THE FALLING AGE OF PUBERTY IN U.S. GIRLS:

What We Know, What We Need To Know

by Sandra Steingraber, Ph.D.

This paper is dedicated to the memories of Catherine Cauffield, physician, and Deborah Tall, poet, who both died of breast cancer during the writing of this paper. From each of you, I learned much. May this work stand as a small gesture of my abiding gratitude.

— Sandra Steingraber

AUGUST 2007

ACKNOWLEDGMENTS

EDITORIAL TEAM

Sandra Steingraber, Ph.D.
Writer

Jeanne Rizzo, R.N.
Executive Director, Breast Cancer Fund

Nancy Evans
Health Science Consultant, Breast Cancer Fund

Kevin Donegan
Director of Communications, Breast Cancer Fund

Janet Nudelman
Director of Program and Policy, Breast Cancer Fund

Brynn Taylor
Program Manager, Breast Cancer Fund

Marisa Walker
Senior Communications Coordinator, Breast Cancer Fund

Dana Oshiro
Communications Associate, Breast Cancer Fund

Design and Production
Fiona Burgess, FiBu Design

Printing
Cooperative Print Solutions

ACKNOWLEDGMENTS

A NOTE FROM JEANNE RIZZO, R.N.,
BREAST CANCER FUND EXECUTIVE DIRECTOR

Over the past few years, studies have revealed that girls as young as two are entering puberty. The reports and images are deeply disturbing. For breast cancer advocates, there is something else that is disturbing: early puberty increases breast cancer risk. When puberty arrives earlier the window of exposure to estrogen opens wider and increases a girl's risk of getting breast cancer later in life.

As a breast cancer organization focused solely on prevention, the Breast Cancer Fund knew it needed to explore this phenomenon. What do we know? What are the possible causes of early puberty? What differences exist among girls of different races? What does it mean for the mental and physical health of our girls as they age? We needed to take a walk upstream to understand the intricacies of puberty.

As an author, biologist and cancer survivor, Sandra Steingraber has walked thousands of readers upstream to illuminate the connections between our health and the environment. She has been called the "poet laureate of the environmental health movement," as well as the Rachel Carson of our generation. Dr. Steingraber shares Carson's gift for crafting vivid images that clarify complex concepts. Who better to help us sort through the phenomenon of early puberty?

In *The Falling Age of Puberty*—the first comprehensive review of the scientific literature on the timing of puberty—Dr. Steingraber explores pubertal development and outlines nutritional, psychosocial and environmental factors that contribute to its timing. She focuses on areas where there is sufficient evidence for us to take public policy action now to protect the health of our girls in the future. And further, she identifies where more research is required.

Is the trend toward earlier puberty beyond our control? We don't believe so. Rather, we believe a greater understanding of this changing biology will lead to precautionary action and exposure reduction that could reverse this trend.

At the Breast Cancer Fund, a national environmental health organization with the sole mission of preventing this devastating disease, we remain committed to eliminating environmental exposures to endocrine-disrupting chemicals— many that mimic estrogen in the body and some that can trigger early puberty—through public policy initiatives and corporate accountability campaigns. We also continue to advocate for research to understand the mechanisms by which synthetic chemicals in the environment trigger early puberty and how early puberty, in turn, increases breast cancer risk.

Due to the multiple influences on early puberty, it is imperative that we work closely with our colleagues in children's health, women's health and environmental health, as well as build new collaborations with those specialists working on the nutritional, behavioral and psychosocial influences on early puberty.

We hope you will join this conversation on the falling age of puberty and join the Breast Cancer Fund as we advocate for change that will protect the health of our children today and in the future.

We are indebted to Dr. Steingraber for her important contribution to our knowledge, and are grateful to reviewers for their dedication to this paper and to the foundations and supporters of the Breast Cancer Fund for providing us with the resources to bring this to the public.

TABLE OF CONTENTS

"Don't try to make me grow up before my time, Meg: it's hard enough to have you change all of a sudden; let me be a little girl as long as I can."

— Jo, age 15, to Meg, age 16, in Little Women *by Louisa May Alcott (1868)*

PREFACE

Why this report?

Early puberty—in particular, early menarche—is a known risk factor for breast cancer. This association has spurred interest within the research community in understanding more about the development of the normal breast as well as the neuro-hormonal mechanism that governs the onset of its pubertal growth. The resulting inquiry has taken on new urgency with the publication of recent studies showing that the advent of breast budding—one of the earliest visible signs of puberty—appears to be arriving earlier and earlier in the lives of U.S. girls. We need to know why.

This report is a review of the published literature on the timing of puberty in U.S. girls. It describes the basic biology of puberty, identifies the various determinants that seem to influence its onset and explores their possible interactions. It is not intended to be exhaustive but instead to spotlight new discoveries and findings in the hope they will inspire fresh ideas for research and show us where to take precautionary action now. Because the potential influences on puberty are manifold and diverse, this report is necessarily interdisciplinary and gathers findings from divergent fields of study. Predictably, it draws on studies from epidemiology, endocrinology, toxicology and evolutionary biology. But it also references publications in sociology, child development, nutrition, veterinary medicine, media studies

and anthropology. (It may contain one of the very few bibliographies in which citations from *Frontiers in Neuroendocrinology* stand next to those from *Journal of Research in Crime and Delinquency.*)

As a biologist, I'm accustomed to distinguishing cause from consequence and consequence from covariable. But in the puberty story, so many variables are interwoven and interdependent that, as I began to trace the threads of causality to their beginning points, I sometimes felt as though I were caught in a Mobius strip. For example, obesity raises the risk of early puberty in girls, but weight gain itself is a consequence of early pubertal development. And risks for both obesity and early puberty are raised by being born too small or too soon—risks which are modulated by maternal exposure to certain environmental chemicals during pregnancy. The intricate interrelationships among pubertal determinants made the organization of this report tricky. Thus, even as I strove to isolate each variable and discuss its relative importance, I found it necessary to return to particular topics several times and in several different contexts. My analysis is deliberately open-ended and suggestive in tone.

This report is written primarily for physicians and researchers who wish to know more about the various aspects of pubertal timing but who may not have the luxury of reading so broadly in the literature. But it is also written for the lay

public and, as such, it attempts to bring plainspoken English to some very complicated neuroendocrinology without doing a disservice to either the language or the science. As a mother of an eight-year-old daughter, I am dedicated to the idea that science should be accessible to all. Readers with less scientific training are invited to tarry in the glossary and in the "Overview of Pubertal Events," which were both written with you in mind. My citations include both primary references and, whenever possible, literature reviews and books from the popular press. The latter may be more accessible to non-scientists who wish to pursue the topic further.

A final note on language: I intentionally use the word "black" rather than "African American" when describing ethnic and racial disparities in pubertal timing because "black" is the demographic category used in such studies. In describing other types of studies, I use "African American." The terms "black" and "African American" are not always synonymous and I have retained the language of the original researchers.

— Sandra Steingraber
Ithaca, New York, June 2007

Girls get their first periods, on average, a few months earlier than girls 40 years ago, but they get their breasts one to two years earlier… The childhoods of U.S. girls have been significantly shortened.

In girls, puberty involves the activation of a signaling pathway that begins in the brain and awakens the ovaries, which begin secreting estradiol. The result is breast development (thelarche) and onset of menstruation (menarche). A second signaling pathway stimulates the adrenal gland, which begins androgen production. The result is pubic hair growth (pubarche). Thelarche and pubarche are early events in pubertal development, while menarche is a late-stage event. Puberty actually occurs twice in human development: its hormonal circuitry is first turned on in utero and then switched off again a few months after birth. The function of "infant puberty" is unclear, but it may prepare the endocrine system for its reactivation in adolescence. Thus, a search for the causes of early adolescent puberty must begin in prenatal life and infancy.

WHAT WE KNOW ABOUT PUBERTAL TIME TRENDS

Thelarche and menarche are occurring earlier and earlier in the lives of U.S. girls, but the age of thelarche is falling more rapidly than the age of menarche. Girls get their first periods, on average, a few months earlier than did girls 40 years ago. But they get their breasts, on average, one to two years earlier. Over the course of just a few decades, the childhoods of U.S. girls have been significantly shortened.

The average age of menarche among U.S. girls declined steadily throughout the first half of the 20th century and continued to decline after that but at rates that differ markedly among racial and ethnic groups. Among U.S. white girls, the average menarchal age has declined slightly over the past four decades and now stands at 12.6 years. Among U.S black girls, average menarchal age is 12.1 years and the ongoing rate of decline is swifter. This is also true among Mexican American girls. Similarly, the average age of thelarche and pubarche, the first clinical signs of pubertal onset, have continued to fall among all groups and with significant ethnic/racial differences. About half of all U.S. girls show signs of breast development by their 10th birthday, with 14 percent attaining breast buds between their eighth and ninth birthdays.

About half of all U.S. girls show signs of breast development by their 10th birthday, with 14 percent attaining breast buds between their eighth and ninth birthdays.

Although studies differ somewhat in their findings, the mean age of thelarche is about 10 for white girls and 9 for black girls. Pubertal onset and menarche are apparently not as tightly coupled to each other as in years past. However, the data quality on onset of thelarche and pubarche, and their changes over time, is not as reliable as that for menarche.

With its multitude of signaling pathways, the neuroendocrine apparatus by which pubertal onset is controlled is inherently susceptible to disruption.

WHAT WE KNOW ABOUT THE CONTROL OF PUBERTAL TIMING

The brain is the driving force that controls thelarche and menarche through the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. The GnRH-secreting neurons (of which there are about 1,000) are themselves regulated by a plethora of chemical cues. Some of these are hormones, some are enzymes and some are neurotransmitters.

Hormones that play a role in stimulating GnRH neurons include leptin, which is produced by body fat, and kisspeptin, which is produced by neurons in the forebrain and appears to act as the central processor. Leptin and kisspeptin appear to interact. Melatonin is an inhibitory signal that responds to light and dark cycles and may also interact with kisspeptin. Insulin and the enzyme aromatase are influential as well. New evidence points to an interactive role for insulin-like growth factor and estradiol.

Also modulating the hormonal drumbeat of the hypothalamus are many neurotransmitters. Two of the most important are gamma-aminobutyric acid (GABA), which is an inhibitory signal, and glutamate, which is an excitatory signal.

Far less is known about the triggering mechanism of pubarche.

WHAT WE KNOW ABOUT RISK FACTORS FOR EARLY PUBERTY

With its multitude of signaling pathways, the neuroendocrine apparatus by which pubertal onset is controlled is inherently susceptible to disruption. Several upstream factors can potentially alter the regulation of the GnRH-secreting neurons and thereby hasten the onset of puberty in girls. These include low birth weight and premature birth; overweight and obesity; and environmental exposures to endocrine-disrupting chemicals. Other factors currently under investigation include formula feeding in infancy; physical inactivity; psychosocial stressors, including father absence and family dysfunction; and television viewing and media use.

Obesity, which has tripled in prevalence among children over the past three decades, is an endocrine disruptor. Obesity dramatically alters insulin, leptin and aromatase levels. Chubby girls tend to reach thelarche sooner than lean girls. But obesity is a consequence of early puberty as well as a contributor. Its role in accelerating thelarche and pubarche is not clear. A potential behavioral pathway by which obesity may lead to early puberty is via increased calorie intake, physical inactivity and television viewing. The association between adverse health behaviors and early puberty makes biological sense. For example, television viewing appears to depress melatonin levels. Evidence does not exist to answer questions about the possible effect of sexualized media

Obesity, which has tripled in prevalence among children over the past three decades, is an endocrine disruptor.

messages on pubertal timing. Breast milk, which contains melatonin as well as fewer calories than infant formula, appears protective against early puberty, but this finding requires further confirmation.

Premature birth and intrauterine growth retardation are also endocrine-altering events that raise the risk for early pubarche. Here, hyperinsulinism and cortisol appear to play a role. Preterm birth and low birth weight, in turn, may be influenced by chemical exposures of the mother (among other important factors).

Psychosocial stressors are also endocrine disruptors that hasten pubertal onset. Family dysfunction and father absence are consistently associated with earlier puberty. Underlying mechanisms require further evaluation.

Evidence suggests that exposures to endocrine-disrupting chemicals also are playing a role in accelerating puberty in girls. The recent demonstration that endogenous levels of estradiol in prepubertal girls are many times lower than previously thought suggests that very small perturbations in levels of sex hormones may have disproportionately adverse effects during childhood. Accidental exposures of girls to known estrogenic chemicals—including polybrominated biphenyls (PBBs) and estrogen creams—have led to demonstrable changes in the timing of sexual maturation. Geographic clusters of early puberty suggest, but do not prove, environmental determinants. Evidence does not exist to answer questions about the speculated connection between early puberty and growth hormones in milk or meat, but there are reasons for concern. Data do indicate that exposure to lead delays puberty while exposure to secondhand tobacco smoke accelerates it. Experimental studies demonstrate that environmental chemical exposures can advance

pubertal onset in laboratory animals at doses to which human children are routinely exposed. Detailed understanding about human effects is hampered by lack of basic chemical safety testing, lack of biomonitoring in human populations and lack of large-scale, longitudinal studies.

WHAT WE KNOW FROM EVOLUTIONARY STUDIES

The reactivity of pubertal timing to environmental signals has a long evolutionary history. In all female mammals, sexual maturation is a trait that responds to cues about both the internal environment of the organism (in particular, its nutritional and immune status) and the external environment it inhabits (in particular, availability of food, a suitable mate and shelter). Both must be favorable for successful reproduction, which, in female mammals, requires an immense commitment of calories and nutrients as resources are diverted to the tasks of making babies, giving birth, making milk and parental care. The contribution of male mammals to reproduction is typically far less.

Against this backdrop, the declining age of menarche in the first half of the 20th century resembles an extension of a natural process: human females developed the ability to reproduce at younger ages in response to less disease and plentiful calories, and environmental conditions of the day accelerated that trend. More recent trends, however, suggest that girls' endocrine systems are also being subtly rewired by stimuli other than good health and sufficient food and that early breast and pubic hair development is a coincidental, non-adaptive outcome.

Evidence suggests that exposures to endocrine-disrupting chemicals are also playing a role in accelerating puberty in girls

WHAT WE KNOW ABOUT THE CONSEQUENCES OF EARLY PUBERTY

Early puberty poses several risks for girls. It raises the risk for breast cancer and is associated with many high-risk behaviors in later adolescence—such as smoking, drinking, drugs, crime and unprotected sex—that have potential life-long consequences. Early-maturing girls are also more likely to suffer violent victimization and psychopathologies such as depression and anxiety. It is not clear whether the social or physiological experience of pubertal change is responsible for these negative outcomes. In either case, interventions that reverse the trend toward ever-earlier puberty in girls are a public health imperative.

WHAT WE NEED TO KNOW

Future research and activism should focus on six areas.

First, the proximate triggers of pubertal maturation in girls require further explication. Epidemiologists need to partner with neuroendocrinologists to identify the full suite of hormones, growth factors, enzymes and neurotransmitters that influence the process of sexual maturation and that may help explain the ethnic and racial disparities in pubertal timing of U.S. girls as well the changing tempo of puberty.

Second, the function of infant puberty—especially as it may prime the circuitry of reproduction—requires further investigation.

Third, longitudinal studies are required to confirm or refute the time trends of pubertal maturation that seem apparent in recent cross-sectional studies, all of which suffer from methodological shortcomings. The National Children's Study, which proposes to follow 100,000 children from birth to age 21, is designed to meet this need.

Fourth, chemicals in commercial use need to be routinely screened for their ability to disrupt the endocrine system. Ongoing ignorance about the extent to which chemical exposures are altering the timing of sexual maturation in children is directly attributable to a lack of basic data on the ability of common chemicals to act as endocrine disruptors. (The U.S. Environmental Protection Agency's Endocrine Disruptor Screening Program was initiated in response to a 1996 directive from Congress to develop a basic screening assay for such chemicals, but the program has been crippled by funding problems and the repeated disbanding of its advisory panel.)

Fifth, right-to-know laws about toxic exposures must be expanded. In order to prevent children's exposures to endocrine-disrupting chemicals, physicians and public health researchers need to know more about the sources, emissions and fate of such chemicals in commercial use. Chemical ingredients in consumer products and their sources should be fully disclosed. Inventories of emissions and monitoring of important routes of exposure—such as air, food and drinking water—should be comprehensive. With such data collected in a complete, accessible and specific way, we would be better able to prevent exposures in humans before they occur. (At this writing, the Toxics Release Inventory, the lynchpin of the Emergency Planning and Community Right-to-Know Act, is set to be scaled back by the U.S. Environmental Protection Agency.)

Lastly, biomonitoring programs need to measure levels of endocrine-disrupting substances in a representative sample of infants,

children and women. The California statewide biomonitoring program holds particular promise for meeting this need. However, because biomonitoring depends on people already exposed to chemical contaminants, it's critical that the California program, as well as other state biomonitoring programs, collect information about sources of exposure that can be matched up with biomonitoring data.

WHAT WE CAN DO NOW

Many actions can be taken on the basis of what is already known.

Strategies to tackle child obesity and inactivity include changes to the built environment that encourage exercise; the resurrection of daily physical education in school; the elimination of high-calorie, low-nutrient foods from school lunch programs and school activities; the development of school and community gardens; the establishment of urban farmers' markets; and partnerships between local farmers and neighborhood supermarkets to provide fresh, local produce in low-income communities. One obesity-prevention program in Boston-area schools already has demonstrated that coordinated efforts to promote healthy eating, increase physical activity and decrease television viewing have the power to delay menarche in sixth- and seventh-grade girls.

In addition to having both good nutrition and

access to prenatal care, strategies to lower rates of preterm and low-weight births include eliminating exposure to tobacco smoke, chemical solvents, sources of air pollution and mercury contamination.

Strategies to lower the burden of endocrine-disrupting chemicals to which girls have documented exposures include phase-outs of phthalates and bisphenol A; investments in organic agriculture; watershed protection; and non-chemical pest control in homes, schools and daycare centers.

Strategies to lower the combined burden of psychosocial, socioeconomic and environmental stressors—which disproportionately affect poor and minority communities, especially African American communities—require community-based solutions, as identified by the National Environmental Justice Advisory Board.

Early puberty is a problem that does not arise from a single toxicant, lifestyle or dietary shortcoming. Rather, many different environmental stressors—some psychosocial, some nutritional, some chemical—interact in the bodies of young girls in ways that result in accelerated sexual maturation with its attendant risks for health and well-being.

One program in the Boston area has already demonstrated that coordinated efforts to promote healthy eating, increase physical activity and decrease television viewing can delay menarche in girls.

Adrenarche: Maturation of the adrenal gland that results in secretion of androgens from the adrenal cortex. Regulated by the HPA axis but activated by unknown factors, adrenarche occurs independently of gonadal maturation and breast development and leads to…

Biomonitoring: Evaluating chemical body burden by measuring levels of contaminants in urine, blood, hair or other human tissue.

Endocrine disruptor: A chemical agent that interferes with the synthesis, secretion, transport, binding, action or elimination of natural hormones in the body.

Gonadarche: Maturation of the gonads (ovaries in girls) that results in a dramatic increase in sex hormone production (estradiol in girls). Gonadarche is the result of the activation of the HPG axis and indicates that puberty has commenced. Gonadarche is less visible in girls than boys.

HPA axis: Hypothalamus-pituitary-adrenal axis. A second signaling pathway involved in puberty. The HPA axis permits the production of steroidal hormones from the adrenal glands (which sit atop the kidneys). These hormones include androgens.

HPG axis: Hypothalamus-pituitary-gonadal axis. This signaling pathway regulates the production of sex hormones by sending chemical messages from the hypothalamus in the brain to the pituitary gland and then, in girls, to the ovary. Its activation marks the onset of puberty.

Infant puberty (also known as "mini puberty"): The period of early development (from late prenatal life through 3 to 9 months) when the HPG axis is active and prior to its repression during the juvenile period. Sex hormones are produced during infant puberty. Unlike adolescent puberty, infant puberty is not tightly regulated.

Insulin resistance: Occurs when increasing amounts of insulin are needed to transport blood glucose into body tissues. The result is hyperinsulinism. Often a precursor of type 2 diabetes.

Isolated premature thelarche: Breast development without activation of the HPG axis and in the absence of gonadarche in girls younger than 7. Isolated premature thelarche may or may not raise the risk for true precocious puberty. The self-limiting or progressive nature of this condition is a matter of ongoing debate (Salardi, 1998).

Menarche: Onset of menstruation and a consequence of estradiol stimulation. It is a late-stage event in the pubertal process. Along with thelarche, menarche is a consequence of HPG activation.

Precocious puberty: Signs of sexual maturation that appear at an age that is more than two standard deviations below the mean. True precocious puberty refers to premature activation of the HPG axis that initiates gonadarche and thelarche. True precocious puberty is five times more common in girls than boys. In the past, true precocious puberty was defined as onset of gonadarche and thelarche before age 8, which was considered the lower limit for normal puberty in girls. In 1999 in the United States, these age limits were revised downward to 7 years old for white girls and 6 years old for black girls (Kaplowitz and Oberfield, 1999).

Pubarche: Appearance of pubic and underarm hair, adult body odor, increased oiliness of skin and hair and, sometimes, acne.

Thelarche: Onset of breast development, also called "breast budding." It is a physical consequence of gonadarche and an early visible event in pubertal development.

