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INTRODUCTION

A. EVOLUTIONARY THINKING IN MEDICINE

Evolutionary medicine is a relatively new discipline at the junction where evolutionary insights clarify medical observations and where the latter offers not only new insights but also research opportunities in evolutionary biology. Yet, the gaps are still wide between evolutionary biology and clinical medicine. Here are some concepts as to where the two vary.

Medical practitioners and medical scientists view organisms as machines whose design has been optimized by engineers to provide good health. The evolutionary perspective asks why those mechanisms are the way they are. It views organisms, instead, as compromises between traits shaped by natural selection to maximize reproduction, not health or the good of the species (helping it to avoid extinction) (Stearns, Nesse et al. 2010). They are the product of inevitable trade-offs. Thus, compromises that increase disease resistance often have costs, and some variations that increase susceptibility have their benefits. Evolutionists like to make the distinction between "proximate," for mechanistic explanation, and "ultimate," for evolutionary explanation, which in medicine is often misunderstood as teleological design of final causes that exist in nature. The synthesis of the two approaches, which is used throughout this book, is that proximate mechanisms evolved through interactions with the environment to shape phenotypes.

Evolutionists place special emphasis on the concept that selection acts on phenotypes, not on genes, and in a similar manner, patients are phenotypes. Doctors do not treat genes; they treat traits that are influenced by genes and their expression. Whereas much of the theory of life history has been developed and tested without reference to the genetic underpinnings of the trait (admittedly, Charles Darwin

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knew nothing about genes), genomics may respond to the question of how a tradeoff that is expressed at the phenotypic level is manifested or modulated at the level of genetic regulation.

The notion that common heritable diseases are caused by a few defective genes is usually incorrect. Rather, many genetic variants interact with environments and other genes during development to influence disease phenotypes (Stearns, Nesse et al. 2010). Genome-wide association studies have failed to explain more than a few percent of the variations in a trait. Such studies have shown time and again that most of the genetic variance of a trait is contributed by mutations at low frequency in the population, and the effects of rare mutations tend to be much larger than those of common mutation; mutations that have strong effects on fitness are likely to be rare in populations and hence difficult to detect; and mutations that are easy to detect have small effects on disease.

Another interface between biological evolution and clinical medicine is the recognition of cultural effects on disease. Population evolution is much slower than cultural change, and diseases arise often from the mismatch of our bodies to modern environments.

Two examples illustrate how evolution has provided important insights to medicine: (1) in the explanation of aging and (2) why humans have more cancers than other species. Both aging and cancer are not adaptations, but by-products of selection for reproductive performance earlier in life. We now live for two decades and more of post-reproductive years that are relatively indiscernible to natural selection; we practice our unique sexuality with countless nonreproductive cycles and contraceptives; likewise, we are not adapted to our rich diet.

B. EVO-DEVO

Evolutionary development biology (evo-devo) addresses the issues of how developmental systems have evolved and probes the consequences of these historically established systems for organismal evolution (Muller 2007). Research in evo-devo has formed around comparative embryology and morphology, evolutionary developmental genetics, and experimental epigenetics. In that respect, it considers the interactions of both microevolutionary processes-changes in traits and gene frequencies resulting from selection and drift in each generation at the populations level-and macroevolutionary processes in deep time perceived in comparisons among species and with fossil evidence and phylogenetic lineages. Micro- and macroevolution explain why species and populations are the way they are, but they do not explain individuals (Stearns and Koella 2008). Understanding individuals requires adding considerations of development: the interaction of genes and environment at each stage of life history, a combination that is now referred to as "evodevo." This treatise takes evo-devo into postnatal life, the realm of clinical medicine, and more particularly, the physiology and pathology of child growth and maturation. Under the evo-devo concept, child growth is a developmental process, and we no longer speak of genetic versus environmental effects and "nature or nurture"; all traits are products of both.

Human populations are usually thought to be poor candidates for the study of basic questions about the evolution and maintenance of fitness traits; the effects

of culture are profound, and environments are variable and far different from those in which the species evolved. Humans, however, are the most investigated species, and clinical observations offer an immense opportunity for the study of evolution. Moreover, special cultural conditions offer something like a natural situation and are used in this treatise to understand the role of the environments on child growth.

