fitness in small-scale societies. Subsistence productivity is influenced by a vector of individual-level variables that affect strength and skill levels, including age, energetic status,

health status, and degree of physical limitations. In the absence of food storage or bank accounts, successful subsistence production relies heavily on cooperation and coordination with other group members to buffer risks of food shortfalls.

Forager diets consist largely of foods requiring high levels of strength and skill (Kaplan et al., 2000). Meat and other important foods (e.g., tubers, larvae, honey, nuts) require extraction from a substrate (often with technology), intensive processing, and assistance from others. Hunting return rates more than double from ages 20 to 40, even though strength peaks in the mid-20s (Walker et al., 2002; Gurven et al., 2006). Lags in peak efficiency relative to peak strength have also been documented for other foods, although not as extreme as hunting and not across all food types (Bird and Bird, 2002; Bock, 2002; Jones and Marlowe, 2002; Tucker and Young, 2005; Gurven and Kaplan, 2006; Crittenden et al., 2013; Stieglitz et al., 2013). The age-profile of net food production over the lifecourse appears to be fairly consistent across small-scale societies, with some variability in the onset of net productivity (Kaplan et al., 2000; Kramer, 2005; Hooper et al., this volume). Large caloric deficits are incurred early in life, and only by the mid to late teens do individuals start producing more calories than they consume. At this point, surplus caloric production increases with age, peaks in the 40s, and then slowly declines until dropping below consumption levels once again after seven decades. High adult productivity enables net transfers from older to younger generations to bankroll prolonged juvenile dependency and to help promote transfers within generations during negative shocks (e.g., morbidity that inhibits work). These transfers increase the likelihood that juveniles reach adulthood, allow parents to rear multiple dependent offspring simultaneously, and reduce adult mortality (Lancaster and Lancaster, 1983; Jaeggi and Gurven, 2013a).

Despite frequent resource pooling to buffer risk, exposure to periods of uncertainty in the food supply was probably common over human evolutionary history. Food anxiety[1] is a commonly reported major life stressor cross-culturally and is associated with several indicators of reduced psychological well-being (e.g., anxiety, depression) (Pike and Patil, 2006; Hadley and Patil, 2008; Weaver and Hadley, 2009). Because the ability to produce and transfer food is strongly age-dependent, prevalence of food anxiety should vary with age, independently of other factors including household need and availability of social support. Food anxiety should also vary with energetic status, since nutrient deficiencies may directly affect psychological well-being. For example, micronutrient supplementation reduces levels

[1]We use the term "food anxiety" to signify psychological distress over lack of food security. The 1996 World Food Summit defined food security as existing when people, at all times, have access to sufficient, safe, and nutritious food to maintain a healthy and active life.

of perceived stress and anxiety in nonclinical Western samples (Long and Benton, 2013). Nutrient deficiencies may also indirectly affect psychological well-being by reducing the capacity to work and subsistence productivity (see below).

Demonstrating a link between productivity and psychological well-being, Figure 9-1 shows the probability of reporting food anxiety by age among Tsimane adults aged 20+, alongside the age-profile of Tsimane net daily caloric production. Food anxiety is prevalent overall (31 percent of adults), and more prevalent among younger adults, despite low household dependency and few deleterious effects of senescence on the ability to produce food. Food anxiety sharply declines with age, as productivity increases, and reaches a nadir at age 46, the same age that productivity peaks. There is also a main effect of body mass index (BMI) in the predicted negative

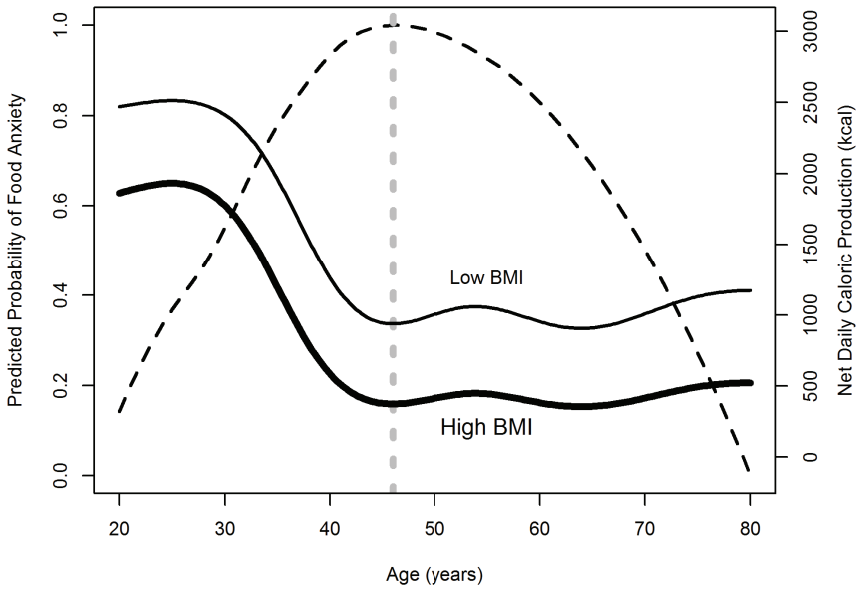

FIGURE 9-1 Predicted probability of reporting food anxiety by age and BMI among Tsimane.

NOTES: Generalized additive mixed model, controlling for sex and repeated measures, n = 1002 adults, 1137 observations. BMI is plotted at 2 SD below and above the mean (mean ± SD = 24 ± 3). Age thin plate spline $p < 0.001$, edf = 5.814, $B_{Male} = -0.31$, $p = 0.02$, $B_{Bmi} = -0.077$, $p < 0.001$. Tsimane daily net food production (production minus consumption) is shown on the second y-axis (averaged across sexes). The nadir in food anxiety corresponds to the age of peak productivity (dashed vertical line).

direction (BMI range = 16-38). At the age of peak productivity, probability of food anxiety is over twice as high for Tsimane with low versus high BMI (0.34 vs. 0.16).[2] Although food anxiety appears to increase slightly at older ages, this increase is not significant (OR/year = 1.03, p = 0.13, including ages ≥ 60 and controlling for sex and BMI). Food anxiety may not increase at older ages as productivity declines because of declining caloric dependency of offspring and grandoffspring (cf. Gurven and Kaplan, 2007).

Aside from food anxiety, other indicators of psychological well-being[3] vary predictably with the ability to produce and transfer resources, as determined by age and energetic status. We find that Tsimane depression score increases with age among adults aged 18+ (controlling for sex, not shown), peaking in the late 70s when caloric production approaches pre-adult levels. Depression score, like food anxiety, is inversely associated with BMI and rises more steeply with age among those with lower BMI (not shown). Large body size may partly offset deleterious effects of aging on psychological well-being by supporting greater subsistence productivity and resource transfers. For example, 59 percent of Tsimane women aged 65+ report being able to get materials from the forest and weave a mat if below median BMI, compared to 83 percent of age-matched women at/above median BMI ($\chi^2 = 5.08$, p = 0.024, n = 73). Among men aged 65+, 6 percent report being able to lift a quintal of rice (~46 kilograms) if below median BMI compared to 22 percent of age-matched men at/above median BMI (Fisher's Exact Test p = 0.046, n = 89).

Morbidity is another impediment to subsistence productivity and food transfers, in addition to age-related physical decline and reduced energetic status as described above. Empirical links between morbidity and reduced psychological well-being are well documented cross-culturally (Cohen et al., 2007; Diener and Chan, 2011; Fagundes et al., 2012; Yanek et al., 2013). We hypothesize that morbidity is causally implicated in the onset

[2]While BMI may be inversely associated with food anxiety in small-scale societies, BMI may be positively associated with food anxiety in large-scale modern societies. In modern societies food anxiety is similarly associated with reduced productivity (e.g., low socioeconomic status or SES), but because low SES is also associated with obesity, positive associations between BMI and food anxiety emerge.

[3]To evaluate depression, we developed a culturally appropriate 16-item interview based on focus groups, 10+ years of ethnographic experience, and a review of validated depression scales used among diverse samples with good test-retest reliability (Beck's Depression Inventory, HAM-D, CES-D). The interview contains most or all of the symptoms contained in previous scales. Adults aged 18+ (mean ± SD age = 54 ± 12) were recruited regardless of their health status, and no individual refused participation. Participants were queried about prevalence of symptoms over the past month (e.g., sadness, guilt, fatigue, changes in sleep or appetite). Responses were given on a self-anchored scale from 1 ("rarely") to 4 ("always"), and items were summed to create a "depression score" (mean ± SD = 38.3 ± 6.8, range = 19-60, n = 849 men and women) (refer to Stieglitz et al., 2014, for further methodological details).

and maintenance of reduced psychological well-being. Indeed, Tsimane depression score varies predictably with self-reported health: adults aged 18+ reporting "extremely poor" overall health score 14 percent higher in depression, on average, than adults reporting "very good" health after controlling for potential confounders such as age, sex, BMI, Spanish fluency, and residential proximity to town (marginal mean depression score = 40.4 vs. 35.3, p = 0.026, n = 579). Less than 1 percent of Tsimane adults aged 18+ report "excellent" overall health, highlighting the pervasiveness of morbidity and its potential to impair psychological well-being in societies with limited access to healthcare. Clinical data indicate that < 10 percent of Tsimane adults aged 18+ are diagnosed as "healthy" in a given year.[4] Common diagnoses include gastrointestinal, respiratory, and skin infections, and arthritis. Older adults also commonly report disrupted sleep quality due to persistent musing over poor health (self or kin) (Gandhi Yetish, personal communication). Poor sleep quality may delay recovery and facilitate a cycle of morbidity, disability, and reduced psychological well-being.

Across diverse societies, subjective well-being is positively associated with self-reported health (see Table 9-1). We propose that this relationship may be especially tight in energy-limited subsistence societies, where direct effects of physical condition on production is stronger relative to sedentary industrialized societies. Managing disability-related production shortfalls with modern technology (e.g., glasses, hearing aids) or by liquidating savings accounts are not options in small-scale societies. In modern societies, unemployment (analogous to reduced subsistence productivity in small-scale societies) is a major cause of depression (Paul and Moser, 2009). Yet even in modern societies with government-subsidized unemployment benefits, employer-subsidized sick leave, or health insurance, functional limitations due to illness, injury, or senescence commonly reduce quality of life.[5] Links between functional limitations and reduced psychological well-being appear to exist in other species, too. For example, captive animals deprived of opportunities to perform preferred behaviors present signs of withdrawal that are similar to signs observed in addictive drug deprivation (Boissy et al., 2007).

Like morbidity, functional limitations can reduce inclusive fitness through multiple pathways including reduced subsistence production, kin transfers, and reproductive opportunities. Functional disability is a

[4]Bolivian physicians diagnosed patient illnesses during annual medical exams as part of the Tsimane Health and Life History Project (THLHP). Diagnoses from the International Classification of Disease (ICD-10) were grouped into gastrointestinal, respiratory, and other ailments for exams conducted from 2002 to 2004. "Healthy" is defined here as not presenting any symptom associated with any ICD-10 code.

[5]Reduced functional ability is increasingly contributing to the global burden of disease, as life expectancies increase, populations age, and the number of disabled individuals increases (National Institute on Aging, 2007).

TABLE 9-1 Mean Subjective Well-Being Score (shown as % maximum possible score) by Self-Reported Health from the Multisite Project AGE

Economy	Site (n)	Self-Reported Health			% increase in subjective well-being from poor/fair to excellent health
		Poor/fair	Average/good	Excellent	
Pastoralist	Botswana (174)	37	53	62	68
Market-rural	Momence, IL, USA (207)	70	77	80	14
Market-rural	Clifden, Ireland (129)	73	80	83	14
Market-suburban	Swarthmore, PA, USA (200)	73	78	82	12
Market-suburban	Blessington, Ireland (170)	72	75	82	14
Market-urban	Hong Kong (192)	57	57	67	18

NOTE: Well-being scores were collected among adults aged 18+ using a modified Cantril Self-Anchoring Ladder. Respondents were asked to select their current position on the ladder, with the highest and lowest steps representing the best and worst possible lives, respectively.
SOURCE: Adapted from Table 5.4 of Keith et al. (1994).

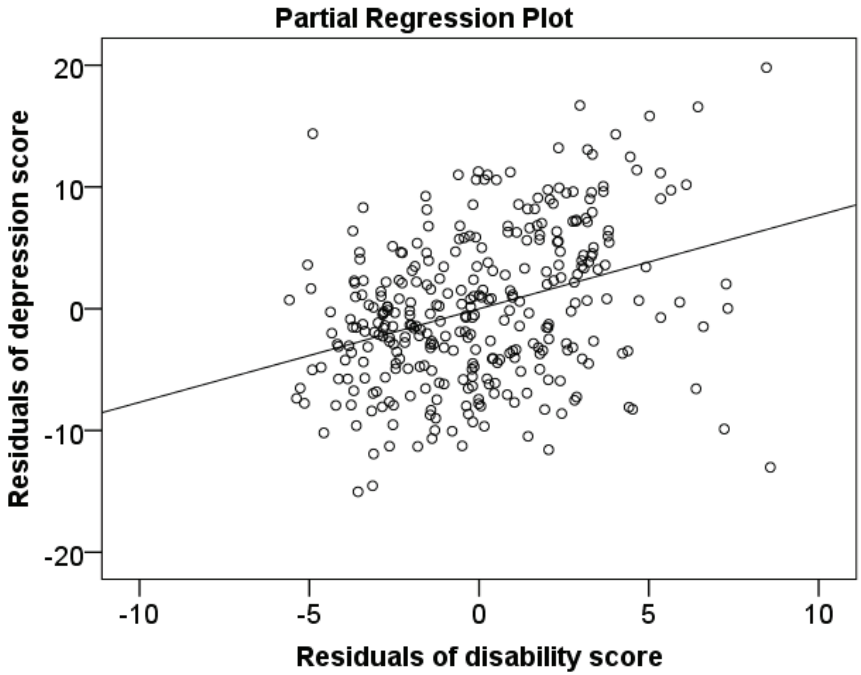

FIGURE 9-2 Depression is associated with greater physical limitations among Tsimane aged 50+.
NOTE: N = 325, controlling for age, sex, BMI, Spanish fluency, and village distance to the market town of San Borja. Methodological details are provided in footnotes.

strong predictor of Tsimane depression: Adults aged 50+ in the top decile of disability[6] score 14 percent higher on depression than those in the bottom decile after controlling for potential confounders ($p < 0.001$) (see Figure 9-2).

Tsimane perceptions of how to improve quality of life support a strong, potentially bi-directional link between productivity and psychological well-being. When we asked 723 adults aged 40+, "If you could change some-

[6]As part of the THLHP's monitoring of functional status in older adulthood, participants aged 50+ performed a modified battery of mild exercises originally used in the MacArthur Studies of Successful Aging. We coded whether subjects experienced any difficulty (yes = 1, no = 0) standing from a chair without using their arms, standing repeatedly, and balancing in the tandem position, and on each leg, without using the arms or body. We also measured time taken (in seconds) to walk three meters, pivot, and return as quickly as possible. Eleven measures were summed to create a "disability score" (mean ± SD = 11.2 ± 2.9, range = 5.5-21.0, n = 325).

thing in your life to make you happier, what would you change?" *higher subsistence productivity* and *lower frequency of illness* were the most common responses for both sexes. Iraqw and Datoga women of rural Tanzania similarly report hunger and morbidity as major life stressors (Pike and Patil, 2006). Indeed, across diverse societies, cross-sectional and longitudinal studies have documented strong positive associations between functional status and psychological well-being (Ormel et al., 1994; Covinsky et al., 2010; Lindwall et al., 2011). We hypothesize that this relationship is mediated in part by resource transfers, as greater functional ability increases economic productivity and the extent of food and other transfers to both kin and non-kin.

Resource Transfers Mediate the Effect of Productivity on Psychological Well-Being

Preferential sharing partnerships are common in small-scale societies, and individuals generally share less with those who give less (Jaeggi and Gurven, 2013a; Jaeggi and Gurven 2013b).[7] Indicators of productivity and generosity are thus highly valued by both sexes in same- and opposite-sex partnerships. Hunting performance and meat sharing may be two of the most important routes to prestige and status among men in hunter-gatherer societies (Kaplan and Hill, 1985; Hawkes and Bliege Bird, 2002; Smith, 2004; Gurven and Von Rueden, 2006; Von Rueden et al., 2008). Women's desirability as a social partner (as perceived by other women) increases with reputation of being hard-working and a good mother (Rucas et al., 2006). Across cultures, preferred mate characteristics including dependability, emotional stability, maturity, good health, and intelligence (Buss et al., 1990) are reliable and valid indicators of current and future productivity for both sexes.

Given fitness benefits of high social status and mate value (see Von Rueden et al., 2008, 2011, and references therein), gaining recognition as a high producer and as generous might be a psychological goal in many cultures. Providing support to others can increase support received during periods of greater need (Gurven et al., 2000), thus increasing resilience to negative shocks including illness or injury. Consistent with the gaining-recognition hypothesis, providing support appears to increase well-being regardless of whether aid is reciprocated. For example, among older married Americans, self-reported support provided to others (kin and non-kin) in the form of assistance with daily tasks and emotional support reduces

[7]Contingency is important in sharing relationships, but dyadic imbalances may be common in the short or long term since sharers may subsequently receive from multiple parties (recipients or nonrecipients) and since exchange may consist of multiple currencies.

risk of mortality prospectively, even after controlling for support received (which did not consistently affect mortality risk) and other confounders (Brown et al., 2003). Similarly, older American adults with greater self-perceptions of "generativity" (concern for the well-being of others) engage more frequently in socializing and providing support, and are also less likely to experience functional disability prospectively (Gruenewald et al., 2012). In contrast, net dependence among older adults can increase risk of depression and further impair functional status rather than improve it (Seeman et al., 1996; Liang et al., 2001). "Feeling burdensome" to others providing support is associated with depression among younger and older American adults (Brown et al., 1999; Liang et al., 2001). Together these results suggest a positive association between support given and received, and between net support given and psychological well-being.

Prolonged social isolation in adulthood was probably rare over human evolutionary history given high fertility, frequent resource pooling, and minimal privacy in kin-based residential groups. While there is some ethnographic evidence of "elder neglect" and practices facilitating hastening of death among frail "net consumers," there is also evidence that such decisions are made by elders themselves, suggesting few conflicts of interest (Glascock, 2009). In pre-demographic transition societies, net food flows are downward, from grandparents to parents to children, and grandparents may also provide nonmaterial contributions by resolving conflicts or adopting roles as leaders, orators, and shamans (Keith et al., 1994; Hawkes, 2003; Gurven and Kaplan, 2006; Kaplan et al., 2010; Gurven et al., 2012). Given a modal age of adult death of about 70 among foragers and forager-horticulturalists (Gurven and Kaplan, 2007), few adults live long enough to be a net burden on kin. This minimizes risk of interpersonal conflicts over time and resource allocations, and risk of social isolation. Whether reduced ability or willingness to provide material or nonmaterial support increases risk of loneliness remains unexplored in small-scale societies. Nevertheless, in a random sample of private residences in the Netherlands, Gierveld and Dykstra (2008) found an inverse association between number of generations supported (financially, emotionally, or instrumentally) and degree of loneliness after controlling for potential confounders. Perceived or real lack of social support and loneliness are well-documented predictors of reduced well-being in modern societies (Steptoe et al., 2013; Teo et al., 2013). The effect of social isolation on mortality risk may even rival effects of well-established mortality risk factors such as smoking, hypertension, and obesity (House et al., 1988; Holt-Lunstad et al., 2010).

In sum, available evidence from small-scale societies suggests that risk of depression increases with age, as health, functional ability, and productivity decline, and is not characterized by a "mid-life crisis" as in modern societies (Blanchflower and Oswald, 2008). There is increasing recognition

worldwide that depression among the "oldest old" (age 85+) may be more common than previously thought (Luppa et al., 2012), yet depression is not an inevitable aspect of aging. Functional ability is an important mediator of age-related change in psychological well-being cross-culturally (Kunzmann et al., 2000; Fiske et al., 2009; Stieglitz et al., 2014). Aside from lowering productivity, functional disability may reduce investment in reciprocal sharing relationships, social status, and mate value, which can independently reduce psychological well-being.

In the next part, we consider marriage as a reciprocal relationship uniquely poised to influence psychological well-being given the central role of production and kin transfers. We focus on the extent to which marital conflict over appropriate levels of paternal investment affects mental and physical well-being of reproductive-aged women.

PART II. SEXUAL COOPERATION, CONFLICT, AND PSYCHOLOGICAL WELL-BEING

Marriage[8] is a human universal and probably the most complex cooperative relationship that humans form. Marriage involves coordinated resource production and distribution, child care, sexual responsibilities, and novel opportunities for resource transfers within and among families. Marriage is a fundamental form of risk buffering as it facilitates a sexual division of labor necessary to provide the adequate complement of resources upon which humans rely. In modern societies, entering into marriage may improve psychological well-being relative to remaining single, particularly early in the union (Musick and Bumpass, 2012). Marital problems can reduce household productivity, increase risk of union dissolution, and potentially affect fitness outcomes for both parental and non-parental caregivers. Self-reported marital problems predict depression for both sexes (Kiecolt-Glaser et al., 1987; Choi and Marks, 2008). Common causes of divorce worldwide include conflicts over relative work effort of either partner, how fruits of labor are divided, and pursuit of extramarital affairs (Betzig, 1989).

Life history models acknowledge cooperative and conflictive elements of marriage (e.g., Borgerhoff Mulder and Rauch, 2009; Gurven et al., 2009; Holland Jones and Ferguson, 2009). These models borrow from household bargaining models in economics (Himmelweit et al., 2013) and illustrate how partners may negotiate investment decisions both within and outside of marriage. Although empirical studies of the causes and consequences of marital conflict in small-scale societies are rare, Stieglitz et al. (2011, 2012a)

[8] "Marriage" refers here to any sexual pair-bond, including noncohabiting and cohabiting relationships.

have recently shown that men's diversion of household resources (e.g., through infidelity) is the most prominent source of intense conflict within Tsimane couples (see below). Throughout the developing and developed world, men are more likely than women to commit infidelity and squander household resources (Haddad et al., 1997; Atkins et al., 2001). Next we briefly review the logic underlying life history models of bargaining in marriage, and we highlight how sex differences in embodied, relational, and/or material capital affect household decision-making and maternal well-being.

Marital Cooperation and Conflict in Small-Scale Societies

Several features of human life histories increase costs to both sexes of switching marital partners, including prolonged offspring dependency, rearing multiple dependents simultaneously, and intense bi-parental provisioning and care of offspring (Winking et al., 2007; Lancaster and Kaplan, 2009). Marriage enables men and women to attain fitness benefits through joint production of offspring, which produces an economy of scale such that the fitness of the pair exceeds the summed fitness of solitary partners. Children are a shared public good in the sense that they are a fitness outcome for both partners, regardless of the investment each provides. Our principal hypothesis is that a primary determinant of marital conflict and reduced psychological well-being of at least one partner in the union is the diversion or withholding of resources by one partner that the other partner expects. We also hypothesize that differential bargaining power between the sexes determines both the extent and resolution of marital conflict.

In small-scale societies lacking material wealth, bargaining power derives from an array of embodied and relational characteristics (e.g., body size, skills, coalitional support). Given men's greater size and strength, intimate partner violence (IPV) may be used as a "bargaining chip" to strategically leverage a selfish outcome, despite potential costs to the victim, aggressor, and offspring. Recently Stieglitz et al. (2011, 2012a) have argued that men use physical violence in marriage to control women's responses to the diversion of household resources, often in pursuit of extramarital affairs (hereafter paternal disinvestment). IPV functions to quell women's objections to paternal disinvestment, maintain maternal investment, and dissuade women from pursuing relationships with other men. Among Tsimane, 85 percent of married women report ever experiencing IPV (n = 110), despite a lack of formal patriarchal institutions and potential risks to abusive husbands of physical retaliation or economic sanctions (e.g., reduced food or labor sharing). Roughly 60 percent of violent incidents directed toward wives (n = 124 incidents) occur during arguments over paternal disinvestment. Physical coercion can enhance male bargaining power by undermining women's productivity or social ties, thus limiting

women's options in or outside of marriage. Well-established health consequences for women experiencing abuse (physical or emotional) include depression and other mood disorders.

Relational capital can increase women's marital bargaining power. Close proximity of the wife's natal kin per se does not increase the extent to which spousal interests converge, but can influence whose interests prevail in negotiations (e.g., Sear and Mace, 2008). One might expect matrilocal residence to improve women's psychological well-being through multiple pathways. Matrilocal residence is associated with increased paternal investment, decreased self-reported marital strife for men and women, and reduced risk of IPV against women (Erchak, 1984; Counts et al., 1999; Stieglitz et al., 2011). Beneficial effects of matrilocal residence on maternal psychological well-being may be especially salient during times of increased household demand (e.g., following birth). Future research should determine behavioral and physiological mechanisms underlying the association between residential status and maternal and child well-being, and the relative importance of various alloparental inputs (e.g., food, childcare, advice), especially among new mothers.

Market Integration Can Exacerbate Gendered Inequalities in Resource Access

In high fertility societies with minimal access to contraception, market integration provides novel opportunities for conflict over men's parental investment decisions, with direct implications for household well-being. Market integration may take several forms including town visits, schooling, sale of subsistence goods, and itinerant wage labor. Wage opportunities are often sporadic and incompatible with provisioning of high-quality childcare because they entail risk or require extended travel and village absenteeism. This discourages women's market participation and increases women's dependence on men for critical market goods and services. Gendered inequalities in access to market wealth can increase the degree of coercive control used and tolerated in marriage. Solitary labor migration mitigates reputational risk of paternal disinvestment (if unknown to others), inhibits retaliation by wives and other interested parties, and may create desires among men for extramarital partnerships to relieve loneliness (Smith, 2007; Wardlow, 2007). Money is fungible, liquid, seldom saved, disproportionately controlled by men, and can easily be squandered at substantial cost to the family without directly risking marital dissolution. Economists have long recognized that reallocating income from fathers to mothers increases children's consumption, nutritional status, and well-being; increases in men's income result in greater expenditures on tobacco and alcohol more than increases in women's income (Haddad et al., 1997).

Tsimane wives often accuse husbands of improper use of wages, resulting in arguments that increase women's risk of experiencing IPV (Stieglitz et al., 2011, 2012a). Unpublished results confirm high levels of wage diversions by married men, although there is much inter-individual variability. In a 2010 survey conducted among men in a village near the market center, 59 percent (20/34) report ever pursuing commercial sex opportunities (9 percent report 1 instance, 29 percent 2-5, 3 percent 6-9, and 18 percent ≥ 10 instances). Wage diversions bear direct health consequences for wives. For example, we find that relative to wives in remote villages, wives residing near the market center experience greater likelihood of trichomoniasis, a sexually transmitted infection (STI), despite having easier access to modern healthcare and schooling (Stieglitz et al., 2012b). Tsimane women's risk of STI appears to be independent of their own sexual behavior, which is consistent with prior research in the developing world identifying men's extramarital sexual behavior as a major source of HIV infection among wives (Silverman et al., 2008).

In sum, in the case of the Tsimane, men's withholding of parental investment and diversion of time and resources away from the family (especially in pursuit of extramarital sex) are the most common causes of marital conflict and physical wife abuse. Sexual conflict over parenting effort appears to increase with market integration and fungible resources for mating effort. At present, we cannot determine empirically whether marital conflict is a source of reduced psychological well-being in adults (and perhaps children, through the indirect effects mentioned above). We suspect that this is the case in light of the fact that worldwide, maternal anxiety, depression, and post-traumatic stress disorder appear to be prevalent mental-health sequelae of reduced family functioning (Campbell, 2002). Yet despite potential costs to women and children of paternal disinvestment, maternal resilience is highly variable and responsive to socioecological factors influencing the importance of bi-parental care and the availability of kin. The extent to which conflict over paternal disinvestment affects maternal well-being, therefore, depends in part on women's alternative sources of parental investment.

PART III. EXISTING MODELS OF DEPRESSION AND FUTURE RESEARCH DIRECTIONS

Darwin hypothesized that mood and emotion[9] evolved by natural selection to motivate responses to recurring adaptive problems (Darwin, 1872). Positive valence motivates continuation of prior behaviors associated with

[9]Compared to emotions, moods are longer in duration and more indirectly associated to specific cues.

its occurrence, while negative valence motivates disengagement and pursuit of alternative strategies (Seligman, 1975; Nesse, 2000). The productive value hypothesis developed here posits that depression is a consequence of reduced ability to produce and transfer resources that are valuable to self and/or kin (see also Stieglitz et al., 2014). The second corollary hypothesis is that the withholding or diversion of resources, relative to expectations of transfers, causes conflict with downstream negative impacts on psychological well-being. Table 9-2 provides a summary of other approaches to depression within an evolutionary framework. While there are some important differences among these approaches, the productive value hypothesis helps unify and organize several shared features.

The common finding across cultures that support given to others and "feeling needed" are associated with indicators of greater mental and

TABLE 9-2 Summary of Previous Evolutionary Hypotheses of Depression

Hypothesis (source)	Benefit of Depression	Some Evidence for Hypothesis
1. Avoiding obsolescence (Brown et al., 1999; de Catanzaro, 1984, 1991)	Minimizes inclusive fitness losses via withdrawal.	Depression, hopelessness, suicidal ideation, and suicide attempts are associated with perceptions of being a burden on kin.
2. Bargaining/"labor strike" (Hagen, 1999, 2002, 2003)	Imposes costs on others as a negotiating tactic designed to improve one's circumstances.	Post-partum depression in women is associated with increased paternal investment.
3. Reduced social risk (Allen and Badcock, 2003)	Avoids exclusion from vital social relationships by inhibiting risk-taking and competitive desire.	Depression is associated with inadequate social support (perceived or real).
4. Analytical rumination (Andrews and Thomson, 2009; Watson and Andrews, 2002)	Ensures availability of cognitive resources to focus attention on problem solving.	Depression is associated with persistent musing over problems prompting the depressive episode.
5. Effective goal pursuit (Nesse, 2000; Price et al., 1994)	Prompts disengagement from unproductive efforts, including social competition.	Depression is common among those pursuing "unreachable goals," or following defeat in competition.
6. Pathogen host defense (Anders et al., 2013; Raison and Miller, 2012)	Conserves metabolic resources to promote immune defenses against pathogens.	Depression is associated with greater immune activation.

physical well-being (e.g., Brown et al., 2003; Gierveld and Dykstra, 2008; Gruenewald et al., 2012) is consistent with a human life history perspective emphasizing the importance of downward net resource transfers in adulthood and old age. Suicide, an extreme manifestation of depression, may be more likely to occur among individuals who are a net burden on kin (de Catanzaro, 1984, 1991). Depression and suicide may therefore mitigate inclusive fitness losses among individuals who extract more resources than they provide (Brown et al., 1999). This "avoiding obsolescence" hypothesis of depression is consistent with the logic of our more general hypothesis linking resource production, distribution, social relationships with kin and non-kin, and psychological well-being. Whether depression helps individuals devise novel strategies for increasing one's industriousness or utility in other domains during periods of declining caloric productivity, thereby reducing the net burden on kin, merits further consideration.

Several adaptive models posit that depression functions primarily to elicit social support, which suggests increased psychological well-being following support received (Table 9-2). For example, depression is hypothesized to solicit greater investment from a social partner by imposing costs on that partner (the "labor strike" hypothesis) (Hagen, 1999, 2002, 2003); avoid exclusion from vital social relationships (Allen and Badcock, 2003); and improve one's ability to solve social or other problems through rumination (Watson and Andrews, 2002; Andrews and Thomson, 2009). Yet the hypothesis that receiving support improves either mental or physical well-being has not been supported empirically (Seeman et al., 1996; Liang et al., 2001; Brown et al., 2003). In light of the Tsimane findings, the links between supports given and received (perceived and real) in core cooperative relationships, the degree and resolution of interpersonal conflicts, and psychological well-being merit further consideration. In addition, whether depression "serves" to elicit support, or is simply an outcome of not receiving it, remains unclear.

As mentioned in the Introduction, a different perspective interprets depression as a maladaptive byproduct of modern lifestyles. This "immune dysregulation hypothesis" posits that reduced infectious microbial exposure during development in Western settings contributes to insufficient anti-inflammatory signaling, which promotes hyper-inflammatory responses to psychosocial or other stressors and induces depression (Raison et al., 2010; Rook et al., 2013). It may be that these factors exacerbate the risk of depression, but we find that reduced subsistence productivity and resource transfers are associated with depression in a small-scale society.

Prospective studies of the causes and consequences of depression are necessary to test unique predictions derived from alternative hypotheses. Empirical evidence that depression leads to improved outcomes (e.g., repaired social relationships) is actually quite scarce. In fact, contrary to this

logic, history of psychological disorder is a strong predictor of subsequent psychological disorder (Kuh et al., 1997). It therefore remains unclear whether depression serves an adaptive function, or whether depression is a pathological extreme of an adaptive mood continuum. Given that depression may not be necessary to combat infection or negotiate social relationships, and that depression may not be reversible even if health or social conditions improve, an adequate adaptive theory must explain why natural selection would favor a depressed phenotype given the costs in a highly social species. A major opportunity cost of depression is foregone economic productivity, yet few hypotheses acknowledge that opportunity costs of depression (and thus whether depression manifests) may be variable within an individual over time, as productivity and the ability to impact well-being of kin change.

Directions for Future Research

This paper provides a framework for linking social relationships and social context to psychological well-being in adulthood. The central prediction is that deviations from expected flows of resources and assistance affect well-being. We emphasize disruptions in resource flows via two routes: (1) the inability to produce and transfer resources, and (2) resource withholding or diversion. The factors affecting each of those two sources are likely to vary over the lifecourse and by context.

One direction for future research is how social context affects psychological-well-being through the first route. How do expectations about transfers vary by age, gender, SES, social network, region, and other factors? What are the primary determinants of those expectations? What factors affect within-population variance in the ability to provide expected transfers, and the willingness to provide transfers at similar levels of ability? Does the lack of recipients of transfers (for example, due to childlessness or distance) have the same effects on well-being as the inability to produce and transfer resources? Do impediments to the ability to produce and transfer resources have purely additive impacts on psychological well-being, or do they interact with other social factors, such as community involvement and government subsidies?

With respect to the second route, similar questions can be asked about expectations, the determinants of their variability, and within-population variation. We have focused primarily on interpersonal conflicts in marriage, derived largely from deviations in expected paternal investment, and the links between expectations, conflict, and psychological well-being merit further investigation. There appears to be significant variability in the degree of psychological resilience in the context of family adversity (e.g., Patterson, 2002). What factors affect bargaining power within the family, and how

do those factors shape both the likelihood of conflict and the downstream psychological consequences of those conflicts?

Lastly, in this paper we have focused primarily on the family and broader kin relationships, because of their centrality in the lives of people. However, as mentioned above, social embeddedness goes beyond the family and kin group. Investigating the relationship between expectations of transfers and psychological well-being in other relationships is likely to be fruitful. Future research should consider the broad scope of social exchange networks across a variety of currencies (e.g., calories, money, information).

CONCLUSION

The productive value hypothesis attempts to explain behavioral mechanisms underlying mood regulation across the continua of valence and arousal, while recognizing that stressors and stress responses vary by phenotypic condition, across life stages, and across ecologies. While this framework requires more development (e.g., we do not consider the role of heritability or identify physiological mechanisms), it is the first to explicitly link physical health, productive capacity, sociality, and mental health in small-scale societies.

Depressive symptomology appears to be regularly experienced under conditions more similar to the ones in which humans evolved and is not simply a by-product of modernity. Poor health appears to be causally implicated in the onset of depression cross-culturally,[10] yet not all sick individuals experience depression. Understanding factors that promote resilience to chronic morbidity and adverse life events is an important scientific and practical goal, as much of the world's population lives in poverty.

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[10]The association may be bi-directional (e.g., if depression induces alcoholism or other adverse health behaviors).

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10

Intergenerational Transfers, Social Arrangements, Life Histories, and the Elderly

Ronald Lee

Because of the historical emphasis on energy flow within individuals rather than among the members of a family, intra-individual tradeoffs have played a much larger role to date than intergenerational tradeoffs. . . . (Stearns, 1992, p. 80)

INTRODUCTION

A transfer is a gift with no quid pro quo. It is not reciprocal; it is not an exchange. An intergenerational transfer is a gift of food or assistance by one generation to another, typically a descendant. The descendant, when mature, then herself makes a similar transfer to her offspring or grandoffspring. The chain of transfers continues downward from one generation to the next, never returning to earlier generations.

Reproduction is an intergenerational transfer. Building an offspring requires energy. Helping it survive and grow takes additional energy, provided in a seed or egg, or as a capital bequest (as when a dung beetle lays its egg on a dung ball or a wasp lays its egg in prey) or through progressive feeding as the offspring grows over an extended period (as in mammalian lactation or a bird feeding its chick). In addition, the parent incurs risks in reproduction and may provide services requiring energy expenditure such as building nests or burrows, guarding, ventilating, fanning, warming, and training the offspring. While reproduction involves costly transfers, it lies at the very heart of evolution and natural selection, and does not require explanation through kin selection or inclusive fitness.

Yet many questions arise about the intergenerational transfers associated with reproduction. How many offspring versus how much investment in each (quantity versus quality)? For how long does an offspring receive transfers, and how are these transfers related to growth and to the age of sexual and economic maturity? Is duration of offspring dependency related to adult longevity? What factors favor the co-evolution of transfers and longevity? How does the marginal fitness value of energy vary across the life span, and how is this age pattern related to transfers and fertility? How are transfers related to sexual dimorphism? Could upward transfers from adult child to older parent evolve? Are intergenerational transfers a form of cooperative behavior? Is menopause related to transfer behavior?

As Stearns (1992) suggested in his classic work, life history theory has focused mainly on intra-individual tradeoffs (the allocation of energy among growth, maintenance, survival, and reproduction) and paid less attention to intergenerational tradeoffs. Yet intergenerational transfers can profoundly alter the energetic budget constraint faced by the individual organism over its lifecourse, since an offspring receiving transfers can consume more than it acquires through its own efforts, in which case adults must consume less than they acquire.

My own research, much of which is joint with Cyrus Chu, and sometimes also with Hung-Ken Chien or Carl Boe, has focused on the role of intergenerational transfers in life history theory. Here I will discuss this topic with heavy emphasis on my own research. In a nutshell, parents invest in the quality of their offspring when such investments yield a higher fitness rate of return than would parental consumption of those resources. Parental transfers permit offspring to grow faster for a longer time to a greater size or complexity (e.g., the brain or body armor) or to mature earlier. The balance between quantity and quality of offspring evolves as well, with orchids and oysters close to the "corner" of maximum number of seeds with minimum size of each, and humans and dung beetles at a low fertility interior optimum with great investment in each offspring.

When evolution raises or prolongs such investments, the age at maturity is postponed and nutritional dependency is extended to older ages. In this case parental death entails the wasteful death of offspring in whom much has already been invested, so selection favors longer adult lifespan, perhaps including post-reproductive lifespan.

When there is long offspring dependency, there is also a fitness reward for cooperative breeding as a form of life insurance, with other adults available to substitute for parents who die. Similarly, there is a fitness reward for cooperative food sharing because it eases the lifecycle squeeze when there are multiple dependent offspring at the same time, a situation that is particularly important for humans (Lee and Kramer, 2002). Thus, investments in offspring quality through substantial and prolonged intergenerational

transfers create conditions that favor the evolution of cooperative breeding. Cooperative breeding itself likewise alters the forces of selection on levels and age patterns of fertility and mortality, and provides some evolutionary opportunities for free-riding.

These basic ingredients provide a foundation for considering the evolution of menopause and post-reproductive survival, time preference, specialization and division of labor between younger and older adults, sexual dimorphism, and some incentives for reproductive cooperation.

SENSITIVITY AND SELECTION

My personal starting point was Hamilton's (1966) analysis of how natural selection molds senescence. Hamilton's study used sensitivity analysis, asking how much a perturbation in fertility or mortality at a given age would affect reproductive fitness measured by the intrinsic rate of natural increase (stable population growth rate). Hamilton assumed that deleterious mutations occur at some rate at birth, with each one raising mortality at a specific age. (He thought this approach was less applicable to fertility since it ignored tradeoffs.) If fitness at that age is highly sensitive to mortality, then such mutations would be deselected from the population rapidly. In the balance reached between arrival of new mutations raising mortality at that age and selection removing them, fewer mutations would be present in the genome, so mortality at that particular age would be lower than otherwise. The accumulation of mutations affecting mortality at a given age is inversely proportional to the strength of selection at that age (see Charlesworth, 1994). The mechanism at work is negative selection on deleterious mutations. Because the sensitivities are calculated based on the observed values of fertility and mortality at each age, which are taken as given, there is an element of circularity in the theory. Furthermore, it has now been shown that the linearity assumption underlying most such calculations leads to incorrect conclusions (Wachter, this volume).