INTRODUCTION

OVERVIEW OF PUBERTAL EVENTS

Puberty is the attainment of fertility. As such, it is a narrower phenomenon than adolescence, which refers more generally to the psychological, emotional and social experiences—as well as the physical changes—of teenage life (Ebling, 2005; Grumbach and Styne, 2003; Pinyerd and Zipf, 2005; Sisk and Zehr, 2005). Puberty is not, however, a single biological event. Rather, it is a parade of hormonally-driven changes that, for girls, commences at about the end of the first decade of life and unfolds over a period of about 4.5 years (Pinyerd and Zipf, 2005).

During this time, many changes occur. In girls, puberty begins with a growth spurt (Grumbach and Styne, 2003). It continues with the onset of breast development (thelarche) and the appearance of pubic hair (pubarche), and it culminates with the advent of menstruation (menarche) and ovulation, which typically follows the first menstrual period by about 10 months (Papathanasiou and Hadjiathanasiou, 2006). Along the way, the pelvis widens, fat accumulates under the skin and over the mons pubis and the skin becomes oilier (Ellis, 2004; Grumbach and Styne, 2003). Less visible anatomical changes also occur during puberty: the vagina lengthens (from about 3 to 4.3 inches), the ovaries grow ten-fold in size and the uterus inflates in the manner of a party balloon—expanding from a small tube into a plum-shaped structure and more than doubling in length. The clitoris likewise enlarges, while the vulval labia blanch from the shiny, red appearance of childhood to the paler pink of adulthood (Grumbach and Stein, 2003).

The brain is also transformed during puberty. New neuronal connections sprout and elaborate, and older pathways retract and are pruned away. New synapses form; others disappear. White matter increases in volume; gray matter decreases. Brain wave patterns change (Dorn and Rotenstein, 2004; Grumbach and Styne, 2003; Sisk and Zehr, 2005). Pubertal re-sculpting of the brain's circuitry is believed to make possible the emergence of abstract thinking, values, autonomy, adult social behaviors and the capacity to consider alternative viewpoints (Grumbach and Styne, 2003; Sisk and Zehr, 2005). The development of higher-order thought does not come without a price: during the course of sexual maturation, the brain loses plasticity and cognitive flexibility. The ability to assimilate complex new skills—such as playing a musical instrument, riding a bicycle or achieving athletic prowess—declines dramatically after puberty (Yun, 2004). After puberty, one can no longer learn to speak a foreign language without an accent (Grumbach and Styne, 2003). The brain's

ability to recover from injury also diminishes after puberty, along with the body's ability to heal without scar formation and regenerate hyaline cartilage (Yun, 2004).

Near the end of puberty, rising levels of estrogens close off the epiphyseal plates of the skeleton. These are the bands of cartilage that lengthen the long bones and thereby contribute to tallness. Once they have ossified, the pubertal growth spurt is over, and the girl has attained her final adult height. The jaw and the chin are the last bony elements to reach adult proportion (Golub, 2000).

THE HPG AXIS—GOVERNING THELARCHE

The signal that launches the above-described sequence of pubertal changes is gonadotropin-releasing hormone. GnRH is produced by the hypothalamus, that part of the brain that sits directly above the pituitary gland and directs its activity. More specifically, the pubertal process begins when GnRH is released in hourly pulses from a small group of about 1,000 specialized cells within the hypothalamus. These cells are called GnRH-secreting neurons (Hughes and Gore, 2007). In all mammals, GnRH is both necessary and sufficient to induce puberty (Ebling, 2005). That is, the administration of GnRH can, all by itself, trigger the events of puberty. Puberty will not occur in its absence. Released from the hypothalamus in intermittent bursts, GnRH is shuttled, via a portal blood system, to the pituitary gland. In response to these pulsating GnRH signals, the pituitary releases its two other hormones—follicle stimulating hormone (FSH) and luteinizing hormone (LH)—which then travel through the bloodstream to the ovaries. Here, they initiate a dramatic rise in the production of steroidal sex

HPG Axis – Governing Thelarche

GnRH — Hypothalamus, Pituitary Gland
FSH
LH
Breast Development (*thelarche*)
Estradiol (*gonadarche*)
Ovaries

HPA Axis – Permitting Pubarche through Unknown Pathway

CRH — Hypothalamus, Pituitary Gland
ACTH
Androgens (*adrenarche*)
Pubarche
Adrenal Cortex of Adrenal Gland
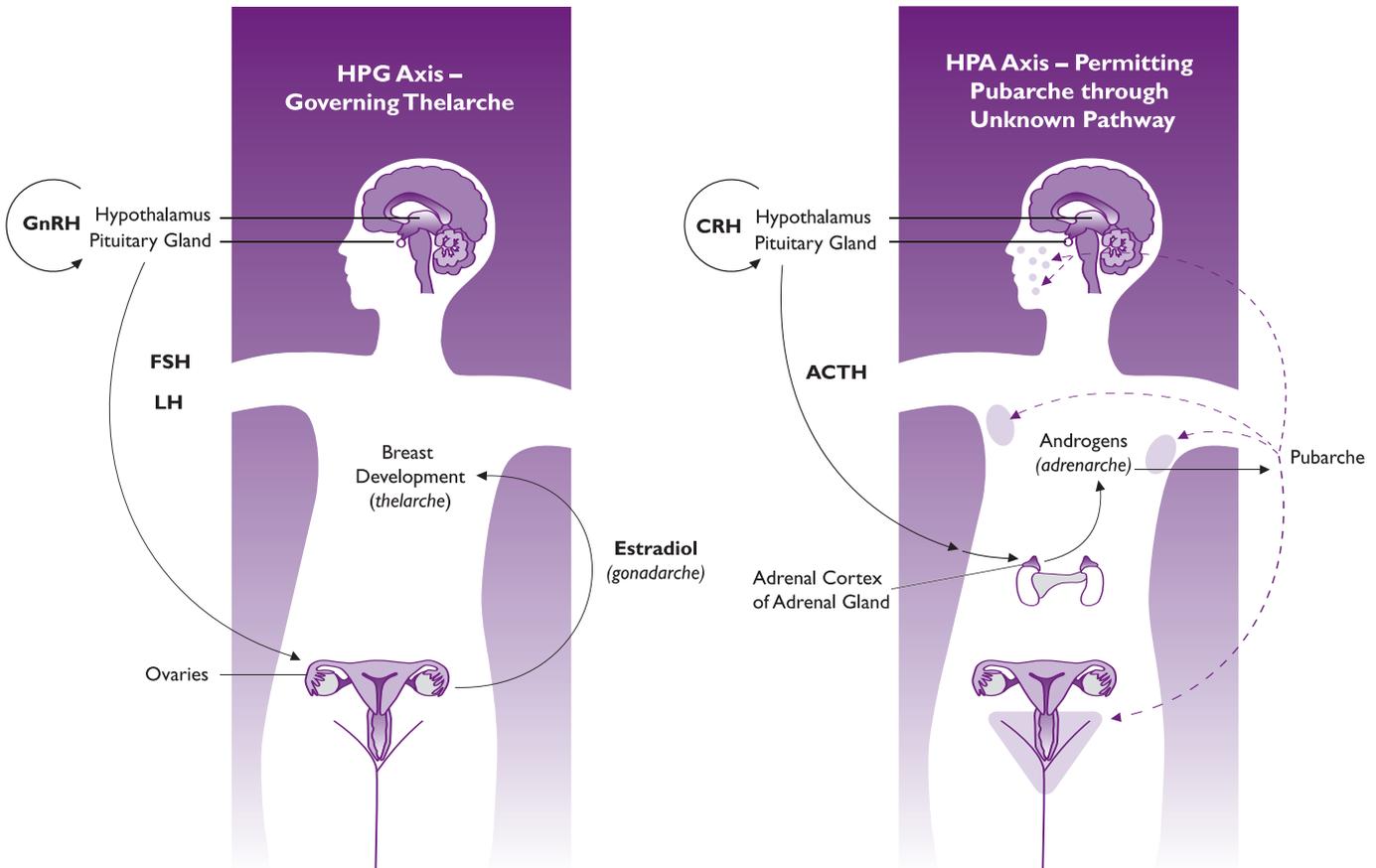
hormones, including a potent form of estrogen called estradiol. The maturation of the ovaries into estrogen-secreting glands (gonadarche) is the definitive event of puberty. Estradiol, in turn, initiates breast development, among other changes. In this way, puberty represents the mobilization of a hypothalamus-pituitary-gonadal circuit that is known as the HPG axis. The changes wrought by the actions of the HPG axis are not immutable. Puberty can be arrested or even reversed if the GnRH is removed from the system or its signals are effectively blocked (Grumbach and Styne, 2003).

THE HPA AXIS—PERMITTING PUBARCHE BUT THROUGH AN UNKNOWN PATHWAY

A second signaling pathway sends hormonal messages from the hypothalamus to the pituitary and then to the adrenal gland. The so-called HPA axis functions independently of the HPG axis. Whereas the HPG axis governs thelarche (breast budding), the HPA axis is involved in adrenarche. During adrenarche, the adrenal cortex matures and takes on androgen-secreting functions. More specifically, for adrenarche to occur, a novel cell type with the ability to produce androgens (male hormones) must arise from within the adrenal glands (Auchus and Rainey, 2004). The outward manifestation of adrenarche is pubarche: the sprouting of pubic hair. Pubarche also involves maturation and activation of the apocrine sweat glands that are located in the armpits, in the pubis area and around the areola of the breast. It is these glands that produce adult body odor.

The initiating mechanism for adrenarche is not known (Auchus and Rainey, 2004). In contrast to the HPG axis, whose activation defines the genesis of puberty, the HPA axis, which has

many critical functions, does not suddenly stir to life at some point during the late juvenile period. Corticotropin-releasing hormone (CRH) from the hypothalamus signals the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which is then received by the adrenal gland. ACTH is necessary for adrenarche, and yet circulating ACTH levels do not rise during its commencement. Thus, ACTH appears to be a permissive rather than a causal agent in adrenarche. The factor that acts as the proximal signal for the onset of adrenarche remains to be discovered. Complicating the search for this signal is the fact that adrenarche only occurs in human beings and some Old World primates (Auchus and Rainey, 2004).

Whatever the initiator of adrenarche, circulating levels of three adrenal androgens (male hormones) begin to increase progressively in girls between the ages of 6 and 8, although visible changes are not typically apparent for some time (Dorn and Rotenstein, 2004). Eventually, pubic hair, underarm hair, body odor and, sometimes, acne emerge. For most girls, breast development precedes the arrival of pubic hair, but about 20 to 40 percent of girls enter puberty with pubic hair first and breasts second. This is considered a normal variation (Papathanasiou and Hadjiathanasious, 2006; Parent, 2003).

CHILDHOOD AS THE HIATUS BETWEEN TWO PUBERTIES

For both boys and girls, the HPG axis is active at birth and for a brief period during early infancy. It is then switched off—through a yet-to-be-identified mechanism—and remains quiescent until it is de-repressed a decade or so later, thereby ushering in the process of sexual maturation (Papathanasiou and Hadjiathanasious, 2006). Hence, by definition,

newborn babies are actually "in puberty" upon arrival. Within the brains of neonates, GnRH secretions are sending pulsatile signals to the pituitary gland, which in turn is stimulating the gonads to produce sex hormones. New parents often notice the startling effects: the genitals of newborns are typically enlarged, red and swollen, and acne may appear. These traits recede and largely disappear by about 3 to 9 months of age.

This so-called infant puberty (or "mini puberty") represents a time when gonadal hormones organize the nervous system—as they will a second time during adolescent puberty (Sisk and Zehr, 2005; Whitlock, 2006). In boys, GnRH secretion during infancy appears important to testicular maturation (particularly to the regulation of Sertoli cell proliferation in the testes) and may also play a role in masculinizing the brain (Ebling, 2005). The function of infant puberty in girls is less clear. However, many researchers believe that infant puberty serves in

Nasal Origins of GnRH Neurons

Curiously, GnRH-secreting neurons in the infant hypothalamus do not originate from central nervous system tissue. Instead, they arise from tissues in the nose. During prenatal life, these cells migrate from the nasal area into the brain, spinning out webs of electrical connections with cells along the medial septum and within midbrain sites as they go. Kallmann's Syndrome, a genetic disease whose hallmark features are infertility and complete lack of smell, results from the failure of GnRH neurons to navigate the nasal passages successfully along with the concurrent failure of the olfactory nerve to develop at all. Individuals with Kallmann's Syndrome never spontaneously enter puberty (Cariboni and Maggi, 2006).

some way to prepare the brain for the later regulation of pituitary gonadotropic function (Ebling, 2005; Whitlock, 2006). The events of infant puberty may thus influence the timing of adolescent puberty.

Childhood, then, from an endocrinological point of view, simply represents the period of time between two puberties. Childhood is a hormonal hiatus made possible by a temporary inhibition of the HPG axis. Biological anthropologist Carol W. Worthman writes that "childhood is created through specific patterns of endocrine regulation in which central mechanisms restrain gonadal and some adrenal function" (1999). Infant puberty and adolescent puberty represent periods of human development during which the brain becomes exquisitely sensitive to hormones, both endogenous and exogenous. However, during infant puberty the HPG axis, while active, is largely unregulated as the neurons of the central nervous system are still getting into place. By contrast, the HPG axis during adolescent puberty is regulated by highly organized neuronal circuitry (Gore, personal communication).

THE PLASTICITY OF PUBERTAL TIMING

While humans enjoy the longest childhoods of any mammal (Grumbach and Styne, 2003), we are not the only species with an HPG axis that goes into juvenile hibernation. Indeed, this is a trait typical of long-lived mammals. We also share with other mammals a remarkable degree of plasticity around the timing of its reawakening. That is to say, it is a trait that is not predetermined at birth but is designed to be shaped by the interplay of various environmental factors. Among the deer family, for example, the timing of sexual maturity is highly variable. Yearlings and even fawns can begin ovulating and

Puberty is less like a clock and more like a musical performance, with our bodies as the keyboards and the environment as the hands of pianist.

become sexually receptive if food is plentiful. If it is not, females won't become sexually mature until age 2 or older (Putnam, 1988; Steingraber, 2006). Similarly, among macaques (a genus of Old World monkeys), menarche can arrive as early as 17 months and as late as 31 months, but the individual must weigh at least six pounds in order to menstruate (Donovan and Van der Werff ten Bosch, 1965). In general, among the mammals, the basic elements of fertility do not appear governed by a built-in clock but are better understood as potentialities that respond to environmental cues that time puberty via particular neural mechanisms (Ebling, 2005). Indeed, the popular "biological clock" image is inappropriate for understanding the process of sexual maturation among any species of mammal, including humans. Puberty is less like a clock and more like a musical performance, with our bodies as the keyboards and the environment (both internal and external) as the hands of pianist. The various evolutionary adaptations that allow for environmentally-cued puberties receive further attention in part four of this report.

Not only is the timing of puberty among human girls widely variable—with the onset of "normal" puberty ranging in age from 8 to 13—the tempo of puberty is also a highly-elastic trait. On average, the pubertal sequence in girls takes 4.5 years, but the range is 1.5-6 years (Pinyerd and Zipf, 2005). Early puberties often unfold more slowly than later-onset puberties (Kaplowitz, 2004). Full breast development takes three to four years, with menarche, on average, occurring two years after thelarche (Pinyerd and Zipf,

2005), but there are emerging signs of a recent decoupling of thelarche from menarche among U.S. girls (Biro, 2006a).

INTRODUCTION TO TRENDS IN PUBERTAL TIMING

Between the mid-19th century and the mid-20th century, the average age at menarche declined sharply and steadily among European girls from 17 to 13. Similar trends are seen in the United States—although good data were not available until the beginning of the 20th century (Marshall and Tanner, 1986; Tanner and Everlyth, 1975; Wyshak and Frisch, 1982). Improved health and nutrition are thought to be the underlying causes of this century-long trend. Over the last half century, in the United States, average age at menarche has continued to fall but at a slower rate and with significant racial and ethnic disparities. In the United States, black girls, as a group, begin menstruating significantly earlier (12.1 years on average) than do white girls (12.6 years on average). Mexican American girls, as a group, also reach menarche earlier than white girls. It is not clear when these racial disparities emerged. Historical data were collected primarily on white girls (Herman-Giddens, 2006).

The onset of puberty itself, as measured by the appearance of breasts and pubic hair, shows signs of a more dramatic ongoing decline for both black and white girls (Muir, 2006; Parent, 2003). Hence, the window of time between commencement of puberty and its conclusion is becoming longer. Average age of breast budding has fallen to just under 10 years for U.S. white girls and just under 9 years for black girls, with a significant portion starting breast development before age 8 (Herman-Giddens, 1997). These patterns are discussed in detail in part two of this report.

Average age of breast budding has fallen to just under 10 years for U.S. white girls and just under 9 years for black girls, with a significant portion starting breast development before age 8.

Not all endocrinologists, however, agree that age of onset of puberty is truly falling in U.S. girls. This is at least in part because of a lack of historical data on the age of breast budding, differing methods among large-scale studies and changing ethnic demographics of the U.S. population. In addition, evidence for a continuing decline in the age of thelarche has not, by and large, been found in other countries.

At the very least, such critics argue, current evidence is insufficient to make such a claim (Dorn and Rotenstein, 2004, for example. For a discussion of how this debate has played out within the pediatric community, see Kaplowitz, 2004). It is, nevertheless, now the opinion of most endocrinologists, including the authors of the leading medical textbook on endocrinology, that the falling age of puberty among U.S. girls is a real and ongoing phenomenon (Euling, 2005; Grumbach and Styne, 2003). That is also the viewpoint of this author.

THE DEBATE OVER NORMALIZING EARLY PUBERTY

The apparent decline in the average age at puberty has compelled the pediatric community to rethink what constitutes precocious puberty (Kaplowitz and Oberfield, 1999). Traditionally defined as the appearance of breast budding before age 8 (Massart, 2006), precocious puberty is now defined as an onset at less than 7 years in white U.S. girls and less than 6 years among black girls (Grumbach and Styne, 2003). It is a problem that affects far more girls than boys. True

precocious puberty—which involves the activation of the HPG axis—is five times more common in girls than boys (Grumbach and Styne, 2003), and it is more common among U.S. black girls than among U.S. white girls (Muir, 2006). Precocious pubarche—the premature appearance of pubic or underarm hair—is 10 times more common among girls than boys. It is now defined as less than 7 years old among U.S. white girls and less than 5 among U.S. black girls (Grumbach and Styne, 2003). Moreover, no apparent cause for precocious puberty can be found for the majority of girls, whereas boys are likely to exhibit a known pathology (Muir, 2006).

The normalization of early puberty in girls is a two-edged sword. On the one hand, girls between the ages of 7 and 8 who show signs of breast development should not, most pediatricians believe, be subject to drastic hormonal interventions in an attempt to arrest puberty (Kaplowitz, 2004). And many girls who show signs of early puberty do not rapidly complete sexual maturation. Instead, they exhibit "unsustained puberty," which is slowly progressive and sometimes spontaneously ceases (Palmert, 1999). On the other hand, a small minority of girls with early puberty may indeed have an underlying medical problem— a pituitary tumor, for instance—which may be overlooked without a medical diagnosis (Dorn and Rotenstein, 2004; Midyett, 2003). They may also be at risk for future reproductive dysfunction (Rosenfield, 2000).

Furthermore, what has become the new norm is not necessarily normal or good. Whether or not a 7-year-old with breasts is labeled with a disorder and treated, the falling age of puberty raises serious public health questions. As is discussed below, early puberty is linked to a variety of high-risk behaviors in girls. Early

Precocious puberty is five times more common in girls than boys.

puberty also raises the risk for breast cancer in adulthood. This effect may be most pronounced when breast budding precedes the appearance of pubic hair (Biro, 2003a, 2003b). For all these reasons, public health advocates need to understand why the average age of puberty appears to be dropping and why such a significant portion of young girls are maturing at ages far below the average (Zuckerman, 2001). Simply declaring early sexual maturation "normal" discourages a full and thorough investigation about what might be driving the trend toward early puberty. As one leading pediatrician notes:

It is difficult to ignore the fact that 15.4 percent of African-Americans and 5 percent of white girls are now presenting to their pediatricians' offices between seven and eight years old with breast budding. This is very different from the 0.06 percent of girls this age that would be anticipated from the previous standards…. The fact that "normality" may have changed does not negate the possibility that the physiological processes leading to these changes are neither normal nor benign (Slyper, 2006).

THE SCOPE OF THIS REPORT

This report closely examines five topics related to early puberty in U.S. girls. Part one looks at the harmful impacts of early puberty on girls, including a potential link to breast cancer. Part two explores time trends in puberty both in the United States and abroad. Part three examines the regulation of puberty, with a focus on what is known about the upstream signals that mediate the HPG axis and thereby control the timing of puberty. Part four looks at the insights offered by evolutionary biology. Part five explores the various possible causes for the declining age of puberty in U.S. girls. These include reduced fetal growth, obesity, low rates of breastfeeding, psychosocial stressors, television viewing and environmental exposures to endocrine-disrupting chemicals. Finally, part six proposes recommendations for research and action based on current evidence.

This report does not analyze the trends for pubertal timing in U.S. boys. While there is some evidence for secular changes in the maturational process in boys, they are much more subtle. Delayed puberty is far more prevalent in boys than girls, whereas precocious puberty is far more common in girls (Hughes and Gore, 2007). Early puberty is a gendered issue.

WHY ARE WE WORRIED ABOUT EARLY PUBERTY IN GIRLS?

