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How It Works: The Biological Mechanisms
that Generate Demographic Diversity

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Abstract

Tinbergen (1963) proposed that a complete understanding of any behavior requires knowledge of its function, evolutionary history, developmental history, and mechanism of operation. This chapter is largely concerned with gaining some insight into the nature of the biological mechanisms generating variation in human fertility and, consequently, demographic diversity within and across populations. My inquiry is informed by life history theory, an analytical framework within evolutionary theory for studying maturation, reproduction, and aging and the associated behavioral and physiological mechanisms underlying the allocation of resources to these processes. Different allocation patterns are referred to as life history strategies (LHSs) and are subject to natural selection. Biological mechanisms can be usefully conceptualized as a set of suitably timed strategic responses to signals. I discuss this and other ideas about the mechanisms that underlie the implementation of LHSs, and introduce the concepts of "ecomarkers" and "the physiological fallacy."

Drawing on empirical studies and theoretical models, I examine some intriguing features of human reproductive physiology that are directly relevant to demographic research in both low- and high-fertility populations. Several points, some contrary to common assumptions, emerge from this inquiry. For example: (1) The marked within- and between-population variation in many features of female reproductive functioning challenges the widespread assumption that there is a universal "normal" human biology. (2) The most likely outcome of a human conception is early loss. This unseen natural selection in the production of offspring may hamper investigations of hypothesized associations of post-natal reproductive success with resources or with offspring quality, even in low fertility populations. (3) Competition between incompatible but essential functions shape the timing and operation of various mechanisms. Some biological, psychological and behavioral functions cannot readily co-occur. Of necessity, successful LHSs must juggle such incompatibilities regardless of the abundance of energy and other resources, therefore some reproductive mechanisms may not depend upon (or be responsive to) energy availability. (4) Biomedically, the absence of ovulation is typically considered a pathology (and in some cases it may be). But from a life history perspective, each option of ovulating/not ovulating is a fork in the reproductive road at which there is a strategic decision to continue engaging in the possibility of reproduction or to forego the current opportunity. Not ovulating in a given cycle can be the best strategy for optimizing lifetime reproductive success.

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"It would be instructive to know... by what physiological mechanisms a just apportionment is made between the nutriment devoted to the gonads and that devoted to the rest of the parental organism..." Fisher (1930)

"Evolution is a tinkerer." Jacob (1977)

Introduction

What must be known if we are to have a thorough understanding of human demographic diversity?

Posed this way, the answer would seem to be, "Everything!" and the goal appears unachievable. Recognizing this, we choose instead to focus on a single feature—perhaps age at menopause or marriage practices or hormonal concentrations. This specialization is necessary and productive but risks losing sight of the bigger questions that first piqued our curiosity.

Nearly 60 years ago, Tinbergen (1963) sought to mitigate this risk within the field of ethology[2] by proposing that a comprehensive and coherent understanding of behavior arises from integrating the answers to four complementary questions. His framing proved to be an enduring guide for the thorough study of any feature of an organism (Bateson and Laland 2013). Paraphrased for more general application, Tinbergen's four questions are:

- What is the function of the feature? (i.e., What is its current and/or former utility?)
- How has the feature evolved over time? (i.e., What is its phylogeny?)
- How does the feature develop in an organism? (i.e., What is its ontogeny?)
- What are the mechanisms that produce the feature? (i.e., How does it work?)

This chapter is largely concerned with the physiological mechanisms generating variation in human fertility and, consequently, demographic diversity across populations.[3] Like most organismal features, individual fertility is variable, but the mean and limits of this variation are characteristic of the species and subject to natural selection. Time, resources, competing demands, and the physical constraints of biological processes all limit individual fertility even in the most successful members of a population and even in the most benign environment. In addition to physiological mechanisms, there are psychological, behavioral, social and cultural pathways that generate variation in human reproductive output.[4] Many of these pathways impact fertility via biological mechanisms.

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[2] A glossary of terms is provided at the end of this chapter.

[3] For additional discussions of evolutionary demography using Tinbergen's framework see Mace (in this volume) on function, Jones et al. (in this volume) on phylogeny, and Sheppard and Coall (in this volume) on ontogeny.

[4] For examples see Blurton Jones (in this volume), Borgerhoff Mulder (in this volume), Dillion et al. (in this volume), Lee and Boe (in this volume), and Tuljapurkar (in this volume).

Reproductive mechanisms can be delineated and studied without recourse to evolutionary theory or a consideration of Tinbergen's other questions. But to do so would be to miss understanding *why* these mechanisms operate as they do. Neither is our understanding well served by simply assuming that all features (or variants of a feature) are evolved adaptations; there's plenty of evidence to the contrary (Williams 1966).

Fully understanding the causes of biological variation necessarily demands incorporating an evolutionary perspective (Tinbergen 1963, Dobzhansky 1973). Doing so, however, doesn't give us leave to accept any seemingly plausible story of the adaptive advantage of some trait or another (Williams 1966, Gould and Lewontin 1979, Caro and Borgerhoff Mulder 1987). Without an understanding of mechanism, we risk spinning "just-so stories" (explanations relying more on our imaginations or preferences than on empirical evidence). Rather, our plausible conjectures are better seen as starting points for generating specific and testable hypotheses about how a thing works and what function it serves.

Mace (in this volume) discusses three ways to test hypotheses about function: experimentation, comparative studies of individuals within populations, and comparative studies across populations or across species. These approaches are equally applicable to investigating mechanisms. Ideally, hypotheses about mechanism are addressed by demonstrating exactly how a purported causal agent is linked to an observed outcome. *How* questions about mechanism are not the only ones worth asking, and they are very rarely the first to be asked. But they must be answered if we are to thoroughly understand *why* human fertility, mortality and health vary, whether due to immediate circumstances or as a consequence of evolutionary processes or, most likely, the dynamic interaction of both.

Evolution through natural selection is often portrayed as a winnowing process that favors individuals with "the best" features for survival and reproduction, a description that gives the misimpression that after many generations most members of a species are nearly identical when it comes to basic functions such as the reproductive system. This misimpression readily lends itself to the false assumption that there's not much variation in the physiological mechanisms enabling human reproduction (and thus such mechanisms appear unlikely to be a significant cause of fertility differentials within and between populations).

To the contrary, there is substantial and compelling empirical evidence of within-species variation in biological mechanisms. Even identical genotypes can produce different phenotypes (variants in morphological, physiological, behavioral, and psychological features), an outcome of developmental and epigenetic processes that facilitate individual adaptation to the environments encountered from conception through death.

Because environments change over time and space, individuals possessing a genotype that adjusts phenotype according to shifting conditions can have an evolutionary advantage over conspecifics who express only one phenotype no matter the conditions encountered. The capacity for a genotype to express a variety of phenotypes is known as "phenotypic plasticity" and the range of possible phenotypes for a given genotype is referred to as the "norm of

reaction" (Via and Lande 1985, West-Eberhard 1989, 2003, Stearns 1989, Vitzthum 1990, 2003, Scheiner 1993). Such plasticity can also be disadvantageous (Dewitt et al. 1988), a reminder of the importance of testing specific hypotheses. Nonetheless, the evidence for phenotypic plasticity across a wide range of taxa and phenotypes supports its importance as an adaptive mechanism (West-Eberhard 2003), and the analyses by Jones et al. (in this volume) suggests that phenotypic plasticity plays a significant role in generating human demographic diversity.

Individual adaptation is achieved through genetic, epigenetic, and ontogenetic processes shaping the organism's phenotypes. Biological evolution is a consequence of natural selection acting on these phenotypes. Many biological mechanisms, including those associated with reproduction, are flexible and exhibit a dynamic response to external conditions. This capacity can cause variation in fertility across the many physical and social environments in which humans live. Examples of this flexibility and the potential impact on demographic diversity are discussed in this chapter.

On a broader note, failing to understand the how and why of biological features can lead to pathologizing natural variation and reifying cultural constructs of what is normal or superior. This error sometimes takes the form of assuming that the average and distribution of some feature found in one's own population is universally true of, or an appropriate norm for, the entire human species (Mead 1947, Vitzthum 2020). But if, like me, your native population is WEIRD (Western, educated, industrialized, rich, democratic), then it represents only 12% of the world's current population (Henrich et al. 2010) and bears little resemblance to the conditions typical of human history during the many hundreds of thousands of years before humans invented agriculture. To help overcome this myopia, there is a fifth question worth adding to Tinbergen's four: How do the features of these mechanisms vary within and across human communities worldwide? Techniques developed over the past 40 years have allowed us to begin to address this question; some of the answers are considered throughout this chapter.

Why is the study of biological mechanisms useful to demographers?

The answer, in brief, is that the identification and specification of biological mechanisms expands and enriches our understanding of how demographic variation is generated. As a case in point, an ever better grasp of mechanisms has been, and will continue to be, directly relevant to improving models of the proximate determinants of fertility.

Demographers' investigations of how fertility, mortality, and migration impact population structure brought to light the marked variation in these processes across human populations. Not long ago, most explanations for this variation concerned the influence of sociocultural and economic factors, giving little attention to the biological processes involved in the production of offspring and the maintenance of a living body. This focus reflected demography's historical roots (Sear et al. 2016, Kreagar in this volume) and the assumption that there was little variation across human populations in such biological processes. As a consequence, much has been learned about the changes in fertility associated with varying sociocultural and economic factors (Balbo et al. 2013, Uggla in this volume) but relatively little about how these factors

might play out through biological mechanisms. Even so, over time and for a variety of reasons, demographers' growing attention to biological processes and evolutionary biologists' keen appreciation of demographers' population data has prompted novel and productive collaborations to address this gap (Sear et al. 2016, Kreagar in this volume, Low in this volume).

Davis and Blake (1956) proposed the first formal demographic framework identifying a finite set of behavioral and biological mechanisms ("intermediate fertility variables") through which all other possible factors (sociocultural, economic, environmental, behavioral) must act in order to influence fertility. Of their eleven direct factors, only two ("fetal mortality from involuntary causes" and "fecundity or infecundity, as affected by involuntary causes") are biological variables, and the latter of these included the entire morphological and neuroendocrinological mechanisms of the ovarian cycle, conception, and implantation. The authors lamented the absence of relevant data that would allow an assessment of the contribution to fertility of either of these two biological intermediate fertility variables.

In 1978, Bongaarts reformulated Davis and Blake's work as a set of eight "proximate determinants of fertility" and proposed a quantitative approach for estimating the contributions of four determinants (#1-4 in Table 1) to a population's total fertility rate. Of these four, the only biological factor is lactational infecundability. Its inclusion in Bongaarts' analyses was a consequence of the by-then large body of data demonstrating that breastfeeding can suppress ovulation (Gioiosa 1955, Perez, 1971, Vitzthum 1994) and thereby contribute to inter-population variation in fertility (these data had not yet been collected at the time of Davis and Blake's work in 1956). Bongaarts also argued that the other four proximate determinants (#5-8 in Table 1) are *not* important contributors to differences in fertility between populations but allowed that the three biological factors might be significant if venereal disease were present.