Hamilton's analysis implies that the force of selection against mutations that raise mortality at a given age is inversely proportional to expected remaining fertility at that age, and predicts a very rapid increase in mortality at ages after reproduction ceases (menopause in human females). The long post-reproductive survival of humans is a puzzle for the theory, although it was understood that post-birth parental care probably played a role. Similarly, the theory predicts that mortality will be low and constant from birth until the age of start of reproduction, and the actual pattern, in which it declines following birth, is a puzzle for the theory.

In Lee (2003), I developed a model that added food and intergenerational transfers to the purely demographic model of Hamilton. In my model, fertility is a positive function of lifetime consumption and mortality

is negatively related to it. Foraging productivity is also positively related to higher lifetime consumption levels, since they would lead to bigger body size, better health, and perhaps better brains. Individuals of all ages live in food-sharing groups in which population age distributions are on average stable and depend on the levels of fertility and mortality determined by the model. Foraging success depends also on overall population density relative to a given resource, so population equilibrates eventually at a particular density, foraging productivity, fertility, mortality, and age distribution. At young ages, individuals may receive transfers from adults and, therefore, consume more than they produce. The overall population age distribution is stable and the analysis is comparatively static.

I then find an expression for sensitivities to perturbations in mortality and fertility in the neighborhood of the equilibrium, drawing conclusions about age patterns of mortality using arguments similar to Hamilton's. In this model, higher survival at post-reproductive ages contributes to reproductive fitness if older individuals make net transfers of food to young members of the population (perhaps offspring or grandoffspring). The force of selection against mortality starts at a low level at birth and rises up to an age between reproductive and economic maturity, so mortality is high following birth, declines until maturity, and then rises throughout adulthood but with substantial post-reproductive survival.

The general conclusion is that the force of selection against higher mortality at a given age is proportional to a weighted average of the share of lifetime net fertility remaining above that age (as in Hamilton) and the share of remaining lifetime net transfers to others above that age. If the species in question makes no transfers after birth, then the weight on remaining fertility is unity and the weight on remaining transfers is zero, giving the classical result of Hamilton (1966). If the species in question makes transfers to the point where the tradeoff between quantity and quality of offspring is optimal, then the remaining-fertility component gets zero weight and the force of selection depends entirely on remaining transfers, which get a weight of unity. Intermediate weights can also occur according to explicit expressions in the analysis.

Based on observed fertility, mortality, and patterns of intergenerational transfers for some hunter-gatherer groups, Figure 10-1 plots actual age-specific mortality, the mortality predicted by the Hamilton analysis, and the mortality predicted by the theory of Lee (2003) incorporating intergenerational transfers. The agreement with the transfer theory is quite striking, but I view this as in part coincidental. There are many empirical difficulties with the estimates of food transfers, and food transfers are only one aspect of the ways older humans help younger ones, and surely many other forces are at play besides those incorporated in the model. Nonetheless, the figure is encouraging.

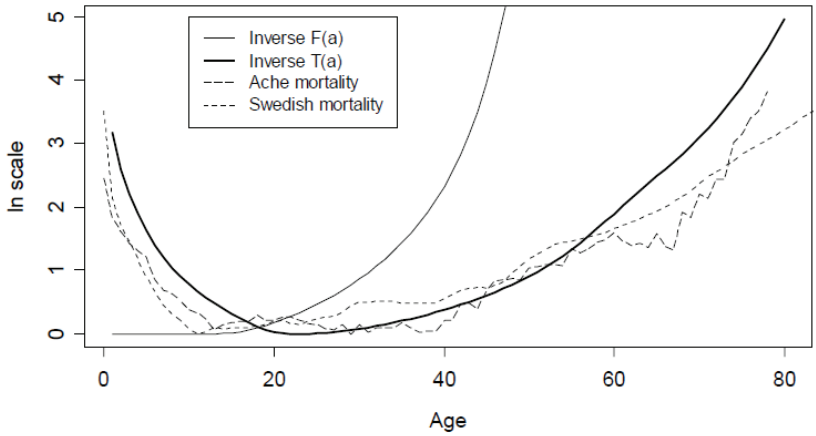

FIGURE 10-1 Comparison of actual mortality schedules for Aché and historical Sweden (1750-1754) with those predicted by force of selection for Hamilton theory and theory including transfers.
NOTE: F(a) is the share of lifetime net maternity remaining at age a, ranging from 1.0 until the age of sexual maturity to 0 at the first age at which fertility reaches 0, at some time before menopause. T(a) is the share of lifetime net transfers to others remaining at age a. At birth (or conception) this zero, since transfers made and received over the remainder of life are equal. From zero this share rises until it peaks at the age when the average child becomes nutritionally self-sufficient and then begins to make net transfers to others, which happens around age 18 or 20 for hunter-gatherers. After this, the share remaining declines with age until death.
SOURCES: Swedish mortality from Human Mortality Database. Aché mortality and fertility from Hill and Hurtado (1996). Transfers T(a) calculated from Kaplan (1994). See Lee (2003).

MICROSIMULATION OF THE TRANSFER MODEL WITH EXPLICIT FOOD-SHARING GROUPS AND RULES

The theory and analysis just described, in Lee (2003), raises questions: How could the populations of sharing groups be stable when individual families would have been tiny, perhaps with only one or two or three members? How could the catastrophic effects of a parental death be reflected in the analysis when in stable populations all ages are always present? How could comparative analysis of outcomes for gene lines be appropriate in the context of a mutation accumulation mechanism that would mean that every individual had a different mix of deleterious genes? These questions motivated a microsimulation approach (Lee, 2008). While Lee (2003) applies to any species, the microsimulation analysis is calibrated for human hunter-gatherers.

The simulations are single sex. Individuals inherit the genome of their mothers, but experience random mutations at birth. They live together in small food-sharing groups within which intergenerational transfers take place. Group membership is built up from membership in "matriarchies" consisting of all the living descendants of a single living female. Different rules for membership in sharing groups are considered, for example: (a) sharing only within matriarchies, which are therefore strongly kin-based or (b) sharing within groups containing up to third cousins, and therefore within bigger groups with weaker kin ties or (c) sharing within groups of 8 to 25 members that contain several distinct third-cousin groups, consistent with hunter-gatherer ethnographies (Lee, 2008). When group sizes fall below 8 members then two groups fuse, and when they rise above 25 members, they fission; or (d) sharing within groups like (c), but with the constituent up-to-third-cousin groups reshuffled every five cycles (25 years) to reflect the actual fluidity of group membership; or (e) sharing at the level of the total population, an unrealistic specification that should mimic the Hamilton results. Within the (b) through (e) type groups, the completeness of sharing among versus within the constituent matriarchies or third-cousin groups can be specified, but typically half of food acquired by a kin group is consumed by it directly, and half is shared with other kin groups. The general setup is guided by descriptions such as Hill and Hurtado (2009): "food provisioning is ubiquitous, generally biased in favour of helping families with large dependency loads and not limited to kin assistance."

Food consumption and the transfers implicit in these sharing arrangements affect reproductive fitness because each individual's fertility and mortality are related to its food consumption. These relationships are calibrated on estimated relations in historical demographic data (Lee, 2008).

Age distributions within sharing groups reflect stochastic births and deaths. Mutations occur randomly at each birth so there is genetic heterogeneity within groups and among kin. Catastrophic effects of maternal death may occur, or the consequences of maternal death may be buffered by the presence of other adults in the sharing groups. In these ways the simulations avoid the questions raised above, but do not avoid a degree of circularity. They can assess the underlying coherence and consistency of an age-patterned set of behaviors—fertility, mortality, and transfers. However, they are based on the observed age shapes of fertility and productivity as inputs.

The basic result is that starting from a flat and very low mortality schedule, after 75,000 years of simulated evolution along the lines described above, the age-specific mortality schedule assumes a shape much like that derived analytically in Lee (2003) and shown in Figure 10-1. The simulated mortality schedules are shown in Figure 10-2, each corresponding to a different assumed social-sharing rule. The schedule labeled "population level

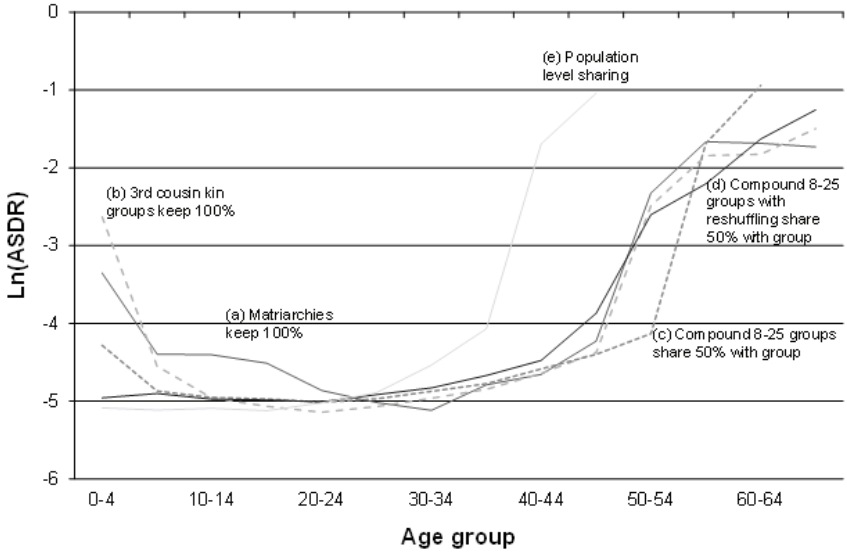

FIGURE 10-2 Simulated evolution of mortality by social arrangement after 75,000 years.
SOURCE: Author's simulations as described in text and Lee (2008) and Lee and Boe (2007).

sharing" assumes that all food is pooled and shared at the level of the total population. In this case, there is no selective advantage to post-reproductive life since sharing is not at all kin-based. In this case, evolved adult mortality conforms to Hamilton's theory: It is shaped solely by remaining lifetime fertility. It rises sharply in the 40s and is completely flat up to sexual maturity.

Schedule (e) mimics the Hamilton results as it should, because here only fertility matters for reproductive fitness, while the transfers that allow the young to survive and grow come from the population at large whether relatives live or die. Schedule (a) assumes food is pooled and shared within matriarchal groups, as defined earlier. In this case, mortality declines after birth and post-reproductive survival emerges. The bulge in mortality from age 10 to 20 reflects child death following maternal death. Schedule (b) assumes all sharing is within third-cousin groups and none between. Here maternal deaths are buffered by help from relatives so the 10-20 mortality bulge disappears, while post-reproductive survival is still selected. Schedules (c) and (d) come closer to actual hunter-gatherer arrangements, and they look quite similar to one another and to the theoretical schedules in Figure 10-1. The different levels and age patterns of mortality above age 45 are largely explained by different probabilities that a surviving adult has

an orphaned grandchild, as shown by a separate analysis of the simulation results.

It is interesting that infant and child mortality is substantially higher in the more closely related groups with 100 percent sharing than in those with less sharing. This happens because with 100 percent sharing within a kin group, when an infant dies, all the foregone future costs of rearing that child are recaptured and reabsorbed by kin and can be used to invest more in siblings or to better nourish the adults. When 50 percent of resources are shared outside the group and received from the other groups, only 50 percent of the foregone future costs of rearing a young child can be recovered by the kin if the child dies. There is therefore greater selective pressure to avoid the child death. Fertility would be expected to be higher when there is sharing outside the kin group, because the costs of raising an incremental child are partially born by non-kin.

WHICH SOCIAL ARRANGEMENTS HAVE THE HIGHEST FITNESS?

In Lee and Boe (2007), we simulated co-existing subpopulations with different social arrangements that interacted only through the influence of total population density (for the sum of subpopulations with all social arrangements) on foraging efficiency. The subpopulations remained totally separate and competed only through their abilities, due to the sharing arrangements, to reproduce and grow at a given density. Other than the sharing arrangements, each evolved over time subject to identical functional constraints and mutation rates. There were three Matriarchal subpopulations, three subpopulations with food sharing within groups with relatedness up to Third Cousin, and three subpopulations with larger sharing groups of 8 to 25 individuals composed of several unrelated Third Cousin groups, in which these groups pooled half of their food and kept half to share with their up-to-Third-Cousin kin. The simulations were run for 15,000 years. Inclusion of three groups of each kind allowed us to assess the role of randomness in the success of the social arrangement.

The clear results for the first 3,000 years are shown in Figure 10-3. The social arrangements in which groups had the fewest sharing adults, that is the Matriarchies with an average of 1.8 members including offspring, went extinct first. The arrangements with Third Cousin groups that had an average of 4.8 members went extinct next. The arrangements with larger sharing groups of 8 to 25 members and an average of 15 members from an average of three Third Cousin subgroups did best and were positively selected. Presumably sharing raised fitness through maternal life insurance and through smoothing of dependency burdens. Social arrangements with broader sharing are able to reproduce successfully at higher densities.

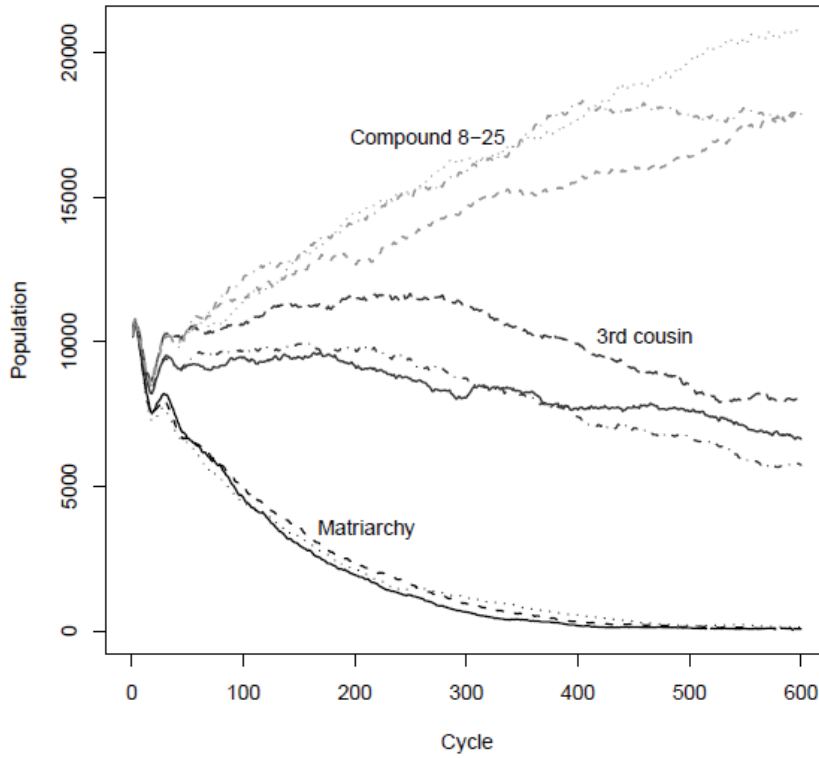

FIGURE 10-3 Evolutionary competition through density pressure on foraging among three types of sharing groups: Matriarchal, Third Cousins, and Compound Sharing Groups with Third Cousin components sharing 50-50 in groups of 8-25.
NOTE: Three subpopulations of each kind are simulated, for a total of nine, over 3000 cycles (15,000 years). Foraging efficiency depends on density of total population of the nine groups, and the kind of group that is able maintain itself at the highest density is selected, while the others go extinct.
SOURCE: Author's simulations as described in text and Lee (2008) and Lee and Boe (2007).

That said, the effect of sharing is to smooth over the demographic variance. In some circumstances, variance might promote fitness rather than inhibit it through inefficiencies. In the simulations shown in Figure 10-3, consumption in childhood was specified to have no effect on productivity in adulthood. In other simulations in which childhood consumption was specified to raise adult foraging productivity, the outcome was the opposite of Figure 10-3: The large sharing groups went extinct first, the intermediate Third Cousin groups went extinct next, and the smallest and most variable

Matriarchal groups won out. The lesson is that variance can be useful, particularly when there is positive feedback. Matriarchal offspring have high variance in consumption while young. For example, high consumption could arise when demographic randomness generates a low dependency ratio due to only one offspring and both a mother and grandmother surviving, and perhaps an aunt. A high-consumption child in the model grows up, by assumption, to be more successful at foraging, and therefore its offspring will themselves consume more and become more successful adults. To quote Clutton-Brock (1991, p. 255): ". . . the effects of variation in parental investment are rarely confined to a single stage of the offspring's life history or a single component of its fitness and can frequently be identified throughout its entire breeding career. Some studies show that the benefits . . . can be transferred across generations, influencing the phenotype and fitness of grandchildren. . . ." Such intergenerational transmission happens in the simulation model (with appropriate settings) and can be strong enough to reward the higher variance in offspring consumption in the Matriarchal units.

The message is that social smoothing of risks can indeed raise fitness, but it can also ensure mediocrity by smoothing out both high success and dismal failure and, in some circumstances, mediocrity may lose.

OPTIMAL LIFE HISTORIES WITH INTERGENERATIONAL TRANSFERS

To get at the more fundamental forces shaping the observed age patterns, I turn to a different approach: finding the optimal life history using analytic methods. This approach avoids the circularity of the mutation accumulation and sensitivity analysis approach. However, one must begin by assuming underlying biological constraints and relationships, and then consider how the organism acquires energy and allocates it among growth, survival, reproduction, and transfers over its lifetime. Here, deleterious mutations are ignored, and the implicit assumption is that a species can evolve to the optimal life history by positive selection on a sufficient variety of beneficial mutations. Because evolution through positive selection of beneficial mutations is implicitly assumed and the analysis is atemporal, the strength of selection does not matter. Only the sign, and not the magnitude of sensitivities, matters. Furthermore, selection is always forward-looking and is therefore conditional on survival to a given age, whereas sensitivities are assessed at birth, as in Hamilton's (1966) analysis. Some baseline conditions for the optimization must be assumed, such as that the organism has a deterministic growth pattern (first growth with no reproduction and then reproduction with no growth) or that the organism has oocytes that tend to decay with age and therefore faces rising costs of fertility with age.

This optimal life history approach is taken in my work with Chu and Chien. While the earlier literature on optimal life histories assumes optimization is carried out over an individual life history, with an organism constrained to consume no more than it produces at each moment, our approach is distinctive in relaxing this constraint by permitting intergenerational transfers. Despite the very different theoretical approaches and assumptions relative to the transfer model described earlier, there are many formal similarities in the results, and the central elements that emerge from the sensitivity approach occur again in the optimal life history approach.

Here are some basic results on the age-shape of mortality across the life span (Chu et al., 2008). If a linear energy budget constraint is assumed for energy expenditures on survival, fertility, and growth, then the optimal life history involves growth without fertility up to some age of maturity, and fertility without growth thereafter, as has been known for some time. This is known as determinate growth, which is characteristic of mammals and birds among others, in contrast to most fish, reptiles, and plants. The results described below are also true of a model with non-linear budget constraints, provided these entail determinate growth.

Consider mortality from birth until maturity. We find that survival from age a to a + 1, p_a, will be proportional to an expression that has in the numerator the weighted sum of two terms. The first term is expected remaining lifetime fertility at age x, the *Hamilton* effect, which is constant across all juvenile ages. The second term is expected remaining lifetime transfers to others at age x, the *Transfer* effect, which rises with age since adult transfers to be made remain unchanged while fewer future transfers will be received as a juvenile approaches maturity. This weighted average is very close to the sensitivity analysis result of Lee (2003). However, there is additionally the possibility of investing in growth before maturity, which is in the denominator of the expression. An investment in growth has a compounded effect because size enables increased energy through foraging and that increased energy is then optimally expended, perhaps on further growth. The compounding is greater for expenditures made at younger ages, with more time for compounding before adulthood. Thus, the denominator declines with age. The rising numerator divided by the falling denominator implies rising survival with age and, therefore, mortality declines from a high level at birth up to maturity.

Now consider adult mortality. The numerator is exactly the same, a weighted sum of the *Hamilton* effect that declines to zero when fertility stops and the *Transfer* effect that gradually declines but remains positive throughout adult life (unless there are net transfers from younger to older in old age). Thus the numerator declines with age but remains positive after fertility ceases. This points to continued survival after completion of fertility as older people raise, through transfers, the fertility and survival of their

descendants and thereby raise their own fitness. By itself, this would imply that survival rates at each adult age were declining and mortality rising.

However, in optimal life history analysis. optimization is forward-looking from each given age, unlike sensitivity analysis, which evaluates a perturbation's impact at birth. For this reason, impact sensitivities for mortality perturbations late in life tend to be small, since relatively few survive to be affected by the perturbation. By contrast, the optimization expression has the probability of survival from birth to age a in the denominator, and this survival declines with age. The declining denominator tends to offset the declining Hamilton and Transfer effects in the numerator, postponing the increase in mortality following maturity and slowing the pace of mortality increase. While the U-shape of mortality remains a prediction of the model, the upswing may start later than maturity. The age schedule of optimal mortality may have a bathtub shape rather than a J-shape, with flat mortality from, perhaps, age 20 to 40, as often found for contemporary hunter-gatherer populations (Gurven and Kaplan, 2007). This flatness could also result from a violation of our determinate growth assumption. Foraging productivity may continue to rise during adult years due to accumulating skills and experience, rather than being fixed at maturity. For example, the hunting productivity of male hunter-gatherers has been found to rise to a peak at age 40.

THE EVOLUTION OF TRANSFERS AND LONGEVITY

In Chu and Lee (2006), preconditions favoring the evolution of transfers include (a) the initial ratio of adults to juveniles is high (and therefore life expectancy is high relative to age of maturity), (b) greater productive efficiency of adults relative to juveniles per unit of body size (and therefore it is efficient when young receive transfers of food that is more easily acquired by adults), and (c) greater efficiency of juveniles in converting energy into body size. Initial low mortality and long life favors the selection of transfers from old to young through (a), but lower mortality itself evolves farther when transfers are greater as discussed earlier. Therefore, longevity and transfers co-evolve in a mutually reinforcing way, as argued in Lee (2003).

THE EVOLUTION OF MENOPAUSE AND INTER-ADULT TRANSFERS

In Chu and Lee (2013), we consider the comparative advantages of younger women and older women, and the efficient division of labor between them. Suppose that for young women, the ratio of productivity in foraging to that in childcare is greater than the corresponding ratio for older women such as their mothers. (If the opposite is true, slightly dif-

ferent results follow, but the principles involved are the same.) Then, in a hypothetical state before the evolution of menopause, it would be efficient if the grandmother spent more time in camp rearing the children and reduced time spent foraging for herself and her children, while the younger mother increased her foraging time and left her children to the care of the grandmother. This efficient division of labor would raise the fitness of both grandmother and her adult daughter, and is the first stage of specialization.

However, the grandmother is less efficient in childbearing as well, with higher costs per birth or lower quality due to the declining quality of oocytes with age. Her continuing childbearing also limits her specialization in providing childcare for her daughter's children. There could be fitness gains for both grandmother and mother if the older woman reduced her fertility and increased her childcare, with the younger mother providing more food. We show that evolution could move the human life history in this direction of further specialization, eventually reaching the reproductive "corner" outcome where the older woman has zero fertility (menopause) and the younger woman has higher fertility, shorter birth intervals, and greater reliance on the older woman's assistance to cope with the increased dependency burden. The older woman would continue to forage for her own subsistence and have no dependent children of her own to feed. This is the second stage of specialization.

However, there is still room for further efficiency gain and increased fitness if the grandmother reduces her foraging even more and relies on food provided by the younger woman, in the limit ceasing to forage altogether and subsisting entirely on upward transfers of food from the younger woman. This is the third stage of specialization.

We show in Chu and Lee (2013) that such a life history pattern could yield higher fitness. Furthermore, under certain parameter restrictions in a two-sex population, the mutations causing this behavior could successfully invade the population. That is, we show that individual selection and not just group selection could lead to this outcome. In this way, menopause, age-specific division of labor, and intergenerational transfers among adults could evolve together. But has this ever in fact occurred?

Ethnographic evidence reviewed in Chu and Lee (2013) suggests that at younger old ages, grandmothers may specialize in foraging rather than childcare, but at older old ages a pattern like the one described above does occur for both men and women. Some species of toothed whales appear to have menopause and extensive post-reproductive survival. The older adults may guard the young while the parents dive to hunt. The adults bring up food to the surface for their young and if some were consumed by the grandparents (I know of no evidence on this point), this would be consistent with the scenario described for humans. However, although such behaviors appear possible and not inconsistent with known facts (for example, for

pilot whales, Orcas, or Sperm whales), they are very far from established, and research on whale life histories is very difficult. Life histories of some other species, such as African hunting dogs or naked mole rats, share some elements of the theory sketched above, although in these the division of labor and reproductive specialization are not based on age but on dominance that may be transitory or by size. There are also some similarities to the reproductive and foraging specialization in eusocial insects.

INTERGENERATIONAL TRANSFERS AND SEXUAL DIMORPHISM

The classic theory of sexual dimorphism, dating to Darwin, begins with the observation that females invest much more heavily in reproduction than do males, starting with the trivial cost of sperm compared to the female egg, and continuing with the costs of pregnancy for viviparous species and birds, and then post-birth care, mammalian lactation, and transfers (although transfers are sometimes shared with males). Consequently, fitness is constrained by the female's resources while the male has resources to spare. Here, the evolutionary path forks. In one direction lie pair bonding, relative monogamy, greater paternity certainty, and male investment of his surplus resources in rearing the offspring, as in the case of humans and many other species.

Down the other fork, the males' surplus energy is devoted to competition for reproductive access to females. Female preferences shape the form of male-male competition, which may be combat based on size, teeth, and horns; sperm competition with large testes and spermicidal weapons; competition by display of colors, claws, tails, dances, or noises; and so on. In this case the male seeks to mate with multiple females, and paternity is highly uncertain. Down the monogamous first fork, sexual dimorphism is slight. Down the second fork, dimorphism flourishes. In Chu and Lee (2012), we develop this classic theory in mathematical form, focusing on the second dimorphic fork, and draw out some new implications. Because successful males father many offspring while most males father none, and because of high paternity uncertainty, the father's transfers would have small fitness value to him, and he has greater incentives to compete for more females, to guard access to the females he already has, and perhaps to protect his purported offspring from lethal assault by other males.

TIME PREFERENCE, TRANSFERS, AND THE MARGINAL VALUE OF ENERGY

Organisms must frequently make decisions about tradeoffs across time, or intertemporal allocations. Most of these are developmental and physiological, and have evolved, but others are strategic and a matter of choice

and decision. Eat a nut now or store it for later? Wait to grow bigger or start reproduction now? Disperse now to breed or postpone this step to remain as a helper at the nest? Search longer for a mate or accept this one now? Bear another litter this year or wait until next?

In general, an incremental unit of energy may have different incremental fitness value at different ages over the lifespan. Often it would have greater fitness impact early in life when it can enhance survival and growth than it would in later adult life when energy is more easily acquired and the perils of early life have already been avoided. Time preference between ages i and j is measured by the number of incremental units of energy at age j an organism could trade for one unit of energy at age i, with no change in fitness (along a fitness isoquant).

Intergenerational transfers evolve in species that have a high rate of time preference between early and adult years. The transfer of resources from the adult to the offspring raises the marginal value of energy to the giver and reduces it for the receiver, tending to equalize them and to move the rate of time preference towards unity across all ages. Paternity uncertainty and the possibility of parental death would likely prevent complete equalization. Chu et al. (2010) develop these ideas in a formal analysis. This general line of theory was pioneered by Alan Rogers and followed by Sozou and Robson.

INTERGENERATIONAL TRANSFERS AND COOPERATION

Individuals in many species cooperate with one another, and their behavior is a mixture of competition and collaboration. A sizeable literature in various disciplines (Bowles and Gintis, 2011; Nowak, 2011) discusses how cooperation could evolve given that defection would often seem to give an advantage, at least in the short term. Cooperation is advantageous because it makes production more efficient, because risk-sharing shifts some resources from those for whom they have a lower marginal value to those for whom it is higher, and because it aids in defense and in acquisition of territory.

The literature appears to be largely about cooperation among adults. An adult who cooperates will on average experience a net individual gain as a consequence. By contrast, an individual adult who makes an intergenerational transfer of food or care to her offspring is permanently worse off as an individual as a consequence. Of course, she raises her reproductive fitness thereby and is therefore better off indirectly, which is why the behavior of transferring to her offspring was selected. But her transfer is not an effort to improve her individual situation. Her recipient offspring will not return the favor to her parent, but will instead herself grow and mature and later make similar transfers to her own offspring. To the extent that the parent

and offspring do help one another reciprocally, the behavior is cooperative or an exchange, not a transfer.

Cooperation resembles a mutually advantageous exchange more than an altruistic act or transfer. Unlike market exchanges, the terms of the exchange are not enforced by rules of the market, police, and a judicial and penal system. Instead, reciprocal behavior develops in the context of repeated interactions that are maintained through mutual benefits, an evolved sense of fairness, and occasional punishment of offenders.

Nowak (2011) discusses five mechanisms through which cooperation could evolve: reciprocity, indirect reciprocity, spatial selection, multilevel selection, and kin selection. Bowles and Gintis (2011, p. 2) define cooperation as ". . . engaging with others in a mutually beneficial activity." As an example, consider a pair of unrelated foragers with families to feed, who are each disabled by illness or injury on 20 percent of the potential foraging days (as estimated in Hill and Hurtado, 2009). They might agree to provide food for one another's family on these days of disability, which would be an example of reciprocity, a form of cooperation that could evolve for foragers who were repeatedly in contact over a long time. (A similar outcome could be achieved in a different institutional setting through formal insurance markets or through money.) Both the foragers and their families are better off with this cooperative arrangement than without.

Intergenerational transfers benefit the recipient but not the giver—other than indirectly through reproductive fitness. Intergenerational transfers are never reciprocal, since by definition there is no quid pro quo. For example, young birds sometimes remain at their parents' breeding site rather than dispersing and assist their parents in rearing their younger siblings as so-called "helpers at the nest." It appears that they do this in exchange for being allowed to avoid risky dispersal by staying at the breeding site, although they may gain a bit through inclusive fitness as well. This is not a true transfer.

In the literature on cooperation, I find very little discussion of fertility, survival, or reproductive fitness (Bowles and Gintis, 2011; Nowak, 2011). To understand the evolution of life histories, in the sense of age-patterning of fertility, mortality, growth, investment in offspring, and behavior over the life span, the evolution of intergenerational relations must be considered. There is remarkably little overlap between this topic and the evolution of cooperation.

COOPERATION AND INTERGENERATIONAL TRANSFERS AS REALLOCATION SYSTEMS

At a general and abstract level, we can consider the possible ways of shifting resources in a population across age and over time. There are only three ways (Bommier and Lee, 2003: (1) saving, accumulation, and then dis-

saving; (2) borrowing, lending, repaying—that is, intertemporal exchange; and (3) transfers across ages or generations. The first, accumulation, can shift resources only forward in time: accumulation (of nuts, berries, a nest or beaver dam, or 401K account) necessarily precedes consumption of the asset or its services. This cannot help a juvenile to grow. The second, intertemporal exchange, is limited in its ability to shift resources from one age to another. It could shift resources to the young only if they repaid those resources at a later age to their elderly parents, which is inconsistent with maximization of reproductive fitness and does not occur in nature, although it does occur in agricultural and industrial human societies. The third possibility, intergenerational transfers, is the only mechanism capable of shifting resources to children to promote their survival and development. A parent may accumulate an asset or capital good, of course, and then give it as a lump-sum transfer to an offspring at birth or at laying, for example a dung ball or paralyzed prey on which an egg is laid. This nonetheless remains an intergenerational transfer.

Cooperation is based on reciprocity. One consequence is that at any instant, the average age of all those contributing and all those benefiting from a cooperative situation are equal. This is obviously true when every participant also simultaneously benefits, since the ages of the contributor and beneficiary are then one and the same. Consider the less obvious case of sharing the risk of disability through food sharing as described above. Suppose hunter X is age A_x, and Y is age A_y. On one day X gives food to Y, and d days later Y gives equal food to X. The average age of givers is $[A_x + (A_y + d)]/2$. The average age of receiving food is $[A_y + (A_x + d)]/2$. Clearly these are equal, and this will be so no matter how circuitous and indirect is the path by which X eventually receives the reciprocal gift. (I call these "gifts" here, but clearly they are not gifts; they are essentially loans to be repaid, directly or indirectly.)

Contrast the case of intergenerational transfers. Suppose each generation is g years older than the next. A parent in generation X makes a transfer to her offspring in generation Y who eventually makes a transfer to her offspring in generation Z. The transfer is always made to someone g years younger than the donor parent. The average age of donors is g years greater than the average age of recipients.

The average participant in the cooperative arrangement, looking to the future, expects to contribute and receive equal amounts. In the language of reallocation systems, there is a zero aggregate credit balance in this system (Lee, 1994; Bommier and Lee, 2002). Individuals who have contributed more in the past than they received, and therefore who expect to receive more in the future than they will contribute, are exactly balanced by those in the opposite situation. The aggregate credit balance is proportional to the difference in average ages of receiving and contributing, which is zero.

The situation is different in the case of intergenerational transfers. Juveniles have already received transfers from their parents, and even if they expect to receive more in the future, at every age after birth these expectations will be outweighed by the transfers they expect to make later when they are themselves parents. For this reason the young have a negative credit balance. As for adults, they expect to continue to make transfers themselves for the rest of their lives so they also have a negative credit balance. In fact, every member of the population expects to make more transfers in the future than will be received. The aggregate credit balance is therefore negative, and indeed is proportional to the difference in average ages of receiving and donating, which is g—one generation. The system of intergenerational transfers enables what would be impossible through exchange, cooperation, and reciprocity. It enables the young to consume more than they produce through their own foraging efforts and therefore to grow faster, larger, and more complex than otherwise. As adults they will never repay their parents, since they received a transfer with no quid pro quo. Instead they will enable their own children in the same was as they were earlier enabled themselves. These points are established in mathematical models and analyses in Lee (1994) and elsewhere.

And what about cooperative breeding? The part of cooperative breeding that involves relatives of the parents and offspring is intergenerational transfers, not cooperation. But in some species, including humans (Gurven 2004; Hrdy 2009), African hunting dogs (Creel and Creel, 2002), and acorn woodpeckers (Koenig and Mumme, 1987), for example, non-kin may assist in provisioning and caring for the young of others. This is a form of cooperative behavior in which the non-kin will expect to receive similar support when they are in similar circumstances, although not necessarily from the same adults that they assisted. In human hunter-gatherer sharing groups, for example, families with higher dependency ratios (more children relative to adults) often receive extra help from others including non-kin (Gurven, 2004).

Lee and Mason (2011, p. 88) report differences between average ages of consuming and producing in hunter-gatherer groups of 11 years and 10 years, based on bio-anthropological studies of contemporary groups in the Amazon Basin (Aché, Macheguenga, and Piro: Kaplan 1994) and the Kalahari (!Kung: Howell, 2010). Multiplying these by one over the aggregate share of transfers in consumption, or by roughly a factor of two, gives the corresponding difference between the average ages of receiving and giving transfers, which would then be 22 and 20 years, respectively. Lee and Mason (2011, p. 92) give estimates of these age differences for private transfers in 17 countries ranging from low-income developing countries to high-income industrial nations, and all are quite similar to these results for hunter-gatherers. Once public transfers are taken into account, however,

the results are dramatically different. Now the average age differences are much shorter, particularly in the rich nations. In two cases (Austria and Hungary), the direction is reversed, with average transfers flowing upwards from young to old rather than the reverse (Lee and Mason, 2011, p. 101). In most rich nations, the average age of consumption now exceeds the average age of earning labor income, and as populations age, these trends will be reinforced.

DIRECT AND INDIRECT GENETIC EFFECTS AND INTERGENERATIONAL TRANSFERS

Intergenerational transfers are all instances of indirect genetic effects, to the extent that the transfer behavior is genetically influenced and therefore heritable. Review articles on indirect gene effects often give maternal care of offspring, the most basic kind of intergenerational transfer, as a lead example of an indirect genetic effect (Wolf et al, 1998; Cheverud, 2003). Certainly the quality and quantity of this care influences the survival, growth, and development of the offspring, in addition to the direct genetic effects operating in the offspring to influence height, speed of growth, body mass, and so on. Later in life, the continued survival and presence of the mother influences her daughters' fertility and the survival and growth of the mother's grandoffspring (Sear and Mace, 2008; Coall and Hertwig, 2011). When the effects of the presence of the mother or grandmother on the survival, growth, development, and reproduction of the offspring are not additive but involve interactions, then there are gene-on-gene (GxG) epigenetic effects that arise through intergenerational transfers. In this case, selection acts on both genes, for example, of mother and offspring, through the offspring trait in question. Therefore the evolution of intergenerational transfer behavior will act through both direct and indirect genetic effects.

HYPOTHESES

1. Longer nutritional and other dependence of offspring on one or both parents is associated across species with longer post-reproductive survival. The length of dependence must be substantial in relation to the lifespan of the mother or parents. In the case of humans, years of dependence for a child, say 18-20 years, is about half of total life expectancy of individuals surviving to maturity. When offspring care is limited to a short time followed by more reproduction, it will be difficult or impossible to separate its effects on longevity from the effects of fertility itself.
2. The male or female parent that is more heavily involved in care and transfers to offspring (if either) will have longer life expectancy,

with due allowance for mortality risks incurred through care and foraging, and for mortality risks incurred in intra-specific competition for access to the other sex. For example, when only the female bird cares for the chicks, she thereby exposes herself to risks of predation while obtaining food for chicks and while attempting to defend the nest against predators. Whether or not she has evolved a lower level of senescent mortality, she typically has higher overall mortality. Unfortunately, it will typically be impossible to make "due allowance" (although analysis of animals in captivity may help), so it may be impossible to test this hypothesis. A study of sex differences in longevity of apes did find that the sex mainly responsible for offspring care did live longer.

3. The period of time in which mortality falls following birth should be associated with the duration of dependency. Unfortunately, it will be difficult to distinguish this hypothesis from the hypothesis that mortality is lowest when reproductive value is highest.
4. In species in which mothers or parents are fully responsible for provisioning and caring for their offspring, in contrast to otherwise similar species in which provisioning and care are provided cooperatively, infant and juvenile mortality will be intrinsically lower in the cooperative groups, by which I mean that mortality will be genetically lower and, therefore, lower than the sharing of food and care could itself explain.
5. Mortality follows a U-shaped pattern, declining from a high level at birth to a low point at sexual/economic maturity, rising to early adulthood and either continuing to rise throughout the rest of life or possibly having a flatter segment for a while following maturity. The flatness may arise in an optimal life history because even in species with deterministic growth like mammals, the accumulation of skills and knowledge may continue after somatic growth has ceased, so the opportunity set may continue to expand (Chu et al., 2008, and references therein). This is not relevant for late life plateaus in mortality.
6. Intergenerational transfers are more likely to evolve in species that (a) have higher ratios of life table person years lived in adulthood to juvenile person years lived; (b) have higher ratios of adult foraging productivity to juvenile productivity; (c) have more efficient conversion of calories received through transfers into somatic growth.

EMPIRICAL ANALYSIS

Consider conspecifics of varying ages and sex, living in a group. They may compete for breeding sites and for food, and members of some age-

sex groups may tend to kill members of other age-sex groups. Offspring in a family may compete with one another for parental care. Some members may assist all others as sentinels or in combating other groups, or defending the group from predators. Some age-sex members may store information and use it to guide group decisions. Others may lead the group. Some may provide food or care for others. It would be impossible to account for all the relevant pathways through which one individual affects the survival and fertility of another. However, the interaction of all these different influences will be a net effect of an incremental member of age x and sex s on the fertility or mortality or fitness of the average member of age a and sex j. A matrix can be formed with all these net effect parameters, for example, for the case of fertility f, where the i,j element is df(i)/dN(j), where N(j) is the number or proportion of group members of age j and f(i) is the average fertility of females age i. This describes an effect evaluated at some given number or population share by age and sex, but the effect may vary depending on the absolute and relative sizes of the cells of the matrix, so we may need more elaborate functions as elements of the matrix. Information on kinship could be added as well, leading to a three-dimensional matrix. In principle, such a matrix could be estimated from data, although there are many pitfalls. A matrix like this expresses the sensitivities described earlier. These sensitivities might then be argued to shape the evolution of life histories.