THE NEGATIVE CONSEQUENCES OF EARLY PUBERTY

Early puberty in girls is associated with a startling number of psychopathologies and health problems. Girls who are the first in their cohort of friends to reach thelarche report more negative feelings about themselves and suffer more from anxiety. Early-maturing girls are more likely to experience depression, eating disorders and adjustment disorders, and are more likely to attempt suicide (Graber, 1997, Martin, 1996; Zuckerman, 2001). Some of these effects are limited to adolescence and others persist throughout young adult life (Graber, 2004) or even into middle age (Celio, 2006).

Early-maturing girls are more prone to early drug abuse, cigarette smoking and alcohol use (Graber, 1997, 2004). They are more likely to be physically and violently victimized (Haynie and Piquero, 2006). Several studies find that timing of puberty affects teenage sexual activity. Earlier puberty is predictive of earlier sexual initiation, with girls' first sexual encounter following closely on the heels of puberty (Martin, 1996). The combination of early sexual intercourse and early substance use places early maturing girls at

a higher risk for teenage pregnancy (Deardorff, 2005). Conduct disorders (Burt, 2006) and delinquency (Celio, 2006; Johannson and Ritzen, 2005) are also higher among early maturing girls, who are disproportionately represented in criminal records (Celio 2006). At ages 27 and 43, women who had early puberties had lower academic education (Johannson and Ritzen, 2005), whereas late-maturing girls performed better in school and were more likely to finish college (Graber, 1997, 2004).

It's always important to keep in mind that these associations apply only to girls as a group, not to individual girls, and that risks can be statistically significant even when only modestly increased. Risk is not destiny. Many early-maturing girls develop into happy, high-achieving adults.

PROPOSED REASONS FOR HARM

The underlying reasons for the elevated risk of psychopathology in early-maturing girls are unclear. One possibility is that pubertal hormones themselves reorganize neuronal circuitry in ways that create distress. A brain that is younger at the time of pubertal remodeling—with its attendant loss of cognitive flexibility and

increasing determinacy—may be more susceptible to psychopathologies than one that has been shaped by more years of learning and experience. One team of researchers refers to the pubertal loss of childhood skill acquisition as "premature plasticity decay" (Yun, 2004).

Another possibility is that early puberty alters a girl's social interactions in ways that produce trauma and erode self-esteem (Sisk and Zehr, 2005). The latter hypothesis is supported by the fact that early-maturing boys do not suffer the same bad outcomes on measures of health and well being as do their female counterparts. Early-maturing boys tend to be treated as leaders by their peers and are admired rather than scorned and harassed, as is often the case for early-maturing girls (Grumbach and Styne, 2003). This gender disparity suggests that the physiological experience of early puberty is less important for the risk of psychopathology than the social consequences that result. It also suggests that early puberty and bad outcomes are probably not simply the coincident consequences of other underlying childhood stressors (Bogaert, 2005). Rather, for girls, the experience of early puberty itself seems to invite trouble.

Confounding factors are nevertheless difficult to tease apart in studies that explore the impact of pubertal timing on mental, physical, social, educational and economic well being. A recent Norwegian study, for example, found that mental distress among girls—which was higher among early maturers—was more strongly associated with dissatisfaction over body weight than with age at menarche (Lien, 2006). In other words, fatter girls entered puberty earlier but it was their unhappiness about being overweight and not the early maturation itself that, according to this study, contributed most to their ongoing anxiety. And yet, because

increased fat deposition itself is part of the pubertal process for girls, these two variables are deeply intertwined. A similar relationship was seen in body image, timing of puberty and weight status among a cohort of black and white U.S. girls. In other words, the stresses of early puberty notwithstanding, being overweight is, by itself, a risk factor for poor mental health (Striegel-Moore, 2001).

EARLY PUBERTY AND BREAST CANCER RISK

Early puberty, as measured by onset of menarche, is a well-established risk factor for breast cancer. As age of menarche decreases, overall risk of breast cancer increases (Anderson, 2007; Clavel-Chapelon, 2002; Hsieh, 1990; Iwasaki, 2007; Kelsey, 1993; Okobia and Bunker, 2005; Rosner, 1994; Shantakumar, 2007; Stoll, 1998). Menarche before age 12, for example, raises breast cancer risk by 50 percent compared to menarche at 16 (Grumbach and Styne, 2003). Conversely, for each year menarche is delayed, the risk of breast cancer declines by 5 to 20 percent (Clavel-Chapelon, 2002; Hsieh, 1990; Kelsey, 1993; Rosner, 1994). One study has reported a connection between menarchal age and risk of death from breast cancer: among breast cancer patients younger than 55, early age at menarche modestly increased mortality (Trivers, 2007).

The mechanism by which early puberty makes a breast cancer diagnosis in later life more likely—and possibly more fatal—is not entirely clear, but two aspects appear to be significant in this regard. First, early puberty is associated with increased lifetime exposure to estrogens. Second, early puberty often expands the interval between first menses and first pregnancy, a period of time that is considered a critical window of vulnerability in the pathogenesis of

breast cancer (Rosner, 1994).

Early thelarche—which is sometimes, but not always, coupled with early menarche—seems to influence breast cancer risk in and of itself. Precocious puberty is associated with increased risk for breast cancer in adult life (Ahlgren, 2004). The tempo of puberty may also affect later breast cancer risk: a long period between breast budding and first ovulation creates a wide "estrogen window" that is thought to be favorable to the future development of breast cancer (Okobia and Bunker, 2005). In a study of twin sisters with genetic susceptibilities to breast cancer, the twin who reached thelarche first was five times more likely to develop breast cancer first (Hamilton and Mack, 2003). Girls who enter puberty with breast budding as the presenting event may be more likely to develop breast cancer in later life than girls whose puberties manifest with pubic hair (Biro, 2003).

EARLY PUBARCHE AND POLYCYSTIC OVARY SYNDROME

Early onset of pubic hair development is also associated with health risks. Once presumed a benign condition, premature adrenarche is now thought to be a forerunner of several adult diseases (Auchus and Rainey, 2004; Ibanez, 2000). Premature adrenarche is linked with

polycystic ovary syndrome—a leading cause of pelvic pain and infertility—and is a predictor of later cardiovascular disease (Neville and Walker, 2005; Grumbach and Styne, 2003). Teens and women with polycystic ovaries are at higher risk for diabetes and impaired glucose tolerance (Auchus and Rainey, 2004). Polycystic ovary syndrome is now thought to involve abnormal activation of the HPA axis. Excessive growth of body hair, due to high levels of androgens, is one of its symptoms, and insulin resistance magnifies its severity (Chang and Coffler, 2007).

CONCLUSIONS

In sum, early puberty raises several risks for girls. It raises risks for mental health problems and self-destructive behaviors that are sometimes transitory but can sometimes persist into adult life and negatively affect educational status. It raises the risk for substance abuse, violent victimization and sexual abuse. Early puberty raises the risk for breast cancer, perhaps especially if thelarche precedes pubarche and perhaps by increasing the time span during which pubertal changes unfold. Early pubarche also raises risk profiles for later disease, most notably polycystic ovary syndrome, which itself is related to metabolic and cardiovascular diseases.

PUBERTAL TIME TRENDS IN GIRLS IN THE UNITED STATES AND AROUND THE WORLD

Had pediatric endocrinologists quietly monitored breast and pubic hair development in representative samples of girls throughout the ages, and had they employed comparable techniques as they went, we would know with more certainty how precipitous the decline in pubertal onset really is. But there are no studies with comparable methodologies that go back even 50 years (Kaplowitz, 2006). The National Health Examination Survey reported on stages of breast and pubic hair development among 2,688 U.S. girls between 1963 and 1970 (Harlan, 1980). Unfortunately, the youngest girls in the study were 12, so it provides limited historical information on pubertal onset.

TRENDS IN MENARCHE

There does exist much historical data on menarche in both Europe and the United States. In Europe, between 1830 and 1960, average age at menarche declined by two to three months each decade, falling from 17 to 13 during this period (Tanner and Eveleth, 1975). By 1970, it had leveled off and has not changed much since. Among European girls, average menarchal age now ranges from 12.3 years in Greece to 13.3

years in Finland (Parent, 2003).

A similar downward trend was seen in the United States, although by the 20th century, U.S. girls were menstruating sooner than their European counterparts. In 1900, average U.S. menarchal age was 14.2 years (Tanner and Eveleth, 1975). In 1922, a prospective longitudinal study was launched that followed 3,650 public school first-graders in three Massachusetts cities for 19 years—well into their adulthoods. In this cohort, average age of menarche was 13.5, which, at the time, was the youngest average age recorded anywhere (Shuttleworth, 1937, 1938). As in Europe, puberty in U.S. girls advanced by a few months per decade during the first part of the 20th century. By 1970, according to data gathered by the National Health Examination Survey (NHANES), the mean age of menarche in U.S. girls stood at 12.8 (Harlan, 1980). More than three decades later, it stands at about 12.6 years for white girls, 12.1 for black girls and 12.2 for Mexican American girls (Kaplowitz, 2006; Herman-Giddens, 2006 and 1997).

A recent investigation that analyzes NHANES data in a novel way provides another way of looking at the ongoing decline in the mean age

Age at Menarche in the US by Race[1,2,5]

Age at Menarche

- ◆ *black*
- • *white*
- — *black*
- — *white*

Year data collection completed
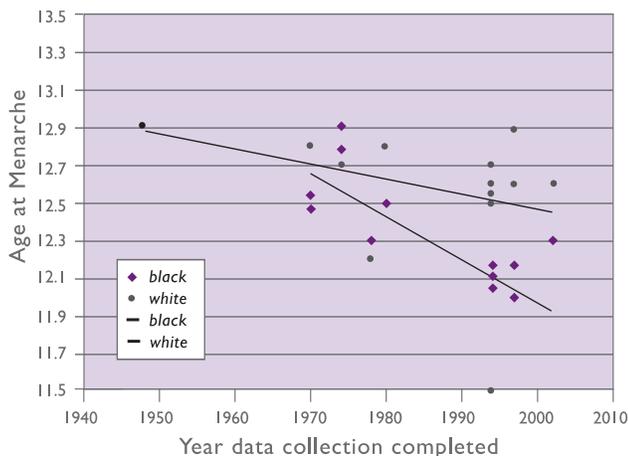
(Anderson, 2003; Parent, 2003; Wattigney, 1999; Freedman, 2002; Foster, 1977; Biro 2006a; Wu, 2002; Anderson, 2005; Freedman, 2002; Herman-Giddens, 1997; Chumlea, 2003; Reynolds and Wines, 1948; Mac Mahon, 1973; Foster, 1977)

Age at Onset of Breast Development in US by Race[1,2,3,5]

Average Age at Tanner Stage B2

- ◆ *black*
- • *white*
- — *black*
- — *white*

Year data collection completed
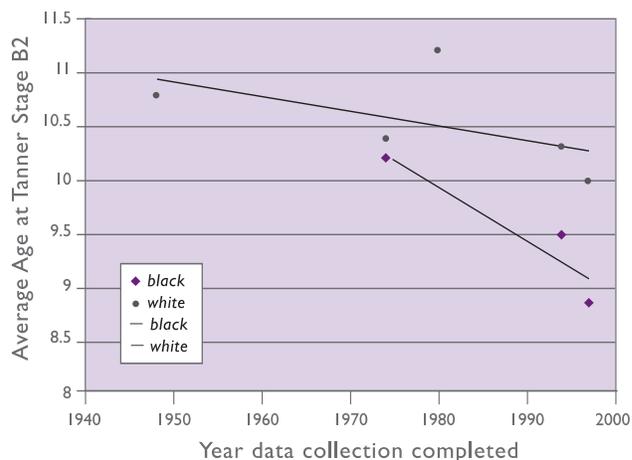
(Foster, 1977; Wu, 2002; Herman-Giddens, 1997; Reynolds and Wines, 1948; Lee, 2001)

Age of Menarche in Europe[4,5]

Average Age at Menarche

Year data collection completed
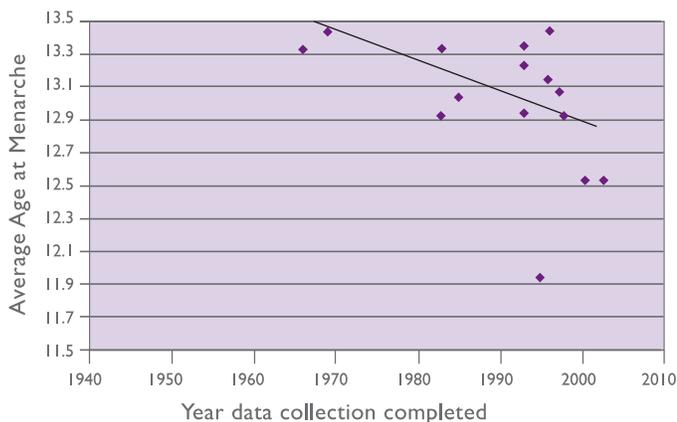
(Marshall and Tanner, 1969; Juul, 2006; Parent, 2003)

Age of Onset of Breast Development in Europe[3,5]

Average Age at Tanner Stage B2

Year data collection completed
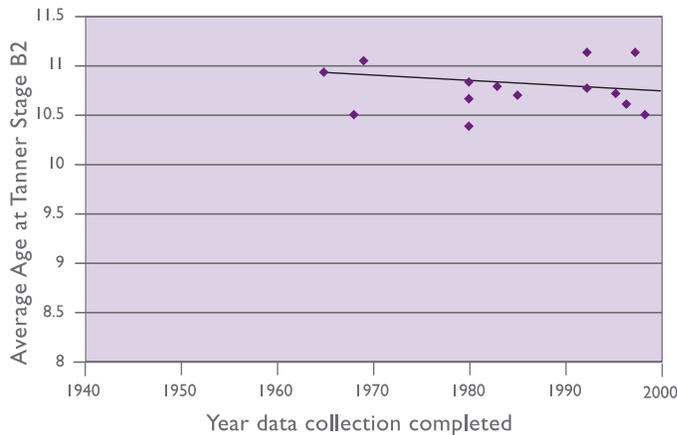
(Largo and Prader, 1983; Juul, 2006; Marshall and Tanner, 1969; Roede and van Wieringen, 1985; Lindgren, 1996; Parent, 2003; Engelhardt, 1995; Mul, 2001; Danubio, 2004)

[1]The population studied by Reynolds and Wines (1948) consisted of 49 girls and was not representative of the general population.

[2]The terms "black" and "African American" are not always synonymous. "Black" is used here because it is the demographic category used by the original researchers in most of these studies.

[3]Onset of breast development is defined here as Tanner stage 2, "Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter" (Marshall and Tanner, 1969).

[4]Most of the data for this graph was drawn from Parent, 2003.

[5]With the exception of data collected in the NHANES study, methods and populations used in studies cited in graphs vary and are not strictly comparable. They are, however, the best available data on age at menarche and onset of breast development. Data used in graphs were collected in a thorough, but not exhaustive, review of the literature.

All graphs by Tamara Adkins.

of menarche among U.S. girls. In this study, researchers grouped women by age cohorts. Those born prior to 1920 were in the oldest group, while those born 1980-84 were in the youngest. The mean age of menarche declined by 10 months from the pre-1920 cohort to the 1980-84 cohort for whites, by 12 months for Mexican Americans and almost 15 months for blacks (McDowell, 2007; Herman-Giddens, 2007). It is also of note that in the oldest cohort—that is, among women now in their 80s

NHANES III (1988-1994)

Non-Hispanic Whites 12.57 years

Non-Hispanic Blacks 12.09 years

Mexican-Americans 12.24 years

Total Population 12.53 years

Race

0   3   6   9   12   15

Average age at menarche
by race/ethnicity *(Anderson)*

or older—blacks had a *higher* average menarchal age than whites (13.6 years versus 13.3 years), which is precisely the reverse of contemporary patterns. That is, over the course of the 20th century, age at menarche fell faster and farther for U.S. black girls than for U.S. white girls.

The conventional wisdom is that these secular trends can be explained by improving health and nutrition. This conclusion is supported by the fact that these declines flatten out during the Great Depression when undernutrition once again became prevalent (Donovan and Van der Werff ten Bosch, 1965). Nutrition has also been invoked to explain urban/rural differences and rich/poor differences that are seen throughout the world. Historically, urban-dwelling girls and girls from wealthier families experience earlier menarche than rural girls and girls from poorer families (Khadilkar, 2006).

And yet nutritional changes and infection control are not able to explain all worldwide trends during the first half of the 20th century. For example, girls in Japan also showed declines in

NHANES III (1988-1994)
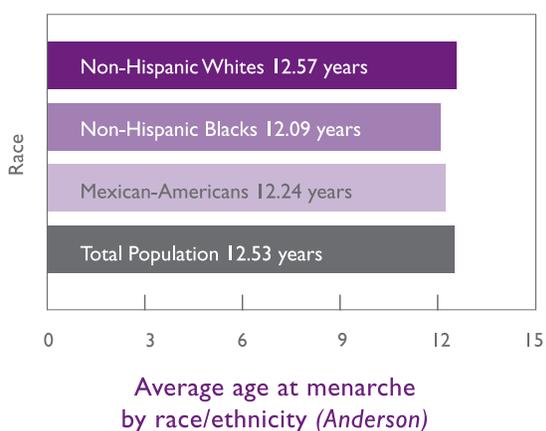
Non-Hispanic Whites

Non-Hispanic Blacks

Mexican-Americans

Total Population

Percent

100

80

60

40

20

0

9   10   11   12   13   14   15
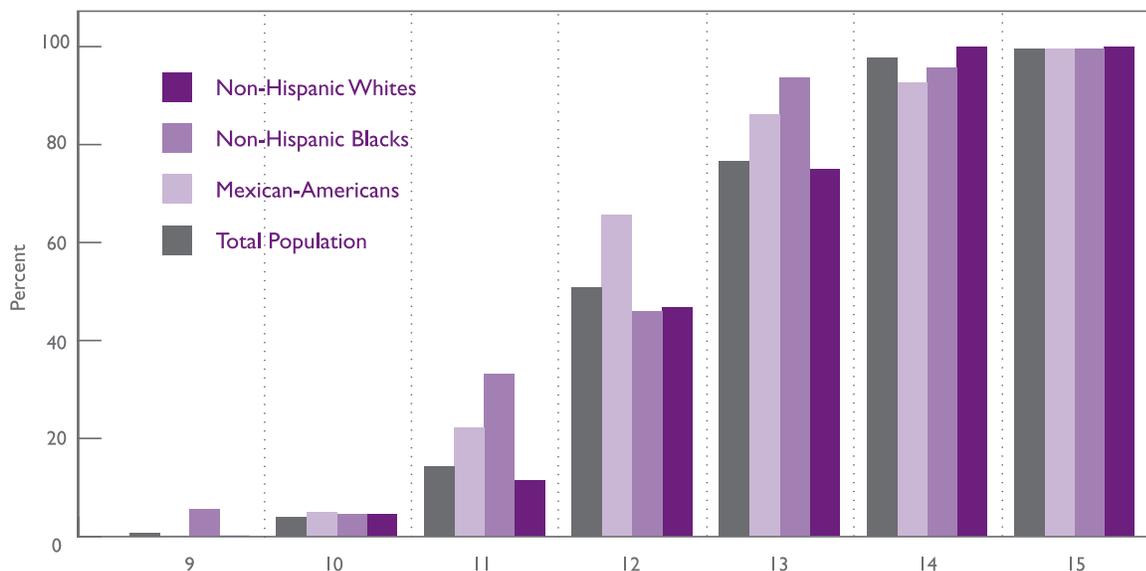
Average age at menarche and percentage of girls who had reached
menarche by race/ethinicity in NHANES III *(Anderson)*

the age of menarche during a period of rapid industrialization after 1900 that ushered in increased poverty, higher rates of infant mortality and tuberculosis outbreaks (Donovan and Van der Werff ten Bosch, 1965). Economic transformations themselves may thus play a role in pubertal timing, albeit through unknown pathways. One researcher has also pointed out that 19th-century declines in menarchal age among European girls correspond to the advent of the gas and chemical industries. The introduction of gas street lamps between 1820 and 1900 created sources of widespread urban pollution as did the dye industries that sprang up as an offshoot (Whitten, 1992). It is interesting to note that in contrast to the menarchal changes seen among girls in rapidly industrializing cultures during this time period, there was no trend toward earlier menarche among Lapp girls living in traditional nomadic cultures between 1870 and 1930 (Grumbach and Styne, 2003). At present, the fastest rates of decline in mean menarchal ages are occurring among countries that are newly industrialized, such as South

Korea, where girls are now reaching menarche more than four years earlier than they did in 1920 (Ong, 2006).

Within the United States, nutrition alone cannot explain the racial differences in age at menarche nor the differences in ongoing rates of decline. U.S. white girls show far more gradual decreases over the past few decades than do black or Mexican American girls (Anderson and Must, 2005; Freedman, 2002; Kaplowitz, 2006).