Plasticity in developmental programming has evolved in order to provide the best chances of survival and reproductive success to the organism under changing environments (Hochberg, Feil et al. 2011). Environmental conditions that are experienced in early life can profoundly influence human biology and long-term health. Developmental origins of health and disease and life-history transitions are purported to use placental, nutritional, and endocrine cues for setting long-term biological, mental, and behavioral strategies in response to local ecological and/or social conditions. The window of developmental plasticity extends from preconception to early childhood and involves epigenetic responses to environmental changes, which exert their effects during life-history phase transitions. These epigenetic responses influence development, cell- and tissue-specific gene expression, and sexual dimorphism, and, in exceptional cases, can be transmitted transgenerationally. Translational epigenetic research in child health is a reiterative process that ranges from research in the basic sciences, preclinical research, and pediatric clinical research. Identifying the epigenetic consequences of fetal programming creates potential applications in clinical practice: the development of epigenetic biomarkers for early diagnosis of disease, the ability to identify susceptible individuals at risk for adult diseases, and the development of novel preventive and curative measures that are based on diet and/or novel epigenetic drugs.

In November 1859, Charles Darwin published the first edition of *On the Origin* of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life. The second edition was published two months later, in January 1860. Chapter 4 of the *Origins* includes the following paragraph, which is as valid today as it was then:

If during the long course of ages and under varying conditions of life, organic beings vary at all in the several parts of their organisation, and I think this cannot be disputed; if there be, owing to the high geometrical powers of increase of each species, at some age, season, or year, a severe struggle for life, and this certainly cannot be disputed; then, considering the infinite complexity of the relations of all organic beings to each other and to their conditions of existence, causing an infinite diversity in structure, constitution, and habits, to be advantageous to them, I think it would be a most extraordinary fact if no variation ever had occurred useful to each being's own welfare, in the same way as so many variations have occurred useful to man. But if variations useful to any organic being do occur, assuredly individuals thus characterised will have the best chance of being preserved in the struggle for life; and from the strong principle of inheritance they will tend to produce offspring similarly characterised. This principle of preservation, I have called, for the sake of brevity, Natural Selection. Natural selection, on the principle of qualities being inherited at corresponding ages, can modify the egg, seed, or young, as easily as the adult. Among many animals, sexual selection will give its aid to ordinary selection, by assuring to the most vigorous and best adapted males the greatest number of offspring. Sexual selection will also give characters useful to the males alone, in their struggles with other males.

Ten years later, in 1871, the German philosopher Schopenhauer remarked (as quoted by Darwin):

The final aim of all love intrigues, be they comic or tragic, is really of more importance than all other ends in human life. What it all turns upon is nothing less than the composition of the next generation. . . . It is not the weal or woe of any one individual, but that of the human race to come, which is here at stake.

C. LIFE-HISTORY THEORY

In simple words, then, the theory of evolution by natural selection claims that the process that causes heritable traits that are helpful for survival and reproduction ("fitness" in the evolutionary jargon—the number of descendents that an organism produces) becomes more common, and harmful traits become rarer. Adaptation occurs through the gradual modification of existing structures. It seemed worthwhile to try to see how far the principles of evolution would throw light on a matter as complex as child growth and maturation.

Variations among species in life history such as growth, maturation, and fertility are extreme. Some species mature within a year of birth and allocate up to 50% of their body mass to reproduction, whereas others take several decades before reproducing and allocate just a small percentage of their body mass to each reproductive episode. Anthropologists attempt to explain how the human species has survived in the face of its unique and apparently impossible life history: a helpless newborn with a short duration of breast-feeding; an extended childhood when the offspring are still dependent for protection and food provision on parental and others' assistance; a juvenile period when they mostly provide for and are able to look after themselves, and when competition with adults for food and space is possible only because the offspring are sexually immature and remain small in size; an energycostly adolescent growth spurt; delayed reproduction into the third and fourth decades of life; menopause, and a uniquely long postmenopausal life.

Life-history evolutionary theory seeks to understand the factors that produce variations in life stages that are found both among and within species. It is another holistic attempt to integrate a wide range of observations of life in human societies; it encompasses the integration of all fields of biology at the molecular, cellular, and organism levels with social sciences, anthropology, evolutionary biology, and psychology, and more recently, clinical medicine. Using a life-history approach, we consider the ways that evolution has worked upon these life stages to produce the adaptations of a society way of life to its environment.