A matrix of effects from theory combined with focused experiments or field studies could be developed, as has been done in a partial way focusing on optimal clutch size for birds, as well as an attempt to estimate the matrix of effects empirically from observations on a group over time. A coefficient matrix of this sort is what economists would call a "reduced form." It does not incorporate theoretical insights. The virtue of this approach is that it is comprehensive. It measures the net outcome of all ways in which the size of one subgroup affects the other. Instead of simple derivatives in each cell, the cells could contain quadratic or other functions, and population shares or ratios instead of absolute numbers could be used to compute sensitivities.

There is a substantial literature for humans on the effect of the presence of specific kin on the survival or fertility of a reference individual in historical and anthropological populations, as surveyed by Coall and Hertwig (2011) and Sear and Mace (2008). The consistent finding is that the mother has a large beneficial effect on outcomes for children while the father does not; for grandparents, the ranking by size of beneficial effect is maternal grandmother, maternal grandfather, paternal grandmother, and paternal grandfather, generally interpreted as reflecting degrees of certainty about relatedness. Some years ago, I estimated matrices for acorn woodpeckers based on a large longitudinal dataset created by Walter Koenig covering many breeding sites and individuals, to which he generously gave

me access. However, there are serious issues of identification in studies of this sort—shared genes, shared environment, and so on.

This sketch of population dynamics as it is influenced by numbers in different age-sex bins is very general. There can be a focus on particular theories and accounting frameworks. The Leslie matrix incorporates only demographic accounting identities, on the assumption that vital rates are independent of the numbers in the bins. This approach is based on Lotka's equation and its precursors. It was used by Hamilton (1966) to develop his theory of how natural selection molds senescence, based on the idea that the force of selection against deleterious mutations would be proportional to the sensitivity of the intrinsic rate of natural increase to a perturbation in the vital rate affected by the mutation. The optimal clutch size analysis would go a step beyond this Hamilton-Lotka approach by taking into account the inter-sibling competition for parental resources and quality of average offspring as a function of the number of offspring. But there are many other kinds of effects that could be incorporated, such as those arising from density dependence if the territory is bounded.

Earlier I described the model of Lee (2003, 2008), which spelled out a structural theoretical model in which incremental individuals affected others not only through the classic demographic accounting identities, but also through density dependence in food acquisition and dependency in kin groups and broader sharing groups. This dependence indirectly affected fertility and mortality of all members of the broader population, as well as had stronger and more focused effects on kin and sharing group members.

Based on these models, a specific matrix of sensitivities could be constructed. Unlike the Leslie matrix, it would have no zeros because it would be filled by indirect effects operating through density, inter-age transfers, and competition for transferred resources. In this setup, genes have both direct and indirect genetic effects on reproductive fitness (Cheverud, 2003; Wolf, 2003), unlike the Lotka setup used by Hamilton in which only direct effects occur. However, other theories could also be considered, each bringing its own set of constraints on the elements of the matrix. It is possible that an empirical approach of this sort would have sufficient power to distinguish between different theories.

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11

Stress and Metabolic Disease

Karen K. Ryan

Persistent exposure to psychosocial stress is linked to an increased risk of metabolic disease, including obesity, cardiovascular disease (CVD), and Type-2 diabetes mellitus (T2DM). Delineating the behavioral, physiological, and molecular mechanisms by which stress adversely affects these endpoints may uncover important opportunities for therapeutic intervention. This paper explores the role of stress-induced activation of the sympatho-adrenomedullary system and the hypothalamic-pituitary-adrenocortical axis as key mechanisms linking chronic stress exposure to metabolic health and disease.

PHYSIOLOGICAL RESPONSES TO STRESS

Stress can be defined as a real or perceived threat to homeostasis or well-being, and it can be either psychological or physical in nature. Threatening stimuli are integrated in the central nervous system (CNS) and recruit downstream effectors to modify behavioral and physiological responses—thereby reducing the expected detriment to the individual. Specifically, the sympatho-adrenomedullary (SAM) system and hypothalamic-pituitary-adrenocortical (HPA) axis are activated, allowing for both immediate (SAM) and sustained (HPA) physiological and behavioral responses, as discussed below. (See Ulrich-Lai and Herman, 2009, and Ulrich-Lai and Ryan, 2014, for a more thorough review.)

The sympathetic nervous system is activated almost immediately upon presentation of an acute stress stimulus and provides for rapid, but tran-

sient, physiological responses via direct catecholaminergic innervation of peripheral organs. Additionally, sympathetic drive to the adrenal medulla elicits the release of catecholamines into systemic circulation (Ulrich-Lai and Engeland, 2002). Together, this increased SAM activity facilitates the mobilization of stored energy, increases heart rate and blood pressure, and redirects blood flow away from reproductive and digestive processes. For example, increased sympathetic drive to adipose tissue results in the release of free fatty acids (Bartness and Song, 2007). Likewise, increased sympathetic drive to the liver promotes glycogenolysis and increases hepatic glucose production (Yamaguchi, 1992). Together, these acute responses facilitate the immediate ability of an individual to flee a predator, fight an aggressive conspecific, mount an immune response to infection, or otherwise deal with the threat at hand.

HPA axis activation provides a relatively slower, but amplified and sustained response to stress. Corticotrophin releasing hormone (CRH) is synthesized in hypothalamic neurons, released at the median eminence, and travels via the portal circulation to the anterior pituitary, where it stimulates the release of adrenocorticotropic hormone (ACTH) into systemic circulation. ACTH stimulates the synthesis and secretion of glucocorticoids from the adrenal cortex. Glucocorticoids act at their receptors to exert a number of effects, including the sustained mobilization of fuels. For example, glucocorticoid-signaling increases lipolysis and the release of fatty acids from adipose tissue (Xu et al., 2009; Campbell et al., 2011) and increases hepatic gluconeogenesis (Baxter, 1976). Glucocorticoid-signaling both decreases pancreatic insulin production and increases insulin resistance, promoting the greater availability of plasma glucose (Lambillotte et al., 1997; Andrews and Walker, 1999). Importantly, glucocorticoids also act at their receptors in the hypothalamus and pituitary to exert negative feedback on CRH and ACTH release, allowing for the eventual resolution of this stress response. Thus, together with rapid SAM action, the somewhat slower and longer-lasting action of glucocorticoid-signaling promotes survival and restores homeostasis across multiple organ systems (Ulrich-Lai and Herman, 2009).

Under conditions of chronic stress exposure, frequent use of CNS stress-regulatory circuits adjusts gene expression and synaptic plasticity, resulting in persistent alterations to stress system function (Ulrich-Lai and Herman, 2009). The result is increased basal SAM and HPA tone. In addition, excitability is enhanced, such that stress-evoked SAM and HPA responses are exaggerated (Akana et al., 1992; Grippo et al., 2002; Ulrich-Lai et al., 2007). Such stress facilitation ensures the continued ability to exhibit appropriate responses to new stressors, despite basal increases in glucocorticoids and changes in immune and endocrine function (Akana et al., 1992).

CHRONIC STRESS AND METABOLIC DISEASE

Chronic stress is linked to increased morbidity and mortality, thought to occur at least in part because, although SAM and HPA responses may be adaptive in the short term, frequent and/or persistent exposure to these physiological processes leads to "wear and tear" on organs and tissues and can predispose to disease (McEwan and Stellar, 1993). Frequent and persistent override of metabolic homeostasis, required to mobilize fuels in response to stressful stimuli, may make metabolic regulatory systems particularly vulnerable to adverse consequences (Ulrich-Lai and Ryan, 2014). Consistent with this possibility, chronic stress alters feeding behavior and promotes obesity, and is thought to be an important risk factor for a number of metabolic diseases, including cardiovascular disease (CVD), Type-2 diabetes mellitus (T2DM), and polycystic ovarian syndrome (PCOS), discussed below. Additionally, stress exposure at earlier life history stages likewise can alter behavioral and physiological responses to acute and chronic stress in adulthood, thereby conditioning the later risk of disease.

Chronic Stress, Feeding Behavior, and Obesity

Glucocorticoids regulate food intake and adiposity via both central and peripheral mechanisms. Glucocorticoid receptor (GR) signaling in the CNS increases caloric intake and stimulates body weight gain (Green et al., 1992; Tempel et al., 1992; Tataranni et al., 1996; Zakrzewska et al., 1999). These effects are thought to be mediated, at least in part, by synaptic changes and altered excitability within canonical hypothalamic circuits important for the regulation of energy balance (Gyengesi et al., 2010). In addition, stress stimulates the selection of calorically dense, highly palatable foods over more nutritious less-rewarding options—further contributing to its adverse metabolic effects (McCann et al., 1990; Oliver and Wardle, 1999; Dallman et al., 2003; Laugero et al., 2011; Groesz et al., 2012; Kim et al., 2013; Tryon et al., 2013b). Stress increases the propensity of both rodents and humans to work for palatable food (Willner et al., 1998; Lemmens et al., 2011), and increases neuronal activation in brain motivation and reward circuitry following exposure to palatable foods (Rudenga et al., 2013; Tryon et al., 2013a). Importantly, this stress-induced consumption of palatable foods can occur even among the subset of people who decrease their total caloric intake in response to stress (Oliver and Wardle, 1999).

In addition to promoting the increased consumption of palatable foods, persistent exposure to circulating glucocorticoids during chronic stress facilitates the redistribution of body fat towards metabolically unhealthy visceral depots (Lönn et al., 1994; Dallman et al., 2003). For instance, chronic job strain was significantly associated with both increased general

obesity and increased central obesity in the Whitehall II study (Brunner et al., 2007). Likewise, chronic stress increased the intra-abdominal fat of cynomolgus monkeys, relative to unstressed controls (Jayo et al., 1993). Because visceral depots are thought to exhibit a greater lipolytic response to adrenergic stimulation (Ostman et al., 1979; Arner, 1995; Hoffstedt et al., 1997), fat redistribution associated with chronic stress may mirror stress facilitation in neural circuits, by ensuring the system can rapidly mobilize fatty acids in response to new acute stressors (Ulrich-Lai and Ryan, 2014). Unfortunately, however, such fat redistribution may also have long-term pathophysiological consequences, since increased visceral adiposity is also thought to contribute to various metabolic diseases, by promoting ectopic fat storage in liver and vascular tissues.

Chronic Stress and Cardiovascular Disease

A large literature now supports that psychosocial factors contribute significantly to the pathogenesis of CVD in human populations (Rozanski et al., 1999; Steptoe and Kivimäki, 2012). This relationship may represent an important target for the development of therapeutic interventions, since CVD remains the leading cause of death worldwide. Work-related stress, marital discord, and caregiver status are chronic life stressors that have been extensively studied with respect to cardiovascular outcomes. As just one example, a recent meta-analysis reports a 1.4 relative ratio of coronary heart disease for men working in jobs characterized by high demand together with low decision latitude, low reward, and/or minimal control (Kivimäki et al., 2006). Likewise, a high demand–low reward work environment is associated with significant 4-year progression of atherosclerosis (Lynch et al., 1997), and marital stress among working women is associated with a 2.9-fold increase in the risk of both recurrent cardiovascular events (Orth-Gomér et al., 2000) and accelerated progression of coronary heart disease (Wang et al., 2007). Moreover, spousal caregivers of patients with Alzheimer disease exhibited higher plasma triglycerides and increased blood pressure compared to non-caregiver controls (von Känel et al., 2011).

Chronic stress is also associated with indices of CVD in nonhuman primates and laboratory rodents. For example, dominant male cynomolgus monkeys housed in an unstable (i.e., stressful) social environment exhibit accelerated progression of coronary atherosclerosis and impaired endothelial function (Kaplan et al., 1983, 1987). Among female monkeys, social subordinates and singly housed individuals had 5 and 12 times the coronary artery atherosclerosis of social dominants, respectively (Shively et al., 1989). In laboratory rodents, both the chronic social-defeat stress and chronic mild stress paradigms induce a pro-atherosclerotic plasma lipid pro-

file (Neves et al., 2009; Chuang et al., 2010) and increase vascular indices of atherosclerosis (Neves et al., 2009).

Such adverse cardiovascular consequences may arise in part from stress-associated changes in food choice and increased visceral adiposity, discussed above. However, other physiological mechanisms likely play a role, since vascular pathology has been observed among stressed rodents and primates that are exclusively maintained on a low-fat, "healthy" laboratory chow (Kaplan et al., 1983; Neves et al., 2009). Classical physiologic adaptations to chronic stress, including increased basal and stress-evoked SAM and HPA tone, are also thought to contribute. For example, stress-induced vascular pathology in male cynomolgus monkeys can be abolished by concurrent treatment with the β-adrenergic antagonist propranolol, supporting that elevated SAM tone is a contributing mechanism (Kaplan et al., 1987). Likewise, chronic exposure to elevated glucocorticoids is associated with hypertension and atherosclerosis in Cushing disease patients (Orth, 1995), and this is recapitulated in a mouse model in which elevated corticosterone is provided chronically in the drinking water (Okutsu et al., 2014). Exaggerated vascular pathology in response to excess glucocorticoids is associated with dyslipidemia, although a thorough understanding of the molecular mechanisms remains to be determined (Okutsu et al., 2014).

Chronic Stress and Type-2 Diabetes Mellitus

Type-2 diabetes mellitus (T2DM) is a chronic metabolic disorder that results from defects in both insulin secretion and insulin action. While the nature of the relationship between chronic stress and diabetes is less-well understood, limited evidence supports that stress may precipitate T2DM or exacerbate its progression. For example, psychological abuse by cohabitating partners significantly increases the risk of T2DM (Mason et al., 2013). Likewise, acute exposure to psychosocial stress impairs post-prandial glucose clearance among diabetic subjects (Faulenbach et al., 2012). Chronic stress may facilitate insulin resistance and/or T2DM by the direct action of glucocorticoids to induce cellular insulin resistance (discussed above), and/or it may act indirectly by promoting unhealthy eating behavior, visceral adiposity, and hepatic steatosis. Duong et al. (2012), for example, report that poor glucose control in T2DM subjects was associated with both high circulating cortisol and "low-quality" dietary choices (Duong et al., 2012).

Chronic Stress and Polycystic Ovarian Syndrome

Polycystic Ovarian Syndrome (PCOS) is a complex endocrine and metabolic disorder characterized by increased abdominal obesity, hyperandrogenism, insulin resistance, hypertension, and ovulatory dysfunction,

and is a common cause of female infertility. The etiology of PCOS is unknown, but its symptoms have been associated with primary defects in the HPA axis and enhanced SAM activity (Reaven et al., 1996; Tsilchorozidou et al., 2004). While it is clear that women with PCOS suffer from increased social and other life stressors, the psychosocial implications of PCOS symptoms (e.g., hirsutism) make it difficult to resolve the cause/effect nature of this relationship in human subjects. Importantly, however, in a rat model of PCOS wherein such psychosocial factors are presumably less prevalent, PCOS females exhibit increased SAM and HPA activity together with ovarian pathology (Stener-Victorin et al., 2005). Such findings suggest that altered stress regulation in PCOS is not entirely secondary to human psychosocial factors and may indeed contribute to the etiology of this disorder.

EARLY LIFE STRESS AND METABOLIC DISEASE

In addition to promoting metabolic disease among individuals as they cope with ongoing chronic life stress, exposure to stress both perinatally and at other early life history stages may also impair metabolic health later in life. Indeed, an abundance of epidemiological, clinical, and experimental evidence now supports this possibility. A more thorough review of this "developmental origins" hypothesis can be found elsewhere (e.g., Bruce and Hanson, 2010; Tamashiro and Moran, 2010; Reynolds, 2013), but is discussed briefly below.

Fetal exposure to high concentrations of maternal glucocorticoids retards intrauterine growth in humans (Goedhart et al., 2010; Reinisch et al., 1978), nonhuman primates, and laboratory rodents, whereas low birth weight is associated with increased risk of developing cardiometabolic disease during adulthood (Edwards et al., 1993; Barker, 1995; Seckl and Meaney, 2004; Gluckman et al., 2008). For example, in a population based study of U.S. women, very low birth weight was associated with a significantly increased risk of obesity in adulthood (Leong et al., 2003). Similarly, in a study of 22,846 U.S. men, low birth weight was associated with increased risk of hypertension and diabetes (Curhan et al., 1996). Low birth weight may also predict the development of PCOS. In a cohort of 948 Australian females, for example, thinness at birth was a significant predictor of hyperandrogenism, menstrual dysfunction, and polycystic ovaries (Davies et al., 2012).

In addition to the effects of prenatal stress and low birth weight, exposure to stress during infancy and childhood also presents a risk for obesity, CVD, and T2DM. In a bonnet macaque model of early life stress, for example, a variable foraging demand (VFD) paradigm was imposed on monkey mothers for 16 weeks, beginning when their offspring were 3-5 months

of age. Despite that VFD had no effect on total food availability or early offspring growth, VFD monkeys exhibited greater body weight, body mass index, and abdominal circumference at puberty, compared to unstressed controls (Kaufman et al., 2007). These findings suggest the adverse metabolic consequences of early life stress are not strictly dependent on early growth retardation. Likewise, persons who reported several adverse childhood experiences exhibited a 1.4- to 1.6-fold increase in the incidence of severe obesity as adults (Felitti et al., 1998). Early life stress among participants in the Helsinki Birth Cohort, who were evacuated abroad during World War II and separated from their parents, were more likely to exhibit both cardiovascular morbidity and T2DM as adults (Alastalo et al., 2009). In a similar manner, a harsh childhood environment and low childhood socioeconomic status predicted hypertension in the Coronary Artery Risk Development in Young Adults sample (Lehman et al., 2009).

The molecular and physiological mechanisms linking early life stress to cardiometabolic disease have not been clearly elucidated, but may be the consequence of organizational changes to the developing HPA axis, which eventually result in altered basal and stress-evoked SAM and HPA tone during adulthood. In a model of maternal separation stress, for example, rats exposed to this early life stressor had exaggerated sympathetic responses in adulthood (Loria et al., 2013). Similarly, when pregnant rats are exposed to restraint stress during the third week of gestation, their adult male offspring exhibit a prolonged corticosterone response to challenge with a novel object (Henry et al., 1994). Likewise, receiving relatively poor maternal care results in lower glucocorticoid-receptor (GR) expression in key stress regulatory brain regions, facilitating enhanced HPA responses to stress in adult offspring (Liu et al., 1997). Altered GR expression likely results from altered epigenetic modification of the GR promoter, since infusing a histone deacetylase inhibitor directly into the brain eliminated these effects (Weaver et al., 2004). In this way, exposure to early life stress may elicit a chronic stress-like phenotype in adulthood—underscoring potential mechanisms that link early life stress to an increased risk of developing metabolic disease.

STRESS, INFLAMMATION, AND METABOLIC DISEASE

As discussed above, exaggerated and persistent SAM and HPA axis activity likely contribute to the development of chronic stress-associated metabolic disease, by driving increased "wear and tear" on metabolic regulatory systems (McEwen and Stellar, 1993). Downstream cellular and molecular mechanisms for this proposed wear and tear are not fully understood, but one important mediator is thought to be stress-induced activation of the innate immune system and inflammatory responses.

The innate immune system is the primary early barrier to infectious agents. It recognizes conserved molecular structures that are essential for the lifecycle of various pathogens, providing a nonspecific response (Kumar et al., 2011). For example, the toll-like receptor 4 (TLR4) is a type-I transmembrane receptor that recognizes lipopolysaccharide (LPS) derived from bacterial cell walls. When it is bound by LPS, TLR4 signaling leads to activation of macrophages and increased production of inflammatory cytokines (Akira and Takeda, 2004; Selvarajoo, 2006; Milanski et al., 2009; Kawai and Akira, 2010). In response to infection (a physical stressor), this coordinated action leads to fever and other appropriate physiological reactions.

Intriguingly, the innate immune system is also activated by acute psychological stressors and exhibits ongoing low-level activity associated with chronic stress (Segerstrom and Miller, 2004). Stress reliably increases inflammation in a variety of contexts (Jaremka et al., 2013). For example, the Trier Social Stress Test, a well-characterized laboratory stressor involving anticipation, public speaking, and mental arithmetic, leads to increased indices of inflammation relative to baseline levels (Bierhaus et al., 2003); this is exaggerated among individuals with a history of adversity early in life (Carpenter et al., 2010). Similarly, low socioeconomic status is associated with both chronic stress and chronic low-grade inflammation (Hemingway et al., 2003; Cohen et al., 2006). Although the origins of this inflammation are not thoroughly understood, stress may facilitate activation of the immune system through direct innervations of lymphatic tissue, release of SAM and HPA hormones that bind to and alter the functions of immunologically active cells, and/or through stress-induced behavioral changes (Cohen et al., 2007). For example, social disruption stress increases spleen weight, macrophage activation, and circulating cytokines in laboratory mice. All of this could be prevented with concurrent administration of the β-adrenergic antagonist propranolol (Hanke et al., 2012), identifying a critical role for the SAM to mediate these effects.

Importantly, a growing body of evidence implicates chronic low-grade activation of the innate immune response in the pathogenesis of various metabolic diseases including CVD, obesity, and T2DM. It is well known, for example, that inflammation plays a key role in the development of atherosclerosis (Cole et al., 2013). Specifically, atherogenesis is thought to begin with an initial insult to endothelial function that promotes accumulation of inflammatory cells in the vessel wall. These cells produce cytokines and growth factors that evoke a cascade of morphological changes, eventually contributing to plaque formation and rupture (Libby et al., 2011). Conversely, therapies that reduce vascular inflammation are effective to reduce the incidence and progression of atherosclerosis. Inflammation in the central nervous system circuits that regulate feeding behavior contributes to the overconsumption of high-fat diets and increases weight gain (Thaler

and Schwartz, 2010; Ryan et al., 2012). Chronic low-grade systemic inflammation also contributes to the increased risk of peripheral insulin resistance associated with obesity (Donath and Shoelson, 2011). This depends at least in part on TLR4 signaling, since mice that lack TLR4 are protected from high-fat diet induced obesity and insulin resistance (Shi et al., 2006; Cani et al., 2007; Tsukumo et al., 2007). Consequently, there has been some interest in the use of anti-inflammatory agents to treat Type-2 diabetes mellitus (Larsen et al., 2007; Fleischman et al., 2008; Goldfine et al., 2008).

Gut Microbiota and the Innate Immune Response

Related to all this, vast communities of commensal microbes inhabit the alimentary tract of humans and other mammals (Dethlefsen et al., 2006). Indeed, gut microbiota outnumber human cells by a factor of 10 and, as a whole, possess 100-fold more genes than the human genome (Hooper and Gordon, 2001). A rapidly growing research enterprise now focuses on interactions between gut microbial ecology, inflammation, and human health (Caesar et al., 2010; Tremaroli and Bäckhed, 2012). One intriguing direction for future research, explored below, is the idea that stress-associated changes to gut microbial communities, and subsequent stimulation of the immune response, contribute to the origin of stress-associated chronic inflammation, providing an additional mechanistic link between stress and metabolic disease.

The innate immune system responds to conserved molecular structures that are essential for the lifecycle of various microbial species—both pathogenic and commensal. In this way, commensal gut microbiota may affect host physiology by modulating inflammatory signaling pathways (Caesar et al., 2010; Chu and Mazmanian, 2013). In addition, the composition of gut microbial communities is thought to significantly affect barrier function of the intestinal wall (Berg, 1999; Tlaskalová-Hogenová et al., 2011), which in turn would determine the infiltration of microbes and/or microbial particles to ultimately modulate innate immune responses. For example, modifying gut microbial communities, by administration of a probiotic, significantly reduced circulating cytokines among patients with rheumatoid arthritis (Vaghef-Mehrabany et al., 2013). Likewise, manipulating mouse gut microbial communities, by adding a pre-biotic fermentable carbohydrate to their diet, reduces intestinal permeability, circulating concentrations of LPS, and systemic inflammation (Cani et al., 2009).

GUT MICROBIOTA, STRESS, AND METABOLIC DISEASE

An explosion of recent research has begun to identify important links between humans' commensal microbiota and metabolic disease. Impor-

tantly, an altered gut microbiota has now been linked with obesity, T2DM, and CVD (see Figure 11-1). Gut microbial communities are altered in obese individuals compared to lean counterparts and can be modified by dietary intake (Ley et al., 2005; Turnbaugh et al., 2009). These patterns may indicate that an altered gut microbiota contributes functionally to obesity, or conversely, that obesity and/or food selection per se alters the gut microbiota. A growing body of evidence from prospective human studies and experimental animal models supports the possibility of a functional association. For example, a prospective Finnish study of 49 individuals sampled as infants identified specific microbial groups that were associated with the development of overweight by 7 years of age (Kalliomäki et al., 2008). In addition, transplantation of the gut microbiota from obese mice into germ-free gnotobiotic mice is associated with weight gain (Turnbaugh et al., 2006, 2008). Finally, changes in gut microbial communities, secondary to an altered local environment, are implicated in the weight loss and other metabolic benefits achieved with bariatric surgery, in both humans (Furet et al., 2010; Graessler et al., 2012) and in rodents (Liou et al., 2013;

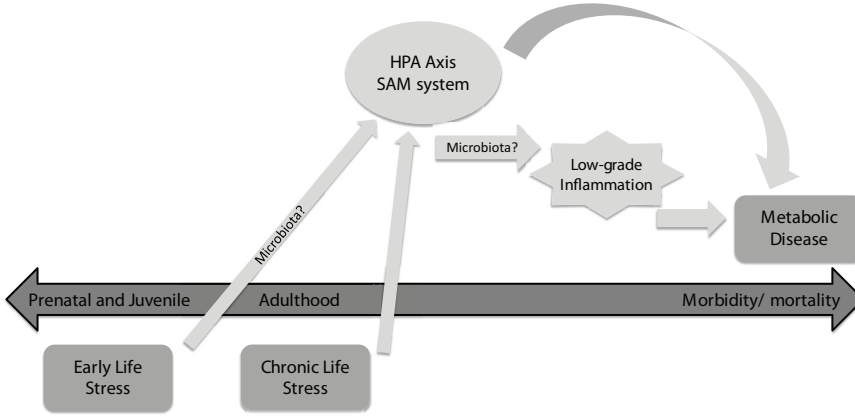

FIGURE 11-1 Potential mechanisms linking stress to increased risk of metabolic disease.

NOTE: Exposure to stress both early in life and chronically, during adulthood are significant risk factors for obesity, diabetes, and cardiovascular disease. This may result from frequent and/or persistent activation of hypothalamic-pituitary-adrenocortical (HPA) and sympatho-adrenomedullary (SAM) stress responses. HPA and/or SAM activity may contribute to the etiology of metabolic disease either directly, or by eliciting mild, persistent activation of the innate immune system. Finally, stress is known to alter the composition of gut microbial communities, whereas differences in gut microbial ecology has likewise been linked to both inflammation and the risk of metabolic disease.

Ryan et al., 2014). Gnotobiotic mice receiving a transplantation of gut microbiota from donors that had gastric bypass surgery gained less weight compared to those that receive a transplant from sham-operated controls, supporting the functional nature of this relationship (Liou et al., 2013).

Both human and rodent studies also implicate the gut microbiota as contributing to the pathogenesis of CVD. For example, commensal bacterial species previously thought to be restricted to the alimentary tract have now been found in atherosclerotic plaques (Koren et al., 2011), implicating increased leakiness of the gut mucosal barrier and likely contributing to increased inflammation associated with CVD. Consistent with this, patients who had experienced an atherosclerotic event had altered abundance of specific gut microbial species, associated with a decrease in the synthesis of the anti-inflammatory metabolite butyrate (Karlsson et al., 2012).

The gut microbiota may likewise link aspects of the Western diet to increased risk of CVD. Specifically, an omnivorous diet is associated with the increased abundance of specific gut microbes that metabolize dietary L-carnitine—a trimethylamine abundant in red meat. A metabolite of this microbial reaction, trimethylamine-N-oxide (TMAO), is associated with increased risk of CVD. Accordingly, the presence of specific microbial species, together with high plasma levels of L-carnitine and TMAO, predicted an increased risk of CVD and the occurrence of adverse cardiovascular events in human subjects. Moreover, supplementing the diet of laboratory mice with L-carnitine both altered cecal microbial composition and increased vascular pathology (Koeth et al., 2013). In this way, the gut microbiota provide an important mechanism underlying the well-established link between high levels of red meat consumption and the risk of CVD.

Gut microbial communities are responsive to host psychological stress. A number of studies now demonstrate that stress exposure, or exposure to stress hormones, significantly alters the composition of the gut microbiota and translocation of gut microbes across the intestinal wall (Tannock and Savage, 1974; Lyte and Bailey, 1997; Bailey et al., 2006, 2011). An altered microbiota is thought to be one link between stress responses and increased systemic inflammation, since stress-induced changes in both gut microbial composition and increased circulating cytokines could be abrogated by concurrent treatment with an antibiotic (Bailey et al., 2007). Thus, one interesting possibility is that activation of the SAM and HPA axis by psychosocial stress facilitates chronic metabolic disease by altering the gut microbiota, thereby activating the innate immune system, although this possibility has not yet been tested.

Furthermore, although the majority of mechanistic research has focused on how social defeat, isolation, and subordination promote disease (discussed above), social relationships may, of course, be both anxiolytic and/or anxiogenic. Therefore, social interactions may be either detrimental or

beneficial depending on the context. In fact, an abundance of epidemiological work indicates that positive social relationships may offer stress relief—contributing to improved health and longevity (Berkman and Syme, 1979). In wild baboons, for example, the degree of affiliation is related to HPA status (Sapolsky et al., 1997). Likewise, lack of attachment with intimate contacts is associated with high resting SAM hormones in young men (Knox et al., 1985). Consistent with the role of the HPA axis and SAM system in facilitating the incidence and progression of CVD, supportive social relationships are associated with better prognosis in coronary artery disease (Williams et al., 1992) and with reduced cardiovascular mortality (Welin et al., 1992). It is interesting to speculate that positive social interactions may blunt SAM and HPA activity in the face of stress, facilitating favorable changes to the gut microbiota, which thereby contribute to these benefits.

In addition to directly blunting activation of the SAM system and HPA axis, social interactions may alter stress system function and/or risk of metabolic disease by facilitating the inter-individual transmission of commensal microbes (Lombardo, 2007; Archie and Theis, 2011). Social transmission of gut microbes has been demonstrated in a variety of animals including iguana (Troyer, 1982), chimney swift (Kyle and Kyle 1993), and mice (Lombardo, 2007). Some evidence suggests this may occur in humans as well, since the gut microbiomes of unrelated adults (typically married partners) living in the same household were significantly more similar to each other than to unrelated individuals living in a different household (Yatsunenko et al., 2012). To the extent that frequent social partners share microbiota, one might hypothesize that individuals with stronger and more diverse social networks possess a more diverse microbiome. Thus, a reduction in the diversity of social relationships that may occur with aging could contribute to the observed aging-associated decline in microbial diversity (Claesson et al., 2011). Accordingly, increasing diversity of the gut microbiome is generally associated with improved health. Increased gut microbial diversity is thought to be protective against a number of diseases, including obesity (Ley et al., 2005), atherosclerosis (Karlsson et al., 2012), and Crohn disease (Manichanh et al., 2006). More directly, gut microbiota are transmitted from mother to offspring during birth (Fåk et al., 2008; Palmer et al., 2007) and lactation (Fernández et al., 2013). In light of the effects of microbiota on metabolic disease, this may provide an alternate mechanism by which maternal stress has long-term organizational effects on the metabolic health of her offspring.

SUMMARY AND FUTURE DIRECTIONS

Although the link between psychosocial stress and metabolic disease has been appreciated for decades, significant work remains to delineate

mechanistic details. A growing body of evidence implicates exaggerated and persistent stress-associated activation of the SAM system and HPA axis, as well as induction of the innate immune system and increased systemic inflammation.

Understanding the potential role of stress-associated changes in the gut microbiota as a source for systemic inflammation and disease is an important avenue for future research that may highlight important opportunities for intervention. For example, gut microbial composition is altered in pregnancy (Koren et al., 2012) and affects the inoculation of newborns. A better understanding of how maternal stress affects maternal gut microbial communities, and downstream physiological consequences for both mother and offspring, will be informative. Importantly, this may represent a critical period for therapeutic interventions aimed at disrupting the connections among maternal stress, low birth weight, and metabolic disease of adult offspring. In sum, this "bottom-up" approach to understanding the relationships among stress, the microbiome, physiology, and social structure/behaviors provides ample opportunity to inform behavioral, nutritional, and pharmacological interventions to combat metabolic disease.

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12

Hierarchy and Connectedness as Determinants of Health and Longevity in Social Insects

Brian Johnson and James R. Carey

INTRODUCTION

It is widely known that health and longevity in humans, the most social of all vertebrate species, have strong sociological determinants ranging from marriage (Waite and Lehrer, 2003) and family (Waite and Das, 2010) to friendship networks (Couzin, 2009) and societal rank (Marmot, 2004). These determinants are the outcome of co-evolved behavioral, demographic, and ecological traits that both animate and link a society, and that are both complementary and mutually affecting. It follows that understanding these traits and the interplay between society, the individual, and individual-level health for any social species, but particularly for understanding these relationships in humans, requires deep knowledge of the roles of social networks and hierarchies (Barry and Yuill, 2012). Inasmuch as it is not possible to manipulate any human society or its individual members in any type of large-scale, controlled study, not only do many questions about the role of social factors in health go unanswered, but also much of the conventional wisdom derived from human studies remains unsubstantiated.

Because of the paucity of information on how social factors, including networks and hierarchies, affect health and longevity in social species in general and humans in particular, our broad goal of this paper is to describe a general research framework for answering questions concerned with sociality and health based on the use of social insects in general and the honey bee (*Apis melifera*) in particular. We begin with a section containing overviews of social insect longevity, evolution of eusociality in

wasps, general principles of social insect biodemography, and a synopsis of the biology of honey bees—the species we focus on throughout much of the remainder of the paper. This is followed with the main section involving mechanisms involved and principles determining aging and longevity in the honey bee. We end with a short section on recommendations for research and hypothesis testing.

SOCIAL INSECTS: CONCEPTS, EVOLUTION AND BIODEMOGRAPHY

Although social insects constitute only 2 percent of the more than 1 million species of insects on earth, they may constitute up to 80 percent of the insect biomass and, in total, outweigh vertebrates by 7-to-1 (Wilson, 1985; Charbonneau et al., 2013). Due to their evolved ability to exploit the concept of division of labor, they are the most ecologically successful groups in nature. They display sophisticated problem solving that emerges from simple individual behaviors that often resemble a voting procedure. Individual workers are adaptively allocated to different tasks (e.g., caring for eggs, larvae, and pupae; building; foraging; defense) in a way that is robust to changes in both task demand and to individual failure. Since the structure and dynamics of the network of interactions will affect overall colony functioning, many of the processes are regulated by interactions between individuals. Thus, the health and longevity of the colony and of individuals is mutually-affecting and complementary. Social insects are excellent models for studying all aspects of sociality as they are an evolved system in which the interacting parts can be individually tracked and manipulated (see Figure 12-1).

Sociality Concepts

Although sociality occurs to some degree in virtually all insect species in the form of the social activities of courting and mating, most biologists consider a species of insect as social only if they exhibit specific types and levels of cooperation including (1) continued care of young; (2) cooperative brood care; (3) reproductive division of labor; and (4) colonies with at least two adult generations (Carey, 2001). The various levels of social organization are thus classified according to combinations of these cooperative behaviors including subsocial, colonial, communal, cooperatively breeding, and eusocial. Although some level of social behavior is found in 12 different groups of insects and acari, eusociality is found primarily in the Hymenoptera (bees, wasps, ants) and Isoptera (termites) with a few "non-traditional" eusocial species also contained in the Homoptera, Coleoptera, and Thysanoptera.

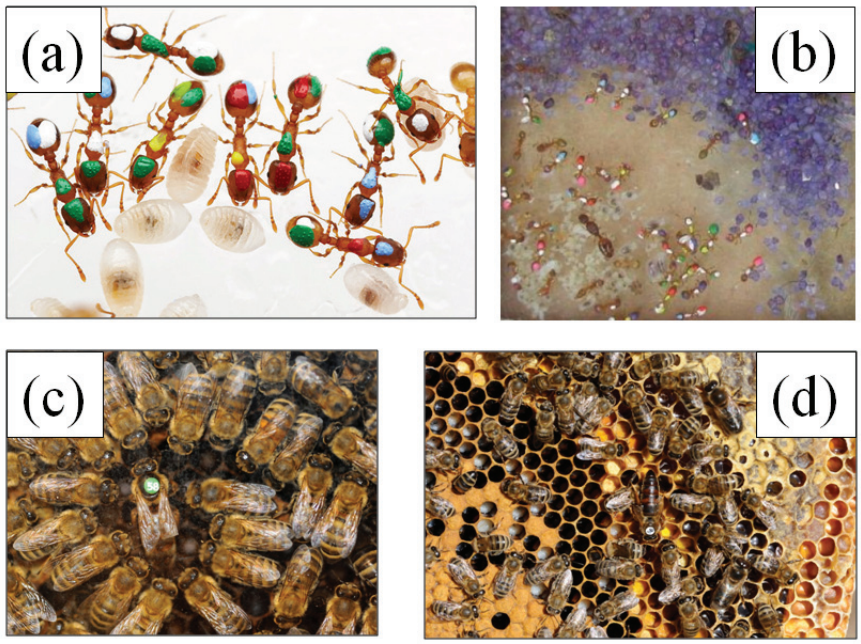

FIGURE 12-1 Social insects—ants and honey bees.
NOTES:
(a) Individually marked ants, *Temnothorax rugatulus*. © Alex Wild, used by permission.
(b) Purple grains of sand built by ants to protect the colony. © Ann Dornhaus, used by permission.
(c) *Queen honeybee retinue*. Older egg laying queens are more attractive to workers than newly mated queens and virgin queens are the least attractive. The workers groom the queen (i.e. retinue behavior) by touching it with their mouthparts, antennae and forelegs. The workers from the queen retinue feed the queen by trophallaxis. During grooming of the queen pheromones are transferred from the queen to the workers attending it and later to other workers in the colony. Whereas worker bees typically live only around 6 weeks, queens are capable of living 6 years or more. © Kathy Keatley Garvey, used by permission.
(d) *Honeybee comb* showing brood chamber with eggs (not visible but in open cells in middle), larvae (see cells to right), sealed brood (closed cells), queen (marked individual in center) and nurse (worker) bees (all other adults). The honey bee hive consists of a single queen, multiple drones and from 10,000 to 40,000 workers. © Kathy Keatley Garvey, used by permission.