NHANES 99-02 (1999-2002)

Average age at menarche by race/ethnicity
(Anderson)

NHANES 99-02 (1999-2002)

Average age at menarche and percentage of girls who had reached menarche by race/ethinicity in NHANES 99-02 *(Anderson)*
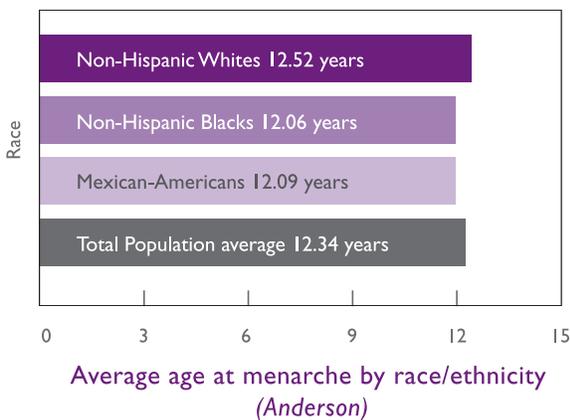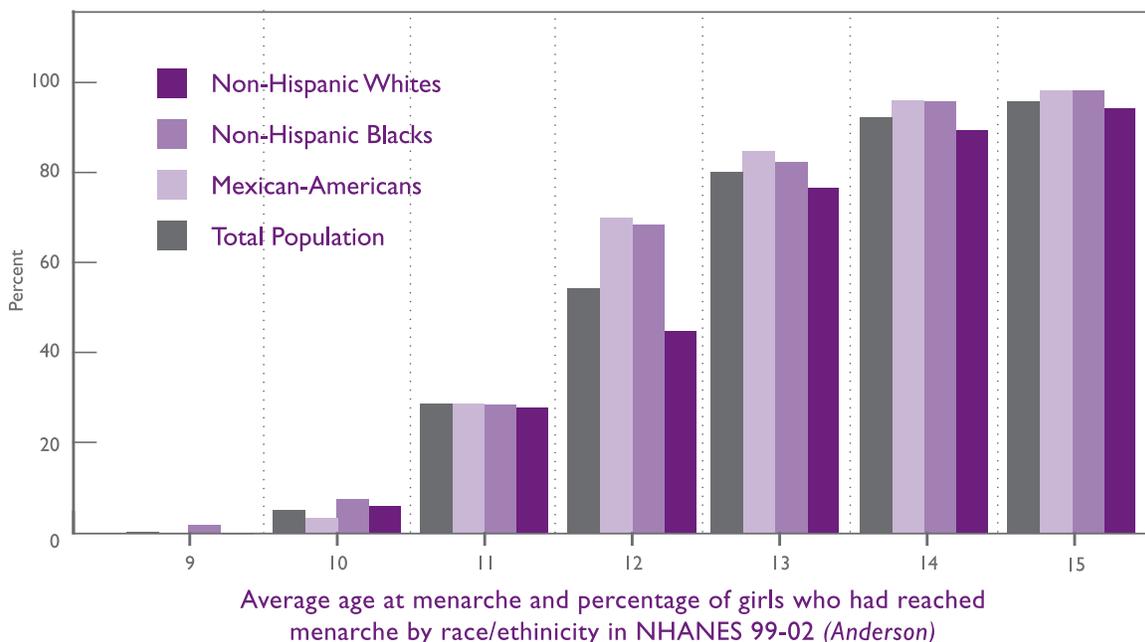
These results highlight the inadequacy of using overall population averages to reveal trends in sexual maturation: overall averages can obscure patterns of change within specific populations of girls and say nothing about what factors may be controlling the menarchal timing of any one individual girl or group of girls living in one geographic area (Anderson and Must, 2005; Biro, 2005).

MENARCHE AS AN UNRELIABLE INDEX OF PUBERTAL ONSET

Menarche is a late event in the march to sexual maturity. Thus, menarche is not a reliable marker for the onset of puberty, as it is only loosely correlated with the timing of thelarche and pubarche, which are puberty's manifesting events. Moreover, the correlation of onset of puberty with age of menarche appears to have decreased over the last few decades. That is, increasingly unique factors contribute to the timing of thelarche and menarche whereas, in the past, the two phenomena had more factors in common (Biro, 2006a). The decoupling of puberty's onset from menarche suggests that environmental signals may be influencing thelarche and menarche in different ways (Kaplowitz, 2006). If so, secular trends in menarche may reveal little about temporal changes in puberty.

Such concerns have prompted several studies of pubertal time trends that revisit the very limited and deficient historical data that are available on the timing of thelarche and pubarche. Various researchers have analyzed these data sets in various ways and have come to sometimes differing and contradictory interpretations (Biro, 2006b; Herman-Giddens, 2004; Herman-Giddens, 1997; Sun, 2005; Wu, 2002). It is beyond the scope of this report to examine the methodological shortcomings, data collection constraints and complex probabilistic sampling techniques of each. What follows is a brief discussion that focuses on points of convergence

Prevalence of Menses
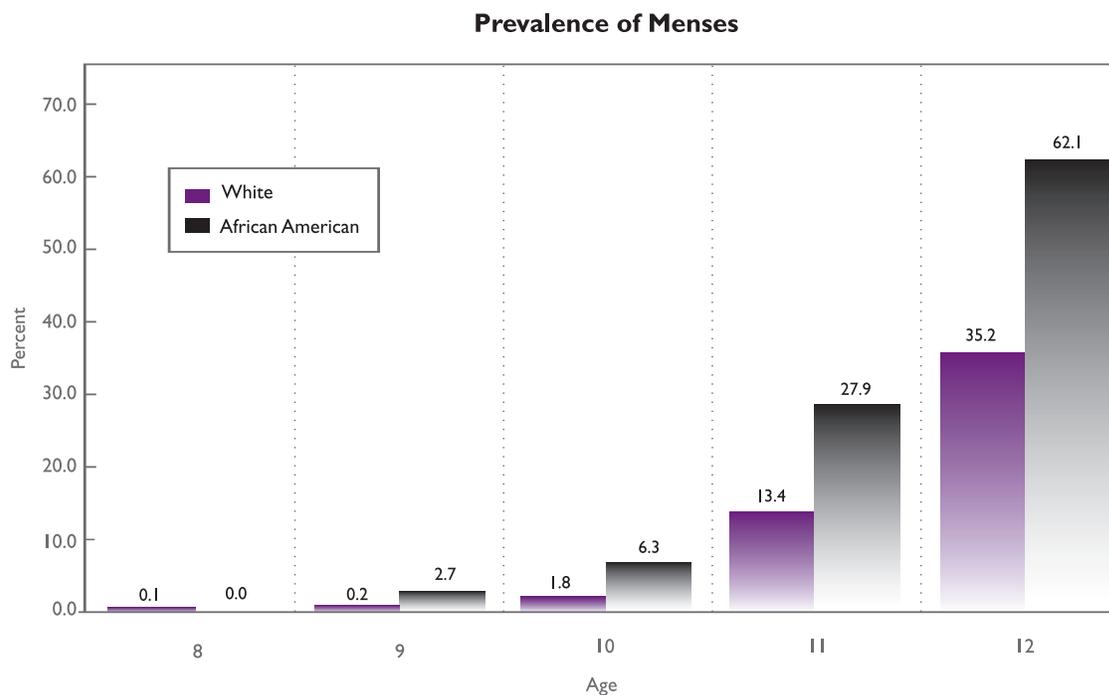
Prevalence of menses by age and race *(Herman-Giddens, 1997)*

and agreement. (For a thorough critique of these studies and their surrounding controversies, see Irwin, 2005; Kaplowitz, 2006; Slyper, 2006.)

TRENDS IN THELARCHE AND PUBARCHE

In the early 1960s, British pediatrician James Tanner and his colleague William Marshall studied the pubertal development of 192 white girls in an English orphanage. In so doing, they refined a system of categorizing and defining stages of pubic hair emergence and breast development that is called the Sexual Maturity Rating Scale for girls (Marshall and Tanner, 1969), which they based on earlier schemas developed by researchers working in Germany (Reynolds and Wines, 1948). While their study subjects were not representative of the English population as a whole, their data were so comprehensive and well-described that their findings became the basis for what is considered normal puberty (Kaplowitz, 2006). Tanner and Marshall reported that mean onset of breast development was 11.15 years.

By the 1990s, many U.S. pediatricians suspected that U.S. girls were experiencing puberty considerably earlier than what Tanner and Marshall had described (Kaplowitz, 2006). Among them was child abuse specialist Marcia Herman-Giddens, who became frustrated at the paucity of recent data on pubertal timing in girls. She launched a large study of more than 17,000 girls and trained pediatricians in 65 office practices to stage breast and pubic hair development using the methods of Marshall and Tanner. She and her colleagues found that mean age of thelarche was 10 in white girls—more than a year younger than what Marshall and Tanner had reported three decades earlier—and 8.9 years in black girls. Pubarche in both white and black girls was also considerably earlier

compared to the Marshall and Tanner cohort. Mean age of menarche had not changed much from the 12.8 years reported in the National Health Survey study from the 1970s (Herman-Giddens, 1997).

On the basis of this study, the Lawson Wilkins Pediatric Endocrine Society argued that existing standards were out of date and proposed changes to the age limits for what constitutes abnormally early puberty among U.S. girls. Under the old guidelines, 14 percent of U.S. girls would be considered precocious (Lee, 2001). In 1999, the cut-off age for precocious puberty, as defined by onset of breast development, was pushed back from 8 to 7 for white girls and from 7 to 6 for black girls (Kaplowitz and Oberfield, 1999). This revision in the age limit for sexual precocity—which was not adopted in Europe—is still considered a highly controversial decision (Parent, 2003). Many who opposed the redefinition pointed to methodological shortcomings in the study on which it was based.

There are two main critiques of the Herman-Giddens study. First, in order to follow the Marshall and Tanner protocols, researchers staged breast development by inspection (although 39 percent of subjects were also palpated). For chubby girls, chest fat can look very similar to breast tissue (Himes, 2006). Also, because of funding limitations, girls were enrolled only up to age 13; thus, late bloomers were excluded (Slyper, 2006). But its major findings were upheld with the publication of another study that analyzed data collected as part of a nationally representative sample called the Health and Nutrition Examination Survey (NHANES) (Wu, 2002). A subsequent analysis of the NHANES data, however, found no downward trends in sexual maturation for black girls or white girls but did uncover evidence for earlier onset of puberty among Mexican

Prevalence of Pubic Hair Development
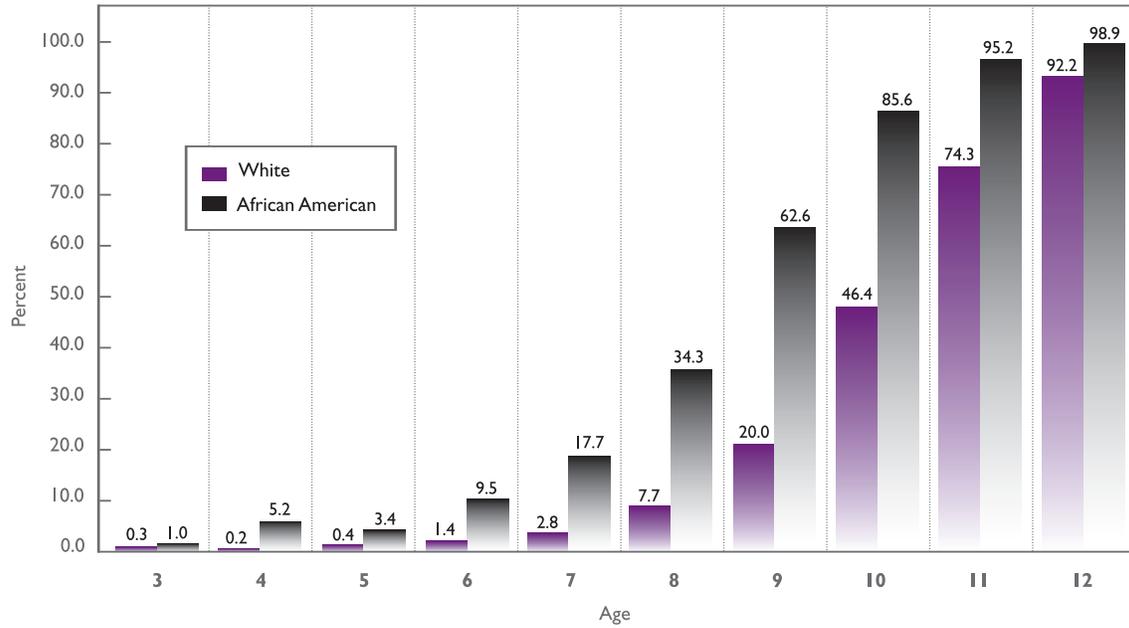
Prevalence of pubic hair development at Tanner stage 2 or greater by age and race
(Herman-Giddens, 1997)

Prevalence of Breast Development
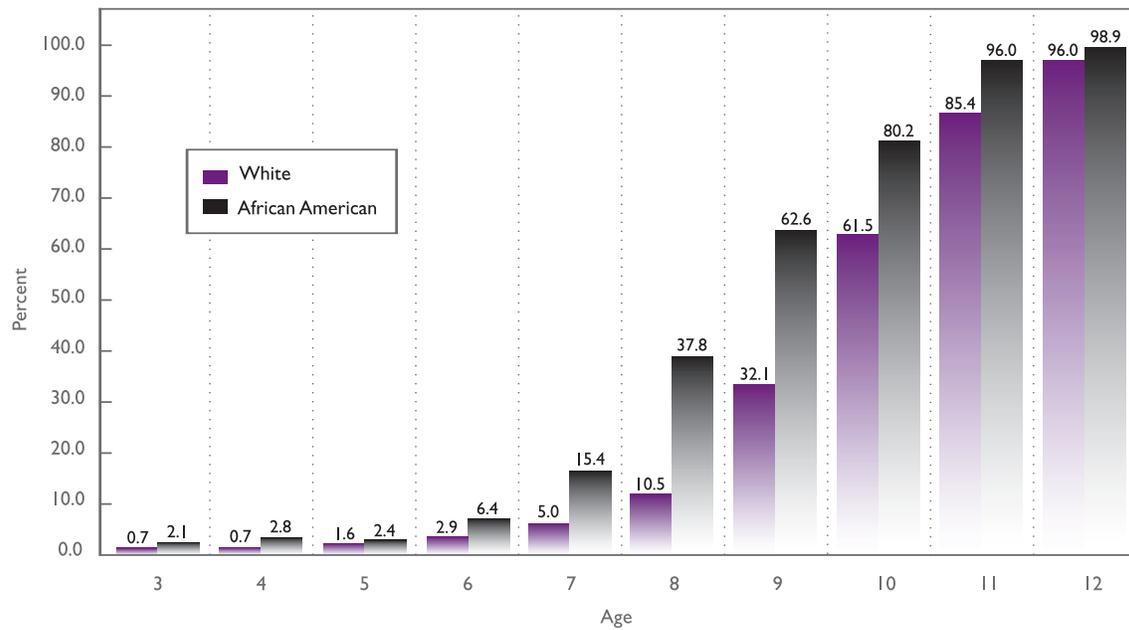
Prevalence of breast development at Tanner stage 2 or greater by age and race *(Herman-Giddens, 1997)*

American girls (Sun, 2005. See also Irwin, 2005). The NHANES data set also, however, suffered from its own sampling deficiencies. For example, it did not include girls younger than 8 and so may have eliminated some early bloomers (Slyper, 2006). In all these studies, statistical corrections were used to compensate for the various omissions in the data sets.

As a group, this suite of studies contains both point of concordance and point of conflict (Herman-Giddens, 2004). Nevertheless, all together, they suggest that U.S. girls are maturing earlier with significant racial differences (Euling, 2005). None of these U.S. studies sheds light on what underlying factors might be driving the trend toward early puberty.

INTERNATIONAL TRENDS

In contrast to U.S. temporal patterns, the trend toward earlier maturation among European girls has plateaued (Parent, 2003; Castellino, 2005).

Denmark and the Netherlands, for example, t have good data on pubertal milestones in girls through the second half of the 20th century. In neither country are there signs of an ongoing decrease in average age at thelarche and menarche. Nor did the incidence of precocious puberty rise in Denmark during the period 1993-2001 (Teilmann, 2005). Indeed, average ages at thelarche and menarche that have remained unchanged for 30 years in Denmark are now a full year later than in the United States (Juul, 2006).

In Lithuania, no evidence was found for an increase in precocious puberty in Lithuanian school girls nor for a drop in average age of thelarche since 1985, despite the fact that the first decade of Lithuanian independence was marked by rapid transition to a market-based economy with intensive advertising of new products and adoption of Western lifestyles, including increases in cigarette smoking and alcohol consumption among children (Zukauskaite, 2005).

Prevalence of menses by age and race *(Tanner, 1962)*
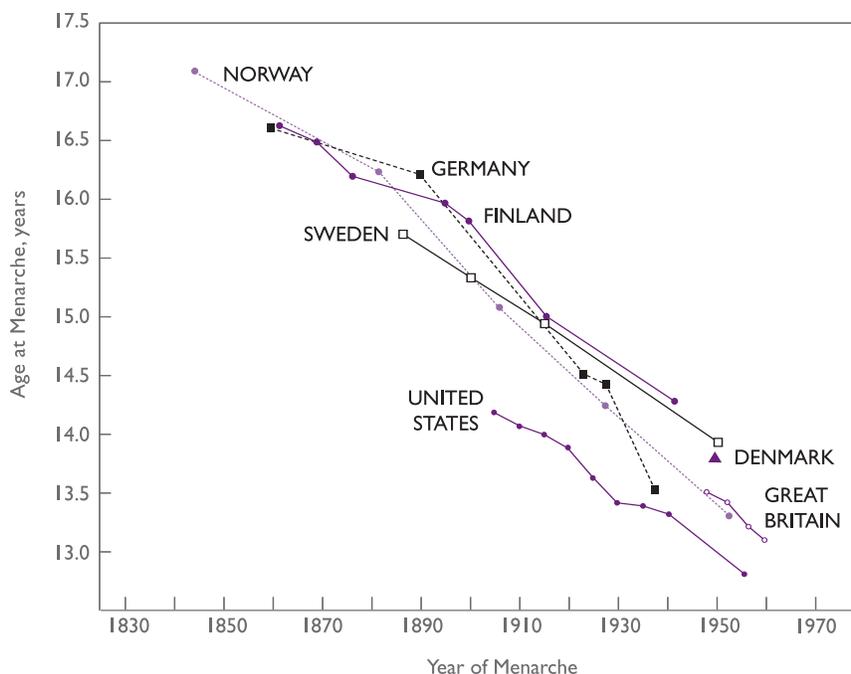
In spite of the stability in mean age at puberty for European girls, there are signs of more subtle changes, such as shifts in the variability of pubertal timing (Parent, 2003). Among Belgian girls, breast development appears to be occurring more rapidly without changes in age of onset. Among French girls, the time between onset of menarche and achievement of regular menstrual cycles appears to be lengthening (De Muinck-Keizer Schrama and Juul, 2006). Moreover, the proportion of European girls with idiopathic precocious puberty—that is, early activation of the HPG axis without evidence of a pathological cause—is increasing (Parent, 2003).

CONCLUSIONS

There are two important conclusions from the studies on the timing of menarche and puberty. First, average age of pubertal onset (as marked by thelarche or pubarche) in U.S. girls appears to have fallen faster during the last half century than menarchal age. Second, pubertal onset and menarche are not as tightly coupled to each other as they were in the past. Indeed, as the age of pubertal onset has fallen, the total time required for puberty to unfold appears to be increasing. That is, puberty is starting earlier and unfolding more slowly than it used to. As stated in the words of two of the leading researchers on this topic:

> In summary, recent U.S. studies show a probable decrease in the mean age of onset of breast and pubic hair of between 0.5-1.0 years between the 1960s and 1990s and a smaller decrease in the mean age of menarche in both white and black girls (Kaplowitz, 2006).

> The correlation of the age of onset of puberty with age of menarche has decreased significantly over the past 50 years. This suggests that although many of the factors associated with onset of puberty and with onset of menarche are similar, there are, increasingly, unique factors that are associated with the development of each over the past 50

HOW THE TIMING OF PUBERTY IS CONTROLLED

"It is important to recognize the onset of puberty not as a gonadal event, but rather as a brain event. Gonadal maturation is initiated by a nervous system that is informed by permissive internal and external signals" (Sisk and Zehr, 2004).

"Episodic release of GnRH is exquisitely governed by the interplay of a plethora of excitatory and inhibitory signals at the hypothalamus" (Papathanasiou and Hadjiathanasious, 2006).

THE ROLE OF GONADOTROPIN-RELEASING HORMONE

GnRH is the proximate cause of puberty. When neurons in the hypothalamus begin translating pulsating neural signals into pulsating chemical signals in the form of intermittent GnRH secretion, the HPG axis stirs to life and puberty begins. At first, the pulsing chemical secretions occur only at night while a girl is sleeping. Gradually, these pulses increase in frequency and amplitude and develop "spontaneous autorhythmicity" (Parent, 2003).

But what sits upstream of the GnRH neurons? What moves the prime mover? And what intrinsic and extrinsic factors modulate its rhythmical work? These questions do not yet have complete answers, although there are many tantalizing clues.

One mystery surrounds the nature of the control mechanism itself. Endocrinologists are not certain whether the HPG axis is actively arrested during the juvenile period (between infant puberty and adolescent puberty) or whether it is simply lying dormant (Ebling, 2005; Ojeba, 2006). In the former case, release from restraint requires the hormonal equivalent of a permissive gate. In the latter case, arousal requires a stimulatory wake-up call. In either case, the HPG axis appears never to lose its capacity for activation. At any point during juvenile period, chemical or electrical stimulation of the hypothalamus will induce the onset of puberty in a wide variety of animal species (Ebling, 2005).

Some researchers have posited the existence of a thermostat-like mechanism—a "gonadostat"—that gradually changes its sensitivity over time. Early in childhood, the very tiny amounts of estrogens that are released by the prepubertal ovary may serve as negative feedback, keeping the HPG axis in a dormant state. Over time, according to this model, there is a progressive decrease in sensitivity within the gonadostat to the suppressive effects of sex hormones. As the gonadostat becomes increasingly deaf to the signals from the ovary, its suppression of the hypothalamus loosens and puberty commences (Ebling, 2005). However, while the gonadostat

mechanism may be part of the story of pubertal control for many mammals, it may not exist for primates: monkeys that are castrated at birth still experience reactivation of the HPG axis in later juvenile life, even in the absence of any gonadal hormones whatsoever (Ebling, 2005). Among primate species, the central nervous system itself appears to provide much of the drive for puberty, independent of gonads. (Gore, personal correspondence; Gore, 2002; Terasawa, 2005).