In the case of hominids, it is best understood in the context of biological rationale and cultural expressions as a solution to an ecological problem posed by the environment and subject to constraints intrinsic to humans (Smith 1992). Among the questions posed in life history research are: Why are organisms small or large? Why do they mature early or late? Why do they have few or many offspring? Why do they have a short or a long life span? Why do they grow old and die at a particular age? This treatise is an attempt to use life-history theory in the understanding of child growth and maturation in a broad evolutionary perspective with a special emphasis on the clinical aspects of this theory.

Two essential assumptions of life-history theory are: (1) there are set measures of fitness (a combination of survivorship and reproductive rate; individuals with

higher fitness propagate more genes to future generations) that are maximized by natural selection, and (2) these are often associated by trade-offs among traits that limit the adaptive potential of a population concurrently or at a later time. Thus, species that maximize life-history traits, such as fertility, typically cannot simultaneously maximize survival, and in the growth domain, species that maximize offspring size cannot maximize offspring number at the same time. Survival is affected among other by investment in immune function and adipose deposits, whereas body size is achieved by, among other things, the function of the growth hormone–insulin-like growth factor-I axis. The latter stimulates growth size, while at the same time depletes adipose depots and suppresses immune function and affects survival. Indeed, transgenic animal studies have shown that excess growth hormone shortens the life span and growth hormone deficiency prolongs it. Thus, a trade-off exists between body size and survival.

D. EVOLUTIONARY PERSPECTIVE IN CHILD GROWTH AND MATURATION

Growth and maturation have strong effects on an individual's fitness, because they affect the individual's reproductive potential, schedule, and efficiency (Stearns 2000). When comparing the growth of a human child with that of a cat, or even that of great apes,¹ the pattern difference is obvious (Fig. 1.D.1). The concave pattern



Fig. 1.D.1. The unique human growth pattern and its energetic resources. Left panel: Lifetime resources allocation in Gambian women. Growth requires as much as a third of the lifetime energy allocation. Right panel: Human height pattern (H, bold line) is compared to cat's weight (F, thin line), and gorilla's weight (G, dotted line). The concave pattern of accelerating infantile growth of both cats and apes is in contrast to the convex pattern of decelerating infantile growth in humans. Note also the brisk growth acceleration during human adolescence. Data from Bogin (1999a).

¹Members of the family *Hominins* consist of humans, orangutans, gorillas, and chimpanzees.



Fig. 1.D.2. The evolution of hominid life history during the first 20 years of life. The existence time is given below [kya (thousands of years ago), mya (millions of years ago)] and the longevity (above). During the evolution of hominids, childhood and adolescence have been added as new life-history stages as compared with apes and presumably the early hominid *Australophithecus afarensis*. The chimpanzee serves as a living representative of the assumed *Australophithecus afarensis* life history. As childhood emerged and prolonged, infancy has gradually cut shorter, and the latest introduced adolescence came at the expense of a shorter juvenility.

(initially slow and accelerating) of nonhuman mammals during their early growth is strikingly different from the convex (initially fast) human growth, followed by a linear growth pattern. This is produced by the uniquely decelerating human infantile growth and the quasi-linear childhood stage.

Whereas several human growth processes are identical to those found in the animal kingdom, hominids' life history is markedly different (Fig. 1.D.2). Humans are born immature, helpless, and defenseless; have a relatively short period of infancy; and are the only species that has a childhood—a biologically and behaviorally distinct and relatively stable growth interval between infancy and the juvenile period that follows. We are also the only species to have true adolescence as a period devoted to puberty and accelerated growth.

Analysis of the height velocity (centimeters per year) in healthy boys and girls of Western European ethnicity, who subsequently become tall or short as adults, reveals the pattern when growth deviates (Fig. 1.D.3). Much of the difference is established early in life during infancy, and some during childhood, where the timing of puberty has minimal impact on ultimate adult height.

The transition from one life-history stage to the next requires a switch mechanism for the onset of the latter, and these switches speak the language of endocrinology, as shown in Fig. 1.D.4 for the sex hormones. Note the rise in sex hormones in early infancy, the so-called mini-puberty, while childhood is characterized by quiescence of sex hormones, followed by a juvenile increase of adrenal androgens, and adolescent increase in gonadotropines and gonadal sex hormones, manifesting as puberty. It is hormones that transduce environmental information to regulate transitions between life-history stages (Hochberg 2009). Indeed, most hormones



Fig. 1.D.3. Tall and short children. Normative height velocity (centimeters per year) data in healthy boys (upper panel) and girls (lower panel) of Western European ethnicity, who subsequently become tall (solid line) or short (dotted line) as adults. Notice that much of the difference is established early in life during infancy and childhood. Data from Veldhuis, Roemmich et al. (2005).