Through the years since, Bongaarts' model has been critiqued and revised (Reinis 1992, Wood 1994, Stover 1998) including a recent "tune-up" (Bongaarts 2015). His quantitative approach has demonstrable utility in addressing certain kinds of demographic questions, and his work

TABLE 1. Proximate Determinants of Fertility

I. Exposure factors:
1. Proportion married
II. Deliberate marital fertility control factors:
2. Contraception
3. Induced abortion
III. Natural marital fertility factors:
4. Lactational infecundability
5. Frequency of intercourse
6. Sterility
7. Spontaneous intrauterine mortality
8. Duration of the fertile period

Source: Bongaarts (1978)

continues to be the most widely applied demographic model of the proximate determinants of fertility. However, Bongaarts (1978, 2015) estimated the contribution to fertility of only one of the four biological proximate determinants, neglecting the others. This may explain why some analyses using this method could not adequately account for observed between-population variation in fertility (Wood 1994). Also, at least some of the omitted biological determinants are likely to generate fertility differences *between individuals*, a possibility that can't be addressed using Bongaarts' approach.

Beginning in 1988, Maxine Weinstein (a demographer), Kenneth Campbell (an endocrinologist), and James Wood (a bioanthropologist) proposed and refined a new model, "the proximate determinants of natural fertility" (Table 2) (Campbell and Wood 1988, Wood and Weinstein 1988, Weinstein et al., 1990, Wood 1994). This framework can accommodate variation among populations, among individuals within a population, and within particular individuals (e.g., over time). Moreover, their approach explicitly models the contributions of a comprehensive, but nonetheless small, set of behavioral *and* biological proximate determinants. This attention to biological mechanisms has revealed, for example, that one of the most important potential sources of inter-population variation in fertility is intra-uterine death. Although most pregnancy losses are undetected (except with a laboratory test), this needn't mean such loss is inconsequential for population structure (see discussion below in "Vote Early, Vote Often: Early Pregnancy Loss").

These theoretical advancements in demographic models of fertility are attributable, in part, to a burgeoning awareness, fueled by empirical and theoretical studies alike, of the variability, complexity, and flexibility of the underlying biological mechanisms that make reproduction possible.

TABLE 2. Proximate Determinants of Natural Fertility

I. Exposure factors:
    1. Age at menarche
    2. Age at menopause
    3. Age at entry into sexual union
    4. Age at onset of pathological sterility
II. Susceptibility factors:
   Fecundability factors:
     5. Length of ovarian cycles
     6. Probability of ovulation
     7. Duration of the fertile period
     8. Frequency of insemination
     9. Probability of conception from a single insemination in the fertile period
   10. Probability of pregnancy loss
   11. Length of the non-susceptible period following fetal loss
   12. Length of gestation resulting in a live birth
   13. Duration of post-partum infecundability

Source: Wood (1994)

The Take-Homes

Before delving into the details, these are the main arguments developed in this chapter regarding the biological mechanisms regulating human reproduction.

Core themes in demography (the causes of variation in fertility and mortality) map well with those of life history theory (LHT). LHT is an analytical framework within evolutionary theory for studying maturation, reproduction, and aging and the associated behavioral and physiological mechanisms underlying the allocation of resources to these processes (Promislow and Harvey 1990, Stearns 1992, Roff 1992, Charnov 1993, Vitzthum 2008a, Hill in this volume, Low in this volume).

Because there are unavoidable trade-offs in the allocation of finite resources (e.g., time, energy, nutrients) over a lifetime, different allocation patterns (referred to as "life history strategies" [LHSs]) can produce variation in the quantity and quality of offspring, thus generating opportunities for natural selection and adaptation.

One useful approach for organizing an inquiry into the physiological mechanisms associated with LHSs is to conceptualize bodily functioning as a set of suitably timed strategic responses to signals. In subsequent sections, I'll use empirical studies and theoretical models of human female reproductive functioning to discuss this and other ideas about these mechanisms. Rather than attempting to catalog all the mechanisms that contribute to the production of offspring, my aim is to gain some insight into the nature of these mechanisms—their shared properties—with an eye towards developing research questions and strategies that help us to search for the physiological keys to human demographic diversity beyond the light from the nearest lamp post. The principle take-home points from this inquiry are summarized below.

(1) Some mechanisms rely more on the detection of change in a condition than on the assessment of a static condition. Because a life history strategy (LHS) is a series of allocation decisions, its success depends both on the relative amounts of resources distributed to competing demands and on strategic timing. Strategic timing necessarily relies on the detection/recognition of reliable signals of endogenous (internal, somatic) and exogenous (external, extra-somatic) current and changing conditions. In some instances, the *change* in conditions may be more readily detected and hence a more salient signal than the specific state of the condition. For example, regardless of the absolute concentration of progesterone at its peak during the menstrual cycle, it is the drop in progesterone which prompts a cascade of biological changes that characterize the ending of one cycle and the beginning of the next.

(2) LHSs are significantly constrained by factors other than energy availability, therefore some mechanisms may not depend upon (or be responsive to) energy availability. Trade-offs in the allocation of finite resources are unavoidable throughout the course of an organism's life. Because life demands energy, considerable research has rightly been devoted to ascertaining when and how energy is apportioned to somatic versus reproductive functions and to the competing demands within each of these arenas. This emphasis on resource distribution has, however, overshadowed the limitations imposed on LHSs by constraints other

than energy availability. For example, there are physical limits to the pace at which biological processes can proceed, and some essential biological, psychological and behavioral functions cannot readily co-occur. Of necessity, successful LHSs must juggle such incompatibilities regardless of the abundance of energy and other resources.

(3) There are often multiple mechanisms involved in the implementation of a given LHS; these mechanisms are connected and communicate ("cross-talk"). Of necessity we speak of "the ovary" or "the reproductive system" as if these were autonomous entities disembodied from the organism. But often an organism must execute compatible responses to a given signal across various bodily components. Such co-ordination is not necessarily reliant on identical responses to a given status of the signal (e.g., a specific hormone concentration), but may be accomplished, for example, through the presence of similar or different types and/or numbers of receptors in the target cells. These differences in signal recognition allow the same absolute concentration of a given hormone and/or the same change in that concentration to elicit distinct yet coordinated responses in these targets. A focus in human research on the absolute concentrations of hormones reflects what we are able to measure, but may not be all that should be measured to understand the mechanisms that generate demographic diversity.

(4) Physiological mechanisms may be conditioned on circumstances experienced during pre-natal and pre-adult development. Boas' measurements in the early 20th century of the morphology of U.S. immigrants and their children suggested the influence of early environments on subsequent adult biology, but the mechanisms were a mystery (Boas 1911). Some 50 years later, physiological studies of humans native to harsh environments (high altitude, the Arctic) strengthened the arguments that adult functioning depended to some degree on conditions during development (Lasker 1969, Leslie and Little 2003). Subsequent epidemiological studies in industrialized countries provided further evidence of these links (Barker 1990), and theoretical and empirical advancements in epigenetics and developmental biology opened a window into the mechanisms by which the environment can alter gene expression (Kuzawa and Thayer 2011). This current state of knowledge prompts testable hypotheses regarding the nature of the neurohormonal mechanisms that regulate physiology. In particular, a physiological response to a specific signal may be essentially constant for all members of a species or it may differ depending upon prior exposure. For example, the responsiveness of adult reproductive functioning to resource scarcity is highly variable between individuals and populations, perhaps as a consequence of differences in resource availability during development (Vitzthum 1990, 1997, 2001).

(5) Ovulation is optional. Although necessary for conception, ovulation is not an automatic feature of a menstrual cycle. In several studies of healthy women, anywhere from 10%-40% of the sample did not ovulate in a given cycle (Vitzthum 2009). Biomedically, absence of ovulation is typically considered a pathology (and in some cases it may be). But from a life history perspective, each option of ovulating/not ovulating is a fork in the reproductive road at which there is a strategic decision to continue engaging in the possibility of reproduction or to forego the current opportunity. In some contexts, not ovulating in a given cycle can be the best strategy for optimizing lifetime reproductive success.

(6) Pre-natal selection of offspring may swamp post-natal differences in offspring quality and/or parental investment. The most likely outcome of a human conception is natural loss (Roberts and Lowe 1975, Holman and Wood 2001, Vitzthum 2008b). At least half of these losses occur before implantation and another quarter in the subsequent 5 to 7 weeks. It has long been assumed that the vast majority of these early pregnancy losses (EPL) are due to genetic errors in the conceptus. But there is now evidence that a substantial portion may reflect a maternal LHS to delay reproduction if the current conditions are sufficiently inadequate for producing a live birth (Weinberg et al. 1994, Nepomnaschy et al. 2006, Vitzthum et al. 2009a). Thus, rather than being difficult for humans to conceive (as some have argued), it is now known that human fecundity (the capacity to conceive) is many times higher than human fertility (production of a live birth). This unseen pre-natal selection in the production of offspring may hamper investigations of hypothesized associations of post-natal reproductive success with resources or offspring quality. Much of the selection has already occurred (i.e., the differential quality and/or subsequent survival among those concepti that have survived to birth is relatively small). In truth, everyone's children really *are* all above average.

Why is Life History Theory Useful for Understanding the Mechanisms that Generate Demographic Variation?

Malthus (1798) envisioned an unflagging human reproductive system, excepting disease or damage. He was mistaken. For example, the absence of ovulation while intensively breastfeeding a young infant is not a failure of the reproductive system but rather the adaptive response of a physiological mechanism shaped by natural selection to reduce the risk of premature investment in the next offspring (Short 1976).

Life history theory offers plausible and, ideally, testable evolutionary explanations for when and why reproductive effort varies. Not reproducing in some contexts may be a life history strategy (LHS) that could yield a higher lifetime reproductive success than would obligate reproduction at every opportunity.

Variation in LHSs within and across populations and generations suggests there are mechanisms for the flexible implementation of LHSs. This inference prompts a cascade of interesting questions about these biological, and perhaps adaptive, mechanisms that create variation in human birth, death, and the experience in between. For example,

- What sorts of mechanisms are likely to underlie implementation of LHSs?
- What signals prompt allocating resources to one of several competing demands?
- Are all allocation decisions typically transient or might some be permanent?
- How are competing signals resolved?
- How does maturation stage interact with these signals?
- What are the constraints on LHSs?

Time is arguably the greatest constraint on LHSs. Because all individuals die, time is a scarce

commodity. Time cannot be stored, created, foraged, harvested, or shared. Social co-operation and/or multi-tasking may or may not mitigate against the scarcity of time, depending on the circumstances (e.g., nine women cannot make a baby in one month). Mortality schedules (the population-specific risk of death for each age or stage of life) express the length of time available for maturation (growth and development) and reproducing, and the pace at which these fundamental biological processes must be accomplished (Stearns 1992, Charnov 1993). Natural selection favors those organisms that respond to the scarcity of time with suitably strategic timing of their allocation decisions. For example, if mortality risk is low and the average life is long, one can afford to postpone the transition to reproductive investment until later, making use of the extended pre-reproductive period to grow larger, build knowledge, acquire skills and/or develop social capital. If the risk of death is high, natural selection tends to favor an early transition from maturation to reproduction (Promislaw and Harvey 1990, Walker et al. 2006).