THE ROLE OF LEPTIN

Leptin, a protein hormone produced by body fat, is almost certainly a player in the timing of puberty. However, it is not the starring actor that many had once predicted. First discovered in 1994, leptin provides information to the hypothalamus about the internal environment of the body. More specifically, it reports on fat reserves and, in so doing, it serves to maintain energy equilibrium. As body fat increases, leptin directs the hypothalamus to decrease calorie intake (through appetite suppression) and increase energy expenditure. Because leptin sends a constant stream of signals to the brain about the size of the body's energy stores (Tena-Sempere, 2006), it is a reliable measure of caloric availability. And because pregnancy and lactation represent enormous calorie expenditures for female mammals, leptin could, hypothetically, serve as the trigger for puberty, as it would guarantee that reproduction would not commence until sufficient fat reserves had been amassed.

But a variety of observations and lab experiments now suggest that its role is more modest. While leptin is required for puberty to proceed, and while it has the power to accelerate the rhythmic pulsations of the GnRH neurons, leptin cannot by itself trigger puberty in lab animals. Furthermore, leptin levels do not rise dramatically at the onset of puberty in girls, and GnRH neurons are located in a different area of the hypothalamus than the cells expressing leptin receptors. Ebling (2005) believes that low leptin levels may serve as a signal to delay puberty in circumstances where food is scarce. If so, leptin may serve more as permissive gate—perhaps in tandem with other upstream factors—than as active trigger. That is, once leptin has reached a certain threshold level, puberty may proceed as long as other needed signals are also in place (Papathanasiou and Hadjiathanasiou, 2006).

THE ROLE OF KISSPEPTIN

One such signal is a protein called kisspeptin. Produced by neurons in two areas of the forebrain, kisspeptin binds to receptors on GnRH neurons in the hypothalamus. In so doing, it stimulates the pulsatile release of GnRH. Furthermore, kisspeptin levels (and their receptor sites in the hypothalamus) increase dramatically at puberty. Thus, kisspeptin neurons in the forebrain appear to act as central processors in the regulation of GnRH secretion, and their signaling may well mediate the events that initiate puberty (Dungan, 2006).

In addition to kisspeptin, leptin, and melatonin, neurotransmitters in the brain also send signals to the GnRH neurons that can cause its hormonal drumbeat to seed up or slow down.

Let's move further upstream. What regulates kisspeptin-making neurons in the forebrain? Here is where the plot thickens. The short answer is that estradiol from the ovary does (along with testosterone from the testes). But it does so in opposite fashion depending on which of the two kisspeptin-releasing forebrain areas one looks at. In one area, estradiol suppresses kisspeptin production. In the other, it stimulates production (Dungan, 2006). Thus, if

kisspeptin neurons indeed serve as the posited "gonadostat," they do so in ways that are complex and incompletely explicated. Furthermore, the sensitivity of GnRH neurons to the stimulating effects of kisspeptin is not a static quality: among laboratory mice, the responsiveness of GnRH neurons to kisspeptin increases dramatically during the transition period from juvenile to adult—far exceeding that shown in both much younger or much older mice (Han, 2005). Ergo, something else upstream must prime the GnRH neuron for a magnified response to kisspeptin when the organism reaches the end of childhood.

Leptin itself appears to affect kisspeptin production. Kisspeptin neurons have receptors for leptin, and kisspeptin production goes down in times of undernutrition. Thus, kisspeptin and leptin seem to play co-starring roles in the metabolic control of puberty. They are, perhaps, subsidiaries of each other. Both are likely partners within a larger nexus of signals that originate from the body's internal environment and report on energy status (Tena-Sempere, 2006).

THE ROLE OF MELATONIN

Melatonin is a signaling agent that reports on the status of the external world. It, too, appears to influence pubertal timing, although its exact role in human sexual maturation is still under investigation (Pandi-Perumal, 2006). Secreted by the pine cone-shaped pineal gland in the center of the brain, melatonin production is regulated by environmental light/dark cycles. More specifically, melatonin is secreted during darkness in response to transduced signals received by the pineal gland from the retina of the eye. In so doing, melatonin levels not only display circadian day/night rhythms but also seasonal patterns. Melatonin thus functions as both clock and calendar. It is the body's "chronological pacemaker" (Pandi-Perumal, 2006).

Melatonin's possible role in puberty is suggested by consistent but circumstantial evidence. The human hypothalamus displays many receptor sites for melatonin. Moreover, melatonin levels remain very high throughout childhood and then drop precipitously during puberty and remain low throughout adulthood. Indeed, the pineal gland itself involutes during puberty and is among the first structures to calcify within the body (Yun, 2004).

These findings suggest that melatonin may function as an inhibitory signal for pubertal development (Murcia, 2002). Some researchers believe that elevated melatonin levels in childhood maintain the dormancy of the HPG axis. The progressive decline in melatonin levels is, according to this model, the activating signal that releases the HPG axis from its quiescence (Murcia, 2002). In support of this model, one Spanish study found significant differences in nighttime melatonin levels among girls with varying levels of breast development. Girls whose breast buds had just started to appear had higher levels of melatonin than girls with more advanced breast development (Murcia, 2002). Melatonin levels are unusually high in female athletes and anorexic girls and unusually low in girls with precocious puberty (Macchi and Bruce, 2004; Yun 2004). When girls with delayed puberty are successfully treated, their melatonin levels fall (Macchi and Bruce, 2004). Tumors in the pineal gland are known to alter the tempo of sexual maturation (Yun, 2004). High melatonin levels are frequently associated with particular kinds of infertility in adults, a finding that has prompted investigation into the use of melatonin as a contraceptive agent (Macchi and Bruce, 2004).

The possibility remains that falling melatonin levels are the consequence of HPG maturation rather than the cause (Macchi and Bruce, 2004). However, very recent evidence in seasonally-

breeding hamsters suggests that melatonin modulates kisspeptin signaling to drive pubertal development (Revel, 2006).

THE ROLE OF GABA AND GLUTAMATE: THE YIN AND YANG OF PUBERTAL INITIATION

In addition to kisspeptin, leptin and melatonin, neurotransmitters in the brain also send signals to the GnRH neurons that can cause its hormonal drumbeat to speed up or slow down. One neurotransmitter critical to the control of pubertal timing is gamma-aminobutyric acid. GABA actively suppresses GnRH neurons prior to puberty and many researchers believe it is the primary signal responsible for the juvenile hiatus of the HPG axis (Gore and Biro, personal communication). Indeed, a series of experiments with monkeys suggests that, for primates, the GABAergic neural system of the brain plays a central role in the timing of sexual maturation (Terasawa, 2005). In opposition to GABA, glutamate—an excitatory neurotransmitter that is also involved with memory and learning— stimulates GnRH production (Gore, 2002).

OTHER PUBERTAL SIGNALS

A constellation of neuropeptides, neurotransmitters and neurosteroids from many parts of the brain modulate the activity of GnRH release and thereby play a role in the timing of pubertal onset. These include opiods, corticotropin-releasing factors, noradrenalin,

epinephrine and dopamine, among many others (Genazzani, 2000). There is also evidence of communication between GnRH neurons and astroglial cells, the star-shaped cells in the brain that provide the neurons with insulation and nutrition (Muir, 2006). GnRH neurons also respond to insulin-like growth factor (IGF-1), a discovery that has prompted some researchers to posit that IGF-1 may be a common signal that regulates both growth and the initiation of puberty (Daftary and Gore, 2005).

CONCLUSIONS

In sum, many parts of the brain participate in the orchestration of puberty. These structures themselves are the receivers of messages streaming in from the internal environment of the organism's body as well as the external environment of the organism's habitat.

Kisspeptin and the KiSS-1 Gene

In spite of catchy headlines such as "Does Puberty Really Begin with a KiSS-1?" the gene and its protein were named not for their apparent role in the awakening of sexuality but after the chocolate candy that is manufactured in the city in which the gene was discovered: Hershey, Pennsylvania. The ability of KiSS-1 to regulate the timing of puberty was not recognized until some time later.

INSIGHTS FROM EVOLUTIONARY BIOLOGY

Humans are the only species of mammal that exhibit a wide variation in age of sexual maturation among normal individuals living in apparently similar conditions (Parent, 2003). We are also the only mammal with a pubertal growth spurt (Grumbach and Styne, 2003). In spite of such differences, lab experiments and field observations of other species offer potential insight into the possible external environmental signals that govern the timing of puberty in our own species and their evolutionary origins. The central lesson from these studies is that, throughout the mammalian class, sexual maturation in females is cued both by internal signals about body energy stores and by external cues about the safety and favorability of the environment, as well as about the availability and suitability of mates. Different species have evolved particular adaptive signaling mechanisms to influence the timing of puberty (Parent, 2003).

LIGHT/DARK SIGNALING

Puberty in seasonal breeders such as sheep is governed both by body size and day/night cycles. Sexual maturation does not begin until a sufficient body size is reached within a proper photoperiod. For the sheep, this means exposure to long days of summer followed by short days of autumn.

Humans are not seasonal breeders, but we used to be, and photoperiodic signals may still influence the timing of our sexual maturation—albeit in ways that are not completely understood (Muira, 1987). Before industrialization, most babies were born in the spring as the days grew longer. (Northern Europeans, with an excess of September births, were the exception to the rule, likely owing to the return of fishermen from the sea each December.) With the advent of industrialization, the spring birth peak shifted and randomized (Muira, 1987). In spite of this, onset of menarche remains somewhat seasonal. Significantly more girls begin menstruating in the winter months than in the summer, suggesting an ongoing role for photostimulation in the timing of puberty (Parent, 2003). In rank order, the distribution of first menses by season is winter, fall, spring and summer (Shuttleworth, 1938).

SOCIAL SIGNALING

For many rodents, the timing of sexual maturation is influenced by social factors as well as light (Foster, 1985). In the house mouse, timing of puberty is delayed when a young female is quartered with other females. It is accelerated in the presence of males (Agosta, 1992). However, family members of both sexes serve to inhibit

Among U.S. girls, absence of a biological father in the home is associated with early puberty. Presence of siblings in the household has been associated with later puberty.

puberty in females, quite likely as an evolutionary hedge against inbreeding, which produces genetically fragile offspring. When a young female mouse is removed from her family unit, puberty commences. Conversely, if an unrelated adult male is introduced into the family unit, puberty occurs (Agosta, 1992). The stimulating effect of the male stranger on female puberty has been documented in many other species including field mice, voles, lemmings, rats, pigs, cows and arboreal monkeys (Vanderbergh, 1983). By contrast, the presence of mothers can have a suppressive effect on puberty, as documented in rodents as well as two species of primates (Vanderbergh, 1983).

To complicate matters, for certain species, the presence of another animal can sometimes have a stimulating effect and sometimes a suppressive effect, depending on crowding (Vandenbergh, 1983; Donovan and Van der Werff ten Bosch, 1965). Among prairie voles, which exhibit boom-and-bust population growth patterns, the introduction of a stranger male triggers early puberty in young females only when population density is low and resource density high. As population density rises and available food falls, stranger males have no such effect on the sexual maturation of young females (Verner, personal correspondence).

PHEROMONES

Among rodents, the mechanism by which social cues time puberty is pheromones—chemical signals that influence the behavior of others.

Some of these pheromones have been identified and even synthesized. Puberty-suppressing pheromones in mice, for example, come from the adrenal gland. When the adrenal glands are removed from a female, she can no longer suppress puberty in her sister (Agosta, 1992). Mice exposed to adrenal-derived pheromones dissolved in water experience delayed puberty (Agosta, 1992).

The presence of pheromones among humans has not been verified. However, a single study has demonstrated that smelling a purified ingredient of male sweat (androstadienone) can alter hormone levels in women (Wyart, 2007). Moreover, some patterns of human sexual maturation are consistent with a pheromonal model. Among U.S. girls, absence of a biological father in the home is associated with early puberty. Presence of siblings in the household— especially sisters—has been associated with later puberty (Hoier, 2003; Matchock and Susman, 2006). Some researchers have speculated that girls who live in tight-knit families might be receiving pheromones that inhibit puberty, perhaps as an evolutionary mechanism to prevent incest and thereby inbreeding. This hypothesis is considered in more detail in Part Five.

CONCLUSIONS

In sum, the evolutionary history of the process of sexual maturation indicates that the timing of puberty among mammals is responsive to various environmental signals such as nutrition, light, family structure and population dynamics.

POSSIBLE CAUSES OF EARLY PUBERTY

What is driving the declining age of puberty in U.S. girls? What are the risk factors for precocious puberty? How can we explain racial and ethnic differences in the timing and tempo of puberty?

The evolutionary history of mammals indicates that sexual maturation among females is governed by a nexus of permissive and inhibitory signals streaming into the brain from both the internal and external environment of the organism. Thus, the answers to these questions will not be found in a simple list of autonomous factors but rather within a network of interrelated and interdependent agents. The discussion below attempts to tease out some of the most important agents while also seeking to understand how they are connected to others, both further upstream and downstream in the process. Many internal factors are themselves modulated by factors external to the organism.

In this, it is clear that heritable factors are not the whole story, although they do play a role in understanding pubertal patterns in families. Identical twin sisters show greater correlation in pubertal onset than do fraternal twins (Muir 2006), and mothers and daughters exhibit similarities in pubertal timing and tempo (Grumbach and Styne, 2003). However, genetics alone cannot explain racial and ethnic differences. Menarche is one full year earlier in U.S. black girls than in black South African girls from well-off families (Parent, 2003). Wealthy black girls in Cameroon also begin menstruation far later than U.S. black girls (Parent, 2003). In Kenya, average age at thelarche is 13, as compared to 8.9 for U.S. black girls. On average, Kenyan girls reach menarche four years later than U.S. black girls (Grumbach and Styne, 2003).

Genetics alone cannot explain racial and ethnic differences. Menarche is one year earlier in U.S. black girls than in black South African girls from well-off families.

A. Low Birth Weight and Premature Birth

Premature birth and low birth weight that results from intrauterine growth retardation are both well-established risk factors for precocious puberty in girls, in particular precocious pubarche (Ibanez, 2006; Neville and Walker, 2005; Parent, 2003; Veening, 2004). That is, birth before week 37 of pregnancy or small size for one's gestational age (less than 5.5 pounds at 40 weeks) both dramatically increase the chances that a girl will develop pubic hair before the age of 7.

COMPENSATORY GROWTH AFTER LOW BIRTH WEIGHT

The reasons for the association between premature pubarche and low birth weight are elusive. It is known that excess weight gain during childhood is a predisposing factor for premature pubarche and that girls born early or small for date often exhibit compensatory catch-up growth that results in chubbiness (Auchus and Rainey, 2004; Grumbach and Styne, 2003). Among French girls with precocious pubarche, 31 percent were obese (Charkaluk, 2004). In a recent Australian study, 65 percent of girls with precocious pubarche were overweight or obese; 34 percent were born small for date, and 24 percent had been premature. However, of the girls of normal weight who exhibited precocious puberty, two-thirds had a history of small for date or prematurity (Neville and Walker, 2005). Thus, with or without subsequent rapid weight gain, entering the world as a very small baby is a predisposing factor for early pubarche.

POSSIBLE MECHANISMS

Hyperinsulinism may underpin the association among low birth weight, early pubarche and excess weight gain in childhood (Neville and Walker, 2005; Remer and Manz, 1999). With rapid weight gain, insulin sensitivity decreases. Blood insulin levels then rise to compensate. But insulin not only regulates glucose uptake, it also regulates the secretion of androgens from the adrenal gland. The adrenal cortex has receptors for insulin and insulin growth factors (Remer and Manz, 1999). The increased blood levels of insulin that result from rapid weight gain may thereby boost androgen production from the adrenal glands (Neville and Walker, 2005). It is these hormones that trigger the growth of pubic hair. Hyperinsulinism may also play a role in altering the timing of sexual maturation in girls with low birth weights who are not chubby or obese. Of note, girls of normal weight with precocious pubarche who were treated with an insulin sensitizer did not go on to develop polycystic ovary syndrome (Ibanez, 2004).

Hyperinsulinism brought on by restricted prenatal growth is part of a sequence of events described by British epidemiologist David Barker as part of his hypothesis about the fetal origin of adult diseases (Barker, 1990), which built on earlier work on fetal programming of the brain (Stein, 1975). In brief, the Barker Hypothesis posits that fetuses respond to prenatal stress by diverting resources to the developing brain at the expense of other tissues. The consequence is not only a small-sized baby at birth but enduring changes in function that predispose the individual for adult-onset diseases. Risks for diabetes, obesity, hypertension and heart disease are all increased with low birth weight. "Fetal programming" is the term used to describe the alterations in genetic expression or genetic imprinting that create functional deficits, which manifest themselves later in life (McMillen and Robinson, 2005).

More recently, the concept of fetal programming has been expanded to consider not only the effects of malnutrition in utero, which was Barker's focus of study, but also the effects of prenatal chemical exposure on gene expression and imprinting and thereby growth and development. For example, exposure to high levels of ambient air pollution in early pregnancy has been linked to low birth weight (Ritz and Yu, 1999), as have prenatal exposures to tobacco smoke, wood preservatives, alcohol and drinking water contaminants (for a discussion of these many studies, see Steingraber, 2001).

The incidence of low birth weight is rising among low-risk, non-smoking mothers in the United States, as is the rate of prematurity (Behrman and Butler, 2006; Martin, 2005; Pew Environmental Health Commission, 2000). These increases may be driving the coincident increase in early pubarche among U.S. girls, for which low birth weight and prematurity are predisposing factors. In the United States, low-weight births have climbed 16 percent and premature births 18 percent just since 1990 (Martin, 2005). Since 1981, premature births have jumped 30 percent (Behrman and Butler, 2006). One in eight U.S. infants are now born before the end of week 37 of pregnancy (Martin, 2005; Hileman, 2001). There are significant racial disparities: 17.8 percent of U.S. black babies arrive prematurely, while only 11.5 percent of U.S. white babies do (Berhman and Butler, 2006).

Like low birth weight, prematurity has many possible causes, one of which is exposure to chemicals that shorten gestation time (Berhman and Butler, 2006). These include industrial chemicals, pesticides and air pollutants (Berhman and Butler, 2006; Hileman, 2001; Steingraber, 2001). Most recently, maternal consumption of mercury-contaminated fish has been demonstrated to shorten human gestation and

contribute to prematurity. In a study of Michigan women who ate fish during pregnancy, those who delivered before 35 weeks' gestation were more likely to have hair mercury levels at or above the 90th percentile (Xue, 2007). Similarly, a phthalate plasticizer used to soften vinyl, DEHP (di-(2-ethylhexyl)-phthalate), has been linked to preterm birth in an Italian study that measured its metabolite (MEHP) in umbilical cord blood. This study relied on a small sample size and therefore requires replication (Latini, 2003). However, the researchers were able to identify a potential mechanism—the inducement of inflammation—by which prenatal exposure to DEHP appears to shorten gestation. Inflammatory response (chorioamnionitis) is a leading cause of preterm birth (Latini, 2006).

CONCLUSIONS

In sum, small size at birth—whether caused by early arrival or restricted growth in utero—makes girls susceptible to early pubarche. Alterations in insulin levels, which affect adrenal functioning, appear to be the likely mechanism. Low birth weight and prematurity are on the rise within the United States, even among low-risk mothers, and emerging evidence suggests that environmental factors may be playing a role in both trends.

B. Obesity and Weight Gain

The trend of increasing body mass for U.S. girls parallels the trend for earlier puberty (Anderson, 2003; Anderson and Must, 2005; Biro, 2006c). On average, children eat 150 to 200 calories a day more than they did 30 years ago (Biro, 2005), and their obesity rates have tripled (Foxhall, 2006). Changes in body mass index (BMI) over the past three decades have been more pronounced in

black girls than in white girls, with a higher percentage of black girls now obese or overweight (Ogden, 2002). As a group, black girls also reach puberty sooner than white girls (Kaplowitz, 2001). A recent national study of pre-school-age children from urban, low-income families found that 35 percent were overweight by the age of three. Hispanic children were the fattest, with 44

percent overweight or obese (Kimbro, 2007). As a group, Mexican-American girls are currently exhibiting the most rapid ongoing decline in age at menarche (Anderson and Must, 2005; Kaplowitz, 2006).

Is the downward shift in pubertal development causally linked to the childhood obesity epidemic—or are these simply coincident trends? Do differences in body mass help us understand racial disparities in timing of puberty? And, if so, is it body fat or rate of weight gain that's more important? Or is it lack of exercise?

EVIDENCE LINKING WEIGHT GAIN TO EARLY PUBERTY

No studies demonstrate direct causality between body mass, fatness or sedentariness and early puberty, but there are reasons to believe that these factors are linked. As we have seen, chubbiness—especially when combined with low birth weight—raises the risk for premature pubarche. In the case of pubarche, rapid weight gain, rather than high BMI per se, appears to be the trigger for early onset. (Remer and Manz, 1999). Many other studies demonstrate that childhood obesity is associated with earlier menarche and thelarche (Anderson and Must, 2005; Biro, 2006c; Parent, 2003). Moreover, pubertal six- to nine-year-old girls have higher BMI scores than prepubertal girls of the same age (Slyper, 2006; Kaplowitz, 2006).