Fig. 1.D.4. Changing sex hormones levels during the first 20 years of human life history. Lifehistory stages of boys and girls (upper panel) may be defined by sex hormone levels (lower panel). Note the rise in sex hormones in early infancy, the so-called mini-puberty. Childhood is characterized by quiescence of sex hormones, followed by a juvenile increase of adrenal androgens, and adolescent increase in gonadotropine and gonadal sex hormones, manifesting as puberty.

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have pleiotropic² and often antagonistic effects on a variety of behavioral, physiological, and morphological traits. Multiple hormone mechanisms may have evolved to activate behavioral and physiological traits at the right time and in the correct context. When traits are expressed throughout the life cycle, hormones may potentially deactivate them for short periods.

E. CHILD GROWTH AND THE ENVIRONMENT

Charles Darwin, in his *The Descent of Man*, cites the 1869 report of over 1 million U.S. soldiers, who served in the "late war" and were measured, and the states in which they were born and reared were recorded. (B.A. Gould, *Investigations in Military and Anthropology Statistics*, 1869). From this astonishing number of observations it was proven that local influences of some kind act directly on stature; and we further learn that "the State where the physical growth has in great measure taken place, and the State of birth, which indicates the ancestry, seem to exert a marked influence on the stature."

For instance, it is established "that residence in the Western States, during the years of growth, tends to produce increase of stature." On the other hand, it is certain that with sailors, their life delays growth, as shown "by the great difference between the statures of soldiers and sailors at the ages of seventeen and eighteen years." Gould endeavored to ascertain the nature of the influences that thus act on stature, but he arrived only at negative results, namely that they did not relate to climate, the elevation of the land, soil, nor even "in any controlling degree" to the abundance or the need of the comforts of life:

When we compare the differences in stature between the Polynesian chiefs and the lower orders within the same islands, or between the inhabitants of the fertile volcanic and low barren coral islands of the same ocean (Prichard's 'Physical History of Mankind,' 1847).

Darwin continues to quote the same source that there was also a remarkable difference in appearance between the closely allied "Hindoos" inhabiting the Upper Ganges and Bengal or again between the Fuegians on the eastern and western shores of their country, where the means of subsistence are very different: "It is scarcely possible to avoid the conclusion that better food and greater comfort do influence stature," and:

Dr. Beddoe has lately proved that, with the inhabitants of Britain, residence in towns and certain occupations have a deteriorating influence on height; and he infers that the result is to a certain extent inherited, as is likewise the case in the United States. Dr. Beddoe further believes that wherever a "race attains its maximum of physical evelopment, it rises highest in energy and moral vigour" ('Memoirs, Anthropological Society,' 1867–69).

With detailed investigations of organisms in their natural environment, one can determine the potential ecological costs and benefits underlying hormone–physiology–behavior interactions that, in turn, shed light on their evolution. Such

²A single factor (or gene) influences multiple phenotypic traits. Consequently, a mutation in the gene will have a simultaneous effect on all traits.

data also indicate a number of problems, trends, and alternatives for hormonal control mechanisms, and hopefully in the future, a more complete understanding of the common mechanisms underlying behavioral–physiological interactions at the cellular and molecular level. Only then will we be able to predict when and where specific mechanisms of hormone-related interactions operate and how they evolved.

The expression "environment" means different things to different people. For sociologists and psychologists, the environment encompasses social group interactions, family dynamics, and maternal nurturing. For nutritionists, the environment refers to calories, food types, macro- and micronutrients, and dietary supplements, whereas toxicologists think of the environment in terms of water, soil, and air pollutants. However, only a few of these environmental influences have been shown to cause DNA sequence mutations and explain altered gene expression or increases in disease frequency in a particular region (Li, Xiao et al. 2002). Evidence is accumulating that all these very different types of environments are able to alter gene expression and change phenotype by modifying the epigenome (more on epigenetic-mediated plasticity in Chapter 10, Section B). Moreover, when these environmentally induced-epigenetic adaptations occur at crucial stages of life, they can potentially change behavior, disease susceptibility, and survival (Jirtle and Skinner 2007).