Lifespans in Social Insects

A summary of the range of lifespans in the four main groups of eusocial insects is given in Figure 12-2. Several aspects of this schematic diagram merit comment (Carey, 2001). First, lifespans of eusocial insect adults differ by 800-fold from the 10-14 days lifespan in some worker ants to the 30-year lifespans of ant and termite queens. As Hölldobler and Wilson note (1990), the longevity of *Camponotus*, *Formica*, and *Lasius* queens, ranging from 18 to 29 years, makes these ants the most long-lived insects ever recorded. Clearly, longevity is a highly selected attribute of the life history of the different species. Second, the extraordinary range in lifespans occurs not simply between the different species, but also within species. For example, queen honey bees are capable of living 3-5 years but honey bee workers only live 6-8 weeks. This is remarkable because the queens do not differ genetically from workers—they are produced through workers constructing special "queen cells" (Seeley, 1995) and feeding the developing larvae

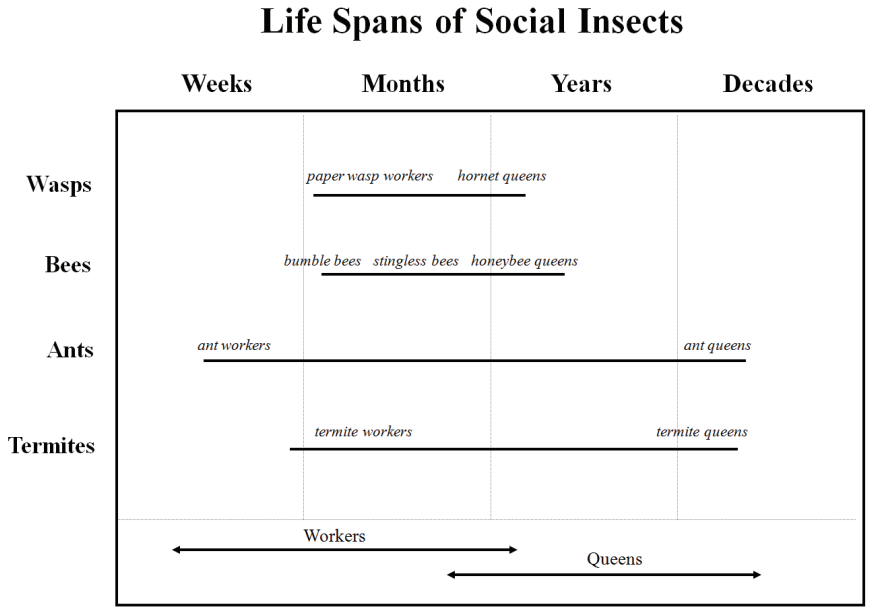

FIGURE 12-2 Lifespan ranges of species within the four main groups of eusocial insects—Wasps, bees, ants, and termites.
NOTE: Arrows in bottom panel indicate range (and overlap) of workers and queens in each of the groups.
SOURCE: Carey (2001).

"royal jelly"—a complex mixture of diet and hormones (Finch, 1990). Third, relatively speaking, males (all workers in the social hymenoptera are female, and males, often called drones, have radically different life histories) have a shorter adult lifespan than either queens or workers (Wilson, 1971; Hölldobler, 1990), mother queens live much longer than workers in all eusocial insects (Keller and Genoud, 1997; Keller, 1998), and ant and termite queens (that are subterranean) experience much greater lifespans than wasp and bee queens (that are terrestrial). Fourth, no correlation is apparent between the degree of sociality of a species (colony size, morphological divergence of queens and workers) and both the absolute and relative longevity of its queens (Hölldobler, 1990). This suggests that the ecology and demography (e.g., foraging patterns, food type) of a social insect species, rather than colonial complexity, is an important determinant of queen longevity relative to that for workers.

Evolution of Sociality in Wasps

Emergence of Wasp Bauplan

Since each successive step in the development is complex, and the success of each is dependent upon the ones that precede, it is not surprising that during the course of evolution there should be a high degree of conservatism in each step (Bonner, 1988), resulting in what is known as the bauplan (Purves et al., 2004)—an assemblage of features (typically morphological) shared by a taxonomic group.

The bauplan for wasps is based on relatively short-lived sawflies, a precursor group of hymenopterans (i.e., bees and wasps) that uses its ovipositor as a precision tool for laying eggs in highly nutritious parts of plants. Short-lived parasitoids evolved from sawfly evolutionary progenitors that used this ovipositor as a "sting" for inserting their eggs into hosts. Parasitoids then evolved into mass provisioning (i.e., lays egg on or in entire host) wasps (Edwards, 1980), their mandibular (chewing) mouth parts preadapted them for nest-building (Jeanne, 1975). Moreover, their wasp waist (i.e., petiole-like) that evolved to enhance their host-stinging ability (i.e., highly maneuverable for precision stinging) restricted wasps to essentially liquid nourishment since only liquids could pass through to the abdominal digestive tract. That, along with progressive provisioning (as-needed feeding using masticated food), then preadapted them for social evolution (and thus long life). Liquid exchange between colony members became a mechanism for within-colony communication (Hunt, 1991).

Co-evolution of Wasp Sociality and Lifespan

A schematic for the progressive evolution of sociality and longevity in wasps can be developed based on the sequence of grades that, according to Hölldobler and Wilson (Hölldobler, 1990), can be logically envisioned to have occurred during behavioral evolution including nest building and guarding, brood care, and provisioning of young. Carey (2001) used the grades of social evolution in wasps outlined in the paper by Evans (1958) as a framework for examining the co-evolution of longevity and sociality in insects (also see Hunt and Amdam, 2005). Several evolutionary grades are grouped into one of three general stages (see schematic examples illustrated in Figure 12-3).

Stage I: Emergence of nest as locus (Figure 12-3a and b). The nest is important in the co-evolution of sociality and longevity because it provides a place to which the female repeatedly returns and thus becomes the locus of activity (Starr, 1991). The nest originated as a site of brood care and development or nursery and thus provides a protected microenvironment for the developing brood, the original female, and the food provisions. As females spend longer periods sitting in the protected nest, different selective factors become important. Mortality due to accident and predation is likely to be reduced, there is selection to reduce rates of senescence, lifespan increases, and mothers are more likely to be alive when some of their offspring reach adulthood.

Stage II: Emergence of parental care (Figure 12-3c). The female brings more prey to the nest, as needed, for the developing larva. She may remain in the nest with her offspring, adding some protection for the young. Later, females may begin to feed macerated food directly to the larvae. The evolution of adult provisioning by social insects enabled pre-adults to grow rapidly towards adult competence under the protection of parental care. This provisioning not only prolongs pre-adult (larval) dependence and accelerates growth, but also it detaches the larvae from the environment—short-term food shortages that would be fatal to larvae not under parental care are ironed out as the mother continues to provision by expanding her foraging activities (Queller, 1989).

Stage III: Emergence of queen/colony concept (Figure 12-3d). The female's life is prolonged and overlaps that of the progeny that remain with her in the nest to form an extended family. Females at this phase lay eggs into an empty cell, a trait that is thought to be important in permitting the evolution of the extended brood care of social wasps. The young females may construct more cells, lay eggs, and care for their own larvae. However, some

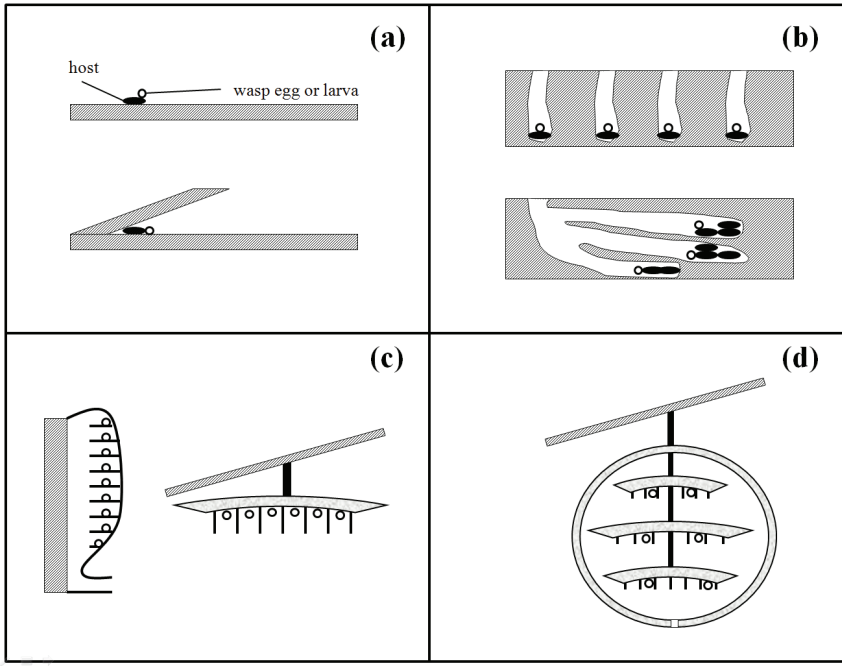

FIGURE 12-3 Schematic diagrams of the nests or prey sequestration behavior of wasps in various evolutionary stages of sociality, all of which alter selection on lifespan (Wenzel, 1991).
NOTES: (a) Parasitoid wasps. Host as incubator of parasitoid larvae (short lifespans with ranges from 14-60 days). Examples: spider wasps, *Notocyphus*; cockroach wasp, *Ampulex*; (b) Nest provides a protected microenvironment for female and brood, thus different selective factors operate; selection reduces senescence rates and increases life span (intermediate lifespan ranges from 30-60 days). Example: sand nesting wasps, *Haploneurion*; *Ammophila*; (c) Extensive parental care increases life span to 1 year; larval and pupal mortality reduced to near zero; this fosters reduction in birth rate; allows females to invest more resource for their own maintenance and for rearing of their offspring (lifespans range 60-365 days). Examples: progressive provisioning *Gorytes* spp. and paper wasps, *Polistes*; (d) Colony and queen concepts. Female's life further prolonged and overlaps with progeny which remain in nest to form extended family (helpers); colony rather than the individuals within it begins to become the unit of selection with the fate of the queen inextricably tied to fate of colony; a new level of individualism emerges (colony) and thus life of queen becomes adaptive to the long-term colony needs (lifespan range: 180-1,000 days). Example: advanced eusocial wasps including yellow jacket, *Vespula* spp.
SOURCE: Carey (2001).

females occasionally care for the brood of another female. Extensive overlap of generations occurs because of extended lifespans and because a clear division of labor and caste systems begins to emerge. A single queen, usually the original foundress, is much more long lived than the workers and monopolizes oviposition (i.e., queen control). As long as the colony remains small and the lifespans of reproductive individuals and helpers are not significantly different, then helpers may be expected to resist evolutionary specialization as workers because this would reduce or eliminate their chances to replace their mother as the sole reproductive female (Alexander, 1974).

Social Insects: Biodemographic Principles

The main principles of longevity extension in social insects, as derived from the wasp evolutionary model include the following (Carey, 2001).

Generation Overlap Is a Prerequisite for the Evolution of Incipient Sociality

One of the prerequisites for the evolution of eusociality in insects is generation overlap—the parents must live long enough to still be alive when their offspring emerge as adults. Evans (1958) noted that an important factor explaining the lack of significant social evolution in sphecid wasps is the relatively short female lifespan, so that the adult lives of mothers and daughters rarely overlap.

Progressive Provisioning Evolved after the Evolution of Extended Longevity

The assumption is that progressive provisioning arose from delayed provisioning. There is no strong evidence that adult longevity depends on progressive rearing but that extended adult longevity is an ancestral trait and that progressive provisioning evolved later (Evans, 1958). This concept is important because it suggests that extended longevity serves as a necessary precondition for the evolution of incipient sociality. Thus subsocial behavior may be an outcome of extended longevity rather than vice versa.

Sociality Provides Insurance-based Survival Advantages

In many facultatively eusocial insects, offspring need continuous care during development, but the life expectancy of adult caregivers is shorter than the developmental period. When a lone foundress dies, her partly reared brood is usually doomed. Helpers in a tropical hover wasp (*Liostenogaster flavolineata*) have an insurance-based advantage over lone foundresses because after a helper dies, most of the brood that she has partly reared will be brought to maturity by surviving nest-mates (Queller,

1989). The consequences of early mortality differ between solitary reproducers and helpers in several *Polistes* spp.—the former that die early will fail to bring any young to independence, while helpers that die at the same age may have made substantial contributions.

Queen-Worker Longevity Differentials Diverge at Advanced Stages of Eusociality

As eusocial colonies become large and long-lasting, mothers become increasingly specialized as reproductives, and offspring as workers and soldiers (Johnson and Linksvayer, 2010). As this happens, daughters have fewer opportunities to become replacement reproductives, both because the mother lives longer and because so many other individuals are available to replace the mother as well. Thus the identity of a queen's replacement becomes a sweepstakes, with each individual having a chance of, perhaps, one in fifty thousand or one in a million. One consequence of increased longevity as a preadaptation to sociality is that the stage is set for the evolution of large colonies (with even longer-lived queens) that have certain advantages over smaller ones, including the ability to organize labor more efficiently, integrate colony activities, defend the nest more aggressively, and exert homeostatic control over physical conditions within the nest. The fitness to the individual worker and the queen is subordinated to the fitness of the colony (i.e., emergence of the super-organism).

SOCIAL INSECTS: MOLECULAR MODELS OF AGING

Operational Framework

We consider the two basic conceptual frameworks for understanding aging in all organisms including social insects—accumulated damage and adaptive senescence (Finch, 1990). The first assumes that molecular damage of various sorts accumulates in the adult organism (who may or may not be post-reproductive) until such time as it impairs function and causes or contributes to death (Muller et al., 2007). Molecular damage is thought to be mainly caused by reactive oxygen species (ROS) that are the result of normal mitochondrial function. Adaptive senescence simply assumes that aging-related decreases in function are caused by genetic changes that occur as a result of a developmental program that has been shaped by natural selection. This is common sense in that it is often the case that relatively closely related organisms have widely different longevity patterns. Hence, lifespan in some sense must be the result of selection for an optimal longevity.

Of course, ultimately these two hypotheses are not mutually exclusive, as an optimal longevity (and a genetic program designed to achieve it)

can be the result of regulating the rate of damage produced by ROS (or other processes) such that they only lead to death at the appropriate age. Generating telomeres of a suitable length would be an example, as would be producing sufficient age-specific levels of antioxidants. We will frame much of our review of the molecular work on aging in social insects such that it either falls under one category or another, with the assumption that ultimately the two are complementary.

Extreme Longevity

Social Insects as Models

Social insects are good models for the study of extreme longevity and the underlying mechanisms for many reasons (Amdam, 2011; Roach and Carey, 2014). First, across species there is wide variation, with some species having lifespans typical for insects (on the order of weeks to months) and some having lifespans on the order of several decades (for queens). Second, within the same species, it is often the case that both patterns are apparent. Workers often have typical lifespans of a matter of weeks to a couple of years, while queens in the same nest can live for an order of magnitude longer. Given that genetic background can be a confounding variable in studies of the molecular basis of aging (Helfand and Rogina, 2003b), having the ability to study radically different aging patterns encoded by the same genome is highly beneficial. Of course, it is also possible to use the comparative method across species to identify genes, and networks that are associated with aging processes, as is done in many other taxa.

Social insects also decouple a fundamental relationship thought to be associated with aging in other species, namely that patterns of senescence are thought to be selected to change strongly before and after reproduction. This is because once an organism has reproduced, there should be little selective force for maintenance of somatic functions (Carey et al., 1992; Vaupel et al., 1998). In the social insects, however, because the queen produces eggs throughout her life (and has no post-reproductive life), this is not the case. Workers can also show atypical patterns of development with respect to hormonal state, reproductive status, and age. Genes that show positive relationships with aging in other insects, such as vitellogenin (the yolk protein), can show the opposite pattern in social insects such as the honey bee (Amdam et al., 2007). These patterns allow an experimenter to decouple the effects of reproduction from aging, something that is impossible in many taxa. In addition, humans, of course, are also social creatures who contribute to the fitness of their offspring, and grandchildren, throughout life, meaning that selection for long life is expected for humans as well. In this way, humans are atypical organisms, like the social insects,

with respect to aging and reproduction. Animal models that share the pattern of decoupling reproduction and senescence might therefore be the best models for the study of human longevity.

With respect to mechanistic studies of extreme longevity in social insect queens, one would like to know by what mechanism queens are able to prolong their lifespan far beyond the norm for insects. With respect to molecular damage, is it by generating large amounts of antioxidants, by slowing down metabolism, or by increased ability to repair damage? Do they continue to upregulate their immune systems for later into life than workers? We review briefly what research has been done, which supports all of these mechanisms (with notable exceptions, such as in the role played by ROS production).

Research has shown in model systems that upregulation of antioxidants causes longer than normal lifespan (Tatar et al., 2001; Helfand and Rogina, 2003a). Parker et al. (2004) tested the hypothesis in ants using the antioxidant gene Cu-Zn superoxide dismutase 1 (SOD1). Contrary to predictions, long-lived queens had lower expression of SOD1 than shorter-lived males. Queens and workers, further, did not differ in expression of this gene. Corona et al. (2005) also found no evidence for higher expression of antioxidants in long-lived honey bee queens relative to short-lived workers. They did find preliminary evidence for variation in ROS production, given their finding of caste-specific expression patterns for key mitochondrial metabolism genes. In sum, these studies support the hypothesis that long lifespan need not be associated with high expression of antioxidants. Decreased production of ROS rather seems a more plausible mechanism for these cases of longevity variation, as has been shown in a number of other systems (Muller et al., 2007).

ROS and Longevity

A variant of the ROS damage hypothesis has recently attracted much attention (Hulbert et al., 2007). This is the hypothesis that the fatty acid composition of cell membranes (ratio of saturated to unsaturated fats) is a major determinant of the rate of oxidative damage to membranes. Further, there are strong correlations between the Peroxidative index (PI) index (a measure of the susceptibility of membranes to peroxidative damage) and longevity across many groups of animals (vertebrates and invertebrates). Haddad et al. (2007) tested the potential for this hypothesis to explain lifespan variation between honey bee queens and workers. They found that the PI index of queens is lower than that of workers (a low index indicates low susceptibility to peroxidative damage). They also found that newly emerged workers have the lowest indexes for workers (still higher than for queens), but that the PI index increases with age. They hypothesized that

the increase in the PI index of workers is the result of pollen consumption, something that the queen is protected against given that she is fed a special nurse bee derived secretion throughout her life. They also found that the difference in PI index between queens and workers is sufficiently large to potentially explain the difference in longevity between these castes. To date, such research is preliminary, in that only correlations have been shown. Although no experimental cause-and-effect studies have been conducted, the data are intriguing and warrant more attention.

Thus far, we have focused on variation between workers and queens in longevity; however, there are also cases of strong variation within the workers on lifespan. In honey bees, the summer bees live about 6 weeks on average, while in the winter bees live up to 6 months (Johnson and Linksvayer, 2010). Essentially, in the summer, the colony is focused on rapid growth and food accumulation and the way they maximize this is by using a system of division of labor (mentioned previously). In the winter, however, the focus switches from growth to survivorship and the physiological specializations of the workers (to be nurses or foragers, for example) disappear. Instead, all the bees go into one physiological condition that is similar to the nurse bee phase (high vitellogenin titer and low juvenile hormone). Much work has taken advantage of this summer versus winter bee phenomenon to study aging processes (Seehuus et al., 2006a; Munch and Amdam, 2010). We will cover one case here related to oxidative damage and then return to the topic of worker aging in later sections.

Foraging honey bees have the highest metabolic rates of any animal measured (Vance et al., 2009). This is not surprising giving that their flight muscle alone makes up a significant portion of their total biomass. Foraging honey bees spend most of their day busily shuttling back and forth from the hive to the field (i.e., loads of nectar or pollen). Williams et al. (2008) took advantage of this phenomenon, and the fact that nurse bees only take one short flight a day, to look at the interaction between ROS production and senescence in honey bees. As expected, flight caused an increase in the production of Hsp70, which is correlated with oxidative damage. Older foragers, however, did not increase their antioxidant capacity after flight (presumably to respond to this damage), while young foragers did (to a modest, but significant extent). Tests for oxidization damage (based on recording protein carbonyl content) after flight (and in young and old foragers in general) did not show oxidative damage in either group. The authors interpreted these results as supporting the notion that ROS production in the flight muscles contributes to functional senescence in foragers; however, it is unclear that a cause-and-effect connection was made, as no damage was detected and older foragers had high antioxidant capacity even if they had no ability to increase it further. Nevertheless, it is the case that high ROS production in forager honey bees is a good context

to explore the mechanisms by which organisms mitigate the effects of high ROS production.

Adaptive Senescence

Adaptive Aging

Worker honey bees have been the focus of much work on adaptive senescence. In short, honey bee workers in the spring and summer have a complex system of division of labor in which workers exhibit different physiological states (castes) that appear to vary in their rates of senescence. There are four castes that occur in a developmental sequence: newly emerged bees, nurses, food storers, and then finally foragers. The nursing phase is most like the queen honey bee in terms of having high vitellogenin stores (and high nutrition levels in general) and low juvenile hormone (JH) titer. Further, bees that are kept in the nursing phase, by manipulating the nest such that they never transition to the next phase, can live for many months, while foragers, in contrast, only live for 2-3 weeks (Dukas and Visscher, 1994; Remolina et al., 2007). After a couple of weeks of foraging, for example, bees display obvious signs of damage (torn wings, damaged flight muscles, etc). There is also some evidence that this decline in foragers may be adaptive (i.e., the result of patterns of gene expression that turn off various pathways important for repairing damage; this is likely associated with reallocation of resources to other more critical functions). Finally, winter bees live throughout the whole winter (up to 6 months) and have a physiology superficially similar to that of nurses. Taken together, these patterns of aging in worker honey bees have been the subject of considerable work. However, several key experiments have not been conducted. Here we review some of the key studies thus far and point out the areas still needing work.

Aging Stasis

In honey bees, an appropriate number of workers in each caste is optimal for a given colony-level growth rate. This is because the different castes work together such that work is either passed from one group to another (foragers collect food, but younger food processors process it), or the work rate of one group is dependent in some more general manner on the activities of another group. The balance of workers in each developmental phase is maintained by workers either speeding up or slowly down their development in response to the colony-level ratios of workers current in each caste. Of chief experimental importance, development can be sped up or slowed down via various experimental techniques. It can be increased, for example, when a large of number of workers in the next phase dies, or it can be

slowed down when new workers are not produced to take the place of older bees (Huang and Robinson, 1992, 1996). Although it does not happen in natural nests, the aging processes can even be frozen by manipulating the ratios of bees in the nest (and the amount of brood in the nest) such that the ratio of workers in each phase does not change (Johnson, 2010). This has been done by removing newly emerged bees (to prevent replacement of nurses) and by adding open brood requiring care. The result is that many bees never seem to leave the nursing phase. Haydak (1963) was able to produce nurses 138 days old in this way. This is equivalent in some sense to freezing the aging of a vertebrate such that it remains a juvenile indefinitely.

Although the biology underlying this frozen development is derived, it is not unique. A similar process occurs in sex-changing fish. In some of these species, individuals all begin as females and a transition to being male only occurs in the fish that is the largest in the group. Hence, most individuals never make the switch. In the case of bees, because their aging is controlled by mechanisms similar to those that control sex in sex-changing fish (Munday et al., 2006), it is thus possible to ensure that some bees never make the transition to some developmental phases. This allows for studying the effects of extreme aging in the context of a body that is working to maintain an optimal functional state. In other words, adaptive senescence should not occur in bees frozen in the nursing phase, but senescence due to unrepairable damage (caused by ROS, for example) should nevertheless occur. Hence, it provides a context to study aging due to molecular damage controlling for the effects of adaptive senescence.

Aging Reversal

Bees that have entered the last of the developmental phases that characterize adult development, the foraging caste, can be induced to revert to the nursing phase by simply removing all the young bees from the nest (Huang and Robinson, 1996). When this manipulation is done, there is a rapid decrease in the JH titer of all the foragers in the nest and then some of the foragers acquire the ability to feed brood. Essentially, they reactivate their brood-feeding glands, and they seem to increase production of Vg, which is required for production of brood food (Amdam et al., 2005). This process is thought to be mediated by chemical signals sent by the foragers to the younger bees (and likely vice versa) that inform the members of the nest as to whether the correct ratio of bees in the different phases is present for optimal colony performance (Huang and Robinson, 1996). The fact that bees can revert from the old phase to the young phase has attracted considerable attention from aging researchers, as it is a natural example of repairing the damaging effects of senescence (Amdam et al., 2005; Amdam and Page, 2005; Seehuus et al., 2006a). It should be possible to learn

about molecular mechanisms (genetic and epigenetic) for the prevention of senescence and for the repair of aging damage by documenting what genes turn on in foragers that have reverted to nurses (Herb et al., 2012; Locket et al., 2012). There is thus much to learn from studying this highly derived pattern of aging in bees. However, as for extending the longevity of nurses, there are still some key experiments missing.

Missing Experiments

The most derived (as distinct from ancestral) patterns of aging are (1) bees can be kept in the nursing phase perhaps indefinitely, and (2) foragers can be induced to revert to the nursing phase, recovering some aspects of nursing physiology (perhaps including increased longevity). With respect to both phenomena, key experiments have not been conducted. Hence, although there is great promise in the study of these two phenomena, there is also some need for caution.

Although it is known that nurses can be kept in the nursing state for a very long period of time, it is also known that young and old nurses have many differences in their physiology (Wegener et al., 2009). Remolina et al. (2007) also found that overage nurses do experience senescence, in that they are less able to handle physiological stresses, such as heat and oxidative damage (relative to younger nurses). It is thus possible that overage nurses are a mosaic of young and old phenotypes. The fact that they live for so long is indicative of anti-aging processes, but the fact that they are more susceptible to physiological stress suggests that the freezing of development is not complete. Much work will be needed to tease apart what aspects of aging are frozen and what proceed at a normal rate in overage nurses.

Although it has been shown that foragers can revert to the nursing phase, and many studies have taken advantage of this phenomenon to study developmental polyphenism, there are several key studies that have not been conducted that must be performed before the utility of this phenomenon for the study of aging can be determined. First, studies showing aging reversal have not controlled for the age of the foragers that revert. It is known that senescence does not start until late in a forager's career. It is possible (and even likely) that the bees that revert from foraging to nursing are only the youngest foragers (and conversely the older foragers might not have this ability). Further, since the young foragers may not have begun the process of senescence, it is not clear that they have reversed the aging process. In contrast, they may simply have changed physiological and behavioral state without having to repair or retard senescence. Studies that control for age of the foragers must therefore be performed. These studies should ensure that only old foragers are present in the nest, and that it is these foragers that revert to the nursing phase.

Second, although it has been shown that foragers can reactivate their brood-feeding glands and change their JH titer to that more characteristic of the younger phase, it has not been shown that this leads to greater longevity. What has been shown, essentially, is that foragers can become nurses, but given that the reverted nurses appear to be rather poor nurses, it is possible that this is a temporary solution for the colony (that is, the reverted foragers will not last long and must be replaced by a new batch of young nurses). Hence, studies must be conducted that show that bees that revert from foraging to nursing can then be induced to stay in the nursing phase for an extended period of time. This will show that the bees reacquire not only the ability to perform nursing tasks, but also the physiological capacity to extend their lifespan for as long as is necessary for the colony. Given that ants that start out as workers and then switch to reproductives can increase their physiological capacity (Schneider et al., 2011) suggests that such a capacity is possible.

Senescence and Immunity: Health in Older Workers

Disposable Castes: Downregulation of Immunity in the Honey Bee?

Foragers in social insect colonies have long been considered the disposable caste. This is because the act of foraging is risky and is associated with a high mortality rate relative to those workers that remain in the nest. Hence, if mortality rates are high, it might make sense to strip the foragers' bodies of all the resources that are not necessary and to store those resources in the nest (either in food stockpiles or in the bodies of younger workers), the result being that if foragers die, there is little cost to the colony. There is evidence to support this notion from several species of ants and bees (Toth et al., 2005; Robinson et al., 2009). Ant and bee foragers, for example, have much lower protein and fat titers than younger workers.

A corollary to the disposable caste idea is that the immune system of workers should be adaptively downregulated in foragers relative to younger bees (Amdam et al., 2005; Seehuus et al., 2006a). In this case, by shutting down the immune system, which is costly to maintain, foragers cost the colony less. Of course, decreased immune function is characteristic of senescence across most organisms (Ames et al., 1993; Sansoni et al., 2008). If the same process of functional decline is observed in forager bees, then this system would be ideal for studying age-related declines in immunity. This is because it is simple to record when a bee begins foraging and, hence, begins to senesce. Precise measurements of the rate of decay of immune function (in its various components) could then be made. Further, because foragers can revert to nurses, it may also be the case that they reactivate their immune systems, allowing one to observe what pathways are turned

back on to recover immune function. Much work has been done on this phenomenon of immune decline in foraging bees (Schmid et al., 2008; Laughton et al., 2011; Helft et al., 2012; Gätschenberger et al., 2013; Jefferson et al., 2013). Early work supported the basic hypothesis outlined above, but more recent work has questioned this simple perspective.

Re-Evaluation of Support for Adaptive Downregulation of Immunity

Early work supported the notion that foragers downregulate their immune system. In support is the long-known fact that nurses have high Vg titers and low JH titers, and foragers have the opposite pattern. Amdam et al. (2004) showed that Vg may act as an antioxidant and protect bees from oxidative damage (Seehuus et al., 2006b). Further, it was shown that foragers have low levels of functional hemocytes, while nurses have higher levels (Amdam et al., 2005). When foragers were forced to revert to nurses, for example, they recovered a higher level of functional hemocytes (and showed a moderate increase in Vg titer). All told, these results supported the notion that foragers actively downregulate immune function. The basic hypothesis could perhaps be expressed as the immune machinery is turned off at the transition to foraging, and then a process of senescence erodes the functional properties of the system.

In these first studies, the circulating level of functional hemocytes was taken as a proxy for the functional properties of the entire insect immune system. The insect immune system is complex, however. In broad strokes, there are humoral and cellular-based defense mechanisms (Lavine and Strand, 2002; Lemaitre and Hoffmann, 2007). The humoral system includes the production of anti-microbial peptides and ROS, while the cellular system is involved in phagocytocis, nodulation, and encapsulation of large foreign bodies. Both nodulation and encapsulation are often followed by melanization, which is associated with the phenoloxidase system (PO). The PO system can also apparently work in the absence of hemocytes (Lemaitre and Hoffmann, 2007). Insects also have an RNAi-based system for defense against viruses. Essentially, the insect immune system is complex with many different components, many of which overlap in function. Hence, it is not clear that a decline in one component (hemocytes of one type) can be a reliable indicator of either overall immune function, or even a particular component of immunity such as the totality of cell-based immune responses.

Work conducted since the original studies by the Amdam lab have generally supported the notion that immunity is not downregulated in foragers. Instead, it appears the immune system is re-modulated such that it retains functionality, but with a different mixture of immune system components playing key roles. It may even be the case that the immune system of

foragers is upregulated (Bull et al., 2012), which would not be surprising given that the foragers are the bees that are exposed the most to pathogens. Supporting this new prospect are a number of studies. With respect to the humoral response, Jefferson et al. (2013) found no decline in the production of antimicrobial peptides with age in honey bees. This barrier line of defense does not apparently decline with age, and this suggests that one component of the immune system (number of functional hemocytes) is not a good proxy for the whole immune system.

With respect to the number of functional hemocytes, Wilson-Rich (2008) found no decline in the number of functional hemocytes with age in honey bees. However, this study misidentified newly emerged bees as nurses, so it is possible that nurses do show higher levels of hemocytes than foragers. This study also found that foragers can encapsulate foreign bodies as well as larva, pupae, and newly emerged bees. Schmid et al. (2008), however, did find that hemocytes decline with age, but not for the reasons initially supposed. They tested whether the decline in hemocytes is specific to the worker caste or whether it also occurs in queens and drones (males). They found that the decline in hemocytes is found in all three castes. This suggests that this decline is not a result of adaptive senescence in workers alone, but is generally true independent of task or even sex. Further, they found that overage nurses also have depressed hemocyte counts, suggesting that aging, independent of functional role, contributes to the loss of hemocytes.

The function of the PO system is to facilitate melanization of pathogens (Lemaitre and Hoffmann, 2007). It is thought that high PO activity can compensate for overall hemocyte losses. In support of this, in the same study in which Schmid et al. (2008) found a decline in hemocytes with age (independent of caste), they found no decrease in PO activity between ages. Laughton et al. (2011), in a similar study, found higher levels of PO in foragers, relative to nurses. Helft et al. (2012) also found no difference in PO expression between young and old ants. This information, taken together with the results of Wilson-Rich (2008) that show that foragers can encapsulate as well as nurses, suggests that the decline in hemocytes found in several studies may not be associated with a decline in immune function. Other components of the immune system are retained, and perhaps are even amplified, to compensate for the loss of functional hemocytes. What is clear based on this mini-review is that the relationship between age and immune system functional senescence is quite complex in social insects, and it will require considerable work to disentangle the many confounding variables.

Lessons to Be Learned

Two lessons can be learned from the ongoing story concerning functional senescence of immunity in honey bees. First, simple interpretation

of gene expression differences alone is prone to error if functional studies are not also conducted (Bull et al., 2012; Gätschenberger et al., 2013). Second, there has been considerable oversimplification of the honey bee's complex system of developmental polyphenism (correlations have been interpreted as causes). With respect to the first principle, Gätschenberger et al. (2013) found that although winter bees are unable to turn on the genetic machinery to cause the formation of nodules for bacterial defense, they are nevertheless equally effective at antibacterial defense as summer bees. This means tests that look for an immune response by looking for increases in expression of genes thought to be central to the process may miss an alternative mechanism supporting the same function. Likewise, Bull et al. (2012) conducted studies in which they challenged bees with bacteria and checked for the ability to increase expression of AMPs (a common bioassay for immune competence). They found that nurses respond to bacterial challenge by increasing expression of many key antimicrobial genes, while foragers do not show a gene expression change. In functional studies, however, foragers survived longer post-infection with a bacterial pathogen than did nurses. It appears that nurses respond strongly with a change in gene expression because their immune system is largely turned off at the point of challenge. Foragers, in contrast, have an already maximally activated immune system: that is, they have already produced much of the required protein and do not need to make more. It is likely the lag time in production of proteins for nurses (relative to foragers that have them already made) that is responsible for the difference in survivorship between nurses and foragers. Hence, the lack of an ability to respond with a rise in gene expression is actually indicative of superior function in this case. The conventional view has been that organisms without the ability to mount a response to challenge (assumed to be based on a rise in expression of key antimicrobial genes) are functionally deficient. Hence, it can be quite problematic to infer function from studies of gene expression alone.

The initial studies by Amdam and others that suggested that Vg is the linchpin underlying functional senescence in honey bees oversimplify the biology of developmental polyphenism in bees. Essentially, high JH in foragers and low Vg (and the opposite in nurses) are two out of thousands of differences between nurses and foragers. Although many correlations were shown suggesting that Vg was a key player in immunity, there were no cause-and-effect manipulations that clearly tie Vg to immunity. A critical test would be to test for various immune functions in drones, since these bees have very low Vg titers at all ages. Gätschenberger et al. (2012) did this and found that drones have competent immune systems in spite of very low Vg. Hence, in general, the developmental polyphenism of nurses and foragers is complex and care must be taken not to overinterpret the significance of differences in the expression of particular individual molecular actors.

RESEARCH OPPORTUNITIES

Because all individuals within societies are interconnected through mechanisms such as social support, social influences, social engagement, individual-to-individual contact, and access to resources, their health and longevity are also interconnected. There is no group of organisms where this is more evident than in the social insects. It follows that social insects are virtually untapped resources for use in answering basic questions regarding the influence of hierarchy and connectedness on health and longevity. Indeed, many behaviors co-evolved in the context of both individual and colony health.

We see at least five areas that hold promise for the use of social insects in future research on the biodemography of health, aging and longevity.

1. *Integration of colony-, organismal-, genetic,- and molecular-level studies on health, aging, and longevity*. The hierarchical organization of insect societies from individuals to the superorganism of the colony provides unprecedented opportunities for research. Bee biologist Rob Page and his co-workers consider social evolution a vertical process from the molecular level through the colony using behavioral and anatomical analyses, physiology, genetic mapping, and gene knockdowns (Hunt et al., 2007; Page, 2013). They map out the phenotypic and genetic architectures of food storage and foraging behavior and show how they are linked through broad epistasis and pleiotropy affecting a reproductive regulatory network that influences foraging behavior, a major determinant of honey bee health and longevity.
2. *Intergenerational transfer, health, and longevity*. In most models of life history theory, reproduction is treated as a purely demographic matter—i.e., birth is viewed as a single event independent of parental care. However, for many social species, continuing transfers to offspring are centrally important for survival, growth, and eventual reproductive success (Duarte et al., 2011). The theory offered by demographer Ronald Lee (Lee, 2003) strikingly shows that only the transfer effect shapes mortality, explaining both post-reproductive survival and why juvenile mortality declines with age. Since this theory also has deep links to kin selection and inclusive fitness, use of social insects to test hypotheses related to parental care and intergenerational transfer of resources has great potential for future research.
3. *Interdisciplinary research at the individual level*. As Charbonneau and his colleagues note (Charbonneau et al., 2013), emerging technologies are facilitating the way for social insect researchers to

gather and analyze data at the individual level (digital tracking). This development is thus fostering interdisciplinary collaboration among population biologists, computer scientists, engineers, and mathematicians, thus creating a synergism in research. There are exciting new possibilities for gerontologists and biodemographers to engage in this exciting development and use social insect models to gain new insight into questions concerning health and longevity in social systems that are relevant to humans.

4. *Comparative biodemography of social insects.* Because of the diversity of life histories and the evolutionary gradations of sociality from subsocial to eusocial within each of the four major groups of social insects (ants, bees, wasps, termites), the potential for comparative studies of concern with evolutionary and biodemographic studies of health, aging, and longevity is vast. Comparative studies have the potential to shed light on the evolutionary interconnectedness of health-related levels of defense including (a) individual defenses, (b) pair-wise defenses such as grooming, (c) colony defenses such as task differentiation, (d) minimizing the entry of infectious agents, and (e) use of environmental (e.g., resins) in colony shielding (Evans and Spivak, 2010). In addition, comparative studies may reveal how selection promotes genes that are most efficient in their ability to produce disease resistance phenotypes, gene products such as proteins and cells that play vital roles in physiological immunity, new groups of individuals that mount collective defenses (i.e., social immunity), and population-level scale disease dynamics (Wilson-Rich et al., 2009).
5. *Honey bee health.* One of the burgeoning fields in social insect ecology involves studies of the determinants of individual- and communal (colony)-level health, respective concepts that are akin to clinical (medical) and public (communal) health in human societies. Even though the history of health studies in social insects and particularly in honey bees extends back well over a century with investigations focused mostly on various brood diseases (e.g., foul brood) or parasites (e.g., Varroa mite), the modern incarnation of health research in social insects emerged with arrival of colony-collapse disorder (CCD) in the mid-2000s, an unsolved decline in bees from parts of the United States, Europe, and Asia (Evans and Schwarz, 2011). Although the causes of CCD have yet to be determined, the efforts have led to the creation of a new framework to study health in social insects at multiple levels, ranging from the immunity of individuals to the defenses at the level of the colony (i.e., social immunity).

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13

Biodemography of Ectothermic Tetrapods Provides Insights into the Evolution and Plasticity of Mortality Patterns

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INTRODUCTION

Evolution acts to shape aging rates within the set of ecological and organismal constraints that individual species experience. Biodemography seeks to understand the shape of age-dependent reproductive and mortality patterns and how they are impacted by these constraints (Carey and Vaupel, 2006). Although model laboratory organisms have been crucial to understanding patterns and causes of aging, there is great value in also studying the underlying evolutionary and ecological forces that shape rates of aging in the environment in which they evolved. In this paper we examine the biodemography of wild populations of three species (a turtle, a frog, and a snake). All are ectotherms, an understudied subset of the vertebrate taxa for understanding aging. Low metabolic rates coupled with a tendency for indeterminate growth, and thus increasing fecundity with age, lead to the prediction that general patterns of aging should be slower in these taxa. We focus on age-dependent differences in mortality (i.e., the shape or trajectory of mortality), describing basic patterns and determining how early-life and late-life exposure to poor environmental conditions shape these patterns.

Classic evolutionary theory of aging predicts that the declining power of natural selection with advancing age will mold the age-dependent trajectory of mortality for a species, or the rate of aging (Hamilton, 1966; Promislow and Bronikowski, 2006). This occurs because fewer individuals are expected to survive to later age-classes due to extrinsic sources of death, and thus alleles that are deleterious at advanced ages become fixed (Medawar,

1946), as do alleles that confer fitness advantages earlier in life despite possible deleterious effects later in life (Williams, 1957). Within this paradigm, a fundamental prediction is the inevitability of senescence as organisms age (Medawar, 1946; Williams, 1957), while relative rates of aging are expected to evolve when the strength of selection is altered across the lifespan (Hamilton, 1966; Promislow and Bronikowski, 2006).

This prediction of universal senescence has been called into question due to problematic assumptions: lack of consideration of the sources of mortality and the role of phenotypic plasticity, and a need for additional mathematical rigor (Abrams, 1993; Lee, 2003; Williams and Day, 2003; Vaupel et al., 2004; Baudisch, 2005; Nussey et al., 2013). At the same time, empirically determined mortality trajectories, such as species-specific Gompertz curves, and notions that animals do not display significant senescence in the wild have been challenged by larger datasets and more sophisticated analyses in many species, including humans (Brunet-Rossinni and Austad, 2006; Carey and Vaupel, 2006; Bronikowski et al., 2011; Jones et al., 2014). Moreover, both the diversity among species and variation within species in the shapes of mortality trajectories have been relatively understudied and remain major unsolved biological questions that have relevance for understanding the evolution of diverse life histories and lifespans (Munch and Mangel, 2006). Taken together, these criticisms and insights suggest that broadening an understanding of the evolution of senescence in diverse taxa, and incorporating analyses that include sex-specific and environment-specific differences, are important for a comprehensive understanding of the constraints governing aging.