Although it is certainly possible that the onset of puberty itself is triggering increased body fatness, at least four longitudinal studies have now found that body fat precedes and predicts pubertal timing. Among 181 white girls in Pennsylvania, those who were chubbier in early childhood were more likely to exhibit earlier pubertal development relative to peers at nine years of age (Davison, 2003). A longitudinal study from

Louisiana found that fatter children tended to experience menarche sooner than thinner children: each standard deviation increase in BMI doubled the odds for early menarche (Freedman, 2003). High BMI during childhood also predicted earlier menarche in a cohort of Australian girls who were followed from prenatal life (18 weeks of pregnancy) to adolescence (12 to 14 years). In this study, lower- than-expected birth weights coupled with rapid weight gain in childhood showed the strongest association with young age at menarche (Sloboda, 2007). Similarly, a University of Michigan study that followed 354 girls from their third birthdays through sixth grade found that higher body fatness at age three was associated with earlier thelarche. Rate of change was also important: the faster that body fatness increased between ages three and six, the greater the chances that breast budding would begin by age nine. In this study, nearly half of the girls in this cohort had entered puberty by nine (Lee, 2007).

Multiple studies show that early maturing girls are more likely to become obese in adulthood (Slyper, 2006), but much of this association is apparently attributable to the greater BMI of the early bloomers: fatter children enter puberty sooner and are also more likely to become fatter adults (Freedman, 2003). Girls who eat more animal protein in early childhood have earlier menarche than those who eat less (Berkey, 2000). A study of Belgian girls found an association between soft drink consumption and age at thelarche and menarche (Vandeloo, 2007).

Girls who enter puberty with breast development first and pubic hair development second tend to be fatter than girls who enter puberty through the pubic hair pathway (Biro, 2003a). This finding is consistent with the fact that body fat itself is estrogenic: fat tissue manufactures the enzyme aromatase, which converts androgens to estrogens. And fat cells secrete leptin. Leptin not

only regulates food intake but also serves as a permissive agent for HPG activation and thereby breast development. Obesity, which represents a dysfunctional energetic state, results in leptin resistance and elevated circulating leptin levels (Mitchell, 2005).

THE ROLE OF HYPERINSULINISM

But there are equally compelling reasons to believe that the increased fatness of U.S. girls is not the whole story behind their falling age of puberty. For example, BMI profiles for six- to nine-year-old children are similar in Denmark and the United States, and yet pubertal onset among Danish girls is a full year later (De Muinck-Keizer Schrama and Juul, 2006). Fatter girls enter puberty sooner, but obesity cannot explain the marked differences between timing of puberty of U.S. and Danish girls (Juul, 2006).

The body mass index for six- to nine-year-old children is similar in Denmark and the United States, yet pubertal onset among Danish girls is a full year later.

Furthermore, within the United States, although early maturing white girls are heavier at the time of puberty, this is not the case for black girls (Slyper, 2006). Leptin levels are higher in blacks, even after adjustment for pubertal stage and fat mass, and black girls still have earlier onset of puberty even when differences in BMI are factored in. Black girls also have decreased insulin sensitivity even after adjusting for body fat (Slyper, 2006; Kaplowitz, 2006, 2004). These racial disparities suggest an alternative hypothesis: the falling age of puberty is not a direct consequence of increasing fatness per se, but is a result of increasing hyperinsulinism among U.S. children (Slyper, 2006).

Calorie-dense diets and sedentary lifestyles certainly contribute to the development of hyperinsulinism and insulin resistance (Slyper, 2006), which can lead to metabolic syndrome and type 2 diabetes. Emerging evidence suggests that exposure to chemical pollutants can also contribute to hyperinsulinism. Chlorinated pesticides and polychlorinated biphenyls (PCBs) have been associated with insulin resistance in non-diabetic adults (Lee, 2007), as have phthalates (Stahlhut, 2007) to which U.S. girls are known to be exposed (see section E below). A number of studies have also found connections between exposure to dioxin-like compounds and risk of diabetes (Porta, 2006). These fat-soluble chemicals bind to genes in the liver that are involved in the regulation of glucose uptake (Remillard and Bunce, 2002). A recent analysis of National Health and Examination Survey data revealed a strong dose-response relationship between blood levels of dioxin-like compounds and diabetes in adults. Prevalence of diabetes was three to five times higher in individuals with higher concentrations of contaminants. Moreover, obesity was a risk factor for diabetes only for individuals with a blood concentration of pollutants above a certain level. In people with very low levels of pollutants, there was no association between obesity and diabetes (Lee, 2006). This finding suggests that obesity may confer risk of diabetes by serving as a vehicle for fat-soluble chemicals (Porta, 2006). This study did not attempt to identify the underlying mechanism of action.

U.S. black girls still have an earlier onset of puberty even when difference in body mass are factored in…The falling age of puberty may be a result of increasing hyperinsulinism among children.

ENVIRONMENTAL ROOTS OF OBESITY

While obesity itself clearly has its roots in dietary choices—both individual and cultural—recent evidence suggests environmental links as well. "Environmental obesogens" refer to chemical contaminants that act to disrupt homeostatic control over energy balance or stimulate the growth of fat cells. Organotins are one. These are a family of chemical compounds made of tin and carbon that are used as antifungal agents, wood preservatives and heat stabilizers in the manufacture of vinyl plastics (Grun and Blumberg, 2006). Mice exposed to the pesticide dieldrin doubled body weight, and hexachlorobenzene had similar effect (Keith 2006). Endocrine disruptors that are anti-androgens may direct more nutrition to a fattier body composition (Keith, 2006). Prenatal exposure to the plastic compound bisphenol A speeds growth in juvenile female mice such that they are heavier at puberty than untreated females (Howdeshell, 1999), and new evidence from mouse studies shows that prenatal exposure to bisphenol A can cause low birth weight followed by rapid, overcompensating growth leading to obesity (vom Saal, 2007). The impact of environmental obesogens on human growth patterns is largely unknown. However, one human study found larger body size in adolescents who were exposed to higher prenatal levels of DDT (Gladen, 2000). The modulation of lipid metabolism is now recognized as yet another route by which endocrine-disrupting chemicals can exert their effects (Tabb and Blumberg, 2006).

CONCLUSIONS

In sum, the increasing fatness of U.S. girls and the ongoing obesity epidemic among children are probably contributing to earlier sexual maturation but in ways that are not entirely clear. These factors seem to place a lesser role in determining the timing of puberty in black girls, for whom obesity rates are higher than white girls. The recent discovery of very high rates of obesity among U.S. Hispanic three-year-olds lends urgency to the need to learn more about the relationship between body mass indices and the falling mean age of menarche among Mexican American girls. Understanding more about the prevalence of hyperinsulinism and insulin resistance in all U.S. girls—but especially black girls—is a high priority for research as is an investigation of the possible links between chemical exposures and altered insulin levels in children. In addition, the contributing role of hyperinsulinism to early puberty is a research topic of great concern.

C. Formula Feeding

FORMULA FEEDING AND PUBERTAL TIMING

Several studies show that formula-fed infants have higher body fat than breastfed babies, a difference that persists into adolescence. Breastfed infants tend to self-regulate their energy intake and are less likely to overeat (Novotny, 2003). Formula-feeding in infancy also alters lipid metabolism in ways that have life-long consequences. Individuals who were formula-fed in infancy have higher blood cholesterol levels in adulthood (Bergstrom, 1995). A recent national study of overweight among three-year-olds found that prolonged bottle-feeding was an important predictor of childhood obesity (Kimbro, 2007). There are deep

racial disparities in breastfeeding rates among U.S. mothers. In 2004, 71.5 percent of U.S. white infants were ever breastfed, as compared to only 50.1 percent of U.S. black infants. Differences between black and white breastfeeding rates existed within most socioeconomic subgroups studied (Centers for Disease Control, 2006).

Is formula feeding a risk factor for early puberty? Only one study has pursued this question directly. In an investigation of 300 girls in Hawaii, those who were formula-fed as infants deposited more fat as adolescents and reached menarche significantly sooner (Novotny, 2003).

Supporting evidence for this study comes from the veterinary literature. In the U.S. dairy industry, precocious puberty among heifers is a desirable outcome. It is accomplished by early weaning of infants followed by confinement and continuous feeding of a high-calorie diet (Gasser, 2006). These feeding practices are roughly mimicked by many human families in the United States, which has the lowest rate of breastfeeding in the developed world and the highest rate of childhood obesity.

Questions about soy-based infant formulas have also been raised. Consumed by one-quarter of U.S. infants at some point during their first year, soy formula contains high levels of phytoestrogens—that is, botanical substances with structural similarities to estrogen (Barrett, 2002). Genestein and daidzein are two such compounds found in soy, and they are known to alter reproductive functioning in laboratory animals at levels similar to those received by soy-fed infants. The human data on the risks and benefits of soy consumption are conflicting for adults and scanty for infants (Tuohy, 2003). Infants fed soy formulas do absorb and excrete phytoestrogens and exhibit alterations in cholesterol synthesis (Cruz, 1994). No

differences in pubertal maturation rates were found in a cohort of women in Iowa who had been fed soy formula as infants when compared with those fed cow milk formula, although those receiving soy as infants did report longer duration of menstrual bleeding in adulthood (Strom, 2001).

Precocious puberty among heifers is a desirable outcome in the U.S. dairy industry. It is accomplished by early weaning of infants followed by confinement and continuous feeding of a high-calorie diet. These feeding practices are roughly mimicked by many human families in the United States.

In addition to providing fewer calories than either soy or cow milk formulas, mother's milk may contribute growth factors that modulate the programming of the HPG or HPA axis during infant puberty, as well as the neural circuitry that both controls and responds to their hormonal messages. Breast milk, for example, contains melatonin—a puberty inhibitor (Macchi and Bruce, 2004).

CONCLUSIONS

The contribution of formula feeding on pubertal timing is a critical question that deserves further study. Breastfeeding appears to protect against early sexual maturation in two ways: certainly because it contributes fewer calories during infancy; and, quite possibly, because it contain hormones and other growth factors that may program the development of the HPG axis in ways that inhibit its premature activation. Lower rates of breastfeeding in black families may partially explain the earlier maturation of U.S. black girls when compared to whites. Cultural and economic barriers to breastfeeding within communities of color need to be identified and addressed.

D. Physical Inactivity

Not only do U.S. girls eat more calories per day than they did three decades ago, they exercise less (Strauss, 2001; U.S. Centers for Disease Control and Prevention, 2004). Physical activity indices are lower for black and Hispanic girls and for girls living in low-income families (Gordon-Larsen, 2000). Physical activity also declines as girls, both black and white, move through adolescence, but activity declines are greater for black girls. By the age of 16 or 17, half of black girls and almost one-third of white girls engage in no habitual physical activity at all (Kimm, 2002). The availability of a community recreation center along with participation in daily physical education (PE) classes both significantly increase moderate-to-vigorous activity patterns among children. However, recess and physical education are a lesser part of school curricula now than in decades past, with only one in five adolescents now participating in at least one day per week of PE in their schools (Gordon-Larsen, 2000). Only the state of Illinois requires daily PE from kindergarten through high school. There is no federal law that requires PE to be provided in schools, nor any incentive to do so (National Association for Sports and Physical Education, 2006).

EFFECTS OF EXERCISE ON THE HPG AXIS

Exercise is protective against early puberty, but through mechanistic pathways that are not clearly understood. As a group, bedridden girls have earlier than average puberties while female athletes have later puberties (Grumbach and Styne, 2003). It is difficult to tease apart leanness from the effects of exercise. Girls with anorexia tend to have

delayed puberties, as do gymnasts, runners and ballet dancers (Grumbach and Styne, 2003). There is some evidence that exercise all by itself is protective against early puberty. Elite swimmers and ice skaters also have later puberties, and these girls are typically of normal weight (Grumbach and Styne, 2003). Sport competition, however, also brings with it psychological as well as physical stress (Parent, 2003), and it is difficult to isolate the relative contribution of each to pubertal timing.

Exercise delays thelarche but not pubarche (Grumbach and Styne, 2003), so the puberty-delaying effects of exercise appears limited to its effect on the HPG axis. Strenuous training all by itself can inhibit the GnRH pulse generator—perhaps by raising melatonin levels (Macchi and Bruce, 2004)—but the role of energy expenditure in pubertal onset is not clear. Some evidence suggests that negative energy balance during intense physical training modifies the set point of the GnRH system in ways that delay pubertal development (Georgopoulos, 2004). Endorphins may also modulate hormonal pulses (Grumbach and Styne, 2003).

CONCLUSIONS

In sum, leanness and exercise appear to work together to delay puberty. These two factors are so tightly associated with each other that it is difficult to assess their individual contribution to the timing of sexual maturation. On a practical level, however, there is enough evidence to recommend individual and social changes—including changes to the built environment and to educational curricula—that encourage the physical activity of girls.

E. Psychosocial Stressors

FAMILY DYSFUNCTION AND CHILD SEXUAL ABUSE

Multiple studies have reported a connection between family relationships and the timing of menarche. As a group, girls in stressful home environments and those who have suffered child sexual abuse reach menarche sooner (Bellis, 2006; Ellis and Garber, 2000; Ellis, 1999; Kaplowitz, 2004; Moffit, 1992, Zabin, 2005). Most of the relevant studies in this area are published in the psychological and anthropology literature, and they rely on questionnaires or interviews to ascertain the timing of puberty. Menarche, rather than thelarche or pubarche, is used a marker for pubertal maturation because the date of its arrival is more accurately recalled by interview subjects. Thus, in spite of the consistency of data on stress/abuse and menarchal timing, there exist very little data about their impact on the actual onset of puberty.

These studies are nevertheless impressive in their consistency across geographic and cultural boundaries, with European data largely corroborating U.S. data. In Poland, for example, girls exposed to prolonged familial dysfunction reached menarche four months earlier than girls living in families free of traumatic events (Hulanicka, 2001). Similar results were reported in French-speaking Canada, where adverse family conditions and high anxiety were correlated with precocious puberty (Tremblay and Frigon, 2005). Childhood sexual abuse lowers age of menarche in New Zealand girls (Romans, 2003). However, war conditions in Bosnia caused delays in menarchal ages among girls so exposed (Tahirovic, 1998). In this case, extreme psychological stress was also accompanied by physical injury and poverty.

FATHER ABSENCE

Father absence—but not mother absence—is consistently associated with early menarche (Ellis, 1999; Hoier, 2003; Maestripieri, 2004; Matchock and Susman, 2006), and the longer the absence, the earlier the first menstruation (Moffit, 1992). More time spent by fathers in childcare, more father-daughter affection and more paternal investment in the family all appear to be protective against early puberty among U.S. girls (Ellis, 1999).

High contemporary rates of divorce and single-parent households not withstanding, it is not clear that father absence is more common now than in previous times. The demands of war, hunting, fishing, farming, shipping, slave labor, wage labor, homesteading and mining—along with death from infectious diseases—have absented countless fathers from daughter-filled households at many points in U.S. history. (Indeed, father absence is the central plot device in that most famous young adult American novel, *Little Women*, with its four pubertal heroines.) It seems unlikely that father absence alone could be responsible for driving down the average age of pubertal onset in U.S. girls during the past half-century. More plausibly, father absence may be contributing to the ongoing racial disparities in pubertal timing among white and black girls, but this is not a question that has been directly examined as yet.

PHYSIOLOGICAL STRESS RESPONSES

The possible mechanism behind the link between early puberty and familial stress has received some attention. Cortisol released as part of a stress response may modulate hormones in ways that encourage early puberty (Bogaert, 2005).

Early childhood experiences are known to shape the basal rhythms of the HPA axis and set its reactivity (Tarullo and Gunnar, 2006). Maltreated children have altered HPA axes and respond to stress differently (Tarullo and Gunnar, 2006).

EVOLUTIONARY CONSIDERATIONS

Other researchers, positing an evolutionary explanation, argue that early puberty in response to stressful conditions is a reproductive strategy that developed early in human evolution (Belsky, 1991). According to this model, "ancestral females growing up in adverse family environments with uncertain futures may have reliably increased their reproductive success by accelerating physical maturation and beginning sexual activity and reproduction at a relatively early age" (Ellis and Garber, 2000). The inhibitory effect of father presence on puberty in daughters may be part of an ancestral mechanism for incest avoidance—as seen in rodents. (For a thoughtful review of the father absence literature, see Macleod, 2007).

This model also predicts that the presence of an unrelated male in the household should accelerate puberty—putatively through pheromonal cues. Stepfather presence, independent of father absence, was correlated with early puberty in one study (Ellis and Garber, 2000) but not another (Bogaert, 2005). A recent study reported that the household presence of half- and step-brothers accelerated menarche, while the presence of sisters, especially older sisters, was associated with delayed menarche (Matchock and Susman, 2006). A German study found that living in a household with younger siblings decelerated menarche (Hoier, 2003).

Do girls exposed to psychosocial stressors eat more as a compensating mechanism? Few studies have examined diet or body mass in the context of father absence and early puberty. One study that has found that father absence significantly contributed to early puberty over and above the effect of weight (Moffit, 1992).

CONCLUSIONS

In sum, child abuse and family stress, including father absence, are consistently linked with early menarche for reasons that have not been fully elucidated. Dietary assessment needs to be part of future psychosocial studies, as does pubertal assessment that examines the onset of thelarche and pubarche and not just menarche. The socioendocrinology of human development—and the posited existence of human pheromones—is poorly understood and requires further investigation.

Child abuse and family stress, including father absence, are consistently linked with early menarche for reasons that have not been fully elucidated.

F. Television Viewing and Media Use

aMany parents have wondered whether the sexualized content of television programming and other media used by children may be serving as a permissive signal to the neurohormonal apparatus that controls pubertal onset. Harvard psychologist and media watchdog Susan Linn has documented a dramatic increase in erotic marketing messages aimed at pre-teen girls—thong underwear for 10-year-olds, for example (Linn, 2005)—and researchers in North Carolina have demonstrated that early-maturing girls seek out

Early-maturing girls seek out sexual media imagery significantly more than late-maturing girls.

sexual media imagery significantly more than later-maturing girls regardless of age or race (Brown, 2005). Exposure to sexy media matter is also known to accelerate sexual initiation among white adolescents (Brown, 2006).

However, the impact of media content on the timing of puberty itself is not a question that has been tested empirically. Indeed, it is difficult to even imagine how such a study could be designed as almost nothing is known about how sensory input of any kind modulates the pace of human sexual maturation. And, in contrast to the wealth of studies that have documented the impact of media violence on boys, scant research has been directed toward investigating the effects of sexualized media on girls (Levin, 2005). A recent report by the American Psychological Association did find that exposure of girls to sexualized media images raised the risk for mental health problems but did not investigate the impact on pubertal timing (American Psychological Association, 2007).

Certainly U.S. children are immersed in media, and their engagement has increased dramatically over the past three decades. Children in the United States watch an average of three hours of television per day. With video games and other media formats included, daily screen time can be far higher (Christakis, 2004; Gentile, 2004). Media use increases with age but is high in all age groups, including among children under two (Certain and Kahn, 2002), although the American Association of Pediatrics openly discourages television viewing before age two and advocates limits of less than two hours per day for older children (American Association of Pediatrics, 2001). Among pre-schoolers, children from non-white families and low-income families watch more TV each week than

white children and those from higher incomes (Dennison, 2002). A national random sample revealed that children ages eight to 18 devote more time to media than any other waking activity—about one-third of each day (Roberts, 2000). In this study, media was defined to include Internet, computer games and personal music devices as well as television, videos, books and magazines.

MEDIA USE AND CHILDHOOD OBESITY

Television/video viewing is associated with overweightness and obesity among both pre-schoolers and school-aged children in a dose-dependent manner. That is, the more TV, the higher the risk for obesity (Dennison, 2002). However, the specific mechanisms are not well understood (Cooper, 2006). Children who watch lots of television are more sedentary (Dennison, 2002) and also have lower energy expenditure while resting (Cooper, 2006). Among U.S. girls, those who averaged more than two hours per day of television viewing had significantly higher body mass indices and were 13 times more likely to be overweight by age 11 than girls who watched less television (Davison, 2006).

MEDIA USE AND MELATONIN

One observational study from Italy has investigated the effects of television and computer viewing on melatonin production. The hypothesis was that light and electromagnetic radiation may disturb melatonin production and thereby accelerate pubertal onset. Researchers found that children ages six to 13 who were denied access to television, computers and videos for one week experienced a 30 percent increase in melatonin levels (Salti, 2006).

CONCLUSIONS

Little is known about the effects of sexualized media content on pubertal timing in girls. Distinct from the message, the medium of television itself (as well as that of video and computer) is potentially relevant to pubertal timing through at least two different routes. Increased screen time is associated with increased obesity and physical inactivity in children, both of which are known to modulate the onset of sexual maturation. Increased screen time may also lower production of melatonin, an inhibitory signal to the HPG axis. The latter association is based on a single pilot study that requires further confirmation or refutation.

....

G. Environmental Exposures

"Are chemicals in the environment causing girls to mature sooner?" —question posed in the concluding paragraph of a recent analysis of pubertal time trends (Anderson and Must, 2005).

As described earlier, chemicals in the environment may indirectly contribute to early puberty by shortening gestation time, lowering birth weight and increasing risks for obesity and insulin disregulation—all of which, in turn, may increase the risk for early puberty. Here we examine how chemical exposures may alter the timing of sexual maturation through direct impact on the HPA or HPG axis.