The myriad allocation decisions that constitute a LHS are not consciously cognitive but rather are executed via biological mechanisms responding to signals of endogenous (internal, somatic) and exogenous (external, extra-somatic) conditions. Strategic timing of allocation decisions requires an organism to process signals that are at least roughly reliable indicators of the current and/or changing status of these conditions.

The simplest conceptualization of a mechanism involves a reliable signal that is recognized by a transponder (receiver/transmitter) which then sends a different signal that elicits an appropriate response. For example, a signal of exogenous conditions (an "ecomarker") is processed through a sensory system and the brain, prompting a change in biology that elicits an investment of resources and time into one of perhaps several allocation options (e.g., a predator's growl prompts downstream responses that include rises in epinephrine and cortisol and will ultimately result in flight or freeze or fight).

At different points in a mechanism, signals may be molecular, electrochemical, morphological, or psychosocial; behaviors of the individual, conspecifics, or other organisms; social, economic, or cultural features of the group; and physical or biotic features of the environment. Signals of endogenous conditions (e.g., fat stores, rises in glucose) typically rely on molecular signaling and often involve neuroendocrine input and coordination (e.g., hypothalamic regulation of reproduction, sleep, hunger, thirst, and body temperature).

An ecomarker may have a direct role in an organism's acquisition and/or distribution of resources, or it may act only as a reliable proxy that conveys information about factors external to the organism that have more direct roles in the organism's life history strategy. For example, in numerous organisms, the duration and intensity of daylight is an ecomarker of extra-somatic conditions that directly influences daily sleep/wake cycles and that also influences longer-term physiological responses to seasonal variation in environmental conditions (e.g., reproductive functioning in response to predicted changes in food availability). These responses are endpoints in a mechanism that begins with absorption of light photons in the cells of the eye's retina causing molecular changes that eventually signal the pineal gland to produce and release

melatonin. Receptors for melatonin are found in many brain regions, the pituitary, gut, ovaries, and blood vessels. Neural receptors likely regulate circadian rhythms, and other receptors likely regulate reproductive function, cardiovascular function, and body temperature (Brzezinski 1997). It is not uncommon for molecular signals to be recognized by many different cells in an organism, each of which responds according to its own function.

Some of these conditions and the accompanying allocation decisions set the course for a lifetime (e.g., early maturation cannot be reversed). Other investment decisions are temporally limited and may incur few costs. For example, in healthy humans, pregnancy loss within a few weeks of conception does not appear to impair the probability of ovulation in the subsequent cycle (Donnet et al. 1990) or increase the subsequent mean waiting time to conception (Kaandorp et al. 2014).

Many allocation decisions re-occur throughout a lifetime as organisms navigate seasonal and circadian variations in environmental challenges and orchestrate the daily scheduling of physiological processes. For example, sleep is now recognized to be more than a means of conserving metabolic energy. Rather, it is an activity during which some necessary biological processes are better undertaken, either to avoid competing for resources with processes that must occur while awake or because of incompatibility with such daytime processes. For instance, memory consolidation is optimized during sleep (Rasch and Born 2013), night suckling has a greater impact on suppressing ovulation than day sucking (Elias et al. 1986, Vitzthum 1994), and aspects of immune and reproductive functioning are modulated by melatonin, released in large measure only under cover of darkness (Nelson et al. 2002).

It merits reminding that which allocation response, if any, is adaptive (favored by natural selection because it increases reproductive success) cannot be assumed by the mere fact that the organism displayed that response. Variations in such responses (i.e., better and worse allocation decisions over the course of a lifetime) are fodder for natural selection and hence the means by which LHSs can evolve in population-specific environments.

The Human Female Reproductive System—A Well-Tuned Machine or a Flexibly Responsive Behavior?

The study of human fertility is biased towards female over male biology because pregnancy duration and other biological constraints limit the number of offspring a woman can produce and thus also, the rate of population growth. Men are not as unavoidably constrained although, for a variety of reasons, neither is their reproductive capacity unbounded (Drea 2005, Moya et al. 2016, Vitzthum et al. 2009b, Borgerhoff Mulder in this volume).

The hypothalamic-pituitary-ovarian (HPO) axis, comprising three endocrine glands and the hormonal communications between these, is the primary pathway orchestrating physiological changes during the ovarian (menstrual) cycle and subsequent to fertilization (if it occurs). The hypothalamus, an almond-sized portion of the brain, links the nervous system to the endocrine

system via the pituitary, a two-lobed pea-sized gland lying near the hypothalamus. The release of a neurohormone (gonadotrophin releasing hormone [GnRH]) from the hypothalamus prompts the anterior lobe of the pituitary to release other hormones into the blood that then circulate to and affect the functioning of the ovaries. The anterior pituitary's hormonal signals stimulate the development of ovarian follicles (the structure surrounding an immature egg cell) and prompt ovulation (the release of the mature egg from a single follicle). Ovulation is followed by transformation of the ruptured follicle into the corpus luteum, which produces the progesterone necessary for sustaining a pregnancy through the subsequent 5 or so weeks. In the absence of a conception, the corpus luteum regresses about a week or so after ovulation, progesterone begins to fall and menstrual bleeding occurs (Figure 1).
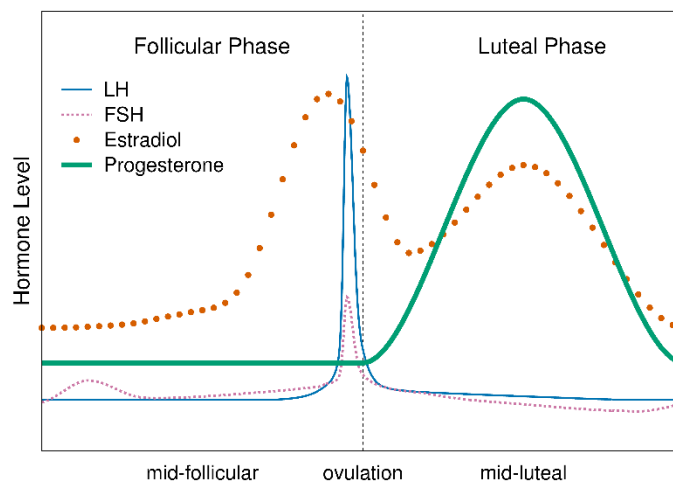
Figure 1. Idealized depiction of hormonal changes (relative to day of ovulation) during the ovarian cycle. Follicle stimulating hormone (FSH) promotes follicle development. The estradiol peak prompts a surge in luteinizing hormone (LH), which binds to receptors on the follicle, thus initiating ovulation. The follicle transforms into the corpus luteum, which secretes progesterone. If a conception doesn't occur, progesterone declines, culminating in menses. In an ovulatory cycle, each phase lasts from about 8 to 22 days (phase durations are not correlated); hormone levels in ovulatory cycles are highly variable between cycles, women, and populations. (Vitzthum 2009)

The more-or-less monthly appearance of menstrual bleeding in most healthy pre-menopausal women (other than those who are pregnant or breastfeeding) tends to bolster the widespread belief that the female reproductive system is unflagging in its cyclical effort to conceive. This idealized view of ovarian regularity derives in part from Descartes' (1637) conceptualization of the body as a machine and is reflected in the work of Malthus (1798), who argued that moral restraint and early death were all that kept a population from outstripping its food supply in a few generations.

The powerful body-as-machine metaphor continues to subtly influence contemporary sciences. This impact is perhaps most evident in biomedicine. The image of a well-tuned machine, necessarily invariant in the form and coordination of its components, readily lends itself to a narrow definition of "normal" biology and tends to perpetuate the classification of variants not

meeting the criteria for "normal" as pathologies that require medical interventions. Such criteria for hormones and other biomarkers typically involve the designation of upper and/or lower thresholds outside of which the biomarker is considered abnormal. Given that medicine's mission is to identify illness and restore the patient to health, arguably such diagnostic practices are acceptable, even desirable, regardless of the underlying misconceptions. Better to recognize all who may be sick, and a few who aren't, than to miss those needing treatment.

But what if the diagnostic threshold derived from a faulty assumption about normal variation has identified a treatment pool comprising more healthy than ill, then what? If this seems far-fetched, consider the "impairment" referred to as luteal phase deficiency (LPD). First described by Jones in 1949, LPD is characterized as insufficient endogenous progesterone for the adequate development of the uterine lining, successful implantation and early pregnancy maintenance. Diagnostic criteria have included a short luteal phase (under the misbelief that a normal luteal [post-ovulatory] phase is 12-14 days) and low progesterone concentrations. But, in fact, the luteal phase varies considerably in cycles from healthy women (WHO 1983) and the Practice Committee of the American Society for Reproductive Medicine (2015) has concluded, "No minimum serum progesterone concentration defines 'fertile' luteal function". Examination of the uterine lining (endometrial biopsy) was thought to be the diagnostic "gold standard" for luteal phase deficiency, however, rigorous clinical trials have concluded otherwise. For example, one large double-blinded study found that about half of the mid-luteal endometrial biopsies were considered "abnormal" according to LPD diagnostic criteria in *both* fertile and infertile women (Coutifaris et al. 2004). In other words, natural variation had been mistakenly perceived as pathology.

Although the body is obviously not a machine, sometimes this imagery can divert us from recognizing the inherently variable nature and flexible capacities of physiological mechanisms. In his essay laying out the four questions, Tinbergen (1963) praised Konrad Lorenz for having "made us look at behavior through the eyes of biologists." In so far as metaphors can aid understanding, it may prove of use to flip the view and look at physiology as an ethologist might. Rather than analyzing features of physiological systems (e.g., hormone concentrations) as if they are species-specific morphological traits that are only modestly variable across populations, it may be more useful to think of physiological mechanisms as responsive behaviors whose range of expression reflects developmental conditions and is contingent on immediate circumstances.

This perspective is consistent with current knowledge of hormone-receptor signaling behaviors. A hormone exerts its effect by binding to a receptor having a molecular configuration suitable for that hormone (rather like a key in a lock). The hormone-receptor complex can then signal to the cell to perform some biological response. Receptors are a large class of proteins encoded in the cell's genes; receptors specific to a cell's function are manufactured by that cell. Regulation of receptor manufacture is affected by several endogenous and exogenous developmental and environmental factors, depending on the specific cell and intended action.

The relative number of receptors to hormone molecules is critical in regulating the cell's

actions. Without receptors, hormones (no matter how high the concentration) cannot directly affect cell behavior. The relationship between hormone concentration, receptor availability and biological response varies by receptor. There can be many different types of receptors for a given hormone, and a given receptor may be able to bind with different hormones.

High affinity receptors (those that form stronger molecular connections with a given hormone) can attract and bind hormones at low concentrations and trigger cell action. In other cases, hormones need to be present at high concentrations in order for enough receptors to be bound and thereby elicit a biological response. The rhythm of change may matter in some pathways (i.e., increases in the amplitude and/or frequency of pulsatile hormonal signaling, rather than a monotonic rise in hormone concentration, are necessary to effect a response in a target cell). In some mechanisms, the presence of the hormone will prompt the cell to produce more receptors and then, once enough hormone-receptor complexes are formed, the cell will perform its action ("upregulation" is the cell's creation of more receptors so that the cell is more sensitive to the hormone). But at other times even high hormone concentrations will not trigger the production of more receptors (e.g., insulin resistance) and the biological response is not performed. In general, when available receptors become saturated (because of hormone binding and/or receptor degradation), the cell becomes less sensitive to the presence of the hormone (a process called "downregulation").