Hormonal changes are evident in transitions from one life-history stage to the next. The transition from infancy to childhood is associated with the setting in of the dominance of the growth hormone–insulin-like growth factor-I axis. The transition into juvenility requires the development of androgen-generating adrenal reticularis. The beginning of adolescent-related puberty is evidently a function of the maturation of the hypothalamic–pituitary–gonadal axis. Evolutionary fitness with regard to hormones requires avoiding potential costs and penalties for hormones that are secreted at inappropriate times. Thus, for example, precocious puberty comes at the cost of a loss in ultimate adult height and a "punishment" in the form of psychological and social derisions.

F. HETEROCHRONY AND ALLOMETRY

Evolutionists speak of "allometry" and "heterochrony" in the process of natural selection. The former implies the pattern of covariation among several morphological traits, such as height and head circumference, or between measures of size and shape, such as the growing human cranium and receding mandible. Unlike heterochrony, allometry does not deal with time explicitly.

Heterochrony is the comparison of ontogenetic trajectories between two species representing ancestors and descendants (Gould 1977), such as the shorter infancy in *Homo sapiens* as compared to our ancestors or the ever-growing size of hominids. The dimension of time is therefore an essential part in studies of heterochrony. In the theory of heterochrony, the end point of ontogeny can be altered by the selection of two initial parameters of development: allometric relationship and relative timing for the onset (or offset) of developmental events.

Both heterochrony and allometry are pertinent to understanding child growth and the evolutionary impact and will be used throughout this treatise to understand growth patterns as the child grows through his life-history stages and transitions from infancy to childhood, then to juvenility, and to adolescence and adulthood. This treatise presents the data and theory of evolutionary predictive adaptive growth-related strategies for transition from one life-history stage to the next and the inherent adaptive plasticity in the heterochrony of such transitions in order to match mostly energy supplies, but also other environmental cues.

G. ADAPTIVE PLASTICITY IN LIFE HISTORY

Phenotypic plasticity is the process by which organisms alter development, physiology and growth, as well as behaviors in response to cues. These responses feature an assessment of both external and internal factors. Physiological sensors compute adaptive trade-offs as a function of energy resources, stress and other signals, and effectors initiate physiological, developmental, and behavioral responses to these determinants. The central nervous system, neuroendocrine circuits, and hormones are critical to growth maturation and development.

I propose the following periods of adaptive plasticity in human's life-history strategies that are related to transitions in life-history stages and child growth:

- Shorter or longer gestation is a plasticity provided as an adaptation for the intrauterine environment, reflected in later metabolic tuning. Thus, among other factors, both preterm and post-term infants are prone to obesity.
- Humans evolved to withstand energy crises by decreasing their body size, and evolutionary short-term adaptations to energy crises utilize a plasticity that modifies the timing of transition from infancy into childhood. A delay in this growth transition, which we refer to as "delayed infancy-childhood transition" (DICT) (see Chapter 4, Section E), has a lifelong impact on stature and is responsible for as many as 50% of children with a normal birth weight and no endocrine disease, who are referred to pediatric endocrine clinics as suffering from "idiopathic" short stature.
- The transition to juvenility is part of a strategy in the transition from the childhood stage of total dependence on the family and tribe for provision and security until self-supply and a degree of adaptive plasticity is provided and determines body composition. It is associated with specific brain effects of the juvenility hormone dehydroepiandrosterone-sulfate (DHEAS) and changes in body proportions.
- The transition to adolescence entails plasticity in adapting to energy resources, other environmental cues, social needs of adolescence, and the maturation to determine the period of fecundity, fertility, and longevity.

Focusing on child growth, this treatise does not cover the transition from adolescence to adulthood, although it certainly entails a degree of adaptive plasticity. This treatise will further postulate that whereas evolutionary fitness is achieved by the interplay of our entire genome and its expression, life-history stages utilize hormones as a major tool and provide distinct periods of adaptive plasticity in setting in and off of life-history-specific endocrine mechanisms to modify body structures and behaviors. The aim of this text is to discuss the implications of this evolutionary–endocrine–anthropological framework for theory building and new research directions.