THE VULNERABILITY OF THE HPG AND HPA AXES TO ENDOCRINE DISRUPTION

Endocrine-disrupting chemicals are substances that disregulate some aspect of the endocrine system. They can exert their effects in a number of ways: by mimicking hormones, blocking their uptake by receptors, altering the rate of their synthesis or secretion, interfering with their metabolism or elimination from the body or altering the number of hormone receptor sites and thereby making the body more or less sensitive to its own hormonal signals. Not only can endocrine disruptors sabotage any one hormonal signal through a multitude of tactics, the HPG and HPA axes are designed to respond to a multitude of hormonal signals. Furthermore, any one hormone can send a variety of messages to these axes depending on the timing of its receipt and its concentration in the bloodstream. For example, estradiol from the ovaries sometimes serves as a negative feedback to the hypothalamus, causing it to slow down the tempo of its GnRH pulse generator. At other times, estradiol serves to accelerate hypothalamic maturation, which quickens the pulse generator's tempo (Massart, 2006). New evidence also suggests that the prepubertal breast responds non-monotonically to estradiol. That is, at low doses, estradiol can induce development of breast tissue, while high doses inhibit it (Vandenberg, 2006). To add to the intricacy, intermittent exposures may have different effects than continuous exposures (Parent, 2003).

In short, the neuroendocrine instrument that controls pubertal

> **Chemicals in the environment may contribute to early puberty by shortening gestation time lowering birth weight, and increasing risks for obesity and insulin disregulation. They may also alter the timing of sexual maturation through direct impact on the HPG axis.**

Dioxin interferes with the production of GABA, a neurotransmitter believed to be the major inhibitor of the HPG axis in early childhood.

timing is, by its very complexity, innately vulnerable to perturbation by endocrine-disrupting chemicals. Such disruption could proceed through any number of pathways and lead to outcomes that are not easily predictable.

Other recent studies demonstrate the exquisite sensitivity of children to sex hormones even during the quiescent period between infant and adolescent puberty. Estradiol concentration in prepubertal girls is very low—one hundred times lower than previously thought (Aksglaede, 2006). However, estrogen receptors are expressed in target tissues throughout childhood. Thus, prepubertal girls are highly sensitive to sex hormone exposures, which may influence the timing of pubertal maturation. Even in infancy, girls respond differently than boys to estrogen exposures, indicating that fetal programming has already begun to organize the endocrine system. For example, although many infants respond to maternal estrogen exposure received in utero and through breast milk by developing palpable breast tissue (which typically recedes by three months of age) transient infant breast development is a much more common phenomenon in girls than boys (Aksglaede, 2006). Indeed, premature thelarche in girls can occur throughout the juvenile period and has been correlated with elevated estradiol levels (Aksglaede, 2006). It is reasonable, then, to predict that girls would be sensitive to estrogenic environmental chemicals, which contribute a higher proportion of sex hormone levels in a prepubertal child than previously thought (Aksglaede, 2006).

SEXUAL DEVELOPMENT AFTER ACCIDENTAL EXPOSURES TO ENDOCRINE-DISRUPTING CHEMICALS

In the absence of controlled testing of hormonally-active chemicals in human subjects, epidemiologic studies of children inadvertently exposed to known or suspected endocrine disruptors offer important clues. One such accident occurred in Michigan in 1973 when estrogenic chemical flame retardants (polybrominated biphenyls or PBBs) were mixed into commercial cattle feed. Before the mistake was discovered, farm families and others, including pregnant and nursing mothers, consumed meat and dairy products from the poisoned cows. Their daughters—now women of reproductive age—have been followed since birth. Elevated PBB levels in mothers were associated with earlier menarche in daughters: the girls exposed to the highest levels of PBBs in utero and in breast milk began menstruating up to a year earlier than girls with lesser exposures. High PBB exposure was also associated with earlier pubarche. The data on thelarche was inconclusive (Blanck, 2000).

In Puerto Rico during the 1970s, 500 children developed isolated premature thelarche or true precocious puberty. By 1991, that number had risen to more than 3000. Some evidence of estrogenic contamination of food was discovered, but no single culprit was ever identified (Partsch and Sippell, 2001).

Three other such studies come from Italy. In 1977, three- to seven-year-old boys and girls who all attended the same school in Milan developed breasts. Elevated blood levels of serum estradiol levels were documented. Poultry and veal from the school cafeteria were suspected sources, but their contamination was

never confirmed (Fara, 1979). Some of the girls in this cohort went on to exhibit early menarche (Parent, 2003). Similarly, in northwest Tuscany, researchers documented a cluster of true precocious puberty among girls living in a particular geographic area with a high density of naval yards and greenhouses (Massart, 2005 and 2006).

In Seveso, Italy in 1976, a chemical explosion exposed residents to the highest levels of dioxin experienced by a human population, including children. Girls eight and younger at the time of the explosion did not show associations between menarchal timing and dioxin exposure, according to a 2005 follow-up study, but pubarche and thelarche were not measured, nor were data collected from women who were exposed in utero (Warner, 2004). When data on women who were younger than five at the time of explosion were looked at separately from those who were six to eight years old, there were signs of early menarche—but the sample size was too small to reach statistical significance (Warner and Eskenazi, 2005; Wolff, 2005). Notably, exposed women in this cohort do have elevated rates of breast cancer (Warner, 2002) as well as an increased risk for early menopause (Eskenazi, 2005). Studies on laboratory animals provide reason for concern about the impact of dioxin on pubertal timing: dioxin is known to interfere with an enzyme necessary for the production of gamma-aminobutyric acid (GABA) in the brain (Hayes, 2002). As described in Part II on page 25, GABA is one of the neurotransmitters that inhibits GnRH secretions, and it is thought by some researchers to be the major inhibitor of the HPG axis in early childhood (Biro, personal communication).

Studies from the United States document cases of breast development in children accidentally exposed to estrogen creams used by their mothers, as well as to ointments, hair tonics or ingested pharmaceuticals. In most cases, symptoms regressed after use discontinued (see reviews in Aksglaede, 2006 and Massart, 2006).

Pubertal activation caused by hormonally active personal care products may be of particular importance in African-American communities in which the use of estrogenic hair products in common.

Likewise, cases of premature pubarche in both male and female children have been triggered by exposure to testosterone creams used by fathers. In most cases, these products were purchased without a prescription and were advertised for enhancing strength, libido or athletic performance. For the affected children, the route of exposure was passive dermal transfer from the father's skin. In one case, the father used the cream at night and then shared the bed with his 5-year-old daughter, who soon developed pubic hair and acne (Kunz, 2004). In a second case, a stepfather, who was wheelchair-confined and often wore shorts, used the cream on his thighs. His 18-month-old stepdaughter, who frequently sat on his lap, developed pubic hair and an enlarged clitoris.

Pubertal activation caused by hormonally active personal care products may be of particular importance in African-American communities in which the use of estrogenic hair products is common (Donovan, 2007; Tiwary, 1998). Greater use of estrogen- or placenta-containing hair preparations may partially explain the predominance of early sexual development among U.S. black girls (Tiwary, 1998).

PUBERTAL DEVELOPMENT IN RESPONSE TO LOW-LEVEL BACKGROUND EXPOSURES TO ENDOCRINE DISRUPTORS

In addition to certain hair compounds, hormonally-active agents are found in many other consumer products as well as in pesticides, packaging and building materials. Hence, apart from accidental, one-time exposures, children are also exposed continuously to low-level endocrine disruptors in their diets, drinking water and air supply. A recent pilot study measured hormonally-active environmental agents in urine of 90 U.S. girls six to eight years old and found a wide spectrum. Levels varied significantly according to body mass and race/ethnicity (Wolff, 2007). Among the chemicals detected were phthalates and bisphenol A, a chemical that was originally developed as a synthetic hormone and that is now used in the manufacture of polycarbonate plastics, in the resin linings of food cans and in dental sealants. Bisphenol A is one of the highest-volume chemicals produced in the world (vom Saal and Hughes, 2005). It easily leaches from food and beverage containers—especially during heating and washing—and has led to widespread human exposure. The U.S. Centers for Disease Control and Prevention found that 95 percent of urine samples from a larger representative sample of U.S. residents contained bisphenol A (vom Saal and Hughes, 2005), so its discovery in the urine of young girls is troubling but unsurprising.

Further identification of the endocrine-disrupting chemicals found in the bodies of infants and children—and understanding how their levels vary by race, age and geography—is necessary but not sufficient for evaluating their impact on pubertal timing. For this, large-scale, prospective, longitudinal studies are required.

In the meantime, a handful of small studies provide clues for further inquiry. In North Carolina, in utero exposure to polychlorinated biphenyls (PCBs) was not associated with menarchal timing in girls, but prenatal PCB levels were related to increased height and weight at time of puberty (Gladen, 2000; Rogan and Ragan, 2003). Thelarche and pubarche did show acceleration at the highest levels of exposure to the metabolized pesticide DDT, but the sample sizes were small (Rogan and Ragan, 2003).

Serum levels of DDT metabolite were associated with earlier age at menarche in one Chinese study (Ouyang, 2005). Similarly, in a study of 151 girls born to Michigan mothers who ate sport-caught fish during pregnancy, increased prenatal exposure to DDT metabolite lowered the age of menarche by one year—but there was no association with PCBs (Den Hond and Schoeters, 2006; Vasiliu, 2004). In Mexico, girls living in an agricultural valley in Mexico where pesticide use is high showed altered breast development when compared to girls from the same Yaqui Indian tribe living in nearby pesticide-free areas. Exposed girls had larger breasts for their body size, but in many cases their glandular tissue was underdeveloped and irregular (Guillete, 2006). Among girls from the Awkwesasne Mohawk Nation that borders upstate New York, Ontario and Quebec, four estrogenic PCB congeners were associated with earlier menarche, but there was no association with other chlorinated contaminants (Denham, 2005).

HORMONES IN MEAT AND MILK

The European Union has forbidden the use of exogenous hormones as promoters of animal growth since 1989 (Aksglaede, 2006). By contrast, estradiol and other natural and

synthetic hormones are still used as growth promoters in the U.S. beef industry. Their impact on pubertal timing of girls who are the consumers of its products remains an unanswered question. Suggesting reasons for concern, some researchers point out that federal risk assessments that have set safe threshold levels for estrogens in meat are based on overestimates of children's own endogenous production of hormones, which are now known to be many times lower than presumed by previous models (Aksglaede, 2006).

In the U.S. dairy industry, recombinant bovine growth hormone (rBGH) has been used to increase milk production since 1993. It is not approved in Canada or the European Union (Chang, 2003). While there are important objections to the routine use of growth hormones by dairy farmers, the potential for rBGH to lower the average age of puberty in U.S. girls is probably not among them. First, the apparent decline in age at thelarche began prior to 1993. Second, dairy intake by U.S. children appears to be down rather than up. Increased cheese consumption partially offsets the declining consumption of liquid milk, but there is still a lower overall intake of dairy than there was three decades ago (Huang and McCrory, 2005).

However, before milk can be eliminated as an environmental determinant in human puberty, much more needs to be known about the potential for its various growth factors to cross the gut wall and interact with human receptor sites. While rBGH itself does not find its way into cow's milk, cows so treated do produce

higher levels of insulin-like growth factor-1 (IGF-1). Identical in structure to human IGF-1, bovine IGF-1 does enter milk. Its ability to cross the human gut and enter circulation, however, is an unresolved question. If IGF-1 exists only as free protein in the whey fraction of milk, it should be fully digested in the human gut. Controversial evidence, however, shows that some IGF-1 may bind to casein (the curds in milk out of which cheese is made), and thereby escape digestion and enter the bloodstream. In this way, dairy consumption could potentially elevate IGF-1 levels in humans (Oransky, 2007). However, variability in IGF-1 levels among individuals is considerable, and no one knows what percent of that variability is accounted for by IGF-1 increases in rBGH-treated cows.

The need to understand more about the influence of milk on IGF-1 levels is underscored by new studies that have documented regulatory interactions between IGF-1 and estrogens. More specifically, neuroendocrinologists have found evidence for cross-talk between IGF-1 receptors and estrogen receptor sites in the brain. Indeed, IGF-1 appears to be a key part of the mechanism for estradiol signaling and is required for the priming actions of estradiol on the HPG axis (Etgen, 2006; Mendez, 2006; Scharfman, 2006). And, as described above, emerging evidence suggests that IGF-1 all by itself plays a role in regulating pubertal onset; certainly GnRH neurons express receptors for IGF-1 (Daftary and Gore, 2005).

The continued discovery of new mechanisms for sex hormone regulation gives reason for precaution about exposure to excess levels of animal hormones and growth hormones.

LEAD EXPOSURE DELAYS PUBERTY

High blood lead levels are significantly associated with later menarche in U.S. girls. These findings are consistent in animal studies in the lab and with occupational studies of lead workers, which found alterations in GnRH levels with lead exposure (Wang, 2005; Wu, 2003). Environmental exposure to lead delayed thelarche, menarche and pubarche in Mexican American and black girls. Among white girls, there were lesser delays that were statistically non-significant (Selevan, 2003). Among Mohawk girls, higher lead levels were likewise associated with older age at menarche (Denham, 2005). Average lead levels among U.S. children have been falling steadily for the past three decades, as lead has been phased out of gasoline, paint and soldered cans (American Academy of Pediatrics, 1999). The possible role of declining blood lead levels in the acceleration of pubertal onset in girls is a question for further study.

TOBACCO SMOKE EXPOSURE ACCELERATES PUBERTY

A recent California study found that girls born to mothers who smoked a pack or more cigarettes daily during pregnancy experienced significantly earlier menarche than unexposed girls. As described above, babies born to smoking mothers are, on average, one-half pound lighter at birth than babies born to non-smoking mothers. Smaller birth size may explain part of this association. It is not the whole story, however, because exposure to passive smoke during early childhood also lowers menarchal age by about four months (Windham, 2004).

EVIDENCE FROM ANIMALS

In contrast to the paucity of human data on the posited link between hormonally-active chemicals and earlier puberty in girls (Partsch and Sippell, 2001), there is a wealth of evidence for such a link from experimental studies with laboratory animals and wildlife. All together, the animal data demonstrate that early exposures to environmental estrogens can advance pubertal onset—through a variety of mechanisms and at doses similar to background levels to which humans are routinely exposed (McLachlan, 2006). It is beyond the scope of this report to provide a comprehensive review all of these studies. (For this the reader is referred to the Web site www.ourstolenfuture.com.) Instead, what follows is a descriptive sampling of a few very recent studies. The intent here is to provide a brief sketch of the state of the science.

Precocious puberty in laboratory animals can be induced via exposure to synthetic estrogens either prenatally or shortly after birth (Massart, 2006). Low doses of estrogens very early in development appear to affect the imprinting of central processes involved in regulating the onset of sexual maturity (Massart, 2006). Similar results have been reported using barnyard animals such as piglets and lambs (Wang, 2005).

Some chemicals push animals into early puberty by increasing their responsiveness to natural estrogens. These chemicals are not estrogen mimickers per se, but work by magnifying estrogen sensitivity. One such chemical is bisphenol A. Prenatal and early-life exposure to bisphenol A can trigger early onset of sexual maturation in female rodents. Stimulation of breast development is a particular target (Howdeshell, 1999; vom Saal and Hughes, 2005). Prenatal and infant exposure to bisphenol A made breast tissue more sensitive to estrogens at

puberty (Durando, 2007). and altered its anatomical development (Munoz-de-Toro, 2005).

A third mechanism by which synthetic chemicals can exert feminizing effects is by interfering with the production of aromatase. This is an enzyme that converts androgens to estrogens, a chemical transmutation that leads to sexual differentiation of key brain structures. One chemical that interferes with the action of aromatase is the phthalate plasticizer DEHP. (This was one of the chemicals detected in the urine samples of six-year-old girls, as described on page 55.) In laboratory experiments, DEHP has opposing effects depending on its concentration: low doses of DEHP suppress aromatase, while higher doses increase its activity (Andrade, 2006).

CONCLUSIONS

The extent to which environmental chemicals are contributing to changes in human pubertal development remains largely unknown (Wang, 2005), but the underlying science is sound and the potential for such effects is real (Rogan and Ragan, 2003).

Evidence from Fish: Ova-pollution

Wild fish populations show signs of altered sexual maturation in rivers and streams contaminated with endocrine-disrupting chemicals.

A nationwide study of hormones and pharmaceuticals in waterways conducted by the U.S. Geological Survey found such chemicals in 80 percent of streams sampled. These included antibacterial agents, insect repellants, nonylphenol (an ingredient in detergents) and sex hormones including estradiol (Kolpin, 2002). Many of these substances don't have drinking water guidelines (Kolpin, 2002) and are not tested for by water treatment plants. The U.S. Geological Survey has also found intersex fish (that is, fish with both male and female sex organs) in many locations throughout the country, including the Mississippi, Rio Grande and Colorado rivers, as well as the Potomac and Chesapeake Bay watershed (Myers, 2006).

The discovery of male bass with ovaries and eggs in the Potomac River, which is a source of drinking water for metropolitan Washington, D.C., prompted a recent congressional hearing on "ova pollution." It is not clear yet if endocrine disruptors are affecting the reproduction of wild fish populations because the methodologies to undertake such a study have not been developed (Mills and Chichester, 2005). However, the endocrine-disruptive chemicals that are known to be in these rivers—such as veterinary hormones—do cause alterations in sexual development and reproduction in aquarium fish (Myers, 2006).

CONCLUSIONS AND RECOMMENDATIONS

WHAT WE KNOW

In some respects, the falling age of puberty appears to be part of a natural process: humans, evolving in hunter-gatherer societies, developed the ability to reproduce at younger ages in response to plentiful calories, and subsequent environmental stimuli have simply accelerated that trend. This remains the best explanation for the falling age of menarche in U.S. girls, as well as European girls, from the mid-19th through the mid-20th century. Increasing access to food and less infectious disease lowers menarchal age (Parent, 2003).

During the last 50 years, however, additional forces seem to have been at work. The evidence suggests that children's hormonal systems are being altered by various stimuli and that early puberty is the coincidental, non-adaptive outcome. The intricate and innately reactive HPG and HPA axes are highly vulnerable to disruption, and this disruption can take many shapes. Obesity is one manifestation of endocrine disruption and may lead to hyperinsulinism, leptin resistance and enhanced aromatase activity. Preterm birth and intrauterine growth restriction—especially when followed by rapid weight gain—is a second kind of endocrine disruptor that raises the risk for early pubarche.

The risk for obesity, preterm birth and low birth weight, in turn, are influenced by exposures to chemical toxicants. Chemical toxicants constitute a third kind of endocrine disruptor when they directly tamper with the HPG and HPA axis. Chemical endocrine disruption can lead to alterations in the timing of puberty by several pathways. It can interfere with the hormonal messages received and sent out by the HPG and HPA axes, for example, or it can alter their sensitivity to hormonal messages. By either route, environmental chemicals may contribute to early puberty in girls. Indeed, stressors of many sorts—nutritional, environmental and psychosocial—all appear to interact in a complex manner and contribute to early sexual maturation in girls.

> **Early puberty is a phenomenon best understood as an ecological disorder.**

As such, early puberty is a phenomenon best understood as an ecological disorder. As described by physician Ted Schettler, an ecological disorder does not result from a single toxicant, or set of toxicants, causing a single disease through a single causal pathway. Rather, it is the consequence of multiple and interpenetrating environmental stressors that exist within a causal web and can thus be defined

as an "ecological manifestation of multiple changes in the dynamic system in which people are conceived, develop, live and grow old" (Schettler, 2006). All of the stressors identified herewith that appear to contribute to early puberty in girls—obesity, television viewing, sedentariness, family dysfunction, preterm birth, formula-feeding, chemical exposures—are higher in poor communities and communities of color where poverty, racism, unemployment and toxic substance exposures are high and access to nourishing food and safe places to exercise is low. In particular, U.S. black children are disproportionately exposed to physical environmental stressors (Hambrick-Dixon, 2002), and it is also this group that reaches puberty earliest among U.S. girls.

WHAT WE NEED TO KNOW

Much basic science remains to be done.
The proximate contributors to pubertal maturation in girls have not all been identified. In particular, the activating mechanism for adrenarche needs discovering. The role of melatonin in human puberty warrants further investigation (Parent, 2003), as does its possible interactions with leptin and kisspeptin. Decoding the communication patterns among leptin, kisspeptin and melatonin would begin to expose the ways in which internal and external environmental signals are integrated in pubertal timing. Indeed, much more needs to be revealed about the entire symphony of HPG and HPA signaling devices—hormones, growth factors, neurotransmitters, enzymes—and their orchestration. At the same time, evolutionary biologists and neuroendocrinologists should collaborate on a fuller investigation of infant puberty, in particular its role in priming the HPG or HPA axis for later sexual maturation. Its disruption via direct chemical exposure

during pregnancy or prenatal growth restriction (or prenatal growth restriction caused by chemical exposure) is a potentially important pathway to premature puberty, but almost nothing is known about this process.

Breast milk swarms with growth factors and hormonal agents. Its influence on infant puberty and the development of the nascent endocrinological system also warrants closer investigation.

Much epidemiology remains to be done.
Discrepancies among the cross-sectional studies that purport to show falling ages of puberty among U.S. girls need to be resolved by large-scale, longitudinal studies (Wang, 2005). The National Children's Study— mandated by Congress in 2000—would meet this need perfectly as it proposes to follow 100,000 children from birth to age 21, gathering data on environmental exposures as well as on the pace and pattern of developmental maturation. The Breast Cancer and Environment Research Centers (BCERC) are recruiting cohorts of young girls who will be followed through their pubertal transition (Biro, 2006b). These studies will directly examine the environmental determinants of pubertal timing as well as nutritional determinants. They will not, however, follow the girls through prenatal life and infancy, and the cohorts are much smaller in number than that proposed by the National Children's Study. The BCERC investigations should help elucidate the nature of the association of obesity with early pubertal onset. It would be useful to incorporate into this work recent discoveries on the new avenues of action for endocrine-disrupting chemicals, including the modulation of lipid metabolism (by so-called "environmental obesogens").