General patterns of mortality may differ both among and within species. Important sources of within-species variation are environmental drivers that lead to differences among individuals in age-dependent mortality and reproductive probabilities (Le Galliard et al., 2010; Peterson et al., 2010). The effect of the environment on demography can manifest as immediate impacts on reproduction and survival of individuals and through long-term ontogenetic carry-over effects that may be realized long after the period of exposure (Madsen and Shine, 2000a). In both cases, the environment in which an individual occurs may shape the pattern of mortality senescence. The literature on compensatory growth in vertebrates has numerous examples of the negative effects of early nutritional stress on growth, reproduction, and survival (Metcalfe and Monaghan, 2001; Hector et al., 2012), as well as the converse notion of a "silver spoon" effect of abundant resource availability during the juvenile stage (Madsen and Shine, 2000b; Mangel and Munch, 2005). For example, recent intriguing examples of an early-age nutritional effect is reported in the lizard *Zootoco vivipara* (Massot and Aragón, 2013), where the first meal of one's life shapes rates of reproduction and survival months to several years later.

Within populations, individuals born in the same year may share the same early life conditions, which can generate common effects on age-dependent mortality for individuals within these cohorts. Cohort effects may either shift the average mortality rate throughout life or interact with age to affect the rate of senescence (Massot et al., 2011). The effects of common environmental conditions on mortality are not limited to early life, but occur throughout life (Eskew et al., 2010). These again may lead to common shifts in mortality across all ages or affect individuals differently based on age-dependent vulnerability to environmental stress (Wikelski and Thom, 2000). In addition, cohort and later-life effects may interact, so that individuals exposed to poor conditions early in life may respond better or worse to later stressors, depending on whether the early exposure has a priming or a weakening effect. Studying factors related to cohort and annual effects in wild populations provides an opportunity to test the magnitude of environmental influences in shaping age-dependent mortality and thereby clarifies the nuances of evolutionary senescence theory.

Natural selection over evolutionary time periods has led to vertebrate species that vary in lifespan by orders of magnitude (< 1yr – 100+ years) (Austad, 2010), whereas the greatest difference achieved via artifical selection in lab mice has been little more than 2-fold (Bartke et al., 2013). Thus, studies seeking to understand how variable lifespans and senescence evolves need to utilize this natural variation. Ectotherm (cold-blooded) vertebrates, including reptiles and amphibians, demonstrate such extensive variation in lifespan among major lineages and species, and include reports of negligible aging (e.g., Congdon et al., 2003; Jones et al., 2014). Amphibians are best known for their transition from aquatic larvae to semi-terrestrial adults accompanied by transformation of the morphology, gut, and respiration systems. In wild populations of reptiles, the oldest adults are often the most fecund and robust (Paitz et al., 2007; Sparkman et al., 2007) in contrast to most mammals (e.g., Alberts et al., 2013); this is a trait that commonly distinguishes species with indeterminate versus determinate growth. Taken together, low metabolic rates relative to mammals (White et al., 2006), coupled with indeterminate growth and indeterminate fecundity, suggest that aging rates, measured as the shape of age-specific mortality, will be slower in reptiles and amphibians than in mammals and birds (reviewed in Schwartz and Bronikowski, 2010). The extensive variation in ectothermic vertebrates in lifespan indicates that forging new links with biodemography holds exciting promise to illuminate evolutionary mechanisms for the origin and modulation of vertebrate aging patterns.

We examined age-specific mortality in populations of three species that have been studied for at least several generations: the Sierra Nevada yellow-legged frog (hereafter, yellow-legged frog; *Rana sierrae*), western terrestrial garter snakes (hereafter, garter snake; *Thamnophis elegans*), and painted

turtles (*Chrysemys picta*). Data for each study derive from long-term mark-recapture studies where environmental factors influencing demography are well characterized and monitored (Miller et al., 2011; Schwanz et al., 2011 Fellers et al., 2013). For each species, we first examine the general age-dependent mortality trajectory. Then we examine how environmental variation influences age-dependent mortality, by focusing on how shared cohort and annual environmental conditions act and interact on mortality patterns. Our goal is to expand the comparative perspective into aging in nonmodel species.

METHODS

Data Collection

Data for yellow-legged frogs were collected from the Summit Meadow population in Yosemite National Park (Fellers et al., 2013). This species has been studied at that site from 2003-present. Animals were marked during 10-15 days each summer where observers conducted systematic searches of the wetland and captured and marked all animals that were at least 40 mm in length. We conditioned aging analyses on the age of maturation (~6 years in this population; Fellers et al., 2013). Based on extensive analysis of growth rates, which included estimating the distribution of individual size at maturity, we classified all individuals that were less than 51 mm at the time of first capture as known-age individuals that matured in the current year and larger individuals as unknown age. Previous work has shown that water availability (as measured by relative precipitation two years previous) has a strong correlation with population size fluctuations (Fellers et al., 2013). To evaluate the role of precipitation on mortality trajectories, we classified individuals exposed to less than average precipitation during the 2 years prior to maturation as coming from "poor" quality cohorts and above average as being from "good" quality cohorts. Similarly, we classified a year as being a "poor" year when precipitation was less than the long-term average and a "good" year as having above-average precipitation. In this way, animals could be either from poor or good cohorts and poor or good recapture years.

Mark/recapture data for the garter snake are from a long-term study in the northern Sierra Nevada (Lassen County, California), in the Eagle Lake basin and surrounding meadows. These populations have been the object of extensive studies from 1976-present. Previous work has shown strong evidence of life-history divergence among populations along a fast-to-slow pace of life continuum, with low-elevation populations characterized by individuals that grow fast, mature early, and have both higher fecundity and shorter median lifespan than higher elevation populations (Bronikowski

and Vleck, 2010; Robert and Bronikowski, 2010), hereafter referred to as "short-lived" and "long-lived" ecotypes of garter snakes. Although observed maximum life spans do not differ (ca. 18-20 years), the age structure is markedly different with low-elevation populations skewed towards younger individuals. For our analyses, we focused on two populations of the long-lived ecotype and one population of the short-lived ecotype for which we had sufficient power to estimate age-specific mortality. Capture effort varied among years, but substantial effort occurred for all populations from 1979–1988 and 1994–1996; thus we use these years for our analyses. Known-age individuals were defined by age/size relationships. Individuals less than 280 mm in long-lived and 350 mm in short-lived populations were considered young of the year and treated as known-age (1-year-olds), and all individuals initially caught at larger sizes were treated as unknown-age. Previous work showed a strong tie between food availability and demography, with precipitation and its effect on anuran prey and water availability being the major driver of annual variation (Bronikowski and Arnold, 1999). We defined "poor" and "good" years following criteria developed by Miller et al. (2011) as years with less than or greater than 500 mm precipitation in the preceding year. "Poor" cohorts were defined to be cohorts that experienced a "poor" first year and "good" cohorts were the opposite. Like the frogs, animals could be either from poor or good cohorts and poor or good recapture years.

Our painted turtle data are from long-term studies of a nesting population of painted turtles on the Mississippi River between Iowa and Illinois (Whiteside County, Illinois). This area has been monitored since 1988, with mark-recapture beginning in earnest in 1995 (Schwanz et al., 2010; Jergenson et al., 2014; Warner et al., 2014). There are two sources of data: females are primarily captured when they move onto land to construct nests or when they are trapped aquatically in fyke and hoop nets. Males are caught almost exclusively in aquatic traps, with the occasional rare male hand-captured on land. Known-age individuals are identified based on pectoral scute annuli when they first return to the breeding grounds (6-8 years of age for females, 3-5 years of age for males). Less is known about what environmental factors drive annual variation in survival beyond the first year of life, in part because adult survival remains fairly stable across years (Jergenson et al., 2014; Warner et al., 2014). Our primary analyses for this painted turtle population do not consider "good" and "bad" recapture years, although adverse winter conditions likely impact individual survival via anoxia. However, previous work (Schwanz et al., 2010) has detected high variability among annual cohorts in hatching success, which is tied to above-average thermal conditions during embryogenesis. Based on this criterion, we assigned individuals from years where less than two-thirds of intact eggs hatched as "poor" cohorts,

with "good" cohorts in years where greater than two-thirds of intact eggs hatched (Schwanz et al., 2010).

Analyses

We estimated age-specific mortality probabilities using standard mark-recapture methodologies to account for detection uncertainty common to monitoring of wild populations (Lebreton et al., 1992; Williams et al., 2002). We first estimated the age-specific mortality schedule from all individuals pooled within each population (i.e., one population of yellow-legged frogs, three populations of garter snakes, one population of painted turtles), with the yellow-legged frog data partitioned further into males and females. Secondly, using only animals of known age, we related mortality to the covariates of cohort quality ("good" vs. "poor") and quality of year in which the animal was recaptured ("good" vs. "poor"). Although the effect of sex was not estimable due to statistical power of our sample size in this second analysis, we were able to test for age-specific cohort and year effects (and their interaction) on known-age individuals. Findings from this latter analysis specifically address the question of whether early-life experiences leave a signature on mortality trajectories, and indeed whether this signature manifests differently among animals that experienced "good" vs. "poor" recapture years.

For the first analysis, we estimated age-specific mortality on data pooled over years for each species (i.e., ignoring variation due to cohort and annual effects, but testing for an effect of advancing chronological age) using the program BaSTA (Colchero and Clark, 2012; Colchero et al., 2012). This program fits models using a Bayesian approach that includes both known and unknown age individuals, as well as accounting for incomplete detection. Models were fit using MCMC. For each population, we fit a Gompertz model of accelerating death rate to the data, reasoning that more parameterized models were not justified given the sparse data. A Gompertz model is defined by $u_x = Aeb_x$ where u_x is the mortality hazard rate, A is the initial mortality rate (*IMR*), and b is rate of increasing death probability with advancing age (referred to hereafter as "aging rate"). We fit models using the complete data sets (i.e., that included both known-age and unknown-age individuals). This approach worked well for the yellow-legged frog and painted turtle datasets, and for the long-lived garter snake populations. We were unable to fit models to short-lived snake populations, likely because of the limited capability of BaSTA to deal with detection heterogeneity and the shorter median lifespan and higher mortality of animals in this population. Thus, we could not estimate mortality trajectories for this population. For yellow-legged frogs we were able to estimate separate mortality functions for males and females, while for the painted turtles,

our data were limited to females. For garter snakes, a large proportion of animals of known age-at-first-encounter (i.e., neonates) were of unknown sex. Thus, we could not test for a difference between the sexes for garter snakes in age-specific mortality.

While powerful, the BaSTA approach has limitations, including an inability to deal with cohort and annual effects on survival, and known-age animals that enter a population at later ages. In addition, the approach makes strong assumptions about a lack of emigration and immigration, no relationship between age and detection variation, and no individual heterogeneity. Therefore, to examine cohort and annual effects, we fit Cormack-Jolly-Seber models (Cormack, 1964; Jolly, 1965; Seber, 1965) for known-age individuals using Program MARK (White and Burnham, 1999). For these analyses, we were limited to the known-age component of the dataset. We again were unable to examine sex-related differences in the painted turtles and garter snakes. Due to data constraints, we also did not consider sex-specific differences for yellow-legged frogs. Other analyses show a high degree of congruence in female and male mortality patterns (Fellers et al., 2013; BaSTA analysis in this study). Our ability to fit complex models for age-specific mortality probabilities was limited when simultaneously considering cohort and annual effects; thus, we grouped data into several age-classes rather than using annual age for each species. For yellow-legged frogs, the age-classes were the first year after reaching maturity (i.e., 6 years of age) and greater than 1 year after reaching maturity (> 6 years of age). Following our previous studies (Bronikowski and Arnold, 1999; Miller et al., 2011), we divided garter snakes from the long-lived ecotype into 1-year-olds (neonates), 2-4 year olds (juveniles), and greater than 4 years of age (adults). Likewise for the short-lived ecotype of garter snakes, we divided garter snakes into 1-year-olds (neonates), 2-year-olds (juveniles), and greater than 2 years of age (adults). Finally, adult female painted turtles were divided into less than 2 years after first breeding (young adult, i.e., 6-8 years of age), 2-4 years after first breeding (i.e., 8-10 years of age), and greater than 4 years after first breeding (i.e., 10+ years of age).

We fit survival models that allowed for variation among age-classes, poor and good cohorts, and poor and good years, along with all two-way interactions among these effects. Our global model took the form of

$$\text{logit(Survival)} = \text{Age-Class} + \text{Cohort} + \text{Year-Quality} + (\text{Age} \times \text{Cohort}) + (\text{Age} \times \text{Year-Quality}) + (\text{Cohort} \times \text{Year})$$

where all explanatory variables were categorical. Age-classes for each species are as explained above. Cohort and year effects are divided into poor and good based on criteria defined in the "Data Collection" section above.

For yellow-legged frogs and garter snakes, we were able to include all the factors in the models. Because we were unable to define poor and good years for adult painted turtles based on an environmental variable, we did not test for an effect of "Year" quality, but did test for effects of age and cohort for this species. We fit models for all possible combinations of two-way interactions and main effects and selected among models using AIC. We present model-averaged estimates of parameters to account for uncertainty in the model selection procedures (Burnham and Anderson, 2002).

RESULTS

We successfully fit age-specific Gompertz mortality models to male and female yellow-legged frogs, female painted turtles, and two populations of long-lived garter snakes of both sexes (see Table 13-1, Figure 13-1). Overall mortality was lower and rates of aging slower for painted turtles than for yellow-legged frogs and garter snakes. Mortality trajectories were similar for both sexes in yellow-legged frogs, with the only difference being slightly higher mortality for males than females. Mortality acceleration was similar in both populations of long-lived garter snakes. One difference between these two populations was that the best model for Population 1 included an age-independent (constant) mortality, i.e., a Makeham term, which is additive with the standard Gompertz model (Table 13-1.) Notwithstanding, rates of aging were quite similar among garter snakes and yellow-legged frogs (range: 0.16-0.22), which corresponds to a mortality rate doubling time (MRDT) of 3.2-4.3 years. The MRDT for female painted turtles was 6.8 years, which is significantly slower than for frogs and snakes (Table 13-1).

When fitting models to determine cohort and annual survival effects, with data limited to only known-age individuals, all populations showed differences in mortality among age-classes similar to the Gompertz analysis (see Table 13-2). In addition, whereas long-lived garter snakes and yellow-legged frogs showed strong evidence of cohort and annual effects on mortality, painted turtles were more resilient and were seemingly buffered against years of poor cohort quality and environmental variance (see Figure 13-2). Overall, mortality of yellow-legged frogs decreased strongly in the first year post-maturity. This was pronounced and consistent for animals from good quality cohorts, regardless of whether their recapture year was of poor or good quality. For individuals who were in cohorts from poor quality years, mortality increased significantly when these poor cohorts experienced poor resource years (Figure 13-2). Growth is still rapid during this first year post-maturation, perhaps contributing to the added mortality in this latter group (Fellers et al., 2013).

TABLE 13-1 Information for Three Species of Ectothermic Vertebrates for Age-Specific Mortality Analyses Including Sample Sizes and Gompertz Model Parameters

Species	Study Years	Group	N	Gompertz Model Parameters ($u_x = Ae^{bx}$)		Oldest Observed Age	Lifespan (yrs) (given survival to maturation)	
				A (IMR /yr) (CI)	*b* (CI)		Mean	90%
Sierra Nevada Yellow-legged Frog (*Rana sierra*)	2003-2013	Male	543	0.153 (0.106, 0.210)	0.22 (0.14, 0.30)	16	8	11
		Female	464	0.130 (0.092, 0.176)	0.21 (0.13, 0.28)	16	9	12
Western Terrestrial Garter Snake (*Thamnophis elegans*)	1978-1996	Short-lived: Male & Female	2176	*	*	15	5	6
		Long-lived: Pop 1 Male & Female	1655	0.25 (0.16, 0.38)	0.16 (0.12, 0.20)	18	9	15
		Long-lived: Pop 2 Male & Female	449	0.10 (0.04, 0.21)	0.20 (0.13, 0.29)	17	9	13
Painted Turtle (*Chrysemys picta*)	1996-2012	Female	1031	0.102 (0.090, 0.116)	0.05 (0.03, 0.07)	23	11	19

NOTES: N is sample size for the Gompertz analysis and includes all individuals of known and unknown age. Gompertz parameters were estimated using a Bayesian mark-recapture estimator. *A* (the Initial Mortality Rate, *IMR*) is estimated at age of maturation for frogs and turtles, and age 0 for snakes. Mean and 90% lifespan are calculated conditioned on attainment of the age-at-maturity. Thus, mean lifespan is the average number of years individuals survive given that they have reached maturity (maturity occurs in the sixth year for frogs, third year for short-lived snakes, fifth year for long-lived snakes, and sixth year for turtles). The 90% lifespan is the number of years until 90% of individuals have died. Lifespan values are calculated from the Gompertz parameters except in the case of short-lived snakes, for which we were unable to fit a Gompertz model and instead estimated mean lifespan from the known-age mark-recapture model. For population 1 of the long-lived snakes, a Makeham term improved the fit: c = 0.23 with CI (0.15, 0.32). Oldest age data observed are from Fellers et al. (2013), Sparkman et al. (2007), and Janzen (unpublished).

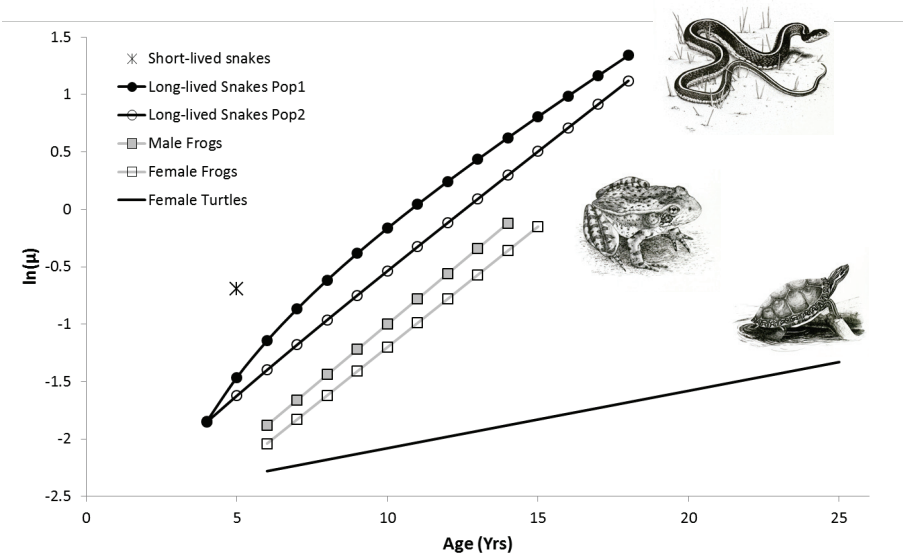

FIGURE 13-1 Age-specific mortality rates for two populations of long-lived western terrestrial garter snakes (*Thamnophis elegans*), male and female Sierra Nevada yellow-legged frogs (*Rana sierrae*), and female painted turtles (*Chrysemys picta*).
NOTES: Estimates are for a Gompertz mortality model (see Table 13-1 for parameters), excepting Population 1 of the long-lived snakes, for which an additive age-independent mortality term (i.e., a Makeham term) was included for improved model selection. For the populations of short-lived garter snakes, we were unable to fit a Gompertz model; the value indicated on the graph corresponds to the point estimate for adult mortality from our analysis of mark-recapture data.
SOURCE: Illustrations by Shawna Snyder, Iowa State University. Used with permission.

Long-lived snakes and yellow-legged frogs exhibited a similar interaction between cohort and annual effects. Mortality for long-lived snakes initially decreased after their first year and then began to increase again once they reached maturity. Individuals from poor cohorts began to exhibit higher mortality starting in their second year and the magnitude of the difference increased for adults. This suggests that poor developmental conditions during the first year of life may lead to greater rates of senescence. In addition, deleterious effects of poor conditions later in life only occurred for individuals from poor cohorts, indicating that early-life stress may reduce the ability of individuals to cope with poor conditions later in life (Figure 13-2).

The model with the strongest support for both painted turtles and short-lived garter snakes only included effects of age (Table 13-2, Figure 13-2).

TABLE 13-2 Mortality Estimates for the Indicated Age-Classes from Cormack-Jolly-Seber Analysis of Mark-Recapture Data

Species	N	Cohort Quality/ Capture Year Quality	Age-specific survival (yrs of age)			
			0-6	6-7	7+	
Sierra Nevada Yellow-legged Frog	366	Good cohort/Good year		0.523	0.952	
		Good cohort/Poor year		0.291	0.749	
		Poor cohort/Good year		0.774	0.813	
		Poor cohort/Poor year		0.576	0.411	
			0-1	1-4	4+	
Western Terrestrial Garter Snake Long-lived	1080	Good cohort/Good year	0.366	0.948	0.942	
		Good cohort/Poor year		0.976	0.926	
		Poor cohort/Good year		0.880	0.872	
		Poor cohort/Poor year	0.395	0.858	0.663	
			0-1	1-2	2+	
Western Terrestrial Garter Snake Short-lived	341	Good cohort/Good year	0.316	0.707	0.627	
		Good cohort/Poor year		0.716	0.648	
		Poor cohort/Good year		0.706	0.629	
		Poor cohort/Poor year	0.323	0.722	0.659	
			0-6	6-8	8-10	10+
Painted Turtle	603	Good cohort		0.811	0.924	0.904
		Poor cohort		0.815	0.922	0.899

NOTES: See Table 13-1 for years studied. Point estimates are from model-averaging.

Overall, short-lived garter snakes showed a similar pattern of age-specific mortality to long-lived garter snakes, with the lowest mortality occurring after the first year of life and prior to maturation. Unlike the long-lived garter snakes, whether cohorts were of poor or good quality did not influence this pattern. Interestingly, the painted turtles had higher mortality in the first 2 years after maturation, decreasing in the next 2 years before starting to increase again in later life, suggestive of a signature of senescence even within these broad age-classes.

DISCUSSION

Evolutionary senescence theory, underpinned by clear expectations from population genetic principles, has guided much of the research in compara-

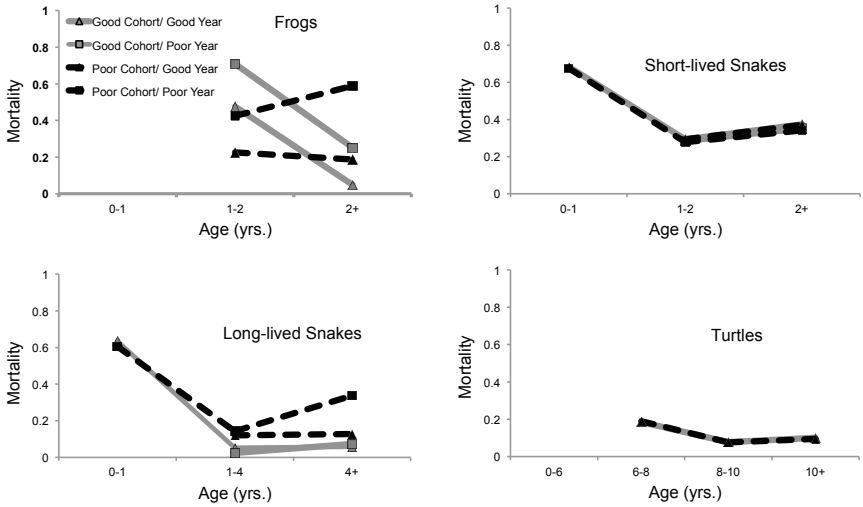

FIGURE 13-2 Tests for effect of early life experience and environmental variation on late life mortality for short-lived and long-lived ecotypes of the western terrestrial garter snakes (*Thamnophis elegans*), Sierra Nevada yellow-legged frogs (*Rana sierrae*), and painted turtles (*C. picta*).
NOTES: Model averaged estimates of mortality are from analysis of mark-recapture models accounting for age, cohort, and annual effects on survival. For yellow-legged frogs and long-lived garter snakes, we found effects of both cohort and year, along with their interaction suggesting that poor developmental conditions are associated with both greater mortality later in life and greater vulnerability to poor conditions at later ages.

tive biodemography for nearly 50 years. Even so, it has become apparent that variation in mortality trajectories demands a deeper understanding of mechanisms, particularly as such variation relates to potential constraints, be they environmental, sex-specific, or otherwise (Austad, 2010). Employing a comparative perspective by examining wild populations of relatively long-lived ectothermic vertebrates, we found that (1) across all three species, there was strong evidence for mortality senescence and (2) environmental factors, including stress, influence age-specific patterns of mortality both in current and later years and therefore produces plastic variation in the shapes of mortality trajectories.

We observed increased mortality with age in populations of all three species—yellow-legged frogs (*R. sierrae*), garter snakes (*T. elegans*), and painted turtles (*C. picta*). Painted turtles aged at a much slower rate than yellow-legged frogs and garter snakes, in agreement with a handful of aging

studies on turtles. However, the results for female painted turtles suggest that contrary to other turtle reports (Congdon et al., 2001; Miller, 2001; Jones et al., 2014), there was measurable aging, though this rate of aging is much slower than in many other taxa (reported here and see Finch et al., 1990; Finch, 2009; Bronikowski et al., 2011).

We found similarities with mammalian studies in the observed rate of aging for yellow-legged frogs and garter snakes. This was surprising, because indeterminate growth and indeterminate fecundity have been predicted to offset declines in the power of natural selection to remove deleterious mutations with late-age phenotypes (Reznick et al., 2004; Bronikowski and Promislow, 2005). The lack of uniformity in aging among our three ectothermic species suggests metabolism and indeterminate growth may not explain evolved differences in aging rates. Future work should evaluate other aspects of comparative aging, including sex-specific dynamics and other mechanisms underlying increasing mortality with advancing age. Such studies should include external sources of mortality (e.g., predation, drought, food availability) and internal mechanisms such as immunosenescence and accumulation of damaged cell components. Such a comparative perspective on biodemography and its underlying mechanisms will provide much needed insights into vertebrate aging.

Our results validate previous observations for the garter snakes, the one species where we had data on multiple populations. Interestingly, long-lived ecotypic individuals are generally smaller bodied and live on average twice as long as the larger-bodied, short-lived ecotypes (Bronikowski and Vleck, 2010). This is consistent with the pattern typically seen in lab rodents and dogs where smaller-bodied genotypes are generally characterized by longer lifespans than larger bodied (e.g., Miller and Austad, 2006).

Due to the limitations of our data, we were only able to examine sex-specific differences in mortality trajectories for the yellow-legged frogs. Not only did males and females in this population exhibit very similar mortality rates, but also the rate at which mortality increased with age was nearly identical between the sexes (Table 13-1). In the case of painted turtles, long-term data were only available for females, while for garter snakes, sex was unknown for the youngest age-classes and could only be determined for individuals recaptured at older ages. Thus, analyzing data for only known-sex individuals would rely on a non-random sample with respect to realized mortality schedules (Miller et al., 2011).

Work is currently under way to characterize survival patterns in male painted turtles, and sex-specific comparisons in this species will be especially interesting. Painted turtles have temperature-dependent sex determination (TSD), where temperatures experienced during a limited period of embryonic development determine the sex of the individual. Thus, since sex-linked genes do not exist in this species, differences between the sexes in

their biology, including their mortality patterns, must derive from environmental contexts or interactions between the environment and sex-specific physiology once gender has been determined.

Many studies on ectothermic vertebrates have demonstrated that environmental conditions in early life, especially during embryogenesis, influence subsequent individual phenotypes (Deeming, 2004), including behavior, physiology, life history, learning, and memory. Our study shows that environmental variation can affect mortality patterns (Figure 13-2). In both yellow-legged frogs and long-lived garter snakes, this is seen as a relationship between environmental quality during early life and an individual's ability to tolerate poor environmental conditions later on. That is, individuals that experienced poor environmental conditions as embryos or neonates had higher mortality when exposed to poor environmental conditions later in life. This pattern suggests that animals stressed early in life senesce more quickly in response to later life stressors. Further work to understand the physiological underpinnings of this relationship could shed light on the mechanisms leading to this pattern. Such an effect was not seen in painted turtles and short-lived garter snakes (Figure 13-2). The apparent buffering of female painted turtles against detrimental effects of early stress may be due to the consistency of food availability that characterizes their habitats and their resilience to extreme environmental perturbations such as flooding (Jergenson et al., 2014). Similarly, short-lived garter snakes reside in close proximity to continuous water and food availability (fish) in contrast to the long-lived ecotype. Thus, the susceptibility to low precipitation may be more pronounced in habitats inhabited by the long-lived ecotype where snakes rely on less reliable breeding anurans for food (Robert and Bronikowski, 2010).

All three species exhibited mortality senescence—increasing mortality with advancing adult age. However, Darwinian fitness is measured not in survival, but as lifetime reproductive success. For a complete understanding of how early life stressors relate to mortality, reproduction, and ultimately fitness, we would need information on how reproductive output changes with age and hence how lifetime reproduction varies with early-life environmental conditions. In the painted turtle population, female reproductive output increases with age until the late age-classes, at which point reproduction falls off quickly (D.A. Warner and F.J. Janzen, personal communication)—a pattern that suggests delayed but measurable reproductive senescence. However, the garter snakes—both the short- and long- lived ecotypes—continue to increase reproductive output with age, although much more rapidly in the short-lived than long-lived ecotype (Sparkman et al., 2007). We have no data for yellow-legged frog reproductive output as they age. However, novel environmental stressors such as pesticide exposure (Sparling and Fellers, 2007; Sparling and Fellers, 2009; Fellers et al.,

2014) and chytrid fungus (Fellers et al., 2001) are likely influencing lifetime reproduction and longevity more than traditional environmental variation.

Finally, we suggest that ectothermic tetrapods, are an underutilized comparative system for understanding the evolutionary forces that shape variation in age-dependent mortality relative to mammals. Ectothermic reptiles may have different mortality and reproduction trajectories across the adult lifespan than seen in many mammals (Lutz et al., 2003; Paitz et al., 2007; Bronikowski, 2008). Evolutionary theory posits alterations in traits that protect the organism from mortality as an ultimate source of variation in species-specific rates-of-aging and lifespan (Bronikowski and Promislow, 2005), and reptiles and amphibians have a number of such evolutionarily novel traits (Schwartz and Bronikowski, 2010). For example, crocodilians, turtles, tuatara, lizards, snakes, and amphibians have evolved the following: an external ribcage (turtles); venom (snakes); toxic secretions (anurans); limblessness (snakes, some lizards, caecilians); extended metabolic shutdown (all); starvation resistance, including remodeling of the digestive tract (snakes); supercooling, freeze tolerance, and heat tolerance (turtles, crocodilians, and some frogs); and extended hypoxia resistance (turtles, crocodilians, lizards) (Robert et al., 2007; Owerkowicz et al., 2009). Thus, mammalian aging and its limits may be best understood by studying variation across all tetrapods.

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14

A Comparative Perspective on Reproductive Aging, Reproductive Cessation, Post-Reproductive Life, and Social Behavior

Peter T. Ellison and Mary Ann Ottinger

INTRODUCTION

The relationships between reproductive aging, reproductive cessation, the emergence of extended, post-reproductive life, and social behavior in humans continue to be topics of both theoretical and empirical interest. Debate continues over the physiological processes underlying human reproductive aging (Downs and Wise, 2009; Perheentupa and Huhtaniemi, 2009; Ferrell et al., 2012), the uniqueness of human menopause (Packer et al., 1998; Herndon and Walker, 2010; Levitis et al., 2013), and the evolutionary forces that may have shaped late life and reproduction in humans (Johnstone and Cant, 2010; Kaplan et al., 2010; Hawkes et al., 2011; Mittledorf and Goodnight, 2012; Chu and Lee, 2013). However, from a comparative perspective, it is critical to recognize the existence of highly conserved mechanisms in these lifelong processes and to identify similarities as well as unique differences across vertebrates. Follicular depletion is widely considered to be the primary cause of the phenomenon of human menopause, as well as of cessation of ovarian function in other birds and mammals (Edson et al., 2009; Perheentupa and Huhtaniemi, 2009; Finch, 2013), but the degree to which this imposes a constraint on evolution is not clear. There is also disagreement over whether the trajectory of follicular depletion in humans displays evidence of significant acceleration prior to menopause (Richardson et al., 1987; Faddy and Gosden, 1995; Hansen et al., 2008; Coxworth and Hawkes, 2010;), as well as over recent evidence

for follicular renewal throughout life (Johnson et al., 2004; Eggan et al., 2006; Faddy and Gosden, 2007; Begum et al., 2008; Kerr et al., 2012).

Other components of reproductive aging, including gonadal senescence in males and changes in hypothalamic-pituitary function in both sexes, are often neglected in these debates. There is also debate over the relative frequency of significant periods of post-reproductive survival in nature and its phylogenetic distribution (Cohen, 2004; Pollycove et al., 2011). Finally, there are theoretical debates regarding the evolutionary origin of the currently observed human pattern of long, regularly occurring post-reproductive life and its relationship to human social behavior, ranging from those who see it as a consequence of intergenerational conflict to those who see it as a consequence of intergenerational cooperation (Mace, 2000; Hawkes, 2003; Cant and Johnstone, 2008; Johnstone and Cant, 2010; Chu and Lee, 2013).

In this paper, we will attempt to bring some of these debates into comparative perspective, focusing particularly on vertebrates. We will first consider the mechanisms of reproductive aging and cessation in vertebrates and particularly in birds and mammals, then the phenomenological distribution of post-reproductive life in captivity and in the wild. In addition, we will consider the insights provided by laboratory or captive populations in order to compare and contrast conserved mechanisms as opposed to unique adaptations in some populations. Finally, we will return to questions of the evolutionary origins of human post-reproductive life in particular.

MECHANISMS OF VERTEBRATE REPRODUCTIVE AGING

Follicular Depletion in Females

In all vertebrates, gonads develop embryologically from the genital ridge mesoderm and are populated by migrating primordial germ cells that give rise to mitotically competent oogonia and spermatogonia in females and males respectively. Spermatogonia are present in the testes throughout life in males of all vertebrate species and respond mitotically to gonadotropin stimulation. In females, however, there are two contrasting patterns. In fish (with a few exceptions noted below), amphibians, and reptiles, mitotically active oogonia remain present in the ovary throughout life, whereas in birds and mammals, they either largely or completely disappear before birth or hatching (Aranzàbal, 2011; Flament et al., 2011; Johnson, 2011; Jones, 2011; Norris and Lopez, 2011; Urbatzka et al., 2011). In birds and mammals, a period of clonal proliferation during embryonic development produces a large supply of daughter cells that become surrounded by a single layer of granulosa cells and commence meiosis I, becoming arrested in prophase where they remain until just before ovulation. At this stage

the cells are known as oocytes and the follicles are referred to as primordial follicles. The only notable exceptions to the phylogenetic distribution of these two modes of oocyte production are certain viviparous species of chondrichthyes, which appear to have a finite oocyte supply from early in development, like mammals and birds (Franchi et al., 1962).

There is some recent evidence that in mice and humans, some stem cells may persist in the ovary capable of generating new oogonia and oocytes long after birth (Johnson et al., 2004; Eggan et al., 2006; Woods et al., 2013), though there is no evidence of clonal proliferation capable of repopulating a depleted ovary with functional primordial follicles (Faddy and Gosden, 2007; Begum et al., 2008; Kerr et al., 2012). This intriguing observation of persistent germinal stem cells may have important medical applications in the domain of assisted reproduction, but does not appear to have any effect on processes of reproductive aging or follicular depletion.

Although birds and mammals are temporally limited in oocyte production, the initial supply of primordial follicles in the ovary at birth is very large relative to the number of potential ovulations over a female's lifespan (see Figure 14-1). In humans, for example, where a female may

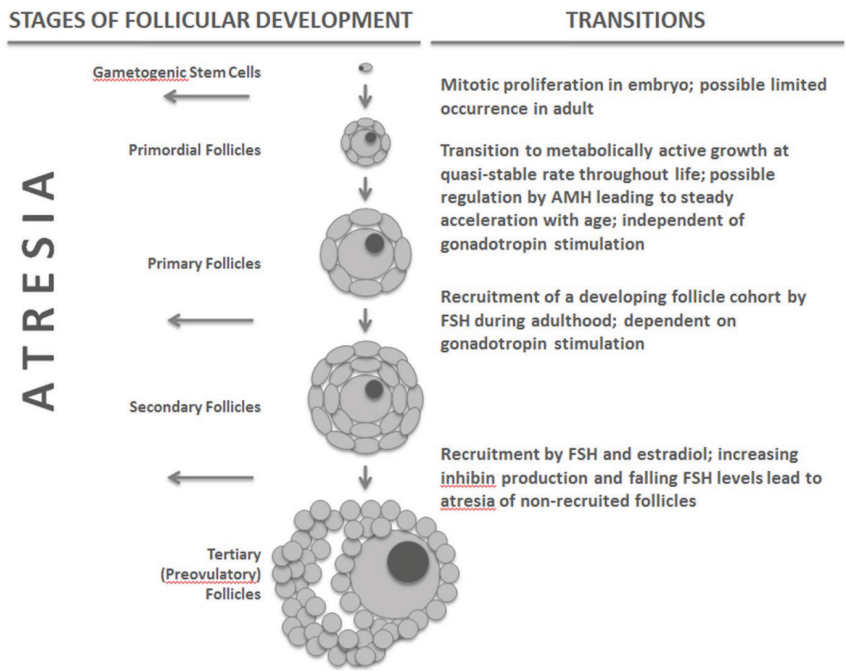

FIGURE 14-1 Stages and transitions in follicular development in birds and mammals. NOTE: AMH = anti-Müllerian hormone, FSH = follicle stimulating hormone.

expect to ovulate a maximum of 500 or so times, follicular supply at birth is typically four orders of magnitude greater. However, from the moment of initial oocyte arrest in meiosis, primordial follicles emerge from a state of metabolic quiescence at a low, quasi-stable rate to become metabolically active, growing follicles known as primary follicles (Fortune et al., 2000). In humans, the annual probability of such a transition has been estimated at 0.118 per follicle. Once past this initial transition, a follicle and its contained oocyte have only two possible fates: ovulation or atresia (regression of the follicle and apoptosis of the oocyte) (Depalo et al., 2003). A second transition, from primary to secondary follicle, depends on appropriate gonadotropin stimulation and recruits a cohort of follicles from the active primary pool in conjunction with mature ovarian cycling (Edson et al., 2009; McGee and Hsueh, 2000). Because this second transition is sensitive to gonadotropin stimulation, it can be affected by neuroendocrine changes in the hypothalamic-pituitary-ovarian (HPO) axis that may accompany aging. The rate of the initial transition from a quiescent primordial follicle to a metabolic active primary follicle appears, however, to be constant or increasing throughout life irrespective of reproductive state. Thus, the vast majority of primary follicles are lost through atresia without ever being recruited for potential ovulation. It is important to note that this loss is independent of the recruitment of follicles during mature ovarian cycling and is unaffected by variation in the timing, frequency, or occurrence of ovarian cycling or ovulation. In humans, approximately 1 percent of the remaining follicular pool is lost each month from birth on. The stages and transitions of follicular development are summarized in Figure 14-1.

There is no evidence that the rate of primordial to primary follicle transition ever abates, but there is some evidence that it may progressively accelerate with age (Gougeon et al., 1994). In humans, evidence of this acceleration was initially misinterpreted as reflecting an age threshold at which the rate of disappearance of primordial follicles shifted in a discontinuous fashion (Richardson et al., 1987; Faddy and Gosden, 1995; Hansen et al., 2008). More sophisticated analyses of the available data suggest that slow but steady acceleration of loss is more likely (Coxworth and Hawkes, 2010). There is evidence as well that the rate of the primordial to primary follicle transition may be subject to feedback regulation from the primary pool via anti-Müllerian hormone (AMH), perhaps as a mechanism to help buffer the size of the available primary pool from the attrition of the primordial stock (Durlinger et al., 2002).