Physiological mechanisms are dynamic and variable, a consequence of evolution's tinkering, using the materials and tools bestowed by previous generations to deal with the task at hand (Jacob 1977, 1994). While some pathways may be conserved (e.g., the link from hypothalamus to pituitary to ovary), features potentially shaped by developmental environments will likely vary (e.g., individuals' hormone concentrations and numbers of receptors). Such systems are rather like an orchestra—a composition (pathway) is typically followed, each instrument coming into play in a fairly predictable fashion, but the rhythm and volume and numbers of each kind of instrument (hormone signal) may vary as can the number of listeners (receptors) who come and go. Sometimes compositions from adjacent orchestras can be heard (cross-talk) and sometimes there's unexpected improvisation provoked by a novel situation (new foods, environmental toxins, glucose overload).

A Delicate Balance: Strategic Trade-Offs of Incompatible Essential Functions

The primary mission of a woman's immune system—to protect her body—is sometimes unavoidably at odds with the evolutionary imperative to reproduce (Abrams and Miller 2011, Alvergne and Tabor 2018). For example, because of sperm's genetic foreignness and the health risks posed by any pathogens in deposited semen, coitus might be expected to elicit a heightened immune defense in women. Yet such a response would potentially harm the sperm required for a conception. Notably, however, sperm's reproductive value is limited to a few days (known as "the fertile window") leading up to and including the day of ovulation.
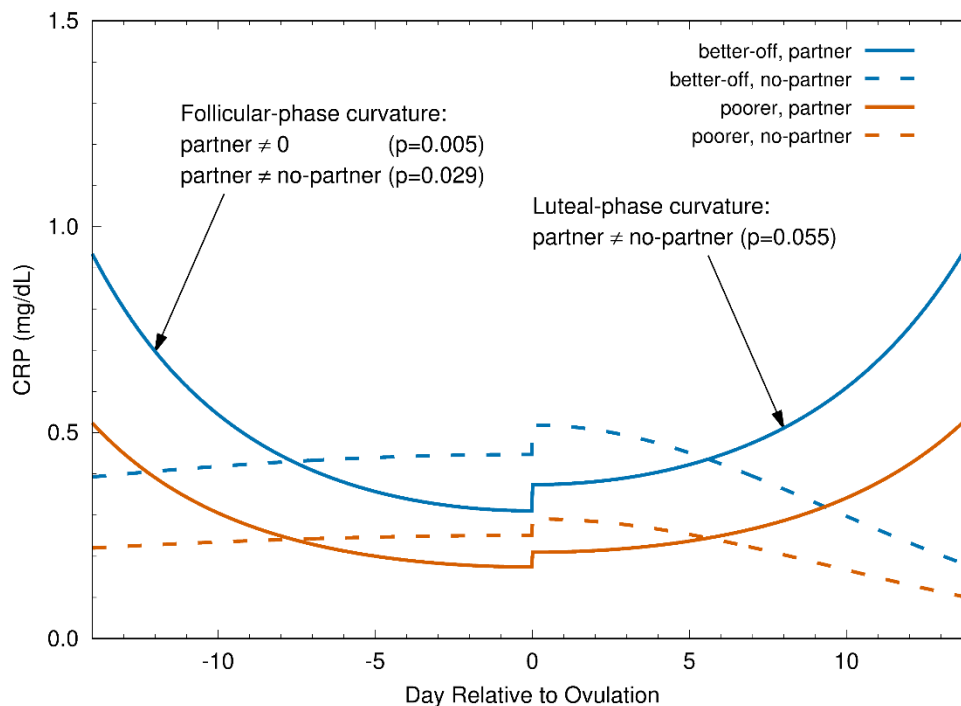
Figure 2. Change in CRP during ovulatory menstrual cycle. Fitted models for the interaction of partnership status and socioeconomic status. CRP is significantly higher during the early follicular and late luteal phases (P = 0.029 and 0.055, respectively) in partnered (solid curves) than in unpartnered (dashed curves) women. In partnered women, CRP is lower around ovulation than at the cycle's beginning (fitted model curvature is significant at P = 0.005). In contrast to partnered women, CRP in the ovulatory cycles of unpartnered women is more stable over time (fitted model curvature is not significantly different from 0). The small increases in CRP at ovulation are not statistically significant in these models. (Lorenz et al. 2015)

The key to balancing these incompatible functions is through the strategic timing of selected immune defenses. Specifically, in sexually active healthy women, we would expect relatively high immune defenses to protect against the risks associated with coitus but also a transient dampening of some immune defenses around the time of ovulation (the fertile window) in order to increase the chances for successful conception. In sexually abstinent healthy women, immune defenses need not be as high as in sexually active women and are not expected to change during the fertile window.

These predictions have been tested and supported in studies of Bolivian women and U.S. women. In Figure 2, the predicted patterns are observed in two Bolivian samples, one of poor women and the other of economically better-off women (Lorenz et al. 2015). The selected immune biomarker (C-reactive protein, CRP) patterns during the menstrual cycle are the same for both samples. Likewise, the pattern is similar in a sample of U.S. women, who are wealthier than both Bolivian samples (Lorenz et al. 2017). The comparability of this pattern across samples with different energetic resources suggests that greater energy availability does not modify the need for dampening some immune defenses at ovulation in sexually active women.

In other words, even though this dampening may come at significant health costs to women (e.g. autoimmune diseases, sexually transmitted infections) (Beer et al. 1996, Whitacre et al. 1999, Wira and Fahey 2008, Wira et al. 2010, Kaushic et al. 2011, Klein 2012), it does not appear to be mitigated by greater access to energy resources.

Which comes first—the coitus or the egg?

The differences in immune-reproduction co-ordination between sexually active and abstinent women are likely a consequence of seminal fluid components (e.g., cytokines) that provoke changes in the female reproductive system (Robertson and Sharkey 2016). The presence of such components is a signal of the possibility of conception and the concomitant necessity of modifying immune responsiveness.

However, if ovulation does not occur, such shifts in immune function in response to seminal fluid are not needed and would be potentially risky for the woman's health. Therefore, one would expect sexually active women to have a higher probability of ovulating than sexually abstinent women (i.e., ovulation is worth the risk from a shift in immunity for sexually active women but is an unnecessary risk in the absence of sex). Consistent with this prediction, Metcalf (1983; Metcalf and MacKensie 1980) observed lower ovulation rates in unpartnered than partnered New Zealand women, and Wilcox et al. (2004) found concurrent increasing probabilities of ovulation and coitus in a sample of U.S. women. However, neither study could specify the direction of the causal arrow (i.e., does coitus induce ovulation or vice versa?).

Now a recent study that included daily documentation of coitus and serial hormonal biomarkers to detect ovulation has yielded strong evidence that coitus increases the probability of ovulation in humans (Prasad et al. 2014). It is plausible (but was not tested in this study) that seminal fluid components are an essential part of the mechanism linking coitus to the physiological decision to ovulate.

This finding flips the causal arrow on the hypothesis that hormonal changes accompanying ovulation in women prompt increases in sexual attraction, desire and/or activity. Most studies of this prediction have failed to demonstrate such an association. The large majority of these studies have assumed, without biomarker confirmation, the timing and occurrence of ovulation during the study cycle. Such assumptions are untenable in light of the evidence that ovulation is not inevitable, that its timing is not restricted to a narrow mid-cycle window (reviewed in Vitzthum 2009), and that coitus itself promotes ovulation.

These observations and arguments, however, raise other intriguing questions. If a woman is not sexually active, why bother to ovulate at all? The fact that there is still an appreciable probability of ovulation in sexually abstinent women suggests that the cost of ovulation is low. One possibility is that once the wheels are set in motion, this low-cost process chugs along unless hindered (perhaps by signals that any risk of conceiving is a poor strategy at this time). Another possibility is that, outside of breastfeeding, there has been little selection against

ovulation but neither strong selection for ovulation, in the absence of coitus. Since sexual abstinence was likely uncommon during human's evolutionary history, opportunities for selecting against or for ovulation in the absence of coitus were relatively few. Even in those few instances, any resource savings in not ovulating may have been more than offset by the value of ovulating on the chance that coitus occurs.

This conjecture then raises the question, "If the cost of ovulation appears to be low, why not be an obligate ovulator regardless of coitus?" Perhaps tying ovulation to coitus is a selectively advantageous mechanism that helps to compensate for the short life of sperm, more closely linking the availability of an egg to the deposition of seminal fluid than would otherwise occur. The timing of coitus may help to explain why the duration of the pre-ovulatory (follicular) phase of the cycle is more variable than the post-ovulatory (luteal) phase. The answers to these questions await further study of the physiological mechanisms regulating ovulation, especially of the links to coitus.

Vote Early, Vote Often: Early Pregnancy Loss

The collective evidence from several studies suggests that only 1 in 5 human conceptions are born. Thus, worldwide during an average day in 2019, there were 360,000 live births, 1.8 million new conceptions, and 1.44 million naturally lost human pregnancies (the vast majority of which were unrecognized by the woman or her clinician) (Vitzthum 2008b).

This unexpected wastage was first brought to light in 1975 by two epidemiologists who estimated pregnancy loss in England and Wales to be 78% based on the marriage rate and reasonable assumptions regarding coital frequency and other relevant factors (Roberts and Lowe 1975). Subsequent studies, though few, have reached comparable conclusions. Boklage (1990) combined the published results of several observational studies of pregnancy loss in industrialized populations and developed a parametric model from which he estimated a total pregnancy loss of about 76%. Holman and his colleagues (Holman and Wood 2001) mounted an impressive study that monitored nearly 500 non-contracepting married Bangladeshi women and collected urine samples, later assayed for a biomarker of implantation, from 1,561 menstrual cycles. With these data, they detected post-implantation pregnancies and losses, and estimated the total pregnancy loss from conception to birth to be about 80%.

Modelled estimates suggest that pregnancy loss is greatest between conception and implantation (about 50-60% of all concepti). But there is little direct evidence because during this early stage women are unaware that they are pregnant, and there is not yet an easy-to-collect reliable biomarker for detecting conceptions prior to implantation. Implantation, which occurs 9 ± 3 days after conception, is recognized by a rise in human chorionic gonadotropin (hCG). Over-the-counter early pregnancy tests are designed to react to the presence of this hormone in urine samples and several studies have made use of this biomarker to estimate pregnancy loss rates. Estimates of loss occurring from implantation through the subsequent month were about 25% to 30% of implanted concepti in several studies in industrialized

populations (Wilcox et al. 1999, Ellish et al. 1996, Zinaman et al. 1996, Wang et al 2003, van Montfrans et al. 2004). In Bolivian women, 31% of implanted concepti were lost within 5 weeks of conception (Vitzthum et al. 2006). Based on hazard models (which produce higher and more accurate estimates), Holman and Wood (2001) estimated loss within 5 weeks of conception to be about 65% in 28-year-old Bangladeshi women. Among settled Turkana agriculturalists in Africa, about 70% of implanted concepti were lost by 10 weeks after conception (Leslie et al. 1993). Several studies have shown that by the end of the second month of pregnancy, the risk of subsequent loss has dropped to only 10-15% (Vitzthum 2008b). In many cultures, women decline to mention to others that they are pregnant until this stage has been reached and the risk of not going to term (i.e., not giving birth) is low.

Roughly speaking, based on the collective evidence, of 100 conceptions, 55 would not successfully implant, 22 would be lost during the month after implantation, and 3 more would be lost in the subsequent months, yielding 20 live births.

Evaluating Offspring Quality

Such apparently wasted effort naturally prompts questions about the causes underlying these losses. The canonical response is that concepti are lost early in pregnancy either because their genetic defects preclude normal development or because maternal mechanisms cull poor-quality offspring unlikely to mature and contribute genes to subsequent generations. Such weeding allows a woman to redirect investments to current or future offspring (Temme 1986; Kozlowski and Stearns 1989; Haig 1990, 1993, 1999). Even given abundant resources, a low-quality conceptus should be rejected quickly to avoid wasting maternal time that could be given to attempting another conception.

Perhaps the most important maternal mechanism for evaluating offspring quality depends on the embryo's own ability to produce sufficient hCG as it begins implantation. Production of this hormone is proof of the embryo's ability to carry out protein synthesis, the most minimal requirement of viability (Haig 1993). In a process referred to as corpus luteum rescue, the embryo signals its presence through hCG binding to receptors on the corpus luteum, which responds by continuing progesterone production to sustain the pregnancy (recall that falling progesterone concentration results in menstruation) (Jabbour et al. 2006).

Timing as well as the volume of conceptus-produced hCG is critical in this mechanism. The rise in hCG that accompanies implantation must occur between 6 to 12 days after ovulation if the conception is to be sustained. The later that implantation begins, and the later that the rescued corpus luteum subsequently produces more progesterone, the more likely it is that the conceptus will be lost during the subsequent month. Failure to produce sufficient progesterone quickly enough is a consequence of the embryo's inability to produce enough hCG rather than any defect in the corpus luteum (Baird et al. 1991; Vitzthum et al. 2006).

In effect, through the mechanism of corpus luteum rescue, the embryo will trigger its own rescue if it can produce, at the right time, enough hCG to assure continually rising progesterone

production by the corpus luteum. An unknown proportion of concepti fail this first test and menstruation renews the cycle. The maternal opportunity cost for having conceived and lost this early is very low. Early pregnancy loss does not appreciably lengthen the time to the next cycle (Vitzthum et al. 2000b), lower the probability of ovulation in the subsequent cycle (Donnet et al., 1990), or increase the subsequent mean waiting time to conception (Kaandorp et al. 2014). Furthermore, menstrual flow is not appreciably greater, which suggests that energy expenditure may not be much higher (Vitzthum et al. 2001).

For embryos that do make it past this first gateway, at least 30% and as many as 50% will be terminated before the end of the subsequent month, by which time another gatekeeping mechanism has come into play. The luteo-placental-progesterone-transition (LPPT), occurring by about 5 weeks since ovulation/conception and 7 weeks since the first day of the last menstrual period, is a developmental period during which the production of progesterone from the placenta (an offspring structure) begins to be greater than that from the corpus luteum (a maternal structure). Because progesterone is essential for the maintenance of the pregnancy, if this shift does not occur, the pregnancy will not continue (i.e., insufficient production of placental progesterone is indicative of a poor quality offspring).

In conceptions that do continue, the LPPT has shifted the locus of physiological control of the pregnancy from the mother to the offspring. It is in an offspring's own interests to sustain the pregnancy and, in large measure, during the LPPT the embryo is becoming the master of its own fate. Once it has the ability to produce enough progesterone without maternal contribution, any maternal interests contrary to those of the offspring may not prevail. Consistent with this prediction, only 10-15% of those pregnancies that survive through the LPPT are subsequently lost before birth.

The LPPT is a well-documented physiological change that occurs during early pregnancy. The evolutionary explanations for the LPPT are predicated on the fact that a mother and her offspring are not genetically identical and hence the optimal degree of parental investment to give and receive are likely not to be identical (Trivers 1974, Haig 1993). At first consideration, the idea of parent-offspring conflict would appear to be at odds with an expectation that it is in the evolutionary interests of a mother to invest in her offspring. Life history theory, however, recognizes that there are trade-offs—what is invested in one offspring cannot be invested in another. For example, in some environments (e.g., those with high infant mortality) it may be selectively advantageous for a woman to have two smaller children rather than one larger child. Therefore, natural selection is expected to favor the maternal life history strategy that produces the number and quality of offspring that will result in the greatest lifetime reproductive success for her under the environmental conditions in which she lives, and even if her LHS is not the optimal investment from the perspective of each offspring (see Strassman and Gillespie 2002 for a notable example).

Evaluating Maternal Quality

Life history theory also predicts that maternal somatic conditions and/or external

environmental circumstances that are inadequate for sustaining a pregnancy through to term may prompt rejection of a conceptus, even if that offspring is not defective (Wasser and Barash 1983, Peacock 1990, Vitzthum 1990). The LPPT imposes a timing constraint on maternal decisions to terminate investment in the current conception. If it is in the mother's evolutionary interests to do so, then termination is best effected while her own physiological mechanisms still regulate the bulk of progesterone production (i.e., before the LPPT). The timing of the LPPT reflects opposing interests. Selection on the offspring favors an early LPPT and the accompanying physiological control of pregnancy continuance. Selection on the woman favors a later LPPT so as to keep her investment options open.

Although it may initially appear paradoxical that a parent would terminate investment in a non-defective offspring, this option may be evolutionarily advantageous given the costs and risks associated with continuing a pregnancy, giving birth, and breastfeeding an infant. A mother's investment in the production of a live offspring is sufficiently high that it can, and sometimes does, cost her life (Vitzthum and Spielvogel 2003). Before the advent of antibacterial sulfonamides in the mid-1930s, an estimated 300-900 women per 100,000 pregnancies died from pregnancy-related causes (Loudon 2000). Currently, about 300,000 women die each year (UNFPA 2019). Mortality is only the tip of the iceberg, with maternal morbidity affecting millions of women each year. With such high costs, natural selection on offspring is expected to be especially high early in gestation (when maternal investments, opportunity costs, and risks are low) and relatively lower after birth (by which point considerable resource and opportunity costs, and much of the cumulative risk to the mother, have already been incurred).

Under the assumption that early pregnancy loss (EPL) is due almost entirely to genetic defects in the conceptus, there have not been many empirical studies of the hypothesis that maternal somatic or environmental conditions are significant contributors to EPL.   Three studies have addressed these questions. The North Carolina Early Pregnancy Study (NCEPS) recruited 221 women who self-collected daily urine samples (subsequently assayed for progesterone and estrogen metabolites and hCG) while attempting to become pregnant naturally (Wilcox et al 1999). Project REPA (Reproduction and Ecology in Provincía Aroma) collected thrice-weekly saliva (assayed for progesterone) and urine samples (tested for hCG) from 191 menstruating rural Bolivian women in a stable sexual partnership (Vitzthum et al., 2004). Twenty-four Guatemalan women self-collected thrice-weekly urine samples later assayed for several hormones (Nepomnaschy et al. 2006). Data from these studies on variability in the risk of EPL, and the environmental and hormonal mechanisms associated with these patterns, suggest life history strategies reflective of maternal factors are also at play in EPL.

In general, genetic defects are expected to occur randomly over time. Thus, if EPL were due almost entirely to genetic defects, EPL would also be expected to be randomly distributed over the course of a year. It was therefore surprising to find seasonal peaks and valleys in the distribution of EPL detected during the NCEPS (Weinberg et al. 1994). Although the pattern was clear—a peak at least four times greater than the trough occurring some time from September through December in three consecutive years—the authors were unable to explain it.

Project REPA also observed seasonal differences in EPL (Figure 3). The arduous planting and harvesting seasons had a 3.7 times greater risk of loss than the other seasons, and agropastoralists were 9 times more likely to experience EPL than those engaged in some other livelihood. The authors attributed the seasonal increase in EPL to the demanding physical labor of farming but also noted that inadequate food reserves and greater psychological or immunological stress could also be contributing.
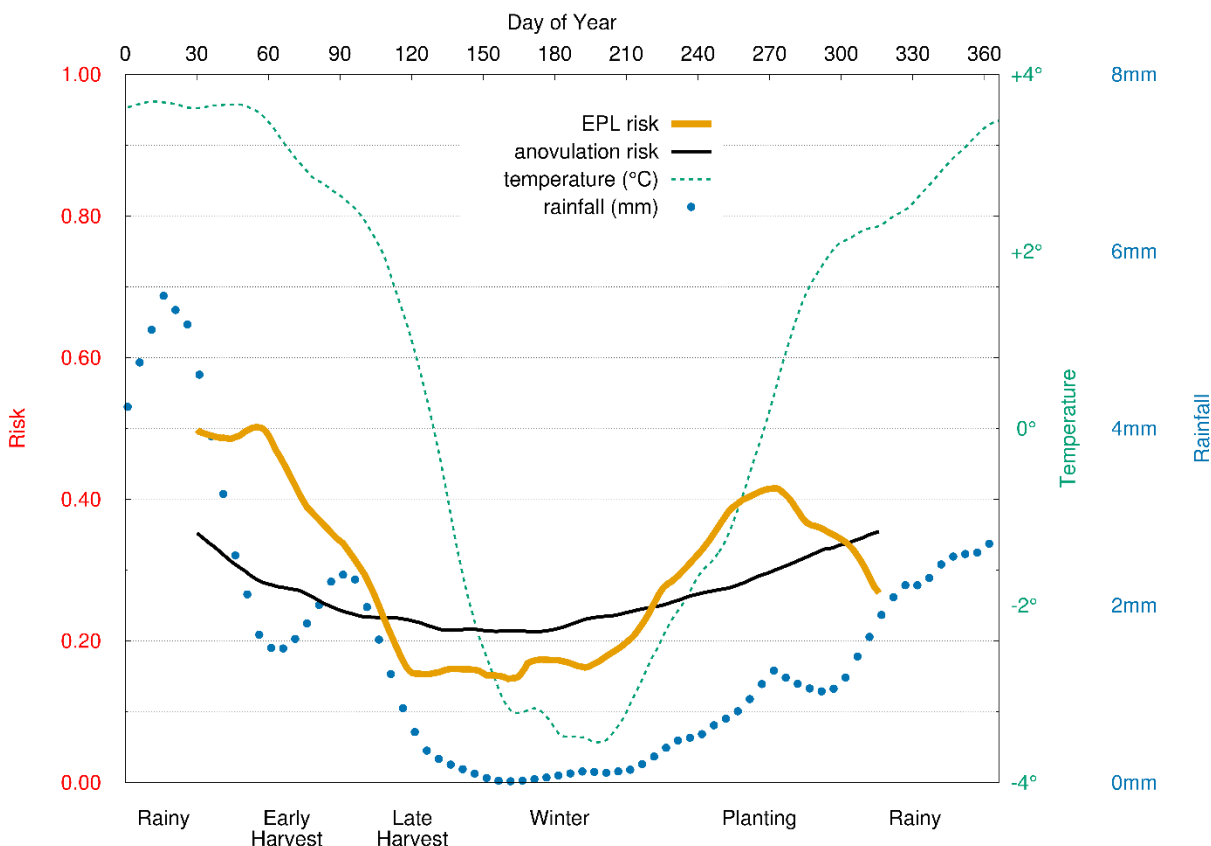