Given the finite supply of primordial follicles and the inexorable rate of attrition in that stock, the follicular supply in a bird or mammal that lives long enough will eventually drop below a threshold level necessary to supply a sufficient cohort of primary follicles for recruitment, and estrogen production by the primary follicles will drop below the levels necessary for

cyclic ovarian function. Data from cows indicate that female fecundity is positively correlated with the size of the secondary follicular pool in a given cycle, which in turn is positively related to the size of the available primary follicular pool (Ireland et al., 2011). Because the primary follicular pool declines in size with age in an inexorable fashion due to the dwindling size of the primordial follicle stock, female fecundity in most species of birds and mammals begins to decline prior to the end of reproductive life (Holmes et al., 2003; Cohen, 2004; Finch and Holmes, 2010).

Neuroendocrine Aging in Females

Characteristic age-related changes occur at all levels of HPO axis regulation in females that interact with declining follicular supply in the ovary. These changes have been well reviewed elsewhere (Brann and Mahesh, 2005; Downs and Wise, 2009; Perheentupa and Huhtaniemi, 2009) and are summarized in Figure 14-2. As noted above, declining numbers of actively growing primary and secondary follicles lead to diminished endocrine feedback to the hypothalamus and pituitary via estrogen and inhibin,

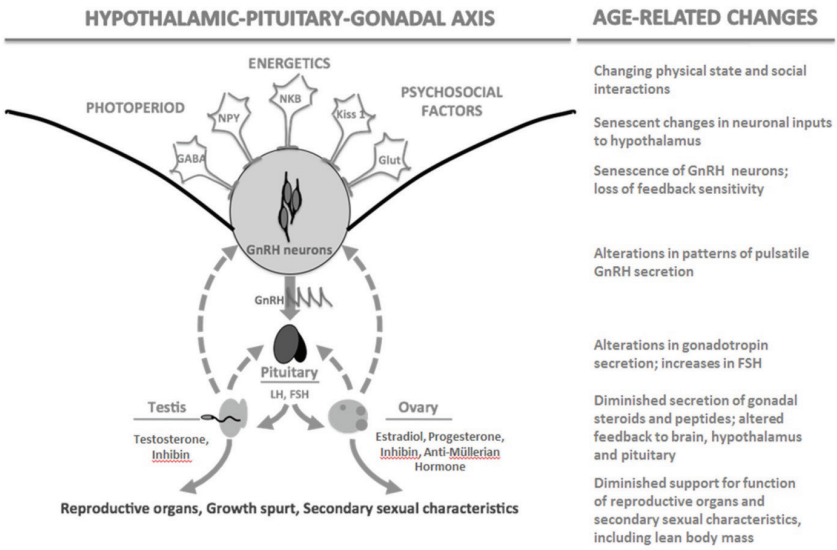

FIGURE 14-2 The hypothalamic-pituitary-gonadal axis in birds and mammals and associated age-related changes.
NOTE: FSH = follicle stimulating hormone, GABA = gamma-aminobutyric acid, Glut = glutamine, GnRH = gonadotropin-releasing hormone, Kiss 1 = kisspeptin q, LH = luteinizing hormone, NKB = neuokinin B, NPY = neuropeptide Y.

resulting in elevated FSH, as well as lower production of AMH. All of these hormones can be used as biomarkers of female reproductive aging. Hypothalamic sensitivity to ovarian steroid feedback may diminish with age as well, either as a consequence of lower steroid stimulation steroid receptor maintenance in the brain or as an independent consequence of neural senescence (Downs and Wise, 2009).

Fitness Value of Mechanisms of Female Reproductive Aging

In most species of birds and mammals, the combination of initial primordial follicle supply, rate of follicular depletion, and balance of neuroendocrine feedback results in a reproductive lifespan in the wild that is at least as long as the natural lifespan. It also provides a system that can be acted upon by natural selection to shape age-specific patterns of female fecundity in response to ecology and other elements of life history. Many, perhaps most, female mammal and bird species show demographic evidence of fertility decline with advanced age, evidenced as increasingly long interbirth or inter-clutch intervals, smaller brood or clutch sizes, and an increasing frequency of failure to reproduce at all. However, there is considerable variability, both between individuals within species and between species, in the trajectory and pace of this decline (Holmes and Ottinger, 2003; Finch and Holmes, 2010). At the species level, more rapid decline in fertility may result from selection to increase fertility earlier in the life history, even at the expense of late-age fertility, by increasing the rate of primordial to primary follicle transition in females. Conversely, sustained fertility late in life may reflect selection for late-age fertility even at the expense of early-age fertility. It is notable, for example, that there is some evidence that fertility in wild chimpanzee females may be sustained in late life to a greater degree than is commonly observed in humans, but that human fertility early in life is on the order of twice as high as that observed in wild chimpanzees (Emery Thompson et al., 2007).

It remains somewhat mysterious, from an evolutionary point of view, why birds and mammals have evolved such a seemingly strange pattern of female gamete production, departing from the ancestral pattern of lifelong gamete renewal followed by females of other vertebrate orders and males of all vertebrate orders. The answer may lie in the reduction in mutational load that results from restricting the number of mitotic generations leading to each ovulated oocyte. Mutational load increases steadily in male gametes due to continuous mitosis. Chromosomal disjunction errors may increase with age in female gametes (though it is not clear whether this is due to the aging of the oocyte itself or to some selective process in follicular recruitment that results in an accumulation of defective oocytes in the ovaries of older individuals), but mutational load does not. This leads to a question

of mutational load in non-mammalian/avian vertebrates and if there would be a prediction of increasing mutational load in aging females. Given current technologies, this hypothesis could be tested using cross-species comparisons. With the necessary restrictions in female fecundity imposed increased investment per reproductive attempt, mechanisms that favor and preserve gamete quality may have been subject to positive selection.

Mechanisms of Male Reproductive Aging

Reproductive aging in human males does not manifest in the same way as in human females. It appears to occur gradually from an early age and without any necessary outer limit imposed anatomically by constraints on gamete supply. Reproductive aging in males is a consequence of age-related changes in neuroendocrine function of the hypothalamic-pituitary-gonadal axis together with senescent loss of function by Leydig and Sertoli cells in the testis (Figure 14-2). Hallmarks of male aging in most birds and mammals include documented declines in circulating gonadal hormones, notably testosterone and 5α dihydrotestosterone (DHT), the peripherally active form of testosterone, as well as decreased hypothalamic secretion of GnRH, and altered pituitary release of gonadotropins (Harman et al., 2001; Moffat et al., 2002; Ottinger, 1998; Veldhuis et al., 2009). Data from primates indicate age-related changes in pituitary function, including circadian production of hormones (Sitzmann et al., 2008, 2010). Testosterone decline can result in weakened muscle function, decreased bone density, and degradation of other physiological parameters associated with aging and potentially important in male reproductive success (Harman et al., 2001; Moffat et al., 2002). Declines in other aspects of male fecundity are also apparent, including mating competence, sperm production, and sperm quality.

Age-related reproductive alterations become apparent in human males after the 5th decade in men, though they may begin much earlier, and include decreasing testosterone levels, loss of potency, increasing sperm abnormalities, and the potential for an increase in birth defects attributable to paternal age. Observations from the Massachusetts Male Aging Study show that total testosterone decreases 0.4-0.8 percent annually, while biologically active free testosterone levels decrease by 1.2-1.7 percent per year starting at the age of 50 (Plas et al., 2000; Henkel et al., 2005). Cross-cultural studies demonstrate a nearly linear decline in salivary testosterone (which parallels free serum testosterone) starting as early as age 30 in a wide range of human ecologies (Ellison et al., 2002). The rate of decline is gradual and in many studies, the variation has led to conflicting conclusions about the age-related loss in circulating gonadal steroid (Ottinger, 1998). Testosterone supports Sertoli cell function and spermatogenesis and is primarily metabolized into biologically active 5-α dihydrotesterone (5-α)

in the periphery and estradiol in the brain, with some aromatization of testosterone into estradiol in the periphery. These steroids are critical for negative-feedback regulation of gonadotropin secretion, adult reproductive function, sexual behavior, metabolism, immune function, bone health, and accessory sex structures. Consequently, diminishing T levels precipitate a cascade that impacts the entire reproductive system, as well as impacting muscle function, bone density, and steroid hormone target tissues.

Although declining testosterone levels do promote some increase in gonadotropin production, this change is not sufficient to prevent the age-related decline in reproductive function. There is evidence for diminishing hypothalamic sensitivity to feedback by gonadal steroids in the aging male and loss of inhibin production by the Sertoli cells (Ottinger, 1998; Zirkin and Chen, 2000; Hardy and Schlegel, 2004; Veldhuis et al., 2009). Reduced Leydig cell steroidogenesis impacts both circulating and intra-testicular testosterone levels and are reflected in altered timing of pulsatile release of hormones and reduced amplitude of these pulses (Syntin and Robaire, 2001; Black and Lane, 2002; Chen et al., 2002; Ellison et al., 2002; Uchida et al., 2006).

Assessing reproductive function and fertility in elderly men has traditionally focused on semen analysis. Based on conventional spermiogram measures, the weight of scientific evidence suggests that increased male age is associated with undesirable changes such as decreased semen volume (Henkel et al., 2005; Kidd et al., 2001), increased DNA fragmentation (Evenson and Wixon, 2006), lower sperm motility (Zubkova and Robaire, 2006), and increased frequency of sperm abnormalities (Kidd et al., 2001; Zubkova and Robaire, 2006), all of which negatively affect male fecundity. In general, however, most measures of male reproductive health exhibit no evidence of a relative age fertility "threshold," but rather display gradual changes over time.

Based on studies in animals, an intriguing aspect of the age-related demise of reproduction in females appears to be a functional loss of pacemakers residing in the hypothalamus and pituitary gland, resulting in diminished amplitude in normal cycles of circulating hormones (Sitzmann et al., 2010). There is evidence that the male brain is steroid hormone responsive, and the age-related testosterone depletion creates a vulnerability to various senescence-related effects of androgen loss (Ottinger, 1998). Women experience a higher incidence of neurodegenerative disease than men during aging and especially following menopause. This raises the question of the utility of specific estrogen receptor modulators (SERMS) as a potential intervention for both disease and for cognitive function.

Fitness Value of Mechanisms of Male Reproductive Aging

Most life history theory is based on one-sex, "female only" demographic models, and human evolutionary biologists are often focused on female menopause as an evolutionary "problem." Male reproductive aging is usually assumed to simply reflect senescence and the decreasing fitness value of investment in the maintenance of reproductive function with age. However, there is no reason to expect that male reproductive aging would not be shaped by ecology in ways similar to female reproductive aging (for instance, changing in response to changes in extrinsic mortality). In species with significant and long-term bi-parental investment, such as humans, it might also be reasonable to expect age-specific patterns of male fecundity to evolve in response to age-specific shifts in the benefit-cost ratios of reproductive effort versus parenting effort. These considerations raise the intriguing possibility that patterns of male reproductive aging may reflect adaptation and not merely constraint. It may serve the male's evolutionary fitness to reduce mating effort with age, even when fecundity is non-zero. Thus, although there is no evidence of abrupt termination of male fecundity in a manner similar to menopause or follicular exhaustion, the rate of age-related reproductive decline may be species and life-history specific.

HOW UNUSUAL IS POST-REPRODUCTIVE LIFE?

The empirical study of post-reproductive lifespan and its taxonomic distribution is complicated by a number of factors, among them a frequent confusion of terms and concepts. Reproductive termination in females can, for example, be defined anatomically, as follicular depletion below some threshold; endocrinologically, as a level of estrogen production insufficient to promote endometrial proliferation or to suppress gonadotropin production to a normal range; phenomenologically, as a cessation of menses, sexual swellings, estrus behavior, or other outward markers of ovarian cyclicity; or demographically, as a cessation of conceptions or births. Of these, only the anatomical definition can be applied in the present, but it is, of course, the most onerous, requiring histological examination of ovarian tissue. All the others only apply retrospectively: that is, only longitudinal data can reveal whether a given menses, birth, etc., was the last in a female's life and even then, only after her death. Nor are these indices of reproductive termination necessarily highly correlated. For example, using the endocrinological or phenomenological definitions, one might conclude that reproductive termination in humans is sensitive to energetic conditions, since energetic conditions independently influence ovarian steroid production. Women under energetic stress may produce less estrogen from a given cohort of follicles than other women and thus fall below the level

required to support endometrial proliferation and menstruation, while still sustaining a significant follicular reserve. Reproductive termination by the demographic definition also may be highly sensitive to energetics, as well as breastfeeding practices, cultural norms, and individual motivations, and thus be quite decoupled from the anatomical and physiological determinants of reproductive cessation.

Reproductive termination in males can similarly be indexed in a number of different, not necessarily correlated ways. Anatomical cessation occurs when the production of viable sperm ceases; endocrinological cessation may occur when testosterone levels are insufficient to support gametogenesis; phenomenological cessation occurs when potency is lost or mating effort ceases; and demographic cessation is marked by the last offspring fathered or pregnancy engendered. In males, none of these indices is usually available outside of a clinical or laboratory context, and inferences from female fertility, mating behavior, or sheer conjecture take their place.

In animals, difficulty in collecting longitudinal data in the wild is also a formidable difficulty, leading to a bias in the available data toward captive samples. Generally, there is an assumption in the literature that data from captivity cannot be used to make inferences about reproductive cessation in the wild, but such data can speak to the existence and degree of phenotypic plasticity in reproductive and total lifespan. Because anatomical, endocrinological, or even phenomenological markers of reproductive termination are rarely available, most animal studies use age at last reproduction (e.g., egg laying, pregnancy, live birth) as the relevant datum. Note that since this datum can only be determined retrospectively, all female animals in a study population must necessarily experience post-reproductive life according to the phenomenological definition, unless they die in the act of parturition or egg-laying. Thus there is an additional layer of complexity in determining whether a given female has died in a state of positive or zero fecundity; that is, did she die physiologically unable to have additional offspring, or merely during a long but potentially closed interbirth interval? The usual approach is to compare the duration of life since the last birth (or hatching) with the *average* interval between births. However, because there is evidence that female fecundity declines significantly prior to death in many, perhaps most, vertebrate species, even this operational approach is problematic. The final interbirth interval may be significantly longer than the average interval. Nevertheless, this approach does provide some basis for controlled comparison.

Post-Reproductive Life in Mammals

There is no systematic survey or sufficient body of data describing the distribution of reproductive cessation or post-reproductive life in mammals.

The best summary available is by Cohen (2004), although some important data have been published since (Alberts et al., 2013). Those data that do exist are spotty, not randomly distributed, and pertain almost exclusively to females.

Other than humans, long periods of post-reproductive life (> 10 years) occurring in a large percentage (> 25%) of females in a wild population have only been attributed to some toothed whale species (Odontoceti), including short-fined pilot whales (*Globicephala macrorhynchus*: Kasuya and Marsh, 1984) and killer whales (*Orcinus orcus*: Olesiuk and Ellis, 1990). Shorter and/or less prevalent post-reproductive lifespans have been reported for wild populations of lions (*Panthera leo*: Packer et al., 1998), polar bears (*Usrsus maritimus*: Ramsay and Stirling, 1988), olive baboons (*Papio cynocephalus*: Packer et al., 1998), and African elephants (*Loxodonta Africana*: Laws et al., 1975), though the claim for reproductive cessation in the female olive baboon and African elephant have been disputed more recently (Moss, 2001; Alberts et al., 2013). Alberts et al. (2013) have recently presented the most complete comparative study of female post-reproductive life in any mammalian group, based on longitudinal data for seven species of nonhuman primates: sifakas (*Propithecus verreauxi*), muriquis (*Brachyteles hypoxanthus*), capuchins (*Cebus capucinus*), olive baboons (*Papio cynocephalus*), blue monkeys (*Cercopithecus mitis*), chimpanzees (*Pan troglodytes*), and gorillas (*Gorilla beringei*). Very few individuals survived significantly beyond their last birth in any of the species studied, and statistical modeling of the rate of senescence in survivorship and fertility indicated that lifespan and reproductive lifespan were essentially coterminous in all seven species.

The data from captivity, including free-ranging, managed populations of animals, stand in some contrast to the data from wild populations and include many examples of species with a significant prevalence of post-reproductive life among females. Females of laboratory species, including mice (*Mus musculus*: vom Saal et al., 1994) and Chinese hamsters (*Chrisetelus griseus*: Parkening, 1982), regularly live for a significant period after reproductive cessation, even by the strictest anatomical definition, and are often used as models of follicular depletion. Females of familiar domestic species, such as cattle (vom Saal et al., 1994), dogs (Anderson, 1965), rabbits (vom Saal et al., 1994), and horses (Comfort, 1979) and more recently domesticated species such as red deer (*Cervus elaphus*: Fisher et al., 1966), also regularly live well beyond the end of reproduction. Post-reproductive life is particularly frequent and well-documented in captive female primates, including marmosets (*Callithrix jacchus*: Caro et al., 1995); tamarins (*Leontopithecus rosalia*: Caro et al., 1995, and *Saguinus* spp.: Tardif and Ziegler, 1992); squirrel monkeys (*Saimiri* sciurus: Caro et al., 1995); various lemurs (*Lemur* spp.: Caro et al., 1995); many macaques

(*Macaca radiata*: Caro et al. 1995; *M. fuscata*: Fedigan, 1991; Nozaki et al., 1995; Takahata et al., 1995; *M. mulatta*: Dyke et al., 1986; Johnson and Kapsalis, 1995, 1998; Tigges et al., 1988; Walker, 1995; *M. nemestrina*: Caro et al., 1995; Ha et al., 2000; *M. sylvanus*: Paul et al., 1993); Hanuman langurs (*Presbytis entellus*: Borries et al., 1991); olive baboons (*Papio cynocephalus*: Caro et al., 1995); chimpanzees (*Pan troglodytes*: Caro et al., 1995); orangutans (*Pongo pygmaeus*: Caro et al., 1995); and gorillas (*Gorilla gorilla*: Caro et al., 1995). In captivity, the general observation is that females enjoy longer lifespans than their wild counterparts, not shorter reproductive spans. Many of these captive primate colonies serve as important models for research on human post-menopausal physiology and disease and have been documented to undergo both endocrinological and anatomical cessation of reproduction in addition to phenomenological and demographic cessation. Thus, it appears that conditions that produce low adult mortality and extended lifespan will very often result in a significant proportion of female mammals living a significant period after their last reproduction and, in primates at least, experiencing both follicular exhaustion and endocrinological menopause.

Post-Reproductive Life in Birds

There are few examples of post-reproductive lifespan in wild birds, though relevant data are sparse and difficult to obtain. In captivity and in domestic species, post-reproductive life is more common. For example, American kestrels maintained in outdoor pens show reproductive decline to the point of cessation at about 10 years of age (Holmes and Ottinger, 2003). Domestic fowl also commonly cease egg-laying well before natural death (Holmes et al., 2003).

Holmes et al. (2003) describe different "themes" or patterns of reproductive aging in birds (cf. Figure 14-3). One pattern, typical of most galliformes (quail, pheasant, chicken, etc.), includes shorter lifespans, rapid decline in age-specific fertility, and relatively common post-reproductive life in captivity and domesticity. A second pattern, typical of songbirds, small raptors, and parrots, includes medium to long lifespan, an initial rise in age-specific fertility after maturity followed by steady decline, and not infrequent post-reproductive life in captivity. A third pattern, typical of coastal and pelagic seabirds, includes very long lifespans and negligible or slow declines in age-specific fertility. A similar pattern of age-specific fertility can be observed across mammals (Cohen, 2004).

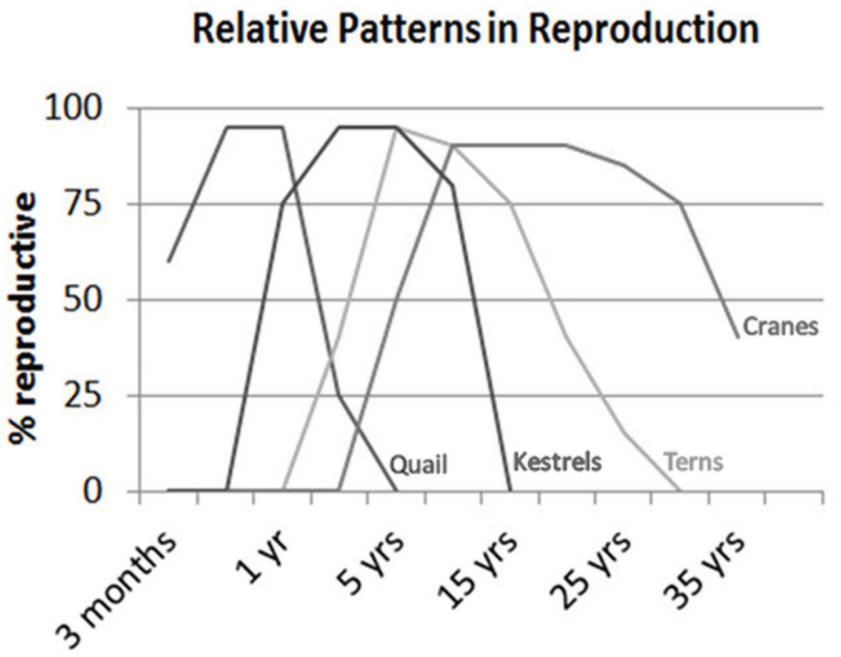

FIGURE 14-3 Variation in age-specific fertility among different groups of birds varying in average lifespan.
NOTE: Similar patterns of variation are observed in mammals.
SOURCE: Ottinger (2007).

Socioecological Correlates of Extended Post-Reproductive Life

Because the only species with well-documented, extended, female post-reproductive life in the "wild" are humans and a few toothed whales, some researchers have postulated that cooperative group living and the opportunity for older females to contribute behaviorally to the reproductive success of their offspring is an important correlate of extended female post-reproductive life (McAuliffe and Whitehead, 2005; Johnstone and Cant, 2010). This suggestion is difficult to test, however, given the paucity of examples of extended post-reproductive life in the wild. Certainly there are many cooperative breeding species of both birds and mammals in which extended post-reproductive life does not occur, as well as large, long-lived, highly social, matriarchal species such as baboons and African elephants (Moss, 2001; Alberts et al., 2013).

The more notable socioecological correlates are captivity and domesticity, which are regularly associated with significant post-reproductive life across a broad range of birds and mammals. Domesticity often alters natural life history in two important ways: It lowers age-specific rates of mortality and, especially in those species that are bred for reproductive output, it increases age-specific rates of fertility. Captivity often results in lower age-specific mortality. These changes in life history pattern almost certainly contribute to the regular appearance of significant periods of post-reproductive life. Lower mortality increases the likelihood that an individual female will outlive her finite supply of primordial follicles. And breeding for increased fecundity may increase the rate of transition from primordial to primary follicles, leading to earlier follicular exhaustion.

It is more onerous to speak of male post-reproductive life, since there is no necessary, physiological terminus to male fecundity. However, there is every reason to believe that male fecundity progressively declines to levels that are demographically insignificant in long-lived species such as humans.

Summary of Observations on the Phylogenetic Distribution of Post-Reproductive Life

The conserved mechanisms of reproductive aging in the females of birds and mammals make post-reproductive life a possibility. The ineluctable decline in primordial follicle supply makes reproductive cessation inevitable *if* an individual lives long enough. The dynamics of follicular stocking and depletion are subject to natural selection, however, and have led to female reproductive lifespans that are at least co-terminous with natural lifespans in the vast majority of birds and mammals. The only notable exceptions in the wild are certain toothed whales. However, many, perhaps most, birds and mammals evidence regular post-reproductive life in captivity and domesticity. These conditions are associated with lowered mortality and (in many domestic species) increased fecundity.

It is interesting to consider the human case against this background. Some researchers are drawn to parallels of social organization between toothed whales and humans as a potential common context in which female post-reproductive life appears. But there are also intriguing parallels between human ecology and captivity and domesticity. In particular, human life histories diverge from those of chimpanzees and other hominoids in two important respects: lower age-specific mortality and higher age-specific fecundity. Both of these traits may be related to the particular nature of human socioecology, including the sharing of food and work, the complementary division of labor among age and sex classes, and the emergence of "pooled energy budgets" to support individual physiology (Reiches et al., 2009; Kramer and Ellison, 2010). These are characteristics of socio-

ecology that are not shared by toothed whales, or perhaps any other vertebrate. The consequences of this socioecology for mortality and fertility patterns are similar to those seen in captive and domestic species. The "self-domestication" of humans may lie at the root of the phenomenon of extended post-reproductive life.

HUMAN SOCIALITY AND THE EVOLUTION OF POST-REPRODUCTIVE LIFE

In most wild vertebrates, and in particular in wild primates, including humans' closest relatives, the chimpanzee, female lifespans and female reproductive spans are closely coterminous. Although it is not unprecedented among wild mammals, humans display a significant and lengthy gap between the average age at death and the average age at last reproduction. A similar gap can often be observed in captive and domestic species. Both in human and in captive and domestic species, this gap appears to be a function of lower adult mortality. With respect to chimpanzees, humans, and wild populations in both captivity and domesticated, it is possible that increased fecundity at younger ages also reflects a more rapid depletion of the primordial follicular supply. Rates of human follicular depletion and ages at reproductive cessation are nevertheless quite close to those of chimpanzees and therefore presumably to the two species' last common ancestor (Jones et al., 2007). Adult mortality rates display considerable environmental plasticity, while rates of follicular depletion that ultimately relate to reproductive cessation in human females do not. The interim conclusions from the comparative perspective adopted in this paper provide the groundwork for any hypothesis construction relative to the evolutionary origins of long post-reproductive life in human females.

Most contemporary hypotheses for human menopause/female post-reproductive life compare the fitness of competing life history alternatives, given various assumptions about relevant costs and benefits. In terms of the adaptive landscape metaphor, this approach is basically a comparison of the height of various adaptive peaks, but does not take account of the available paths to those peaks. That is, little attention is given to the context in which this novel life history pattern would emerge from that of humans' last common ancestor with chimpanzees. It is one thing to posit a fitness advantage to the provisioning behavior of post-reproductive females, for example, but that behavior cannot be used to explain the existence of post-reproductive females capable of doing that provisioning, nor can putative effects of this behavior on their post-reproductive survival explain the existence of a significant cohort of extant individuals at the average age of menopause. Only changes in the rate of adult survival *before* reproductive cessation can account for the initial existence of a significant number

of post-reproductive individuals. This also presumes that there is some heritable phenotypic variation in the age at provisioning and continuing this function into old age, which could depend on increasing the somatic longevity of those individuals. One set of hypotheses, developed by Chu and Lee (2013), does adopt an incremental approach, conceiving of the evolution of the current pattern through a series of intermediate steps, the first of which is the emergence of a division of labor based on age. But the Chu and Lee hypotheses assume that the evolved characteristic in humans is an early termination of reproduction relative to its ancestral state, whereas it seems clear that the evolved characteristic is prevalent and extended post-reproductive life, not premature reproductive cessation.

It seems to us that the most appropriate starting point to posit for the current life history pattern would be the regular appearance of a phenotypic gap between female lifespan and reproductive cessation, a gap similar to that observed in contemporary captive populations of primates (Ellison, 2010). Such a gap would occur as a natural expression of phenotypic plasticity when proto-human socioecology led to a reduced adult mortality rate without (yet) involving any change in the genetic basis of senescence or mortality. It is quite possible that such a change would have occurred with the intensification of social cooperation that led to regular food sharing and division of labor based on age and sex, all of which imply a model of cooperative energy pooling. An intensification of social cooperation of this kind features in virtually every scenario of human evolution. Given the prevalence of environmental plasticity in mortality and the lack of it in reproductive senescence, the opening of a phenotypic gap between female lifespan and reproductive cessation would be inevitable.

Once such a phenotypic gap emerged, it would have immediately imposed new selective pressures, since post-reproductive adults of zero reproductive value would be competing for shared resources with reproductive adults and immatures with positive reproductive value. From this formative location on the fitness landscape of human life history evolution, three paths lead to higher ground. That is, there are three directions in genetic change that could lead to greater fitness in the new socioecology. The three paths might be termed the "path of accelerated somatic senescence," the "path of extended reproductive life," and "the path of indirect reproductive effort." Natural selection takes the path with the steepest initial ascent in fitness, not the one that necessarily leads to the highest adaptive peak.

The "path of accelerated somatic senescence" would increase fitness by increasing the rate of adult mortality through genetic change, shifting the norm of reaction so that lifespan and reproductive span are once again coterminous. This would eliminate the "parasitism" of post-reproductive individuals. The degree of fitness increase achieved via this path would depend on the seriousness of the parasitism, since it would only restore whatever fitness

had been sacrificed with the appearance of post-reproductive individuals. The phenotypic gap would be closed by genetically shortening lifespan.

The "path of extended reproductive life" would increase fitness by generating positive reproductive value for the post-reproductive individuals through genetic change. These changes would either have to increase the initial supply of primordial follicles or slow the rate of follicular depletion so that a sufficient follicular reserve would exist to support reproduction beyond the ordinary age of follicular exhaustion. For many evolutionary theorists, it seems clear that this path should lead to the highest adaptive peak, but it is not clear that its initial slope would be very steep. Because the rate of follicular depletion is exponential, changes in initial follicular supply would need to be prodigious to significantly extend reproductive life. The equivalent of two additional ovaries would be needed, for example, to delay follicular depletion by 3–4 years. In this context, it is notable that the African elephant, the only land mammal whose reproductive lifespan is thought to exceed the human by more than a decade, has an ovary that is an order of magnitude larger, while the human ovary remains approximately the same size as a chimpanzee's. It would be interesting to have a clear comparative dataset that relates ovary size to longevity as well as to predicted number of offspring typical for that species. Changes in the rate of follicular depletion would potentially have a much stronger effect in shifting the age at follicular exhaustion, but their effect on fitness would be complicated by a countervailing decrease in fertility before that age caused by a consequent reduction in the size of the pool of growing follicles. Thus, although the path of extended reproductive life might eventually lead to the highest adaptive peak, its initial rate of ascent might be quite slow.

The "path of indirect reproductive effort" closes the phenotypic gap by selecting for behavior on the part of post-reproductive individuals that increases their inclusive fitness by increasing the reproductive success of relatives, either through direct contributions of time and energy, or through contributions to the common pool that result in benefits to their relatives as well as others. Because this "reproductive effort" is indirect, it must be discounted by effective degree of relatedness relative to potential direct reproductive effort. But the opportunity for contributions of this kind would likely be readily available, generated by the same shifts in socioecology that opened the phenotypic gap in the first place. Note, however, that in contrast to the standard formulation of the "grandmother hypothesis," in this scenario it is the phenotypic occurrence of post-reproductive life that creates selection pressure for old age contributions to the reproductive fitness of younger relatives, not the other way around. Given the presence of post-reproductive individuals arising due to the phenotypic gap between lifespan and reproductive cessation, those who engage in indirect reproductive effort will contribute more copies of their genes to future generations than those

who do not. Once begun, this path is then likely to be reinforced by positive feedback, since as positive reproductive value accrues to post-reproductive individuals, weak selection in favor of delayed somatic senescence will be generated, extending lifespan even further.

The most important aspects of this analysis in comparison to previous treatments are (1) a foundation in the comparative biology of reproductive cessation and post-reproductive life that leads to an appreciation of the likelihood of a phenotypic gap appearing between female lifespan and reproductive cessation, and (2) an attention to the selective pressures generated by this phenotypic gap and the potential for initial increases in fitness due to different responses rather than a comparison of ultimate fitness peaks. We conclude that the path of indirect reproductive effort may have provided the path of steepest initial ascent, and that the path of extended reproductive life may be compromised by insensitivity to changes in initial follicular supply and fitness tradeoffs associated with decreases in the rate of follicular depletion. The result is that the derived life history trait in humans is extended post-reproductive life, supported by indirect reproductive effort, not any change in the trajectory of follicular depletion.

Our analysis is compatible, though derived differently, with hypotheses that suggest that menopause was "uncovered" by an evolved extension of lifespan and not a novel feature of ovarian physiology. It is also compatible with data used to support the "grandmother hypothesis," though as noted, our analysis suggests that post-reproductive life selects for "grandmotherly" behavior, not the other way around. A notable corollary is that indirect reproductive effort need not be confined to post-reproductive individuals. Immature, "pre-reproductive" individuals might also engage in indirect reproductive effort by contributing time and energy to the reproductive success of relatives. Another anomalous feature of human life histories is that the rate of reproduction has increased since the last common ancestor with chimpanzees, while the rate of maturation has decreased. Ordinarily across mammalian taxa, rate of growth during immaturity and rate of reproduction once mature are highly correlated, representing the same metabolic effort net of survival and maintenance. In humans this is not the case. This anomaly may be partly explained by immature individuals diverting some metabolic effort to indirect reproductive effort in advance of their own reproductive maturation. They may, in effect, be "grandparents before their time," performing menial, unskilled tasks that leverage the skilled, more productive efforts of older individuals.

CONCLUSION

The physiological mechanisms that underlie reproductive aging in vertebrates are highly conserved. Prominent among these mechanisms in birds

and mammals are the sexually dimorphic patterns of gamete production and the integrated nature of the neuroendocrine control of reproduction. The phylogenetically ancient pattern of temporally restricted production of a finite pool of primordial follicles in birds and mammals is particularly notable and evolutionarily curious. But since this pattern of female gamete production has evolved, no mammal or bird species is known to have lost it. Hence its fitness value must be high and tightly bound to the reproductive biology of birds and mammals, or it must be a pattern that is very difficult to change due to developmental constraint, or both.

This pattern of female gamete production, involving both a finite primordial follicle supply and an ineluctable attrition in that supply with age, makes female post-reproductive life possible and even predictable, should a female live long enough. Post-reproductive lifespan appears to be rare in wild birds and mammals, though the necessary data are difficult to obtain and not widely available. Ecologies associated with reduced mortality rates, such as captivity and domesticity, commonly result in significant rates and durations of post-reproductive life. No other socioecological correlates manifest such a regular association with post-reproductive lifespan.

Human females do manifest regular and lengthy post-reproductive life. They also manifest lower age-specific mortality and higher age-specific fertility than expected for a hominoid of their size. Hence humans fit the socioecological pattern established by captive and domestic birds and mammals. In order to understand how this life history pattern may have emerged from that of a chimpanzee-like hominoid ancestor, it is necessary to consider what might have led to changes in age-specific mortality that would have created a "phenotypic gap" between reproductive and total lifespan in females, and then what the novel selective forces resulting from that "phenotypic gap" would have been. We argue that the pathway of steepest initial increase in fitness (as distinct from the pathway leading to the greatest ultimate level of fitness) would have favored "indirect reproductive effort" on the part of the newly emerged age-sex class of post-reproductive individuals. Thus, extended lifespan would have selected for indirect reproductive effort, not the other way around.

We also suggest that, although male gamete production does not lead ineluctably to age-related sterility as in the female case, age-related decline in male fecundity may not simply be a matter of senescence. It may be adaptive in its own right, especially in a long-lived, social species with bi-parental care and extended parental investment, like humans. Selection for reduced mating effort with age in human males may lead to "effective" post-reproductive life under the same socioecological conditions that generate it in females. If so, post-reproductive males would also be subject to selection for indirect reproductive effort, although perhaps to a lesser degree than females, due to the continued possibility, at least theoretically, for direct reproductive effort.

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15

The Male-Female Health-Survival Paradox: A Comparative Perspective on Sex Differences in Aging and Mortality

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INTRODUCTION

The male-female health-survival paradox—the phenomenon observed in modern human societies in which women experience greater longevity and yet higher rates of disability and poor health than men—has far-reaching economic, sociological, and medical implications. Prevailing evidence indicates that men die at younger ages than women, despite better health, because of both biological and environmental differences that include behavioral, cultural, and social factors (Wingard, 1984; Verbrugge, 1985, 1989; Kinsella and Gist, 1998; Kinsella, 2000; Case and Paxson, 2005; Oksuzyan et al., 2008; Lindahl-Jacobsen et al., 2013). The male-female health-survival paradox is very well documented in late 20th century high-income countries (Crimmins et al., 2011; Thorslund et al., 2013; Oksuzyan et al., 2014). For instance, cross-national comparisons between the United States, Europe (Denmark), and Japan found consistent but opposite sex differences in survival and health: Men had higher mortality rates at all ages in all three countries, but men also exhibited a substantial advantage in handgrip strength and in activity of daily living at older ages—phenotypes that in both sexes are positively correlated with survival (Oksuzyan et al., 2010).

The mortality part of the paradox, the female survival advantage, has been well documented earlier than the 20th century. In fact, in the very first

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lifetables that were categorized by sex, estimated by Struyck (1740) and Deparcieux (1746), female life expectancy exceeded that of males. More than 250 years later, Thorslund et al. (2013) reported on life expectancy data at age 65 for 16 Western countries and Japan, covering various parts of the period from 1751 to 2007. During the 19th century in Western societies, women generally had a constant, higher life expectancy than men at age 65, although the difference was less than 1 year. The 20th century saw rapid country-specific rises in life expectancy, increasing the male-female gap to approximately 4 years, but with variance across countries. During the last three decades, however, all 16 countries experienced a simultaneous narrowing of the gap to 0.5-1 years. This suggests that country-specific factors may have driven the rise in female advantage in life expectancy, whereas factors shared by all countries may underlie the simultaneous fall (Thorslund et al., 2013). There is general agreement that changes in cigarette smoking is the largest identifiable factor in explaining changes in the sex gap in mortality in the developed countries (Pampel, 2003; Payne, 2004; Preston and Wang, 2006; Jacobsen et al., 2008; Leon, 2011; Lindahl-Jacobsen et al., 2013).

With regard to the health part of the paradox, the female disadvantages in health and functioning, research on contemporary populations generally suggests that men are physically stronger, report fewer diseases, and have fewer limitations in the activities of daily living at older ages than women. However, the issue of sex differences in morbidity is more complex than the pattern in activities of daily living and physical performance tests because of variation in the definitions of diseases, diagnostic procedures, and age-related change in incidence and prevalence of many diseases. For example, the incidence of coronary heart disease starts to rise earlier for men than for women, but the sex difference in heart disease is small at the oldest ages. Women generally have a significantly higher mean number of reported disabling, nonlethal conditions than men (Hjertestatistik, 2004; Crimmins et al., 2011). Hence, sex differences in morbidity depend on disease definitions, the measure of severity, and age trajectories of the particular diseases.

It is generally not clear whether sex differences in health also occur in populations that experience living conditions and cultures very different from contemporary Western societies. For instance, historical populations with very different cultural practices, such as low-risk male behavior combined with high fertility (and hence high risk of female mortality), might have experienced much less of a male-female health-survival paradox than modern human populations, which are characterized by high-risk male behavior but relatively low fertility. As another example, in human populations with extremely high male mortality relative to female mortality, male health might also be more compromised than it is in high-income Western societies.

It is even less clear whether the male-female health-survival paradox is preserved across species: Somewhat surprisingly, no systematic investigations of the paradox exist for nonhuman animals. Research on aging in wild or semi-natural vertebrate populations has generally focused on demographic senescence alone (increases in mortality rates with age), rather than on declines in health or functioning with age (Brunet-Rossinni and Austad, 2006). Research on aging in insects has focused on the molecular basis of aging variation across species and between males and females (reviewed in Keller and Jemielty, 2006) and more recently on how the social environment influences aging, particularly in honey bees (Amdam, 2011). In spite of the significant advances made by these various studies on vertebrates and invertebrates, much remains unknown about the evolutionary significance and proximate mechanisms underlying male-female differences in lifespan. Studies of mortality in animal populations suggest that males experience higher mortality than females in many species, particularly mammals (Promislow and Harvey, 1990; Forsyth et al., 2004; Clutton-Brock and Isvaran, 2007), but they also suggest that this may not be a general rule in either vertebrates or invertebrates (McDonald, 1993; Allman et al., 1998; Carey, 2003). Data regarding the second element of the paradox, sex differences in health, are sparser than mortality data. Some data have arisen from animal models of particular human traits or conditions (e.g., menopause: Bellino and Wise, 2003; memory loss: Picq, 2007; Parkinson disease: Smith and Cass, 2007), but such studies rarely involve systematic investigations of sex differences in these health measures with age.