Figure 3. Seasonal variation in anovulation and early pregnancy loss (EPL). Risk (left-hand scale) of anovulation and EPL, and daily rainfall (far right-hand scale), and minimum-temperature (near right-hand scale) as functions of time (top scale, day of year). Agricultural activities (bottom scale) are positioned relative to day of year. Risk of EPL and anovulation are elevated during the most energetically demanding periods. (Vitzthum et al. 2009a)

Two proposed physiological mechanisms that might link poor maternal conditions to EPL have been tested. Reflecting the important role of ovarian steroids in preparing the uterine lining for implantation and sustaining a pregnancy, one hypothesis predicted that ovarian steroid concentrations would be lower in conception cycles that end in EPL than in conception cycles that are not lost. Data from NCEPS and Project REPA failed to support this prediction. In both studies, the ovarian steroid profiles of the successful and lost conceptions did not differ from ovulation through early pregnancy (Baird et al. 1991, Vitzthum et al. 2006) (Figure 4).
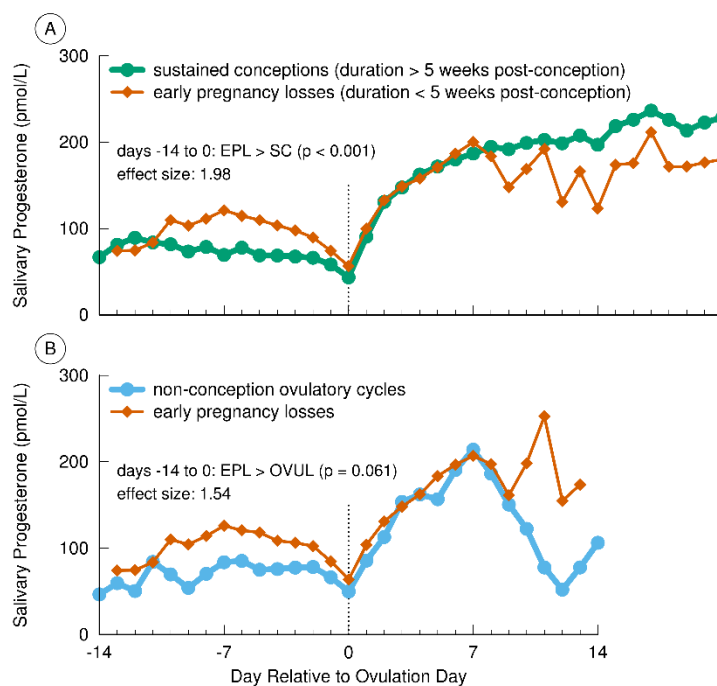
Figure 4. Progesterone (P4) concentrations in sustained conceptions, early pregnancy losses (EPL), and non-conception cycles in Bolivian women. Post-ovulation P4 did not significantly differ between EPL and conceptions persisting for at least 5 weeks after conception (Panel A). In contrast, preovulatory P4 was significantly higher in EPL compared with sustained conceptions (Panel A) and compared to non-conception ovulatory cycles (Panel B). (Vitzthum et al. 2006)

A second plausible mechanism for maternal evaluation of conditions involves cross-talk between the HPO-axis and the hypothalamic-pituitary-adrenal (HPA) axis. During the pre-ovulatory phase of the ovarian cycle, the adrenal cortex is the main source of progesterone, typically produced at levels much lower than those of the progesterone produced by the ovaries following ovulation. However, under stressful conditions (e.g., increased physical activity, food restriction, psychosocial stress), the adrenal glands increase production of cortisol and adrenal progesterone. Elevations of these hormones early in the ovarian cycle may disrupt normal ovarian functioning including development of the follicle, ovulation, implantation and/or sustaining an implanted conceptus (Vitzthum et al. 2006).

Evidence from the Guatemalan study and from Project REPA suggests this mechanism underlies at least some EPL. In the conception cycles of the Guatemalan women, those with high cortisol concentration were 2.7 times more likely to end in EPL than those with normal cortisol concentrations. In other words, 90% of those conceptions with elevated cortisol were lost as compared to only 30% of those with normal cortisol concentrations (Nepomnaschy et al. 2006). In the conception cycles from the Bolivian women (Figure 4, Panel A), adrenal progesterone during the follicular phase was significantly higher in those pregnancies that terminated prior to the LPPT compared to those that persisted beyond this transition.

The findings from these three studies are consistent with the life history prediction that, in

addition to the quality of the offspring, maternal somatic status and environmental conditions are potentially important determinants of whether or not to continue investment in a new conceptus. Although energy stores (adipose tissue) and seasonal energy availability can be major factors in maternal reproductive decisions, psychosocial, micronutrient, and immunological/disease conditions may also trigger termination of reproductive investment regardless of maternal energy adequacy.

A Pair of Paradoxes and the Physiological Fallacy

"Honorable errors do not count as failures in science, but as seeds of progress…" Gould (1998)

Beginning in the late 1970s, an intellectual dispute arose between demographers and biologists (bioanthropologists, physiologists, medical scientists, evolutionary biologists) regarding the role of energetics (caloric intake and expenditure) in human reproduction.

Biologists, on the one hand, had both good theoretical arguments and considerable data in favor of the position that energetics is a major determinant of fertility. In particular, studies of U.S and European women who were following calorie-restricted diets and/or regular strenuous exercise regimes (either in or outside a laboratory setting) were observed to experience disruptions in their menstrual cycles including reductions in reproductive hormone concentrations. Furthermore, with increasing energetic severity, the disruptions could become so pronounced that ovulation and menses ceased all together (dubbed "exercise associated amenorrhea"). Although some observers considered these changes to be pathologies, Jerilyn Prior (1985a, 1985b, 1987) and a few others argued that these were adaptations to spare women from conception when energetically stressed, a condition that could increase maternal and offspring risks for morbidity and mortality.

Demographers, on the other hand, had a world's worth of compelling population-level demographic data that supported the position that energetic stress (other than starvation) has only a trivial impact on human fertility. Bongaarts (1980) laid out the data and arguments in a widely influential paper in *Science*. Perhaps his most convincing point was that many of the very populations experiencing the most significant energetic stress were also those with the highest fertility.

Faced with a seemingly unresolvable paradox—physiological data demonstrating energetic impacts on individuals in industrialized countries yet no apparent impact on population-level fertility parameters in energetically stressed populations—the two sides, for the most part, retreated to their respective domains.

A technological development and more data, however, revived the discussion in the late 1980s. The first studies of possible differences between populations in the concentrations of reproductive steroid hormones (progesterone, estrogens) were largely motivated by an interest in finding the causes of marked population differences in the risks for breast and other cancers.

In general, these studies found lower concentrations of these hormones in Asian compared to U.S. and U.K. "white" populations (Dickinson et al. 1974, MacMahon et al. 1974, Trichopoulos et al. 1984, Bernstein et al. 1990, Key et al. 1990, Shimizu et al. 1990, Wang et al. 1991). There was little, if any, suggestion in the published literature from these epidemiological studies that the observed hormone differences might also cause population differences in fertility.

The first study by bioanthropologists of reproductive hormones in African populations also observed lower concentrations compared to those observed in European and U.S. samples (van der Walt et al. 1978). However, these investigators explicitly argued that the lower concentrations were indicative of lower fecundity and were perhaps evolutionary adaptations to energetic stress. The development of salivary hormone assays (an alternative to blood-based assays) allowed other anthropologists to collect data from several energetically stressed rural populations (Democratic Republic of the Congo, Nepal, Bolivia, and Poland) all of which proved to have average salivary progesterone concentrations significantly lower than the average observed in a sample of U.S. women (Ellison et al. 1989, Panter-Brick et al. 1993, Jasienska and Ellison 1998, Vitzthum et al. 2000a).

These additional observations generated a second paradox. Although these energetically stressed populations had relatively lower progesterone concentrations, they did not necessarily have low fertility. For example, women in the rural Bolivian population, with an average progesterone concentration only 70% that of U.S. women, had an average of 7 live births with some women reporting as many as 13 offspring (Vitzthum et al. 2004).

The resolution of each of these two paradoxes was not simply a matter of figuring out who was right and who was wrong (the various studies had, in fact, been well executed by competent scientists). Rather, we needed to re-think our assumptions and interpretations of the available data with fresh eyes. This re-assessment involved taking the empirical data at face value—specifically, (1) women in industrialized populations had relatively high progesterone concentrations and experienced ovarian cycle disruption, including lower progesterone, when energetically stressed, and (2) women living in energetically stressful conditions had relatively low progesterone concentrations but nonetheless were having lots of babies—and examining these biological patterns within an evolutionary framework. The following assessments arose from this approach (Vitzthum 1990, 1997, 2001, 2009, 2020).

First, there is no scientific justification for assuming that hormonal data from U.S./European women are a normal or desirable standard against which to compare all other populations. The fact that interpopulation hormonal variation does not correspond to interpopulation differences in fertility strongly suggests that there is no species-specific "normal" progesterone concentration necessary for reproducing. Comparable to the misdirection taken in medicine by assuming that statistically defined thresholds are genuine markers of normalcy, so have efforts in reproductive ecology been led astray by assuming that higher concentrations of reproductive hormones necessarily equate with higher fecundity and fertility.

Second, acute and chronic energetic stressors are not necessarily biologically equivalent. The

timing (whether pre-natal, pre-adult, or during adulthood), duration and magnitude of a stressor can all impact how an organism responds to the challenge. The disruption in ovarian function that accompanies an acute energetic demand is a temporary cessation of reproductive investment in favor of temporarily increased somatic demands. If the organism never resumes reproductive investment before dying, it is likely to be at a selective disadvantage compared to individuals who do reproduce. Therefore, if an acute temporary demand persists, the organism may become less sensitive to this demand so as to resume the normal array of bodily functions (a physiological state called "homeostasis"). Unlike acute demands, chronic energetic demands must be managed differently because these stressors are the very nature of the environment in which the organism lives and must reproduce. The organism must have a life history strategy that results in successful reproduction in these tougher conditions.

Third, between-population differences in reproductive hormone concentrations are not necessarily equivalent to the within-person reductions in hormone concentrations associated with an acute energetic stressor. This mistaken equivalency —a "physiological fallacy" somewhat analogous to the "ecological fallacy" (Robinson 1950, Selvin 1958)—ignores both the processes that generate a given hormone concentration and the units of analysis, and hence misidentifies the absolute level of the hormone as the necessarily salient signal in biological mechanisms. Rather, at least as regards the role of ovarian steroids in mechanisms that implement LHSs, the current evidence suggests that it is the temporal *change* in the hormone's level that transmits information about changes in the factors that influence reproductive investments. If change is the (more) salient signal, then it's likely there's not strong selection for specific hormone levels. Rather, there is the potential for high, yet nonetheless normal, variability in absolute hormone concentrations within and between populations (Figures 5, 6).
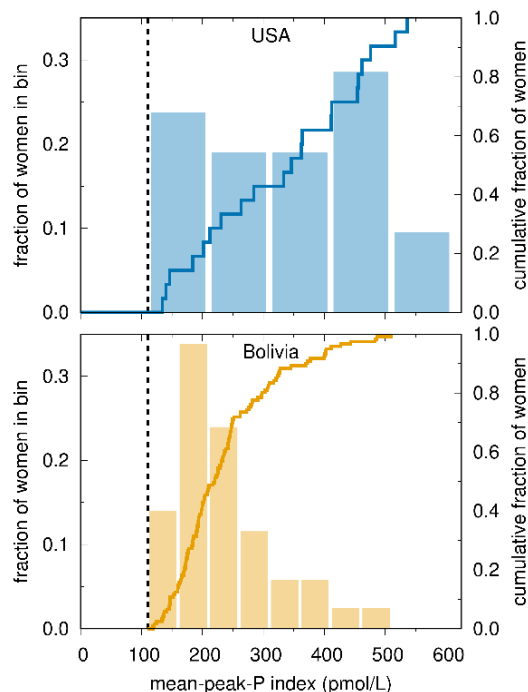

Figure 5. Progesterone variation in ovulatory cycles. Histogram (left scale) and cumulative distribution (right scale) of a mid-luteal index of hormone concentration (mean-peak-progesterone). Progesterone concentrations differ substantially between the two populations and between women within each population (Vitzthum et al. 2004).

The prediction that marked hormonal variability is normal is supported by empirical studies demonstrating that different reproductive hormone concentrations are functionally equivalent across individuals and populations. Although progesterone concentration is significantly lower in Bolivian than in Chicago women, Bolivians successfully conceive at these lower concentrations (Figure 6) (Vitzthum et al. 2004).
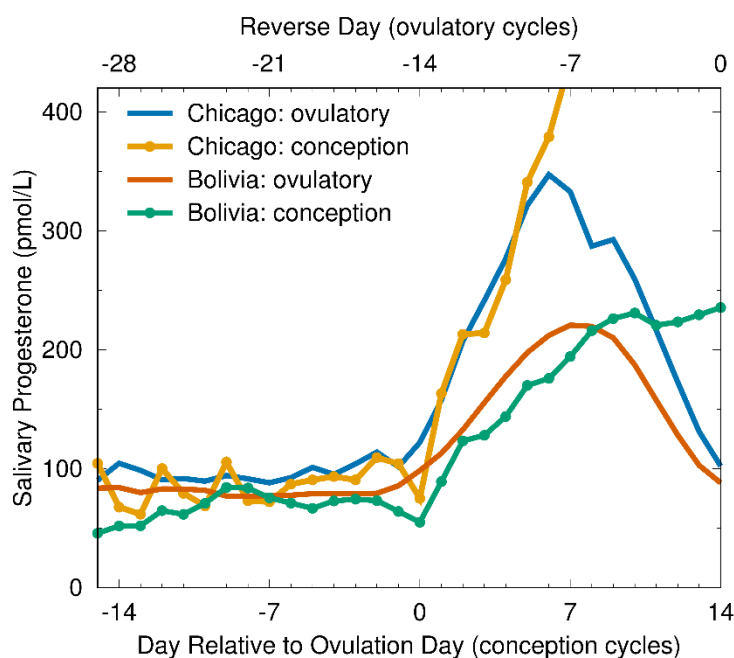

Figure 6. Salivary progesterone profiles in conception and ovulatory non-conception cycles. Progesterone concentrations in ovulatory cycles are significantly lower in women from Bolivia than in women from Chicago throughout the ovarian cycle, and also lower during and subsequent to ovulation in conception cycles. (Vitzthum et al. 2004)

In the search for mechanisms that regulate LHSs and generate demographic diversity, the largely unexamined assumption that there are necessarily species-specific "normal" concentrations of a given hormone has led us down blind alleys and obscured our understanding of how the HPO axis works. Dropping this assumption has both resolved previously inexplicable paradoxes and suggested novel models that better reflect how physiological mechanisms transform signals and implement LHSs.

Evolving Research Directions for the Study of Mechanisms

It has been nearly a century since Fisher reflected on what might be gained by knowing something of the physiological mechanisms underlying resource allocation strategies and more than half a century since Tinbergen re-emphasized the centrality of determining mechanism in our efforts to thoroughly understand a behavior. Yet we've just begun to delve deeply into the unexpectedly complex details of exactly how an organism achieves successful trade-offs

between survival and reproduction. This recent progress is possible because of advancements in biomarker measurements and field-friendly methods for collecting longitudinal as well as cross-sectional data in community-based studies. The expansion of complex statistical models and greater computational capacities have also improved analyses of this wealth of data. Although the investment can be high, the pay-off is often impressive.

Theoretical developments are as necessary as better technologies for discovering the origins and functioning of a specific mechanism underlying a life history strategy (LHS). For example, recognition of parent-offspring conflict regarding optimal parental investment explains *how* pregnancy loss can be a successful LHS in some circumstances and *why* there are maternal mechanisms to test offspring quality. The evolutionary insight that pregnancy is more akin to a Greek play laden with conflict than a pas-de-deux laced by harmony deepens our understanding of human biological variability and potentially prompts re-evaluations of explanatory models in related fields (e.g., medicine, reproductive technologies, demography).

Below I briefly describe two of the many research areas concerning life history mechanisms that deserve attention as we move forward.

Adaptations, Cross-talk, and Trade-offs: More is Needed on the Mechanics of Mechanism

Whether short-term (a day, a season) or long-term, resource allocations are potentially subject to natural selection (i.e., they may be adaptive responses that have evolved to increase lifetime reproductive success in a given set of population-specific conditions). Testing whether or not a life history strategy or some specific investment decision is adaptive is a daunting task, especially in the long-lived human species. Knowledge of the specific mechanism by which a given resource allocation is accomplished facilitates testing adaptation hypotheses and can enlighten efforts to address the other three of Tinbergen's four questions.

Although it's obvious that there must be considerable coordination of actions among the various systems of an organism, for the most part we've understandably ignored those interactions in favor of tackling (relatively) manageable questions. It's now evident that we must begin to venture out beyond these imagined borders and grapple with how various systems inter-communicate and thereby effect responses that are potentially adaptive for the organism.

To accomplish this goal requires figuring out the details of how a mechanism is engaged and operates. For example, at a particular point in a specific pathway, is the salient feature of a signal its absolute status (e.g., hormone concentration) and/or a change in its status (e.g., a rise or fall regardless of the signal's baseline concentration)? What are the specific contexts and factors (nutrient or time limits? mechanical or physiological incompatibility?) that tend to prompt one response over another? By what signals and pathways is this response recognized and responded to by other organismal components?

In addition, although this chapter has focused on the physiological mechanisms by which life history strategies are implemented, resource allocation strategies may also involve somatic, behavioral, or extra-somatic mechanisms. Maintaining body fat stores, food caching (whether buried nuts or dried agricultural surplus), and building reciprocal social networks all demand time and resources diverted from immediate reproductive investment, but each of these strategies can mitigate the risk inherent in variable environments and thereby potentially increase lifetime reproductive success (Lee and Boe in this volume). How, then, do such non-physiological mechanisms become an integral component of the organism's LHS and thus influence the workings of physiological mechanisms and reproductive output? At least part of the answer to these questions involves learning more about the precise mechanics of the pertinent mechanisms.

Linking (Adult) Mechanisms and (Pre-adult) Ontogeny

In their tribute to Tinbergen, Bateson and Laland (2013) emphasized that consideration of "mechanism always requires specification of a point in development." Ontogeny rightly comprises the entire developmental history of the organism up to the time at which a behavior is occurring, and the causes of that behavior may trace back to the organism's conception (Tinbergen 1963).

It has been recognized for some time that early conditions can shape an organism's functioning during its subsequent life. This calibration of individual physiology to local environments is necessary for an organism to mature and to execute a successful LHS. We have only recently begun to identify the epigenetic processes involved in this ontogenetic preparation for the future. The conditions experienced early in life are the best predictors of those likely to be experienced throughout life, and hence the LHS shaped by that early environment is likely to be the most advantageous LHS in later life (Vitzthum 1990, 1997, 2001, 2009).[5] This process does not require any conscious decisions by an organism. Rather, among the ways in which an organism's biology might respond to environmental signals, natural selection will favor those responses that result in a relatively greater reproductive advantage.

Thus population-specific environmental conditions experienced during an individual's pre-adult development are likely to affect her reproductive functioning throughout adulthood. Women who developed in energetically demanding environments may be biologically acclimated to such conditions and hence are less likely to experience ovarian cycle disruption under a given energetic stressor than would a woman who developed in a more benign environment (Vitzthum 1990, 1997, 2001, 2009). Metaphorically, women in industrialized populations are akin to hothouse flowers, cultivated under ideal conditions—small perturbations can have large negative effects until the ideal conditions are restored. In contrast, wildflowers must successfully reproduce in the typical environments in which they have grown, even if those

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[5] Similar arguments have been made independently regarding the psychological mechanisms underpinning animal behaviors that are flexibly responsive to environmental cues (Gigerenzer et al. 1999; Hutchinson and Gigerenzer 2005; McNamara and Houston 2009; Fawcett et al. 2012).

conditions are more demanding compared to a hothouse. From the perspective of life history theory, there is nothing necessarily paradoxical about high fecundity and fertility under conditions that are energetically demanding (compared to some other environment) if these are the conditions in which the individual developed and which are likely to persist for the rest of the individual's reproductive life. (This argument acknowledges that there are minimum energetic requirements for somatic maintenance and pregnancy below which successful reproduction does not occur.)

The centrality of age-specific mortality risk in the evolution and execution of population-appropriate LHSs suggests there are mechanisms that convey information reflective of mortality schedules. These mechanisms likely involve epigenetic and other physiological processes that influence reproductive physiology. But the specific endogenous or exogenous signals that generate suitable epigenetic modifications of the genetic regulation of reproductive maturation and functioning are unclear. How does reproductive physiology become attuned to the local population's mortality schedule or, put another way, how do mortality schedules become embodied within an individual?

For example, the timing of puberty, marking a shift of resource allocation from growth to reproduction, varies by several years within and between human populations and can change markedly in a single generation. What signal(s) prompts this transition at an age that is likely to be advantageous given the current population-specific mortality risks? Whatever these signal(s) may prove to be, they likely have the following attributes:
(1) Because of the evolutionary history of extant taxa, the same signaling mechanism is likely shared across multiple phylogenetic lineages (e.g., all primates or all mammals).
(2) The signals must be acting early in life (before maturation is complete) so that the organism can grow and mature at the strategically "best" pace and age.
(3) The signals are proxies for mortality schedules rather than having experienced death itself (by which point the signal is of no use to the organism).
(4) Most (perhaps all) such signals are likely to be non-specific as to the causes of death because (given a specific time of death) the cause of death is irrelevant to one's lifetime reproductive success.