A relatively recent evolutionary framework predicts that, in many species, males will tend to have worse health than females of the same age, as well as shorter lifespans, because in many cases the most important component of male fitness is mating success rather than investment in health maintenance (Rolff, 2002; Zuk and Stoehr, 2002; Stoehr and Kokko, 2006). This framework thus posits an explicit tradeoff between investment in mating activity and investment in somatic maintenance. Furthermore, males in many species gain substantial fitness benefits from seeking additional mates while females generally do not (Bateman, 1948). The energetic demands of obtaining additional mates will often require the sacrifice of somatic maintenance in general and immune function in particular. The consequence is that males are predicted to show compromised immune function and health relative to females, while females maximize fitness by investing in immune function and thus enhancing longevity. Importantly, this framework, sometimes called "Bateman's Principle for Immunity," predicts no health-survival paradox, but instead predicts that females in many vertebrate species will experience both greater health and greater longevity than males. Nonetheless, it represents one of the few well-developed evolutionary frameworks for predictions about male-female differences in

health, and has received some empirical support; for instance, Nunn and colleagues (2009) found a positive association between sex differences in a measure of immune function and sex differences in investment in mating. However, very few data on health and functioning over the lifespan exist for animals of either sex in any species.

OBJECTIVES

Here we provide a comparative perspective on the male-female health-survival paradox. First, we examine health and survival patterns in humans living in unusual demographic circumstances to determine whether they show a non-paradoxical pattern. Specifically, we summarize recent evidence on the health-survival paradox in a 20th century Russian population and on female survival advantages in the late 19th and early 20th century Mormon population and other historic and prehistoric populations.

Second, we examine age-specific changes in health-related measures in a nonhuman primate in which male life expectancy is short relative to females, to determine whether they conform to the paradoxical pattern described in humans. Specifically, we provide a detailed analysis of age-related declines in health and physical functioning in a wild baboon population in southern Kenya. Baboons are a good choice of species from a comparative evolutionary perspective because baboons, like humans, are diurnal, ecologically flexible omnivores that evolved in a savannah environment. Males in our study population experience both a higher initial mortality rate than females at the beginning of adulthood and a faster acceleration in age-specific mortality with increasing age (Alberts and Altmann, 2003; Bronikowski et al., 2011). By comparing the health trajectories of males and females, we examine whether baboons, like many human societies, experience a health-survival paradox.

RESULTS: HUMAN STUDIES

At the beginning of the 21st century, it is well established that females, on average, outlive men in all countries around the globe (Barford et al., 2006). In high-income countries, they generally do so despite more disabilities and worse self-reported health. In this section, we explore patterns of all-cause mortality in four sets of populations, working our way backwards in time to shed light on whether:

1. the male health advantage is present in a contemporary Russian population with extreme excess male mortality;
2. the female survival advantage was present in the late 19th and early 20th century Mormon population living in Utah, in which

male risk-taking behavior was minimized by societal norms and fertility was high;
3. the female survival advantage was present in other 19th and 20th century populations; and
4. the female survival advantage was present prior to the 18th century using preliminary paleodemographic data.

The Male-Female Health-Survival Pattern in a Contemporary Russian Population

Life expectancy in Russia is lagging behind that in the United States and Europe, and this difference has been very pronounced since the 1960s (Shkolnikov and Meslé, 1996; Meslé, 2004; Oksuzyan et al., 2014). In Russia in 2009, life expectancy was 74.7 years for women and 62.7 years for men. The female-male gap in life expectancy in Russia increased from 8.3 years in 1953 to the maximum level of 13.6 years in 2005 with a decline in 1986-1987 (to 9.4 years) in connection with Gorbachev's anti-alcohol campaign and a steeper reduction in male than female mortality (Human Mortality Database; Field, 2000). Although a narrowing of the sex difference in life expectancy in Russia has occurred since 2006, the sex gap of 11.9 years in 2009 was second only to Kazakhstan as the highest in the world.

In Russia, the main contributors to the declining life expectancy for younger and middle-aged adults from 1988 to 2000 were deaths due to cardiovascular diseases, violence, accidents, and alcohol-related causes (Meslé, 2004; Zaridze et al., 2014). Also, higher mortality rates were observed in Russia at older ages than in other European countries, suggesting worse health in Russia than in old-aged populations elsewhere. A study conducted in the 1990s showed that middle-aged Russians and Swedes had similar prevalence of poor self-rated health and disability, but after about age 45, the prevalence of good general health and the level of physical functioning were substantially lower in Russia compared to Sweden (Bobak et al., 2004). Another study of Russian men and women in the 1990s showed a much steeper decline with age in the probability of being healthy, in comparison not only to the populations in Western Europe, but also to the former communist Eastern European countries (Andreev et al., 2003).

Recently, we have studied sex gaps in mortality rates in Denmark, Russia, and Moscow, as well as sex differences in several health outcomes in Denmark and Moscow among individuals aged 55 to 89 years (Oksuzyan et al., 2014). Pronounced male excess mortality in Russia led us to expect smaller male advantages in selected health domains in Russia compared to Denmark.

The Human Mortality Database and the Russian Fertility and Mortality Database were used to examine sex differences in all-cause death rates in Denmark, Russia, and Moscow in 2007-2008. Self-reported health data were obtained from the Study of Middle-Aged Danish Twins (n = 4,314), the Longitudinal Study of Aging Danish Twins (n = 4,731), and the study of Stress, Aging, and Health in Russia (n = 1,800). In both Moscow and Denmark there was a consistent female advantage in survival at ages 55-89 years and a male advantage in self-rated health, physical ability, and depression symptomatology. Only on cognitive tests did men perform similarly to, or worse than, women. In other words, on the large majority of health indicators, Muscovite males performed better than females. This occurred despite Muscovite men having twice the mortality of Muscovite women at ages 55-69 years, a male-female ratio almost twice as large as that seen in Denmark. Hence, the male-female health-survival paradox is very pronounced in this contemporary Russian population.

Sex Differences in Survival in the Late 19th and Early 20th Century Utah Population

Behavioral factors have been proposed as a key source of female-male differences in mortality, with risk-taking behaviors—including cigarette smoking and alcohol consumption— occurring more frequently among men than among women. Cigarette smoking is the largest identifiable factor in explaining changing sex gaps in mortality, but it is well known that cigarette smoking alone cannot explain the sex difference in mortality; for instance, male non-smokers have higher mortality than female non-smokers (Wang and Preston, 2009).

With this background, we hypothesized that the late 19th and early 20th century Utah male-female survival difference should be among the lowest observed and smaller than that in Denmark and Sweden (Lindahl-Jacobsen et al., 2013). This hypothesis is based on the fact that many residents in Utah in this period were active in the Mormon Church, which proscribes the use of alcohol and tobacco, and whose members would therefore have a healthier lifestyle than the general population with regard to typical male risk factors. This lifestyle was common among members of the Church during the early settlement years, though it was not enforced until the 1860s (Alexander, 1981) and was not institutionalized until 1906 with the Word of Wisdom (Bush, 1993; Alexander, 1996). Females, on the other hand, had a very high fertility level, which was associated with increased maternal mortality risks (Skolnick et al., 1978). We anticipated that the female longevity advantage would grow over the last half of the 19th and early part of the 20th centuries, as their elevated fertility declined during the demographic transition. Denmark and Sweden were chosen as com-

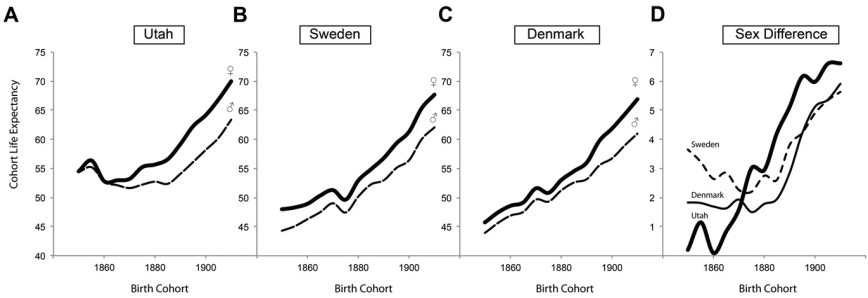

FIGURE 15-1 Cohort life expectancy in Utah (A), Sweden (B), and Denmark (C) and the sex differences in each population (D).
SOURCE: Lindahl-Jacobsen et al. (2013).

parison countries because many descendants of both nations were widely represented among the early migrants to Utah and because these countries have high-quality cohort mortality data spanning back as early as 1850.

As seen in Figure 15-1 and contrary to our expectation, the sex difference in cohort life expectancy was similar or larger in Utah than in Denmark and Sweden, except during the early frontier settlement era (1850-1870), which was distinguished by a series of food shortages and hardships associated with migration and the vagaries of establishing communities (Skolnick et al., 1978). Active male Mormons had longer life expectancy than other groups in Utah (approximately 2 years at age 50), while the difference was minimal for females, suggesting that male Mormons benefitted from a healthy lifestyle. Still, sex differences in cohort life expectancy at the age of 50 years were similar for individuals actively affiliated with the Mormon Church and for individuals living in the general population in Denmark and Sweden. This comparison confirms that even under the particular circumstances found in Utah during the historical period, women had a survival advantage similar to that seen in European populations at that time.

The Female Survival Advantage Was Present in Other 19th and 20th Century Populations

The male-female life-expectancy gap was smaller in the past than it is today, as indicated for time periods in Figure 15-2a for France, and as illustrated for cohorts in Figure 15-1d. In the 1850s, the male-female gap in e_o (life expectancy at birth, a measure of mortality conditions in a given year of birth; see Figure 15-2) was 1.6 years for France and only 0.4 years for Belgium. The gap was 1.8 years in the Netherlands and 2 years in

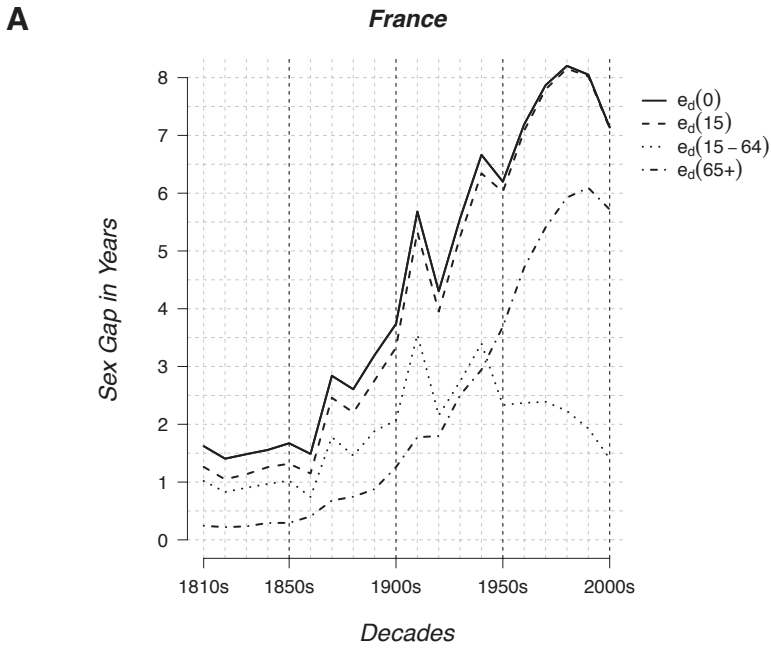

FIGURE 15-2 Male vs. female life expectancy over time (A) and male vs. female death rates over age (B and C).

NOTES: In A, for the French population, the difference plotted is female minus male life expectancy (e_o for females - e_o for males $= e_d$) at ages 0 ($e_d(0)$), 15 ($e_d(15)$) and 65 ($e_d(65+)$) as well as the difference in partial life expectancy between age 15 and 65 ($e_d(15\text{-}64)$). Each point pertains to a decade of data: for example, the point for 1850 pertains to 1850-9. In B the ratio of male to female death rates is plotted for five populations. In C the difference between male and female death rates is plotted for the same five populations. Note that A, B, and C all pertain to mortality conditions in the specified decades, whereas the graphs in Figure 15-1 pertain to cohorts followed from birth through time. In contrast to the cohort life expectancy values in Figure 15-1, which reflect the lifespans of people born in various years, the period life expectancy values in Figure 15-2 are measures of mortality conditions in the specified decade.

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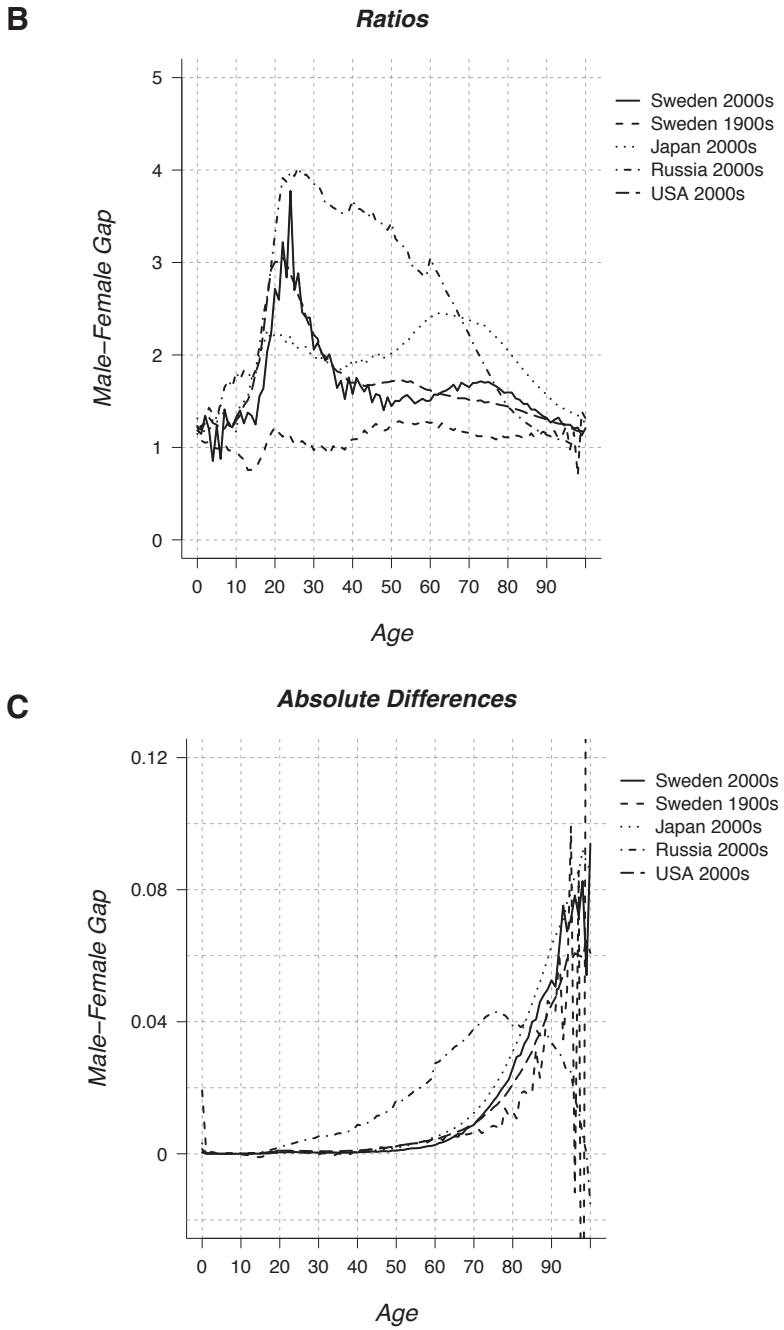

FIGURE 15-2 Continued

England and Wales. The gap in Sweden was higher, 4.1 years, but it fell to 2.3 years by the 1920s. Preliminary analysis suggests that when e_o started to rise in European countries in the 19th century, the female e_o tended to increase faster than the male e_o, widening the initially small gap. As shown in Figure 15-2a, the e_o gap in the 19th century was largely due to the gap in remaining life expectancy at age 15. The rise in the gap in the second half of the 19th century was fueled in roughly equal measure by a rise in the gap at ages 15-64 and the gap in remaining life expectancy at age 65.

The Swedish gap of 2.3 years in the 1920s rose to almost 6 years in the 1980s, followed by a fall to less than 4 years in 2010-2012. In France, as shown in Figure 15-2a, the gap rose to more than 8 years in the 1980s and then fell to 7.2 years in the first decade of this century—with the rise in the gap entirely due to the rise in the gap in e_{65}. The radical rise and recent fall in the gap can be seen in nearly all the countries in the Human Mortality Database. The main underlying factor is almost certainly the rise of male cigarette smoking followed by the more recent rise in female smoking (National Research Council, 2011a, 2011b).

Most of the research to date on discrepancies in age-specific male vs. female death rates has focused on the ratio of male to female rates, as shown in Figure 15-2b for five populations. Several features merit discussion. The age-specific ratios are close to 1 for Swedes in the first decade of the 20th century—this is also true for Swedes earlier and for other countries in the 18th and early 19th centuries. Indeed at some ages and for some countries (e.g., for Swedes in 1900-1909 at ages 8 to 17), it is males that experience lower mortality than females. The low values of the ratios strongly contrast with the much higher values shown in Figure 15-2b for the first decade of the 21st century, a pattern that also held in the mid- and late-20th century and for other countries.

The rise in the ratio starting around puberty, the very high peak in Russia as opposed to Japan, and the secondary maximum for Japan and Sweden in 2000-2009 among older adults (probably due to smoking) are noteworthy, as is the dramatic decline in the Russian ratio from a peak of 4 to a value under 1 at age 100. This Russian pattern may be partly due to mortality selection in a heterogeneous population: The few Russian males who survive to advanced old age may be exceptionally robust. The pattern, however, may partially be an artifact of smoothing algorithms, based on the Kannisto mortality model, that are used by the Human Mortality Database.

It is uncommon to study age-specific differences in male-female death rates, as shown in Figure 15-2c. Hence, for many researchers, including some experienced demographers, it may come as a surprise that the ratio of male to female death rates declines toward 1 but the difference increases exponentially (Wisser and Vaupel, 2014)—except for Russia at older ages, when the impact of heterogeneity and of data artifacts may be dominant.

Also worth noting in Figure 15-2c is the high level of the difference between male and female infant mortality for Sweden in 1900-1909. To put this difference into perspective, the gap arises because the male infant mortality rate was 10.2 percent compared with a female infant mortality rate of 8.3 percent

The Female Survival Advantage Was Present Prior to the 18th Century Using Preliminary Paleodemographic Data

There is general agreement that life was short in the prehistoric past (e.g., Hassan, 1981). Given the deficiencies of published paleodemographic lifetables (Hoppa and Vaupel, 2002), it is not clear for particular populations whether life expectancy at birth was around 20, 25, or 30. The biases in published lifetables may affect males and females in a roughly similar manner. If so, it may be possible to use the available data to assess whether female life expectancy was higher than for males. Jesper Boldsen has done so, based on data from careful studies of single-site mortality patterns (Milner et al., 1989) and reanalysis of archived data for many populations (Boldsen and Paine, 1995). Boldsen's hypothesis (described in Boldsen and Paine, 1995) is that male and female life expectancies were approximately equal for hunter-gatherers prior to and during the Mesolithic period. In the Neolithic period, many people lived in more permanent villages and relied heavily on agriculture to supplement hunting. In the Bronze and Iron Ages reliance on agriculture intensified. As humans began to settle down, fertility increased, which resulted in higher female mortality from complications of pregnancy and childbearing. Furthermore, infectious disease mortality increased, which dramatically increased death rates, especially for older children. Women, who spent almost all their time in the villages, suffered more from this than men, who frequently left the villages for hunting. Hence, Boldsen believes that male life expectancy during the Mesolithic and Neolithic remained roughly constant, but that female life expectancy fell. Starting some 1,500 to 2,000 years ago in Northern Europe, in the Iron Age and thereafter, with increasing levels of trade and of manufacturing, Boldsen thinks that female survival improved more than male survival. Hence, he hypothesizes, the male life-expectancy advantage gradually diminished, with female life expectancy reaching male levels about 500 years ago in Northern Europe.

Until better skeletal data become available, Boldsen's hypothesis must be viewed as an unproven conjecture that is only partly consistent with data on contemporary hunter-gatherers. The Aché of Paraguay during the "forest period" (Hill and Hurtado, 1996) show similar life expectancies for men and women, with men experiencing higher mortality than women only in middle to old age. However, the Hiwi of Venezuela show substantially

higher male than female mortality among middle-aged and older men (Hill et al., 2007), and among the Hadza of Tanzania, women have substantially greater life expectancy than men (Marlowe, 2010).

RESULTS: BABOON STUDIES

In the Amboseli baboons, males experience both higher initial adult mortality and more rapid acceleration of mortality during adulthood than females, resulting in greater longevity in female baboons than in males (Alberts and Altmann, 2003; Bronikowski et al., 2011). However, while the prediction that females live longer than males is supported in this population, the other component of the health survival paradox—better health among males than among females during aging—does not seem to be well supported. To establish this result, we examined several indicators of health and functioning in the Amboseli baboons and compared changes in these indicators with age for males and females. We found that, unlike humans, age-related declines in health and functioning tended to either be similar in both sexes or more extreme in males than in females. This pattern was also true for two measures of individuals' social circumstances that are linked to health in human populations: social status and social connectedness (Holt-Lunstad et al., 2010). Male baboons experienced more rapid age-related declines than females in both of these measures, with potentially negative effects on health during aging. Below we describe our results for each of our measures of health and social circumstances.

Health Indicators for Which Females and Males Experienced Similar Declines with Age

Physical Condition

In humans, very low body mass index is a known risk factor for mortality, particularly among the elderly (Harris et al., 1988; Wilson, 2001; Corrada et al., 2006). We tested for age-related changes in body mass index (BMI), a mass-for-stature measure calculated as a baboon's body mass divided by the square of its crown-rump length. We collect both of these morphological values when we anesthetize animals for blood draws, which we do with only a subset of the population; consequently, these one-time measures yield cross-sectional rather than longitudinal analyses (Altmann et al., 2010). In a linear model, with a quadratic term for age, males and females both exhibited a decline in BMI with age, after reaching a peak BMI in early adulthood ($R^2_{adj.} = 0.68$, $p = 2.2\times10^{-16}$, $b = 2.204$ for age, $b = -0.080$ for age^2: N = 83 measures for adult females and 99 measures for adult males; Figure 15-3a). As expected, males had a significantly higher

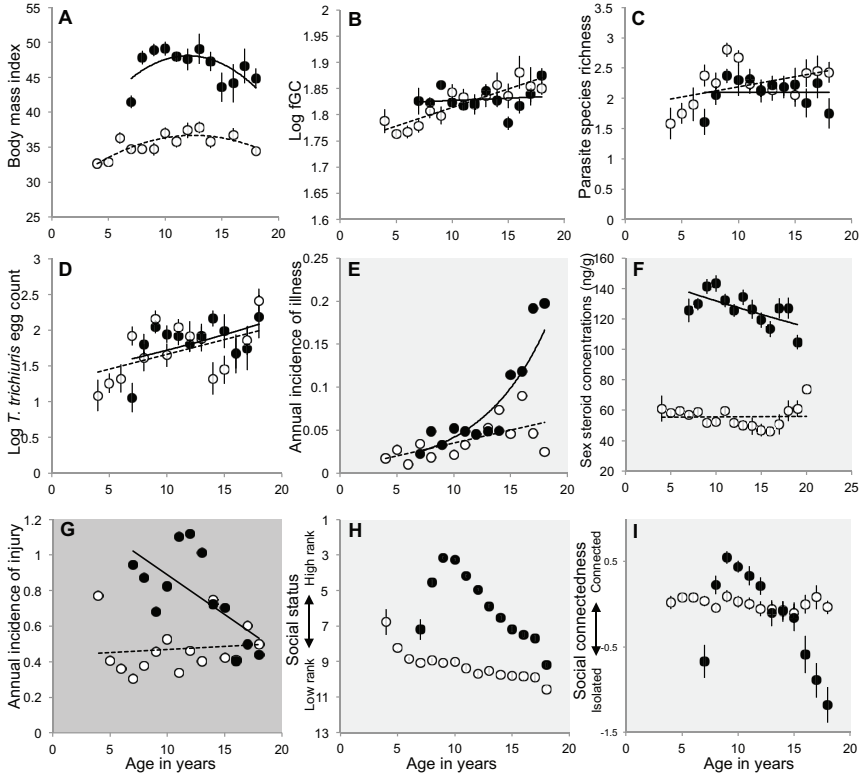

FIGURE 15-3 Changes in health indicators and social circumstances as a function of age.

NOTES: Presented for male (filled circles, solid line) and female (open circles, dashed line) baboons, including: (A) body mass index (BMI), (B) concentrations of fecal glucocoticoid hormones, (C) richness of gastrointestinal parasite species, (D) burden of whipworm parasites (log-transformed eggs per gram), (E) incidence of observed illnesses, (F) concentrations of fecal sex steroid hormones, testosterone and estrogen, (G) incidence of injuries, (H) social status (i.e. dominance rank), and (I) social connectedness. Plots with white backgrounds indicate traits for which males and females experienced similar changes with age; light gray backgrounds indicate traits for which males declined more rapidly than females, and dark gray backgrounds indicate traits for which females declined more rapidly than males.

BMI than females (b = 9.8 for sex; $p < 0.001$), but we found no significant sex-by-age interaction, indicating that males and females did not differ in their pattern of decline in BMI with age (b = –0.001, p = 0.8 for the sex-by-age interaction term in the linear model).

Glucocorticoid Concentrations

Like humans, male and female baboons exhibit age-related hypercortisolism; for instance, Sapolsky and Altmann (1991) reported age-related increases in both serum cortisol concentrations and dexamethasone resistance in Amboseli baboons that had been temporarily immobilized for blood draws. Here we report changes in glucocorticoid hormones measured via fecal metabolites of glucocorticoids (e.g., Khan et al., 2002; Altmann et al., 2004; Gesquiere et al., 2005). Fecal samples are collected on an opportunistic basis from known individuals, and we typically collect several samples per individual throughout the year. In the baboons, we found that both sexes exhibited significant increases with age in concentrations of fecal glucocorticoids (fGC), and we found no evidence of sex differences in the age-related fGC increase. Specifically, in a general linear mixed model (GLMM) including individual identity as a random effect, we identify a significant age term (b = 0.012, $p < 0.0001$) but no significant sex-by-age interaction (p = 0.498; N = 1,941 monthly values for 165 adult females and 3,602 monthly values for 161 adult males; Figure 15-3b).

Gastrointestinal Parasitism

Like most wild animals, the Amboseli baboons are infected with gastrointestinal macroparasites; such infections are a widely recognized measure of health in wild animal populations (Gulland, 1992; Craig et al., 2006; Gillespie, 2006; Hillegass et al., 2010). We used standard methods for fecal flotation and sedimentation to count eggs of different parasite species (Gillespie, 2006; Bowman, 2009). These data were used to examine two measures of the severity of parasite infection: (1) the number of different pathogenic parasite species infecting an individual, including *Trichuris trichiura*, *Abbreviata caucasica*, and the strongyle-type parasites *Trichostrongylus axei* and *Oesophagostomum bifurcum*, and (2) the burden (as eggs per g of feces) of the especially common and pathogenic parasite *T. trichiura* (whipworm). Both males and females exhibited increased evidence of parasitism with age. Specifically, older animals were infected with a greater number of species with known pathogenic effects (GLMM including individual as a random factor; b for age effect = 0.032, p for age effect < 0.001; N = 232 samples from 90 adult females and 209 samples from

68 adult males; Figure 15-3c). In addition, older animals had increased burdens of *T. trichiura* (GLMM including individual as a random factor; b for age effect = 0.052; p for age effect < 0.01; 232 samples from 90 adult females and 209 samples from 68 adult males; Figure 15-3d). However, contrary to the expectations of the health-survival paradox, we found no evidence for sex-differences in rates of increase with age; that is, there was no significant sex-by-age interaction for either parasite richness (p = 0.728) or *T. trichiura* burden (p = 0.135).

Health Indicators for Which Males Declined More Rapidly than Females with Age

Incidence of Observed Illness

Records of illness in the Amboseli baboons are collected as part of our long-term records and are based on visually observed signs of illness, including diarrhea, vomiting, cachexia, lethargy, respiratory problems, and other pathologies. These data are not clinical diagnoses, and the dataset is necessarily small; however, these data present an intriguing picture of greater vulnerability in older males than in older females—a pattern quite different from that seen in humans. Specifically, while both sexes exhibit increasing incidence of illness with age (b = 0.113, p < 0.001 in a GLMM of the annual incidence of illness, including age, sex, and individual as a random effect; N = 59 illnesses in 244 adult females and 48 illnesses in 246 adult males; Figure 15-3e), we also observed a marginal sex-by-age interaction (p = 0.07), with males experiencing a sharper increase in the incidence of illness in old age relative to females (Figure 15-3f).

Sex Steroid Hormones

Patterns of decline in sex steroid concentrations (measured as fecal metabolites of testosterone in males and estrogen in females) are quite different in the two sexes. Males show a marked decline in T concentrations with age (b = –0.023, p < 0.001 in a GLMM including age as a fixed effect and individual identity as a random factor; N = 3,602 monthly values in 161 adult males; Figure 15-3f). In contrast, estrogen levels are relatively stable in females as they age (b = –0.001, p = 0.504 in a GLMM including age as a fixed effect and individual identity as a random factor; N = 1,941 monthly values for 165 adult females; Figure 15-3f). These sex differences correspond with a marked decline in male reproductive activity with age, but the maintenance of relatively high female fertility well into old age.

Health Indicators for Which Females Deteriorate More Rapidly Than Males with Age

Incidence of Injury

The only health measure for which females appear to experience more rapid age-related deterioration than males with age is the rate of injury. For both sexes, most injuries occur in the context of conflict with conspecifics. In males, injuries actually declined markedly in old age, perhaps because older males are less engaged in conflicts over reproductive opportunities than young males. In contrast, for females, the risk of injury increased as they aged (GLMM including individual as a random factor: b = 0.028, p = 0.01 for age, b = 1.093, p = 0.0001 for sex difference (males versus females), b = –0.040, p = 0.053 for age-by-sex interaction; N = 625 injuries in 241 adult females, 568 injuries in 234 adult males; Figure 15-3g). However, the increase in risk that females experienced brought them to the same level of risk as their male age-mates, indicating that even though females experienced a more detrimental *change* with age than males, they did not experience a more detrimental *level* of injury risk in old age.

Social Conditions Deteriorate More Rapidly During Aging for Males than Females

In addition to the health indicators described above, we also analyzed two important measures of an individual's social circumstances that are likely to influence changes in health with age: social status (i.e., dominance rank) and social connectedness to group members. In humans, low social status and social isolation both pose considerable health risks (Berkman and Glass, 2000; Blazer, 1982; Holt-Lunstad et al., 2010; Marmot, 2004; Marmot et al., 1991; Olsen et al., 1991; Uchino, 2004, 2006). In baboons, we found that both of these features declined with age, and that they deteriorated more rapidly for males than for females.

Social Status

Social status is a particularly important trait for both males and females of many species of primates, with consequences for access to food, mating opportunities, and other resources. Consequently, social status is linked to several key life history outcomes (Sapolsky, 2004; Alberts, 2012; Pusey, 2012;). Social status (specifically, social dominance rank) depends partly upon fighting ability and physical strength. In Amboseli, both sexes experience a decline in social status with age, but we saw a much steeper decline with age in male social status than in female social status (GLMM including

individual identity as a random factor: ($b = -10.42$, $p < 0.0001$ for sex difference, $b = 0.20$, $p < 0.0001$ for age, and $b = 0.52$, $p < 0.0001$ for sex-by-age interaction; N = 8,279 monthly rank values for 373 adult males and 19,410 values for 357 females; Figure 15-3h). This steeper decline in male social status may arise, in part, from the fact that female social status, for baboons and other cercopithecine primates, has strong familial influences. Hence, support from relatives may keep females from the precipitous declines in social status during old age that males experience. Moreover, the decline in social status with age likely carries more severe health consequences for males than females. This is because social status is a strong predictor of stress hormone levels (particularly glucocorticoids) for male baboons (Gesquiere et al., 2011), but not for females (Weingrill et al., 2004; Engh et al., 2006). Low-ranking male baboons also experience slower wound healing than high-ranking males (Archie et al., 2012), a pattern that is, again, not true for females (social status has no effect on wound healing in female baboons; Archie et al., 2014). Hence the precipitous decline in male social status with age, in combination with the negative health effects of low social status for males, may result in a more precipitous health decline for aging males than for aging females.

Social Connectedness

We measured social connectedness in the Amboseli baboons as an individual's age-specific frequency of grooming with group mates, relative to all other same-sex adults present in the population in the same year. Grooming is a major social activity in many species of social mammals, and grooming in primates appears to be key for establishing and maintaining affiliative relationships and reducing tension and aggression between individuals (reviewed in Aureli et al., 2012; Lonsdorf and Ross, 2012; Silk, 2012). Relative grooming frequency is commonly used as a quantitative measure of the strength of dyadic social relationships (Lazaro-Perea et al., 2004; Silk et al., 2006). Like social dominance rank, social connectedness also declined more rapidly with age for male baboons than for females in Amboseli (Figure 15-3i). While both sexes experienced a decline in social connectedness with age, males exhibited a much steeper decline than females (GLMM including individual as a random factor: ($b = -0.011$, $p < 0.035$ for age effect, ($b = 1.66$, $p < 0.0001$ for sex difference, and ($b = -0.14$, $p < 0.0001$ for the sex-by-age interaction; N = 8,279 monthly rank values for 373 adult males and 19,410 value for 357 females; Figure 15-3i). As with social rank, the steeper decline in social connectedness for Amboseli males may put males at greater risk for health declines during aging.

CONCLUSIONS

Our objective was to investigate the male-female health-survival paradox with two new approaches. First, we examined male-female mortality and health differences in human populations that experience living conditions and cultures very different from contemporary Western societies, and the female survival advantage since the 19th century. Second, we examined components of the health-survival paradox in a natural population of nonhuman primates. In doing so, we hoped to achieve two goals. First, we wished to probe the historical limits and extent of the paradox in human populations, by asking how universal is the female survival advantage—one fundamental component of the paradox—in historical and modern human populations. Second, we wished to provide an evolutionary context by asking whether components of the paradox occur in wild nonhuman primates.

Our first approach yielded strong evidence that a female survival advantage is a typical feature of nearly all human populations for which serviceable vital-statistics data are available. Indeed, with the exception of a few ages in a few cohorts and periods (as illustrated here by ages 8-18 in Sweden in the period 1900-1909), females had lower mortality than males across all ages and all populations in the Human Mortality Database, which includes several countries since the mid-1800s and Sweden since 1751. Even in unusual demographic circumstances, our evidence suggests that both the female survival advantage and the health-survival paradox persist. The 20th century Russian population was characterized by exceptionally high male mortality (largely driven by cardiovascular disease and alcohol-related deaths), and yet women reported poorer health than men and showed poorer performance on physical tests, conforming to the paradox seen in more typical Western societies. The late 19th and early 20th century Mormon population, in contrast, was characterized by social proscription of alcohol and tobacco use; yet even in the absence of these male-biased risk-taking behaviors, women had a survival advantage over men.

Prehistorical periods are less clear, because data on age-at-death are difficult to acquire from skeletal data, but Boldsen and Paine (1995) have proposed that women lost ground relative to men during the early agricultural era, when fertility and density-related disease epidemics were presumably both on the rise and negatively affected women more than men. In contrast, they propose that men and women had similar life expectancies during the hunter-gatherer period. Existing skeletal data are too problematic to conclusively test this hypothesis, and the idea is only partly supported by data from the few modern hunter-gatherers for which mortality is known. Hence, whether females tended to live longer than males over most of human existence up to a few hundred years ago is uncertain. Importantly, chimpanzees, the closest nonhuman primate relative of humans, are charac-

terized by greater female than male longevity, as are most other nonhuman primates living in the wild (Bronikowski et al., 2011).

Thus, most existing data point to a long evolutionary history of a human (and nonhuman primate) female survival advantage, albeit with periods and places in which the female survival advantage waned. Concomitant health data are not available for most human populations living before modern times, or for that matter for nonhuman primate populations. However, based on the ubiquity of the health-survival paradox in the contemporary West and the evidence that it was equally robust in the unusual demographic circumstances in Russia in the 20th century, we predicted that we would see a health-survival paradox in baboons, with females experiencing more marked declines in health with age than males. This prediction was informed not only by the human data, but also by our data indicating that the energetic costs of reproduction, which female baboons bear throughout their lives in a constant cycle of conception, birth, and lactation, are substantial. After birth, females bear the double burden of milk production and of carrying infants, which they do almost constantly for the first two months of life and then intermittently until the infant weighs 15 percent of the mother's body mass, over average daily distances of 8–10 km (Altmann and Samuels, 1992). The costs of lactation and infant-carrying appear to be partly met by metabolizing body tissues, which in turn delays future reproduction: Lactating females weigh less than cycling females, and lactating females with the lowest body masses take longer to achieve their next conception (Bercovitch, 1987). Finally, wounds heal more slowly for a female baboon when she is lactating than at other times (Archie et al., 2014). Male baboons, in contrast, bear reproductive costs primarily in the form of transient, rather than sustained, energetic demands associated with fighting and with mate guarding when females are in estrous (Alberts et al., 1996).

Our prediction was not supported. Not only do male baboons experience higher mortality than females (Alberts and Altmann, 2003; Bronikowski et al., 2011), but also they experienced a greater increase in the incidence of illness with age than females, and a steeper decline in sex steroid hormones with age (Figure 15-3). On several other measures—an age-related decline in body mass index and age-related increases in glucocorticoid concentrations and vulnerability to parasites—males and females were similar. On only one measure—incidence of wounding—did females experience a greater deterioriation than males, but this deterioration put them at a level of wounding equivalent to, not greater than, males in old age. In other words, we found no evidence of a male-female health-survival paradox in this nonhuman primate species.

Hence, our data suggest that while the female survival advantage has a long evolutionary history, the male health advantage that contributes to

the health-survival paradox does not. Across many human and nonhuman primate populations, females experience lower mortality than males, but we find no evidence, at least in baboons, of a male health advantage. We propose two possible explanations for this. First, age-related changes in sex steroid concentrations are marked and abrupt in women over the age of 50, but are strikingly absent in female baboons, who maintain high sex steroid concentrations and reproduce well into old age (Altmann et al., 2010). This difference may contribute to human-primate differences in whether males or females experience a health advantage in old age. Second, a number of the measures used to document the male health advantage in humans—specifically, measures of physical strength (e.g., grip strength and functioning ability) and self-reported measures of health—are impossible to collect in wild primate populations. Our results call for comparative data on a broad, multifaceted set of noninvasive health measures that are strictly parallel in both humans and nonhuman primates, in order to more clearly understand the evolutionary history of the male-female health-survival paradox.

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16
Of Baboons and Men: Social Circumstances, Biology, and the Social Gradient in Health

Michael G. Marmot and Robert Sapolsky

Position in the social hierarchy is closely related to health and risk of disease. The result is a social gradient in health—worse health the lower the social position. The question is why: How does social position affect biological pathways to cause disease? Destitution is bad for health. Inadequate nutrition, lack of sewerage and clean water, and conditions that foster the spread of microorganisms all contribute to illness. The effects on disease of such material deprivation are exacerbated by lack of appropriate preventive and curative medical care. Yet the social gradient in health also exists where everybody is above this level of absolute destitution. The differences are large. In the Scottish city of Glasgow, for example, there is a 28-year difference in life expectancy between the most and least salubrious areas (Hanlon et al., 2006). Similarly, among the poorer neighborhoods of Washington, DC, life expectancy is 16 years shorter than in the wealthier suburbs (Murray et al., 2006).

We propose that psychosocial processes linked to social experience constitute a major reason for the health gradient. An important part of the evidence for this proposition comes from nonhuman primates. There have been polarized views of the relevance of research on animals to understanding humans. Alexander Pope wrote "that the proper study of mankind is man." By contrast, Darwin said: "He who understands baboons would do more toward human metaphysics than Locke." One of us has spent his research life studying men and women; the other, baboons. Yet we are more with Darwin than with Pope. This is not to imply that there is a simple read-across from monkeys or apes to man. Humans are not simply baboons

in clothes or killer apes with sophistication, and the differences, as will be discussed, can be highly instructive.

The crucial issue is the insight to be gained by studying variation, both in different human societies and among different primate species. There is a naïve idea that as humans spent 99 percent of their existence as hunter-gatherers on the savannah, the species' true nature can be understood by studying savannah primates such as baboons. This is quite profoundly wrong. It was not time spent as savannah baboons, but as savannah hominids. There are marked differences among primate species, including Homo sapiens. The study of this variation is illuminating in the way Darwin presumably had in mind. We contend that by studying when and how hierarchies are related to health in other primate species, we understand better how psychosocial factors generate the social gradient in health in humans.