In 1993 Chisholm proposed a life history model linking childhood experiences of stress (as reasonable proxies for mortality schedules) and later reproductive strategies. Subsequent papers (Chisholm et al. 2005, Coall and Chisholm 2010, Sheppard and Coall in this volume) provided additional support for the model including evidence for mediation of the physiological pathways through the HPA axis. Working from different data and premises, Geronimus (1992) proposed the "weathering hypothesis" to explain ethnic differences in the USA population in the timing of fertility. She attributed this and ethnic health disparities to the negative impacts of various stressors mediated by the HPA-axis (Geronimus et al. 2006). That these different models point to the same physiological mechanism linking mortality, health, and reproduction to present and past conditions suggests that more study of the HPA-axis (in particular, its cross-talk with other physiological systems and epigenetic processes) could shed light on the links between ontogeny and the responsiveness of life history strategies to mortality schedules.

Concluding Remarks

The 150th anniversary of Darwin's publication in 1859 of *On the Origin of Species by Means of Natural Selection* was marked by worldwide celebrations of his far reaching contribution. Mostly forgotten was that by 1900, for want of evidence, natural selection had relatively few supporters (Bowler 1983). Rather, mainstream biology favored several alternative explanations for evolution.

It is now a century since the beginnings of "The Modern Synthesis", the integration of Darwin's ideas about evolution and Mendel's work on heredity. This merger of theory and mechanism by Fisher (1918), Haldane (1924), Wright (1932), and others is rightly considered the foundation of contemporary evolutionary biology (Huxley 1942), having spawned innumerable theoretical and empirical advancements in biology and other fields. Of late there have been calls for an "extended evolutionary synthesis" and other elaborations (Pigliucci and Müller 2010, Jablonka and Lamb 2014, Laland et al. 2015) of the Darwinian-Mendelian model that had been catapulted by the modern synthesis. In large part, these newest developments are an outcome of investigations into the mechanisms that build an organism and manage its functioning from conception through growth and reproduction to death.

Like the modern synthesis, these extensions and the empirical evidence supporting them are worthy of demographers' attention. Collectively they provide a roadmap to understanding the variability and plasticity of human biology and behavior from within an evolutionary framework without resorting to gene-centric reductionism or genetic determinism (which often yield unsatisfactory explanations for complex bio-behavioral phenotypes). While it's evident that humans, like any biological entity, are subject to and the result of evolutionary processes, behavior within and between human populations is typically more than the simple expression of "a gene for" this or that phenotype (the same can be said for non-human species).

Obviously, an organism's behavior is never fully independent of its body. Behavioral and biological mechanisms share a fuzzy boundary across which a signal from one side of the border can prompt a cascade of responses on the other. Unpacking the interactions of biological and behavioral mechanisms is one particularly promising strategy for better understanding how extra-somatic as well as somatic factors influence reproductive functioning and generate demographic diversity.[6]

Consider, for example, lactational suppression of ovulation, a flexibly responsive bio-behavioral mechanism that is the very essence of being a mammal and one of the most influential determinants of variation in fertility. Breastfeeding in humans (WHO 2009) is a coordinated behavioral repertoire of two persons: mom holds and guides the baby, who must latch on to and suckle the nipple. Mothers typically learn their part through repeated observation or active teaching from relatives and midwives. Reflexes in the infant's central nervous system prompt suckling, itself the physical stimulus that initiates the cascade of neuroendocrinological

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[6]Recall that *extra-somatic* refers to social, cultural, economic, physical, and biotic factors, and behaviors of others.

sequelae in mom's body that inhibits ovulation. But only to a point—mom could decide to breastfeed for years but nonetheless ovulation would return much sooner. This is not a consequence of her behavior but of the mechanism itself, which has been shaped by natural selection to return her to a fecund state despite nursing an older infant. Mom could also decide not to breastfeed at all, but this can have negative health consequences for mom and baby alike, and for mom's reproductive success. Leaving aside additional points regarding the somatic and extra-somatic factors that influence a mother's decisions regarding nursing (Tully and Ball 2011), it is evident that lactational suppression of ovulation is neither a strictly biological nor strictly behavioral mechanism and thus its effect on fertility cannot be accurately assessed without considering both sides of the coin.

At the beginning of this chapter I proposed adding a fifth question to Tinbergen's four: How do the features of mechanisms vary within and across human communities worldwide? Quite a bit, as it turns out. Ages at menarche and at menopause vary by many years. Ovarian steroid concentrations in ovulatory cycles of healthy women differ severalfold without accompanying differences in fecundity or fertility. Rates of ovulation and early pregnancy loss vary seasonally and between populations.

This phenotypic variability reveals the flexibility of individual responses to local ecologies and the workings of life history strategies. Optional ovulation is a life history mechanism that prevents premature diversion of resources from a nursing infant or risky shifts in immune defenses in a sexually abstinent woman, or allows foregoing the current opportunity for conception until conditions improve. Conception is not an irrevocable maternal commitment to reproduction. Gate-keeping mechanisms operating during implantation and the subsequent weeks prior to the LPPT afford opportunities for maternal termination of investment (early pregnancy loss) if the conceptus is flawed, or maternal status or extra-somatic conditions are not favorable. At these early stages, human reproduction is a "rent-to-own" contract with low exit costs.

There's practical as well as theoretical value in recognizing that physiological mechanisms have context-dependent outcomes, exemplified by the attempts to develop breastfeeding behavior into a natural contraceptive. Much effort was invested in determining the best nursing pattern (suckling frequency and/or duration) for suppressing ovulation for the longest time post-partum (NFP 1991). This goal proved unattainable. Researchers found that the same breastfeeding pattern did not have comparable impacts on fecundity in different women and populations, and that very different nursing patterns had similar suppressive impact (in mathematics, this is known as a "many-to-many mapping" from nursing pattern to ovulation suppression). This complex variation in signal and outcome precluded proposing a specific regime as a contraceptive. Nonetheless, if a baby's only food was from being breastfed whenever hungry, ovulation was suppressed for an extended period, though exactly how long was not predictable with the available data. Although frustrating for health care providers, these findings are consistent with life history theory (Vitzthum 1994).

Numerous examples of phenotypic plasticity within and across populations challenge notions of

a universal "normal" human biology. While there are barriers to good health in all human populations, it should not be assumed that all deviations from such norms (especially those established with data from WEIRD populations (Heinrich et al 2010)) are necessarily pathologies requiring fixing. Furthermore, we should not necessarily expect there to be a universal "best" adaptation in all populations to an identical challenge to reproduction or survival. For example, Beall (2006) has documented three quantitatively different phenotypes in response to low barometric pressure among indigenous high-altitude populations in the Andes, Tibet, and Ethiopia. These phenotypic variants likely reflect the different biocultural histories of the populations and may also be moderated by other features of the local ecologies.

Cross-population studies have also prompted interesting questions regarding ecomarkers (signals of extra-somatic conditions). In some instances, the change in an ecomarker may be more readily detected and hence a more salient signal than the specific state of the condition. In either case, the utility of the ecomarker will likely differ across contexts (for example, directional changes in photoperiod would be a reliable ecomarker of changing seasons at high latitudes but not near the Equator).

The physiological mechanisms that underlie LHSs operate in ways that vary both within and between populations, and this variation can have profound demographic consequences. These mechanisms have evolved to respond to the changing availability of resources and the finite time during which an organism must develop and reproduce. Some essential biological, psychological and behavioral functions cannot co-occur; successful LHSs must juggle such incompatibilities regardless of the abundance of energy and/or other resources.

It turns out that evolutionary processes are more numerous and nuanced than a mere culling of the less fit and, as a consequence, reproductive functioning is more like a flexibly responsive behavior than a well-tuned machine. The details of "how it works" are, as yet, only partially understood. Clearly there's much work left to be done and exciting revelations await.

Acknowledgements

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Glossary

biomarker: "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group 2001); examples include hormone concentrations, birth weight, blood pressure, and many others; biomarker choice and interpretation depends on many factors (Worthman and Costello 2009)

C-reactive protein (CRP): an acute-phase protein produced by the liver in response to signals from immune agents. Low circulating concentrations of CRP reflect a broad array of processes related to ongoing baseline somatic maintenance, but rise abruptly within about 2 hours of an acute insult

conspecific: members of the same species

corpus luteum: the transformed follicle that had enclosed the egg cell prior to ovulation

cross-talk: biomolecular communication between two signaling pathways

downregulation: in the context of hormones and their targets, the cell becomes less sensitive to the presence of a hormone because available receptors have become saturated due to hormone binding and/or receptor degradation (also see upregulation)

early pregnancy loss (EPL): natural termination within the first few weeks of conception

ecomarker: a reliable signal of extra-somatic conditions

endocrine system: comprises the internal organs that release hormones directly into the circulatory system in order to affect the functioning of more distant target organs

epigenetic: refers to structural changes of the chromosome that alter the expression of the genotype (and thus modify phenotype) without changing the DNA sequence

ethology: the study of behavior (usually refers to non-human animal behavior)

extra-somatic: external to the body (e.g., social, cultural, economic, physical, and biotic factors, and the behavior of others)

fecundity: refers to the capacity to conceive

fertility: refers to the production of a live birth

follicle: the structure surrounding an egg cell prior to ovulation

follicular phase: the pre-ovulatory segment of the ovarian cycle

genotype: the genetic sequences in an individual that result in a phenotype

gonadotrophin releasing hormone (GnRH): is synthesized and released by the hypothalamus; stimulates the synthesis and release of gonadotrophins (LH and FSH) from the anterior pituitary

human chorionic gonadotropin (hCG): produced by the conceptus; binds to receptors on the corpus luteum which, as a consequence, maintains its production of progesterone essential to sustaining the pregnancy

hypothalamic-pituitary-adrenal (HPA) axis: the physiological system comprising the hypothalamus, pituitary, and adrenal gland; plays a central role in responding to stressors

hypothalamic-pituitary-ovarian (HPO) axis: the physiological system comprising the hypothalamus, pituitary, and ovary; plays a central role in the regulation of reproduction

life history strategy (LHS): a pattern of maturation, reproduction, and resource allocation that is subject to natural selection

life history theory (LHT): an evolutionary framework for studying maturation, reproduction, and aging, and the associated mechanisms underlying resource allocation of to these processes

luteal phase: the post-ovulatory segment of the ovarian cycle

luteal phase deficiency (LPD): a disorder that is said to be caused by insufficient progesterone during the luteal phase but that lacks definitive diagnostic criteria

luteo-placental-progesterone-transition (LPPT): a shift in progesterone synthesis during pregnancy from the corpus luteum to the placenta

norm of reaction: the range of possible phenotypes for a given genotype

ontogeny: the development of an organism from conception until death

ovulation: the release of the mature egg from a single follicle

phenotype: a morphological, physiological, behavioral, or psychological feature of an organism; a phenotype may be determined only by genes, or solely by environmental factors, or by the interaction of genes and environmental factors

phenotypic plasticity: capacity for a genotype to express a variety of phenotypes

phylogeny: the evolutionary relationships among current and extinct species

somatic: referring to the body (also see extra-somatic)

upregulation: in the context of hormones and their targets, the cell's creation of more receptors so that the cell is more sensitive to the hormone (also see downregulation)