In this review, we consider the ways in which studies of rank and health in nonhuman primates aid in understanding of the health gradient in humans. Specifically, we will (a) review the ways in which the health gradient is grounded in psychosocial factors; (b) consider how this gradient is anything but simple, and the numerous modifiers of it can only be appreciated in the context of psychosocial factors; (c) examine how some similar health gradients exist in nonhuman primates that, importantly, lack the lifestyle risk factors of humans (e.g., smoking, differential health care access); and (d) explore the enormous variability in the primate realm of social status/health relationships. We contend that circumstances under which subordinate animals suffer health disadvantages have their equivalents among humans. The crucial understanding from the nonhuman primate studies is of the links between social circumstances and biology.

VARIED HEALTH GRADIENTS

We seek to understand the causes of the human health gradient. In order to do so, it is helpful to ask two initial questions of the human evidence: Is the health gradient everywhere; if so, even if why it exists can be understood, is it not inevitable?

Taking life expectancy, or all-cause mortality, as the measure of health, the gradient appears to be widespread (Marmot, 2005), being observed in countries rich, poor, and intermediate (Victora et al., 2003; Hurt et al., 2004). A measure such as education can be used with some universality across societies. It is a general finding that the higher the education, the longer the life, although the magnitude of the difference varies, as illustrated in Figure 16-1. Where the data are available, similar gradients are seen with socioeconomic classifications based on occupation, income, parents' social class, or degree of affluence of area of residence (Marmot, 2004). While there is an undoubted effect of poor health in determining

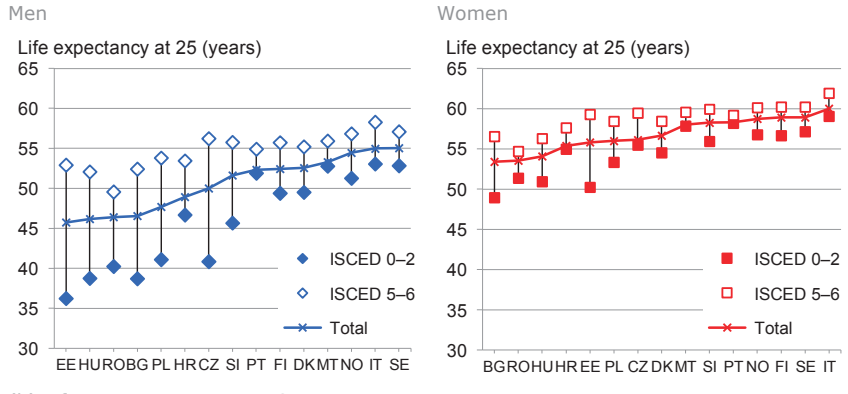

FIGURE 16-1 Life expectancy) at age 25 by education.
NOTES: ISCED = International Standard Classification of Education; Level 0-2 = pre-primary, primary and lower secondary education; Level 5-6 = tertiary education. Countries: EE = Estonia, HU = Hungary, RO = Romania, BG = Bulgaria, PL = Poland, HR = Croatia, CZ = Czech Republic, SI = Slovenia, PT = Portugal, FI = Finland, DK = Denmark, MT = Malta, NO = Norway, IT = Italy, and SE = Sweden.
SOURCE: Marmot (2013).

socioeconomic position, a wealth of evidence points to the effects of social circumstances linked to status having a powerful influence on health (Smith, 1999; Marmot, 2004).

When we turn attention to specific conditions, this universality of the social gradient does not apply. For example, among women in rich countries, obesity follows the social gradient— low status predicts a high prevalence of obesity. However, the gradient is reversed in low-income countries (Gross National Product under US $745): The more education women have, the higher the prevalence of obesity (Monteiro et al., 2004). It is not a surprise, therefore, to find that Type II diabetes and cardiovascular disease are more common in women of high status in poor countries (Chang et al., 2002). This reversal of the gradient for obesity may result from the fact that in poor countries, the challenge for the poor is to get enough food; in wealthier countries, the challenge for the poor is to get enough healthy food. There may be other influences at play that will be dealt with under "Relevant Variables" below. Yet for the diseases responsible for the bulk of loss of life in such poor countries, there is the familiar social gradient. It is worse to be at the bottom than at the top (Victora et al., 2003).

In richer countries, a social gradient is found for most causes of death, including cardiovascular diseases, several cancers, respiratory and gastro-

intestinal diseases, and accidental and violent deaths. There are exceptions, notable among which have been breast cancer, malignant melanoma, and leukemia (Drever and Whitehead, 1997). Among the specific causes of death that do follow the social gradient, the majority, the steepness of the slope varies: that is, the strength of association between social position and disease can be greater or less. Coronary heart disease (CHD) in richer countries tends to show a fairly large social gradient. In countries, such as those in southern Europe where CHD is a less important contributor to overall mortality than in northern Europe, the social gradient in all-cause mortality is less (Marmot, 2013).

This variability in the social gradient leads in to the answer to our second initial question: Is some version of the social gradient in health inevitable? Variation in the magnitude of the gradient suggests that not taking the health gradient as a given. There is not a simple one-to-one relation between rank in the social hierarchy and health. The relation is contingent on what hierarchy means in a given society. In a low-income country, low place in the hierarchy may mean insufficient dietary calories and high burden of infection, and hence low obesity and low cardiovascular disease, but high mortality in infancy and childhood, high rate of violent deaths, and high rates of tuberculosis.

In richer countries, where "diseases of poverty" are not the major cause of death and the major burden of disease is noncommunicable disease and violent deaths, most people are not suffering from the ravages of destitution. In such circumstances, it is our contention that psychosocial factors play a major role in generating the social gradient in health. But this, too, does not imply inevitability of the social gradient. The meaning of hierarchies varies across societies.

The health implications of this variation are the focus of this paper. For this focus, there will be a heavy emphasis on the fact that there is a relationship between health and social dominance rank in other primate species. Initially, it will appear as if the relationship is straightforward, with low dominance rank associated with poor health. However, as will be reviewed, there is great variability in social structure among the numerous primate species and rank/health relationships vary accordingly. Moreover, recent work has demonstrated that differences in social milieu in different populations of the same primate species produce differences in the rank/health relationships.

Of course, one way the health effect of hierarchies can vary is through different links between position on the hierarchy and health behaviors such as smoking, diet, alcohol and physical activity. These all are important, but results from the two Whitehall studies of British civil servants suggest that these behaviors, and blood pressure and plasma cholesterol levels, account for less than a third of the social gradient in cardiovascular disease

(Marmot et al., 1997; van Rossum et al., 2000). Similarly, while differences in medical care loom large as potential explanations for the link between low status and health in the United States, or in low-income countries with poorly developed health systems, they are less likely as explanations in countries with universal provision of health care such as Finland, Sweden, and the United Kingdom. Instead, both the human and nonhuman studies to be reviewed emphasize the importance of psychosocial factors and the extent to which low rank can be a surrogate for large degrees of psychosocial stress. Differential access to high-quality medical care can potentiate health inequalities, but lack of medical care is not the cause of inequalities in the occurrence of disease.

VARIED HEALTH GRADIENTS IN VARIED PRIMATE SOCIETIES

Baboons, Hierarchies, and Health

A frequent feature of social primates (as well as of other social mammals) is the existence of dominance hierarchies. Regardless of the richness of an ecosystem, resources are finite and are often divided unevenly. Dominance hierarchies formalize and ritualize such inequalities, obviating the need for overt competition for each contested resource. In many primate species, linear hierarchies occur (i.e., A > B > C > D . . ., rather than circularities, where A > B > C > A), with rankings that remain stable ranging from months to the lifetime of the individual, and where rank shapes quality of life in numerous ways.

Researchers have demonstrated that a primate's dominance rank is related to its state of health. Much as with the human social gradient literature, it is rank that predicts physiological differences, rather than the reverse. Probably the most detailed study of this issue has been of a population of wild savannah baboons (*Papio anubis*) living in the Serengeti ecosystem of East Africa. This study is notable for its duration (approximately 30 years of longitudinal data), the range of health-related physiological endpoints examined, and the relatively rare reliance on a wild, rather than captive primate population.

Savannah baboons live in large stable troops of 50–150 individuals. Male baboons, which have been the primary subjects of this study, leave their natal troop at puberty, typically then spending their lives in 1-2 other troops. Males form dominance hierarchies that are fairly stable over time, with individuals typically rising in the hierarchy as they approach early adulthood, and declining beginning in late adulthood. Dominance rank is predictive of access to desirable food items (e.g., kills), preferred resting sites, social grooming, and mating opportunities. Importantly, when the hierarchy is stable, dominant males have considerable control and predict-

ability in their lives, as well as ample outlets for frustration such as social grooming, or displacing aggression onto a lower-ranking individual. In contrast, under such circumstances, social subordination is marked by a disproportionate share of stressors. Typically, attaining high rank involves escalated aggression; savannah baboons have among the highest rates of aggression of any primate and an individual typically rises in rank (and, in particular, achieves alpha status) by decisively winning a key fight. By contrast, maintaining high rank is more dependant upon social intelligence, skill at forming of coalitions, psychological intimidation, and impulse control (i.e., ignoring some provocations). As will be described below in the section "Personality," males that are particularly successful in this realm tend towards certainly personality styles associated with low basal cortisol levels.

This picture of sustained social stress for subordinates has pathophysiological correlates. In a dominance hierarchy in a typical savannah baboon troop, subordinate males demonstrate, relative to dominant males: (a) high basal levels of cortisol and resting blood pressure, sluggish endocrine and cardiovascular stress-responses, and sluggish recovery of cortisol levels and blood pressure following the end of a stressor; (b) a testicular axis more easily suppressed by stress; (c) suppressed levels of HDL cholesterol; (d) fewer circulating lymphocytes; (e) lower levels of insulin-like growth factor-1; and (f) greater activation of endogenous benzodiazapine signaling (Sapolsky, 1993a; Sapolsky and Share, 1994, 2004; Sapolsky and Spencer, 1997).

A key question, of course, is whether the physiological profile of subordinate animals is sufficiently adverse to actually impact health and lifespan. This is extremely difficult to answer for at least two reasons. First, because rank among male baboons shifts over time, a high-ranking male may have a very different rank a few years earlier or later; thus, the lifelong impact of rank must integrate the shifts in status. Second, because of the completely wild nature of this population, it is rarely possible to determine the cause of death of an individual or even, given the migratory nature of male baboons, whether an individual has actually died or merely emigrated to a different troop. Nonetheless, these rank differences may be meaningful. For example, wounds heal more slowly in subordinate male baboons in these feral populations (Archie et al., 2012), and the basal hypercortisolism of subordinate males is in the range known to adversely impact blood pressure, insulin sensitivity, and immune function (Sapolsky et al., 2000).

While poor health can certainly lead to low social rank, the longitudinal data in these studies demonstrate that the pathophysiological correlates of subordination follow, rather than precede, the establishment of a rank. We argue that, as with the human health gradient, this rank/health link is mostly psychosocial in nature. For one thing, the bulk of the stressors dis-

proportionately experienced by subordinate males are psychosocial, rather than physical. Food is plentiful and easily obtained through foraging, so that, in the absence of a drought, subordination does not come with a nutritional cost. Differential access to food is limited to "luxuries," particularly kills (which contribute an extremely small percentage of calories for even a dominant male baboon). Furthermore, subordinate animals are predated at the same low rates as are dominant animals. In addition, despite the picture of baboons as being highly aggressive, the vast majority of dominance interactions involve not overt aggression but only threats of aggression or, even more often, psychological intimidation. Moreover, the physiological correlates of rank track more closely with the psychosocial stressors of the rank than with the physical stressors. This is shown in an examination of reversals of the direction of dominance in an interaction among these males, for example, when Male #5 in the hierarchy, typically dominated by Male #4, instead wins a dominance interaction with Male #4. A high rate of such dominance reversals between Males #4 and #5 indicates that the two may soon be switching ranks. In this study, increasing rates of dominance reversals with a male one step below the subject in the hierarchy (i.e., an increasing likelihood of a demotion) were associated with higher basal cortisol levels, whereas increasing rates of dominance reversals with a male one step above the subject (i.e., an increasing likelihood of a promotion) were not. This difference occurred despite the two patterns of dominance interactions (i.e., with the male above, or the male below) involving the same rates of escalated aggression, likelihood of injury, disruption of feeding, and so on (Sapolsky, 1992).

Thus, the pathophysiological price of being a low-ranking male baboon is strikingly similar to that of a low-socioeconomic status (SES) human (Steptoe and Marmot, 1992). This suggests an easy conclusion, namely that these findings regarding baboons are sufficient for extrapolation from the rank/health literature in primates to the social gradient in humans. This would be quite incorrect, and for two important reasons. First, this rank/health profile in baboons occurs only in certain circumstances, and the exceptions are both logical and informative. Second, savannah baboons are not some sort of generic representatives of "social primates" as a whole. Instead, there are more than 150 different species of social primates, each with a distinctive social system. Rank/health relations have been studied in a number of them, and many of the correlates uncovered are dramatically different from those seen in savannah baboons (Abbott et al., 2003). Once again, such variability is logical and potentially quite illuminating for making sense of the health gradient in humans. Thus, while the savannah baboon studies are, arguably, the most detailed in the primate rank/health literature, these other studies are vital and will be given equal weight in the subsequent sections.

In the next section, we will consider some of the key factors that predict the nature of rank/health correlates in different primate species and populations, and how the rules of such variability give insights into the health gradient in humans. Throughout the review of this literature, a particular strength of the primate studies will be apparent. As stated above, we drew the conclusion that neither risk factors associated with lifestyle nor differences in medical care were the major causes of the health gradient in humans. Critically, the great strength of the studies of nonhuman primates is that issues of health care access and lifestyle risk factors (e.g., smoking) can be entirely ruled out. In addition, individuals within the same primate social group will typically have virtually identical levels of activity, and rank-related dietary differences are typically trivial. For example, while access to meat is almost exclusive to high-ranking male baboons, it still constitutes less than 1 percent of their diet.

In what follows, it will be noted that much of the literature on the health gradient in humans has disease, mortality, or life expectancy as the object of study. It is supplemented by smaller scale studies of physiological reactions to stress. The literature on nonhuman primates, on smaller numbers of animals than the human studies, more typically has not disease as an "outcome" but physiological indicators that plausibly indicate risk of disease. Moreover, it should be noted that this nonhuman primate literature has overwhelmingly focused on measurement of cortisol as an endpoint (despite the possibility of measuring additional hormones in the blood, urine, or fecal sample that has been obtained). If one were to choose a single physiological endpoint to serve as a surrogate for the effects of stress on health, measurement of cortisol seems a reasonable choice, given the pathogenic effects of cortisol excess (including inducing insulin resistance, hypertension, immunosuppression, and reproductive impairments). We shall use the term rank/health or social gradient in health in both cases. For shorthand, we shall use the term "primates" to refer to nonhuman primates.

The Relevant Variables

Stability

As outlined, hierarchical systems in primates often take the form of ranks potentially shifting over time. Typically, this involves fairly local changes (e.g., Ranks #3 and #4 switch positions), while the overall structure remains the same. Occasionally, instead, there can be periods of dramatic shifts in the hierarchy, with changes up and down the ranks. Commonly this arises due to a major demographic event, such as the death of a key individual. During such a rare time, it is unlikely that, for example, a very

high-ranking individual will switch positions with a very low-ranking one; instead, as before, the changes are quite local. What characterizes the instability, however, is the sheer number and transience of such local changes—e.g., shifts in rankings daily, rather than over, perhaps, a season—and the amounts of aggression and social tension that accompany the instability.

In many Old World primate species (such as savannah baboons), being high-ranking in a stable hierarchy carries with it tremendous psychological advantages. As outlined above, this includes considerable amounts of social control and predictability, and the low basal cortisol levels and low incidence of atherosclerosis typical of dominant individuals at such times are commensurate with these low levels of psychological stress (Sapolsky, 2005).

During periods of hierarchical instability, however, the picture changes markedly, with the bulk of the social tensions, unpredictability, and aggression centered on the higher end of the hierarchy (Sapolsky, 2005). Not surprisingly, then, during times of such instability, it is dominant individuals that display the highest basal cortisol levels along with the highest incidence of atherosclerosis. This dichotomy between stable and unstable hierarchies has been demonstrated in one wild primate population, namely the baboon studies, and in numerous captive ones. The latter cases are particularly striking, in that they are derived from the situation where a social group of captive animals is first formed; the immediate period afterward models an instability in the wild, in that the animals spend an intensely competitive and aggressive period forming a first hierarchy. Over the course of months, stable ranking relationships emerge. Studies of primates of both sexes demonstrate that during the first period of unstable relations, the most severe stress-related pathologies are associated with dominant animals; it is only when ranks stabilize, typically over the course of a year, that the situation reverses (Sapolsky, 1993b, 2005). Importantly, the stressfulness of periods of rank instability may not so much reflect the frequency with which ranks are changing as much as the frequency with which the status quo is being challenged (regardless of whether the challenge results in a shift in rank) (Gesquiere et al., 2011; Sapolsky, 2011).

Is this stable/unstable dichotomy relevant to understanding the health gradient in humans? The greater degree of control and predictability in the lives of high-ranking animals among Old World primates has its counterpart in human societies. In theory, threats to this control and predictability would weaken the health advantage of high status individuals. One such threat is unemployment. Unemployment, like most uncontrollable threats, is more common in low-status individuals than in high. There is evidence from the United Kingdom, however, that when high-status individuals do become unemployed, their mortality rate rises to a higher level than that of the men immediately below them in the hierarchy who do not experience

unemployment (Moser et al., 1987). As in the primates, the high-status individuals are not protected from the health consequences of threats such as unemployment. Unlike in the primates, the turmoil of unemployment does not change the health gradient. In the end, it is the high-status individuals who have more options.

In the former Soviet Union and countries of Central and Eastern Europe, whole societies were in turmoil as communism tottered and finally collapsed, and before a new social order took hold. Mortality rose. In Russia there was evidence that the rise in mortality was more rapid in areas that were marked by social turmoil, as measured by labor market turnover, unemployment, marriage, and divorce rates (Bobak et al., 1998b; Cornia and Paniccia, 2000). As the new societies have formed, the social gradient in mortality increased. In the Czech Republic, a case control study of myocardial infarction in the 1990s showed a clear social gradient, with men with low education having higher risk. Much of this social gradient could be explained by lack of control in the workplace (Bobak et al., 1998a). The importance of lack of control is a direct parallel with the primate literature.

We noted earlier that obesity shows the familiar inverse association with social status in rich countries but high-status people tend more to obesity in poor countries. Clearly obesity is related to calorie imbalance, but why should calorie imbalance show these patterns? One type of explanation is knowledge and opportunities for healthy behavior. In rich countries, high-status people are more likely to have the knowledge, and financial and other resources, to indulge in healthy eating. In poorer countries, being fat may still be a sign of health and the wealth to engage in conspicuous consumption.

A second possibility may involve stress pathways. The evidence points strongly to greater uncertainty for people of low-SES position in rich countries: threats of unemployment and job insecurity, economic shocks due to illness, and other stressful life events. As evidence that stress pathways may be involved in obesity is the finding of a clear inverse gradient in central adiposity—high waist-hip ratio (Brunner et al., 1993)—that has been linked to hypercortisolism (Brunner et al., 2002). It is difficult to imagine a life more stressful than that of a low-income person in a low-income country, but with insufficient calories to eat, such stress is unlikely to result in obesity.

Rank Maintenance

How position in a social hierarchy is attained and how it is maintained are two very different issues. Depending on the species and sex, there are a variety of mechanisms by which animals achieve positions of dominance varying from intense aggressive interactions to inheritance. It has been

observed that low-ranking male baboons that initiate a lot of fights with dominant individuals, and are thereby actively attempting to rise in the hierarchy, have higher basal cortisol levels than rank-matched subordinate individuals that do not initiate many fights (Virgin and Sapolsky, 1997). There is, however, little evidence that the mode by which dominance is achieved affects the rank-health relationship.

In humans there is evidence that rank, however achieved, is related to health. People whose high status is conferred by coming from privileged backgrounds have better health, in general, than those from more humble origins (Davey Smith, 2003). Independent of childhood social class, those in higher status positions in adulthood have better health than those in lower (Marmot et al., 2001).

Among primate species where rank can shift over time, a key question is what is involved for a dominant individual to maintain that high rank. The strategies utilized can be broadly dichotomized. At one extreme, dominance must be regularly reasserted, and in overt ways, for example, frequent aggressive attacks upon subordinates, regardless of whether being explicitly challenged. In such situations, as is seen among the ring-tailed lemurs of Madagascar, it is dominant individuals that have the highest rates of aggression and of dominance interactions. Such high-ranking animals, by definition, win the vast majority of such interactions, that is, they remain dominant. Despite that, in such cases, it is the high-ranking individuals that show the greatest physiological indices of stress (Cavigelli, 1999).

In contrast, at the other extreme are dominance systems in which dominant individuals maintain their status with a minimum of aggression or overt physical subordination of other individuals. In these cases, maintenance is accomplished instead through psychological intimidation, such as repeatedly standing close enough to a subordinate and making direct eye contact so as to disrupt whatever the low-ranking individual was doing and forcing the animal to move away. In such settings, high-ranking individuals have among the lowest rates of overt aggression. In primate social systems where dominant individuals reassert their dominance with minimal overt effort, it is subordinate animals with the greatest physiological indices of stress (Abbott et al., 2003). High-ranking males do not have particularly high testosterone levels, and high rates of aggression among such individuals are often a sign that their position is teetering.

A fine-tuned analysis of rank/physiology correlates in baboons makes this point about rank maintenance with particular subtlety (Gesquiere et al., 2011). This extensive multiyear study of multiple troops of a different wild population of baboons replicated the general finding of elevated basal cortisol levels in subordinate males. The lowest levels were observed, however, in the second-ranking males (in hierarchies consisting of approximately 15 adults). Alpha males, in contrast, had cortisol levels that were elevated

in the range typical of the lowest-ranking cohort; the authors speculated that the elevated levels reflected the metabolic costs of the frequent fighting on the parts of alpha males. Thus, being generically high-ranking (e.g., in the upper-ranking quartile) and being the alpha individual can be qualitatively quite different.

The relevance to human society is clear. In a society where men fought each other physically for status, one would expect a physiological toll on high-status individuals. But that is not how complex stratified societies work. High-ranking individuals maintain their rank, in general, without resort to violence; instead, when they use violence for their ends, they send lower-status individuals to do it on their behalf. Their dominance is maintained, therefore, without the physiological costs that overt physical aggression would entail.

In human societies, the best-known examples of using violence to maintain status are in lower-income urban settings. Daly and Wilson show a link between homicide rates in Chicago and the degree of income inequalities. Their interpretation of this finding is that threats to status under the shadow of income inequality are met with violence (Daly and Wilson, 1988; Wilson and Daly, 1997). There is the obvious health effect of high mortality from violent death in these communities. Such aggressive behavior is also likely to have physiological consequences (Cohen and Nisbett, 1996).

The Vividness and Frequency with Which Subordination Is Experienced

Under certain circumstances, there is a dose-response relationship between the intensity of a physical stressor and the magnitude of the resultant stress-response (for example, between the extent of blood loss in experimental hemorrhages and the extent of increased cortisol secretion [Gann, 1969]). Similarly, there can be a correlation between the intensity of a psychological stressor and the magnitude of the stress-response; for example, between increasing gradations of novelty in an environment and increased corticosterone secretion in a rat (note that corticosterone is the rat equivalent of cortisol) (Levine et al., 1989). This approximation of a dose-response relationship also appears in the rank/health literature. For example, the more often female baboons were harassed by a highly aggressive male who had recently transferred into the troop, the greater the extent of immune suppression (Alberts et al., 1992).

Thus, it is likely that the strength of the rank/health relationship can be modulated by the ease with which individuals can take refuge from their stressors. This is shown most clearly when considering animals of the same species either living ferally or in captivity. In the wild, particularly in ecosystems such as rain forests, a subordinate individual may be able to evade the presence and notice of a dominant individual. In contrast, within the

closer confines of captivity, this option is greatly restricted, potentially increasing the stressfulness of that rank. Commensurate with this idea, social subordination is associated with elevated basal cortisol levels in captive populations of wolves, but not in feral populations (Creel, 2001).

While novelty is stressful for a rat, there is no evidence to suggest anything similar in humans. In a work situation, for example, learning new things is part of human development and may well be associated with better health. What appears to be stressful is not stimulation or novelty, but psychological demands in the absence of control over work (Marmot, 2004).

In humans there has been much interest in Wilkinson's findings that degree of income inequality is related to overall population health (Wilkinson and Pickett, 2010). Some take issue with these findings on empirical grounds, finding that inequality is correlated with other variables that could account for the association (Deaton and Lubotsky, 2003). Others interpret the findings as meaning that jealousy of those better-off is responsible for the worse health of those lower in status—and reject this interpretation as simplistic (Lynch et al., 2000).

It could be thought that if income inequality is important, then relative position in the hierarchy would be most important for health, rather than absolute socioeconomic level. In support of this position is the famous quote from Karl Marx: "A house may be large or small; as long as the surrounding houses are equally small, it satisfies all social demands for a dwelling. But if a palace rises beside the little house, the little house shrinks to a hovel."

We do not interpret that as meaning that low relative position is, of itself, the crucial determinant of health. In our view, the human and nonhuman data are consistent: It is not place in the hierarchy per se but what place in the hierarchy means in a given situation. In humans, as the Marx quote implies and as economists from Adam Smith to Amartya Sen have made clear, it is not so much what individuals have that is important but what they can do with what they have (Marmot, 2004). Smith emphasized taking one's place in public without shame (Smith, 1776/2003), Sen places emphasis on capabilities (Sen, 1992), and Fogel speaks of egalitarianism of spiritual resources (Fogel, 2000). All of this implies that relative position is important for health to the extent that people lower in the hierarchy are disadvantaged with respect to psychosocial factors. Control over life is one crucial factor, both at home and at work, as shown by, for example, path analyses demonstrating these as variables mediating rank/health relations (Bobak et al., 1997; Marmot et al., 1997; Chandola et al.. 2004; Horton. 2004). Another may be dignity linked to fair treatment (Horton, 2004; Kivimaki et al., 2004).

There has been much speculation that if perceived relative position were important for health, it might be worse for a disadvantaged person

to be living in an affluent neighborhood than in a uniformly poor one. While the data are not entirely consistent, studies in the United States and Britain nevertheless show that health of poorer people is even worse when they live in a poor neighborhood (Diez Roux et al., 2001; Stafford and Marmot, 2003).

Resource Inequities

Primate species differ as to how equally resources (e.g., food, safe resting places) are divided along the lines of rank. Among the South American primates that are cooperative breeders, the hierarchy is considered to be egalitarian, insofar as there is not a particularly steep gradient of resource acquisition as a function of rank. In contrast, Old World primates such as savannah baboons and rhesus macaques have "despotic" hierarchies, in which there is highly unequal resource acquisition. As noted, subordination is associated with hypercortisolism in despotic hierarchical species, but not in egalitarian ones. However, no studies have been able to demonstrate how much the specific issue of resource inequities contributes to this difference.

The issue of resources matters greatly when material resources mean the difference between starvation and adequate nutrition, or between unsanitary conditions and a salubrious environment. Improvement in resources for health provides an explanation for the great improvement in health in the 20th century in the developed countries. At a time when infant mortality in England and Wales, for example, is as low as 6/1000 live births in the bottom social group, compared with 250/1000 a century ago (Rowntree, 1901), resources matter in a different way.

Quoting Sen, we said that in a society where material needs for good health are met, what is important is not so much what one has but what one can do with what one has: capabilities. Adam Smith, father of modern economics, emphasized that the "necessaries" for life include whatever the customs of society render it indecent for "creditable" people to do without. In a society where family background mattered greatly "necessaries" may be less closely linked to income than in a society where prestige, status, and "necessaries" were more strongly linked to current income. In a study in post-communist Hungary, for example, we showed that reported ill-health was more strongly related to lack of luxury goods than it was to lack of goods that might be considered more basic for good health (Pikhart et al., 2003).

Coping Outlets

An extensive literature examining the building blocks of psychological stress shows that the extent to which psychosocial circumstances can

activate the stress-response reflects, broadly, two halves of an equation: the extent of psychosocial stress to which the individual is exposed, that is, frequency and severity of circumstances of loss of control and predictability, and the coping outlets available to the individual (Levine et al., 1989).

The social coping outlets available to psychosocially stressed primates can be positive or negative in nature. Positive outlets include the stressed animal seeking physical contact with an individual with which it is socially affiliated or initiating a bout of grooming with that individual. Among bonobo chimpanzees, a species distinct from the better-known common chimpanzee, sexual behavior is also used to decrease psychosocial stress (de Waal, 2005); in contrast, sexual behavior increases the risk of further psychosocial stress in most primate species. A small literature suggests that greater amounts of such positive outlets are associated with better health among primates. As one example, among savannah baboons, for the same social rank, basal cortisol levels and rates of positive affiliative behaviors are inversely correlated (with, it should be noted, no direct evidence of causality) (Sapolsky et al., 1997). As another example, in a meta-analysis encompassing all the primate species in which rank/cortisol studies have been carried out, the availability of such positive coping outlets to subordinate individuals was significantly, albeit mildly, predictive of their basal cortisol levels (Abbott et al., 2003).

Findings such as this bring up the key issue of sex differences. There is tremendous variation among primate species as to differences, or lack thereof, between the sexes in social systems. Of most relevance here are the Old World primate species (e.g., savannah baboons and rhesus macaques), in which (a) males control a disproportionate share of resources and females are frequent targets of displacement aggression; and (b) females typically have numerous female relatives in their social group (in contrast to the situation for males). Among females of such species, the stressful consequences of male behavior can be buffered by the social affiliation afforded by other females, with protective effects coming preferentially, but not entirely from the females that are related. For example, the elevated basal cortisol levels reported among socially subordinate female macaques do not occur in a troop with atypically high levels of social affiliation (Gust et al., 1993). As another example, females most able to take advantage of close grooming relationships during periods of being subject to escalated male aggression had the smaller increases in cortisol levels (Engh et al., 2006). Very intriguing is one report that in such circumstances, the cortisol-lowering effects of grooming were a function of the frequency with which an individual groomed other animals, rather than the frequency with which she is groomed back (Shutt et al., 2007).

Thus, an array of positive coping outlets can be physiologically protective among primates and, in stable hierarchies, higher-ranking individuals

typically have far more opportunities for such outlets, particularly social grooming.

Negative social outlets also, in theory, can be protective, and this most often takes the form of displacement aggression (i.e., where an individual, having experienced a stressful psychosocial situation such as losing a dominance interaction, will then aggressively attack an innocent bystander). An ample literature with laboratory rodents shows that such displacement aggression can reduce the pathophysiological impact of an external stressor (Levine et al., 1989). Similarly, in one relevant study, socially subordinate male savannah baboons with a strong tendency to displace aggression (on the few animals to which they could do it) had lower basal cortisol levels than rank matched subordinate males without that tendency (Virgin and Sapolsky, 1997).

Thus, among primates, both positive and negative coping outlets can blunt the health consequences of a stressful social rank. No studies to date have examined the critical issue as to whether the positive or negative outlets are more powerful in modulating the rank/health relationship.

There is a rich literature in humans on the protective effects of social interaction and affiliative behavior. The evidence is strong, particularly at the individual level: Individuals who have multiple social ties have lower mortality rates and better health than those who have fewer social ties (Berkman and Glass, 2000). Social isolation appears to be harmful. The literature is mixed on the degree to which there are main effects—social networks simply associated with lower mortality—or buffering—social networks protective in the context of high levels of other sources of stress (Cohen et al., 2000). Social ties are relevant to the social gradient. There is ample evidence that, with the exception of links with family, most other social ties are less frequent as the social hierarchy is descended (Marmot, 2004).

It is reasonable to speculate that human primates may have evolved to be sociable. Across the ~150 primate species, a significant predictor of the relative size of the cortex is the size of the social group: that is, big cortexes and big social groups go together, with orangs as a striking exception in that they are solitary. In other words, on a certain level, the primate cortex evolved for the purpose of gossip and politics.

Much has been made of the importance of reciprocal altruism in the evolution of social systems in many species, including a great deal of work related to the critical issue of how stable reciprocity is first established. It is plausible that altruism evolved as an adaptive strategy: An animal will expend valuable energy to help another as there is likely to be reward coming the other way in the future. In humans an important part of living in society is indulging in socially generative behavior that will be rewarded (Ridley, 1996). An individual expends effort on behalf of others, and there is an expectation of reward for effort expended. A situation where effort is

not matched by appropriate reward is likely to be stressful. Evidence for this comes from the workplace. People whose work is characterized by imbalance between effort expended and reward received are at increased risk of coronary heart disease (Siegrist and Marmot, 2004), mental illness (Stansfeld et al., 1999), and decrements in functioning (Stansfeld et al., 1998).

These results on effort–reward imbalance are consistent with the insights from the primate studies on the balance between stressors and coping mechanisms. However, humans have many more and more subtle means of coping than are available to other primates. In addition to social affiliative behavior, there is the question of religiosity. An extensive literature suggests considerable health benefits to religiosity, but this conclusion has been confounded by the fact that some forms of religious observance can involve different health behaviors (such as in Mormons and Seventh Day Adventists), and that virtually all forms provide community, independent of religious content (McCullough et al., 2000). However, the interaction between the extent and type of religiosity as a coping mechanism, and the social gradient, remains understudied.

In humans there is much speculation and some evidence that affiliative behavior may also operate at the group level in the form of social capital or collective social efficacy. This is taken up below in the section "Social milieu and Culture."

Personality

The magnitude of the stress-response is not only modulated by the intensity and nature of the stressors, psychosocial or otherwise, and the availability of coping outlets, but also by personality factors that influence whether and how those stressors and coping outlets are perceived. Thus, an anxiety-prone personality can be thought as including a tendency to overestimate the menace intrinsic in a particular stressor; a depression-prone personality can involve a failure to perceive the efficacy of a coping outlet, i.e., a sense of helplessness. The term "personality" is used in a similar way by primatologists and formalizes the fact that individual primates have strong and stable differences in temperament and social reactivity. The extent to which such personality arises from genetic versus environmental factors is as unclear as in humans.

Some of these personality factors can modulate rank/health relationships. For example, in social systems where dominance is associated with better indices of health, this advantage is blunted in high-ranking males that are particularly reactive to novelty, that is, have their ongoing behaviors disrupted, and are least adept at behaviorally distinguishing between neutral and threatening interactions with rivals (Sapolsky and Ray, 1989). Conversely, in social systems where subordination is associated with less

favorable indices of health, low-ranking males who are particularly adept at taking advantage of social coping outlets were spared the hypercortisolism typical of their rank (Virgin and Sapolsky, 1997).

If we generalize from personality to the enduring effects of early life on psychological patterns in humans, there is ample evidence that circumstances in adult life, related to rank, affect individuals differently. Two examples suffice. The first illustrates that stressors may be unequally distributed in the population depending on an individual's prior characteristics. The second illustrates that the effect of the stressor on health may vary according to the individual's prior characteristics.

The first can be well illustrated by unemployment. Unemployment rarely strikes at random. A study in Britain has followed a group of people from their birth in 1958 to the present, gathering data as they went through each stage of the lifecourse. Unemployment is more common in people who have experienced unfavorable family circumstances and have less educational attainment (Bartley et al., 1999). Of course, if the population unemployment levels are low, such individuals would not spend as much time out of work. There is, therefore, an interaction between susceptibility of the individual and what is happening in the wider environment.

The second example concerns the genetics of neuropsychiatric disorders. Specifically, it concerns the finding in numerous, but not all studies, of a gene-environment interaction between a particular variant of the serotonin transporter gene and early life stress in increasing the risk of depression (cf., Caspi et al., 2003).

Social Milieu and Culture

As emphasized throughout, there is no single generic primate species but, instead, phylogenetic variability as to social system across the primates. What has been slower to be recognized is that within a single species, there is considerable variation in social behavior and atmosphere from one group to the next. In some cases, the source of the variability is obvious and not particularly interesting; for example, it is to be expected that groups living in harsher environments, and thus forced to spend more time foraging, will spend less time socializing than groups in lusher settings. In other cases, the source of the differences could be genetic. However, considerable social variability emerges as a function of the vagaries of group demographics and personalities of group members. Thus, it is not surprising that the basal hypercortisolism typical of low-ranking female macaques is not observed in troops with lower rates of displacement aggression aimed at such subordinates (Gust et al., 1993).

In some cases, local populational differences in behavior can be transmitted multigenerationally. Such instances, when occurring independent of

ecological or genetic factors, meet the formal definition of "culture," a term now widely used by primatologists. Most examples of culture in primates are rather narrow (e.g., a particular, regional style of social grooming or of tool use) (McGrew, 2004; Whiten, 2005). However, there have been cases of an entire social milieu being transmitted multigenerationally as a group culture.

The most-studied case involved a troop of savannah baboons where, because of a historical accident arising from proximity to a human settlement, the 50 percent of adult males that were most aggressive and least socially affiliative were all killed (Sapolsky and Share, 2004). This produced a troop social milieu markedly different from that of typical baboon troops, with low levels of displacement aggression and high levels of affiliative behaviors. As new (unrelated) adolescent males migrated into the troop from elsewhere, the novel social culture would be assimilated within about 6 months, and has been transmitted for more than a decade past its founding generation. Furthermore, females in this troop are more willing to chance a spontaneous affiliative gesture with a newly transferred male than is the case in other troops, a pattern that appears to be a driving force for the cultural assimilation of these new males. This female tendency, perhaps implying a greater level of trust in the general benevolence of the social environment, seems a rough approximation of the concept of "social capital" in humans.

Strikingly, this local culture had distinctive physiological correlates. Specifically, the hypercortisolism found among subordinate males in typical baboon troops is not observed in this one. Thus, even within the same primate species, the rank/health relationship will vary as a function of local social milieu.

An enduring question in the study of the social determinants of health is whether the environment in which an individual lives and works has an impact on health over and above the socioeconomic characteristics of the individual. As indicated earlier, the answer appears now fairly clearly to be yes (MacIntyre et al., 2002). In the United States, for example, both individual socioeconomic characteristics and level of deprivation of the area of residence influence risk of coronary heart disease (Diez Roux et al., 2001). In the Whitehall II study of British civil servants, there is evidence that deprivation of the environment of residence has a larger effect on the health of low-status people than of higher (Stafford and Marmot, 2003).

The protective influence of social support on health may have its counterpart at the level of populations. In other words, it is not only that individuals with a high degree of social connectedness have better health, but also societies that are characterized by higher degrees of social cohesion are healthier. In Chicago, neighborhoods with a high degree of collective social efficacy had lower homicide rates than less cohesive areas. It has been

suggested that social capital may provide a link between income inequality and health (Kawachi and Kennedy, 1997). Studies in England show a link between measures of social capital and health. The animal literature here provides little guidance.

CONCLUSIONS

The social gradient in health is a pervasive feature of health in populations. To take action to deal with it necessitates understanding of how it comes about. One strategy for doing this is large-scale studies of human populations. Indeed, in recent years, a large body of research has started to address this question. A different, complementary strategy is to study the health gradient in nonhuman primates.

We began this review with the proposition that humans are not simply apes with sophistication. Chimpanzees may be machiavellian but no ape was ever Machiavelli, or Shakespeare, or even the man on the Clapham omnibus. There is no simple read-across from nonhuman primates to people. To go to the other extreme and deny the lessons from studying primates would be perverse. We have put forward the case that variations across primate societies aid understanding of the links between status and health. We take it further. The circumstances under which subordinate animals suffer health disadvantage have their counterpart in human societies.

One clear advantage of studying nonhuman primates is their very nonhumanness. Many of the candidates put forward to explain health inequalities in humans simply are not seen in other species. Baboons don't smoke, eat fast foods, or have differential access to health care depending on ability to pay.

A stressed primate, however, will have similar physiological responses to those of a stressed human. There is insight to be gained not only in understanding the biological pathways by which social position affects health, but also in understanding the circumstances under which these physiological responses are evoked. They lend credence to our claim that psychosocial factors play a major role in generating the social gradient in health.

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