Much chemical testing remains to be done.
Currently, chemicals are not tested for their ability to disrupt the endocrine system before they are allowed into the marketplace. Lack of basic endocrinological information on chemicals in everything from lawn treatments to shampoos prevents epidemiologists from knowing what kind of studies to design. More than a decade ago, as part of the reauthorization of the Safe Drinking Water Act and also in the text of the newly-minted Food Quality Protection Act, Congress directed the Environmental Protection Agency to develop a battery of endocrine-disruptor screening tests for pesticides and other environmental chemicals and gave it a 1999 deadline. This deadline has now been pushed back until the end of 2007, and the program's top endocrine disruptor advisory panel has been dissolved for the fourth time. At this writing, not a single chemical has been tested under the EPA's Endocrine Disruptor Screening Program.

Much chemical tracking remains to be done.
In order to trace routes of exposure to endocrine-disrupting chemicals—and then act to prevent them before they occur—we need to know more about the sources, emissions and fate of such chemicals in commercial use. Expanding our right to know about environmental chemicals requires a two-pronged approach. First, we need full disclosure of chemical ingredients in consumer products, especially those to which children are in direct contact. Second, we need more comprehensive inventories of emissions and better monitoring of important routes of exposure—such as air, food and drinking water. The Toxics Release Inventory is the lynchpin of these efforts (www.scorecard.org). Part of the Emergency Planning and Community Right-to-Know Act of 1986, the Toxics Release Inventory (TRI) was

designed to inform communities of toxic chemical emissions in their neighborhoods and hold polluters responsible for their management. Currently, releases of about 650 toxic chemicals are reported under TRI by the responsible industries to the Environmental Protection Agency, which then makes the information available to the public. However, in December 2006, the Bush administration curtailed the program to exempt small and mid-sized businesses from reporting (Pelley, 2007). This diminishment of the TRI removes from public view a great deal of data on chemical releases. It also makes public health research much more difficult. For example, we know now that the urine of U.S. girls contains phthalates, but despite this knowledge, we have not yet identified their source or the routes of exposure.

Much biomonitoring remains to be done.
Evaluating the influence of chemical exposures on pubertal timing is difficult in the absence of a baseline for chemical exposure in infants and children. Biomonitoring also helps prioritize research on emerging chemicals of concern. The U.S. Centers for Disease Control and Prevention (CDC) monitor chemical contaminants in a representative sample of the U.S. population, and its fourth report—which will disclose results for some 300 chemicals—will be released sometime in 2007. However, the CDC's program collects very little information on infants and young children (National Research Council, 2006). The National Children's Study will collect these data, although they will not be available for many years. The CDC's biomonitoring effort also does not target highly exposed communities for testing. In contrast, the California Environmental Contamination Biomonitoring Program does have this ability. In September

2006, California became the first state to mandate a statewide biomonitoring program. When implemented, it will test for the presence of environmental chemicals in the bodies of representative sample of Californians throughout the state as well as initiate localized studies in communities of concern. Daughters of farm workers would be one subpopulation that could potentially benefit from biomonitoring.

Because it relies on after-the-fact exposures and reveals little about the pathways by which exposures occur, biomonitoring should be coupled with efforts to increase disclosure of chemicals and expand their inventories of emissions and releases.

WHAT WE CAN DO NOW

There is sufficient evidence for the contribution (direct or indirect) of body mass to pubertal timing in girls to support efforts that combat childhood obesity. Any campaign to address this problem should begin with the promotion of breastfeeding. Breast milk safeguards against obesity. At 12 months, breastfed babies are leaner than formula-fed babies, a difference that persists into later childhood (Dewey, 1998; Mayer-Davis, 2006; Schack-Nielsen and Michaelsen, 2007). Breastfeeding is most important for children born small for gestational age or premature, for whom rapid weight gain raises additional risks for obesity and early puberty.

For older children, successful battles are being waged at local and regional levels even as national efforts remain mired. A number of

school districts around the country have begun working to eliminate sugary, high-calorie foods from cafeterias and school events—and continue doing so without federal funding or support from the school lunch program (Foxhall, 2006).

Some school-based obesity-prevention programs have already demonstrated an ability to delay menarche. One is Planet Health, a school-based intervention designed to decrease among school children television viewing and consumption of high-fat foods while increasing exercise and consumption of fruit and vegetables. After two school years, sixth- and seventh-grade girls in the Boston area who attended schools randomly selected for this curriculum had lower average body mass indices, lower body fat, higher levels of physical activity and decreased screen time compared with their counterparts at non-participating schools. They were also 32 percent less likely to have experienced menarche during the 19-month study than girls in control schools (Chavarro, 2005). Such programs need to be replicated widely.

Breast milk safeguards against obesity

The success of school-based interventions such as Healthy Planet can be carried out to the community at large. Since 2005, there has been a dramatic increase in efforts to improve access to healthy foods in urban, low-income areas through the creation of farmers' markets and community gardens (Foxhall, 2006). Persuading schools, neighborhood stores and convenience markets to source with local, organic farms is a decentralized grassroots campaign whose efforts are relevant to protecting girls from early sexual maturation.

Strategies to lower rates of preterm and low-weight babies include eliminating exposure to

tobacco smoke and chemical solvents as well as eliminating sources of air pollution and mercury contamination. Strategies to lower the pediatric body burden of endocrine-disruptive chemicals include phase-outs of chemicals such as bisphenol A and phthalates, to which girls have documented exposures. Supporting organic agriculture not only lowers the burden of hormonally active residues in food, it protects watersheds from contamination by pesticides, herbicides, animal hormones and antibiotics, which flow from farm, ranches and manure lagoons into rivers and streams. Buying organic thus protects drinking water, another potential source of exposure. The Healthy Schools Network has spearheaded the effort to bring non-chemical pest-control practices into schools and daycare centers.

Because it arises from a combination of many different stressors in several different aspects of the environment—psychosocial, nutritional, behavioral, chemical—early puberty in girls is not a trend that will be reversed by single actions by single-purpose agencies. It is a multi-causal threat to the well-being of girls and women that ultimately requires a comprehensive, integrated, unified response. The problem with health issues that cross

multiple environmental media is that they fall between regulatory and activist cracks. On the one hand, addressing all the root causes simultaneously raises the risk for programmatic and regulatory fragmentation and leads to inertia. On the other hand, addressing one problem at a time does not begin to unknot the tangle of its interrelated causes.

The environmental justice community, with its long experience with cumulative risks and impact, has many insights to offer here. Any meaningful attempt to mitigate the problem of early sexual maturation in girls must draw on the collective wisdom of its leadership. Environmental justice activists, for example, have developed methods for response that are able to ascertain and mitigate multi-media stressors swiftly. Incorporated into their analytical framework is the recognition that health disparities, such as obesity or low birth weight, are both an outcome of and a contributor to vulnerability to environmental toxicants. Known as "bias for action," this early identification and response approach, which is community-based and collaborative, holds much promise for addressing the problem of early puberty in U.S. girls (National Environmental Justice Advisory Council, 2004).

LITERATURE CITED

Agosta WC, *Chemical Communication: The Language of Pheromones* (New York: WH Freeman, 1992).

Ahlgren M et al., "Growth Patterns and the Risk of Breast Cancer in Women," *New England Journal of Medicine* 351 (2004): 1619-26.

Aksglaede L et al., "The Sensitivity of the Child to Sex Steroids: Possible Impact of Exogenous Estrogens," *Human Reproduction Update* 32 (2006): 341-49.

American Association of Pediatrics, Committee on Public Education, "Children, Adolescents, and Television," *Pediatrics* 107 (2001): 423-26.

American Association of Pediatrics, Committee on Environmental Health, *Handbook of Pediatric Environmental Health*, 1999, pp. 131-43.

American Psychological Association, *Report of the APA Task Force on the Sexualization of Girls*, February, 2007.

Anderson SE et al., "Relative Weight and Race Influence Average Age and Menarche: Results from Two Nationally Representative Surveys of U.S. Girls Studied 25 Years Apart," *Pediatrics* 111 (2003): 844-50.

Anderson SE and Must A, "Interpreting the Continued Decline in the Average Age at Menarche: Results from Two Nationally Representative Surveys of U.S. Girls Studied 10 Years Apart," *Journal of Pediatrics* 147 (2005): 753-60.

Anderson WF et al., "Estimating Age-Specific Breast Cancer Risks: A Descriptive Tool to Identify Age Interactions," *Cancer Causes and Control* 18 (2007): 439-47.

Andrade AJM, "A Dose-Response Study Following In Utero and Lactational Exposure to di-(2-ethylhexyl)-phthalate (DEHP): Non-monotonic Dose-Response and Low Dose Effects on Rat Brain Aromatase Activity," *Toxicology* 227 (2006): 185-92.

Auchus R and Rainey WE, "Adrenarche—Physiology, Biochemistry and Human Disease," *Clinical Endocrinology* 60 (2004): 288-96.

Barker DJ, "The Fetal and Infant Origins of Adult Disease," *British Medical Journal* 301 (1990): 1111.

Barrett JR, "Soy and Children's Health: A Formula for Trouble?" *Environmental Health Perspectives* 110 (2002): A294-95.

Behrman RE and Butler AS, eds., *Preterm Birth: Causes, Consequences, and Prevention.* Report from the Institute of Medicine's Committee on Understanding Premature Birth and Assuring Healthy Outcome (Washington, D.C.: National Academies Press, 2006).

Bellis MA et al., "Adults at 12? Trend in Puberty and their Public Health Consequences," *Journal of Epidemiology and Community Health* 60 (2006): 910-11.

Belsky J et al., "Childhood Experience, Interpersonal Development, and Reproductive Strategy: An Evolutionary Theory of Socialization," *Child Development* 62 (1991): 647-70.

Bergstrom E et al., "Serum Lipid Values in Adolescents Are Related to Family History, Infant Feeding, and Physical Growth," *Atherosclerosis* 117 (1995): 1-13.

Berkey CS et al., "Relation of Childhood Diet and Body Size to Menarche and Adolescent Growth in White Girls," *American Journal of Epidemiology* 152 (2000): 446-52.

Biro FM et al, "Pubertal Correlates in Black and White Girls," *Journal of Pediatrics* 148 (2006a): 234-40.

Biro FM, "Puberty—Whither Goest?" *Journal of Pediatric and Adolescent Gynecology* 19 (2006b): 163-65.

Biro FM, "Influence of Obesity on Timing of Puberty," *International Journal of Andrology* 29 (2006c): 272-77.

Biro FM, "Stone-Age Genes, Space-Age Times," presentation at the Breast Cancer and Environmental Risk Factors scientific symposium, East Lansing, MI, November 2005.

Biro FM, "Secular Trends in Menarche, *Journal of Pediatrics* 147 (2005a): 725-26.

Biro FM et al., "Pubertal Maturation in Girls and the Relationship to Anthropomorphic Changes: Pathways through Puberty," *Journal of Pediatrics* 142 (2003a): 643-46.

Biro FM, "Puberty and Genetic Susceptibility to Breast Cancer [letter]," *New England Journal of Medicine* 349 (2003b): 1088-89.

Blanck HM et al., "Age at Menarche and Tanner Stage in Girls Exposed *in Utero* and Postnatally to Polybrominated Biphenyl," *Epidemiology* 11 (2000): 641-47.

Bogaert AF, "Age at Puberty and Father Absence in a National Probability Sample," *Journal of Adolescence* 28 (2005): 541-46.

Brown JD et al., "Sexy Media Matter: Exposure to Sexual Content in Music, Movies, and Magazines Predicts Black and White Adolescents' Sexual Behavior," *Pediatrics* 117 (2006): 1018-27.

Brown JD et al., "Mass Media as a Sexual Super Peer for Early Maturing Girls," *Journal of Adolescent Health* 36 (2005): 420-27.

Burt SA et al., "Timing of Menarche and the Origins of Conduct Disorder," *Archives of General Psychiatry* 63 (2006): 890-96.

Cariboni A and Maggi R, "Kallman's Syndrome: A Neuronal Migration Defect," *Cellular and Molecular Life Sciences* 63(2006): 2512-26.

Castellino N et al., "Puberty Onset in Northern Italy: A Random Sample of 3597 Italian Children," *Journal of Endocrinological Investigation* 28 (2005): 589-94.

Celio M et al., "Early Maturation as a Risk Factor for Aggression and Delinquency in Adolescent Girls: A Review," *International Journal of Clinical Practice* 60 (2006): 1254-62.

Centers for Disease Control, "Racial and Socioeconomic Disparities in Breastfeeding—United States, 2004," *Morbidity and Mortality Weekly Report* 55 (2006): 335-39.

Centers for Disease Control, "Participation in High School Physical Education—United States, 1991-2003," *Morbidity and Mortality Weekly* 53 (2004): 844-47.

Certain LK and Kahn RS, "Prevalence, Correlates, and Trajectory of Television Viewing Among Infants and Toddlers," *Pediatrics* 109 (2002): 634-42.

Chang E, "Tempest in a Glass; Synthetic Hormones in Milk Don't Speed Puberty, Say Experts," *The Washington Post*, Oct. 7, 2003, p. F1.

Charkaluk ML et al., "Premature Pubarche as an Indicator of How Body Weight Influences the Onset of Adrenarche," *European Journal of Pediatrics* 163 (2004): 89-93.

Chavarro JE et al., "Effects of a School-Based Obesity-Prevention Intervention on Menarche (United States)," *Cancer Causes and Control* 16 (2005): 1245-52.

Christakis DA et al., "Television, Video, and Computer Game Usage in Children Under 11 Years of Age," *Journal of Pediatrics* 145 (2004): 652-56.

Chumlea WC et al, "Age at Menarche and Racial Comparisons in US Girls," *Pediatrics* 111 (2003): 110-113.

Clavel-Chapelon F et al., "Differential Effects of Reproductive Factors on the Risk of Pre- and Postmenopausal Breast Cancer. Results from a Large Cohort of French Women," *British Journal of Cancer* 86 (2002): 723-27.

Cooper TV et al., "An Assessment of Obese and Non-obese Girls' Metabolic Rate During Television Viewing, Reading, and Resting," *Eating Behaviors* 7 (2006): 105-14.

Cruz ML et al., "Effect of Infant Nutrition on Cholesterol Synthesis Rates," *Pediatric Research* 35 (1994): 135-40.

Daftary SS and Gore AC, "IGF-1 in the Brain as a Regulator of Reproductive Neuroendocrine Function," *Experimental Biology and Medicine* 230 (2005): 292-306.

Danubio ME et al, "Age at Menarche and Age of Onset of Pubertal Characteristics in 6-14-year-old girls from the Province of L'Aquila (Abruzzo, Italy)," *American Journal of Human Biology* 16 (2004): 470-8.

Davison KK et al., "Cross-sectional and Longitudinal Associations Between TV Viewing and Girls' Body Mass Index, Overweight Status, and Percentage of Body Fat," *Journal of Pediatrics* 149 (2006): 32-37.

Davison KK et al., "Percent Body Fat at Age 5 Predicts Earlier Pubertal Development Among Girls at Age 9," *Pediatrics* 111 (2003, 4 Pt 1): 816-21.

Deardorff J et al., "Early Puberty and Adolescent Pregnancy: The Influence of Alcohol Use," *Pediatrics* 116 (2005): 1451-56.

Denham M et al., "Relationship of Lead Mercury, Mirex, Dichlorodiphenyldichloroethylene, Hexachlorobenzene, and Polychlorinated Biphenyls to Timing of Menarche in Akwesasne Mohawk Girls," *Pediatrics* 115 (2005): e127-34.

Den Hond E and Schoeters G, "Endocrine Disruptors and Human Puberty," *International Journal of Andrology* 29 (2006): 264-71.

Dennison BA et al., "Television Viewing and Television in Bedroom Associated with Overweight Risk Among Low-Income Preschool Children," *Pediatrics* 109 (2002): 1028-35.

de Muinck Keizer-Schrama SM and Juul A, "Role of Environmental Factors in Timing the Onset and Progression of Puberty," *International Journal of Andrology* 29 (2006): 286-90.

de Muinck Keizer-Schrama SM and Mul D, "Trends in Pubertal Development in Europe," *Human Reproduction Update* 7 (2001): 287-91.

Dewey KG, "Growth Characteristics of Breast-fed Compared to Formula-fed Infants," *Biology of the Neonate* 74 (1998): 94-105.

Donovan BT and Van der Werff ten Bosch JJ, *Physiology of Puberty* (Baltimore: Williams and Wilkins, 1965).

Donovan M et al., "Personal Care Products that Contain Estrogens or Xenoestrogens May Increase Breast Cancer Risk," *Medical Hypotheses* 68 (2007): 756-66.

Dorn LD and Rotenstein, D, "Early Puberty in Girls: the Case of Premature Adrenarche," *Women's Health Issues* 14 (2004): 177-83.

Dungan HM et al., "Minireview: Kisspeptin Neurons as Central Processors in the Regulation of Gonadotropin-releasing Hormone Secretion," *Endocrinology* 147 (2006): 1154-58.

Durando M et al., "Prenatal Bisphenol A Exposure Induces Preneoplastic Lesions in the Mammary Gland in Wistar Rats," *Environmental Health Perspectives* 115 (2007): 80-86.

Ebling FJP, "The Neuroendocrine Timing of Puberty," *Reproduction* 129 (2005): 675-83.

Ellis BJ, "Timing of Pubertal Maturation in Girls: An Integrated Life History Approach," *Psychological Bulletin* 130 (2004): 920-958.

Ellis BJ et al., "Quality of Early Family Relationships and Individual Differences in the Timing of Pubertal Maturation in Girls: A Longitudinal Test of an Evolutionary Model," *Journal of Personality and Social Psychology* 77 (1999): 387-401.

Ellis BJ and Garber J, "Psychosocial Antecedents of Variation in Girls' Pubertal Timing: Maternal Depression, Stepfather Presence, and Marital and Family Stress," *Child Development* 71 (2000): 485-501.

Engelhardt L et al, "Sexual maturation in East German girls," *Acta Paediatrica* 84 (1995):1362-1365 (as cited in Juul, 2006).

Eskenazi B et al., "Serum Dioxin Concentrations and Age at Menopause," *Environmental Health Perspectives* 113 (2005): 858-62.

Etgen AM et al., "The Role of Insulin-like Growth Factor-I and Growth Factor-associated Signal Transduction Pathways in Estradiol and Progesterone Facilitation of Female Reproductive Behaviors," *Frontiers in Neuroendocrinology* 27 (2006): 363-75.

Euling SY et al., "Environmental Factors and Puberty Timing: Summary of an Expert Panel Workshop," *The Toxicologist* 84 (2005): S-1.

Fara GM et al., "Epidemic of Breast Enlargement in an Italian School," *The Lancet* 2(8137) (1979): 295-97.

Foster DL et al., "Internal and External Determinants of the Timing of Puberty in the Female," *Journal of Reproduction and Fertility* 75 (1985): 327-44.

Foster TA et al, "Anthropometric and maturation measurements of children, ages 5 to 14 years, in a biracial community – the Bogalusa Heart Study," *American Journal of Clinical Nutrition* 30 (1977): 582-591 (as cited in Juul, 2006).

Foxhall K, "Beginning to Begin: Reports from the Battle on Obesity," *American Journal of Public Health* 96 (2006): 2106-2112.

Freedman DS et al., "The Relation of Menarchal Age to Obesity in Childhood and Adulthood: The Bogalusa Heart Study," *BMC Pediatrics* 3 (2003): 3.

Freedman DS et al., "Relation of Menarche to Race, Time Period, and Anthropomorphic Dimensions: The Bogalosa Heart Study, *Pediatrics* 110 (2002): e43.

Gasser CL et al., "Effect of Timing of Feeding a High-Concentrate Diet on Growth and Attainment of Puberty in Early-Weaned Heifers," *Journal of Animal Science* 84 (2006): 3118-22.

Genazzani AR et al., "Neuropeptides, Neurotransmitters, Neurosteroids, and the Onset of Puberty," *Annals of the New York Academy of Sciences* 900 (2000):1-9.

Gentile DA et al., "Well-child Visits in the Video Age: Pediatricians and the American Academy of Pediatrics' Guidelines for Children's Media Use," *Pediatrics* 114 (2004): 1235-41.

Georgopoulos NA et al., "Growth, Pubertal Development, Skeletal Maturation, and Bone Mass Acquisition in Athletes," *Hormones (Athens)* 3 (2004): 233-43.

Gladen B et al., "Pubertal Growth and Development and Prenatal and Lactation Exposure to Polychlorinated Biphenyls and Dichlorodiphenyl Dichloroethene," *Journal of Pediatrics* 136 (2000): 490-96.

Golub MS, "Adolescent Health and the Environment," *Environmental Health Perspectives* 108 (2000): 355-62.

Gordon-Larsen P et al., "Determinants of Adolescent Physical Activity and Inactivity Patterns," *Pediatrics* 105 (2000): e83.

Gore AC, "Gonadotropin-releasing Hormone (GNRH) Neurons: Gene Expression and Neuroanatomical Studies," *Progress in Brain Research* 141 (2002): 195-210.

Graber JA et al., "Is Pubertal Timing Associated with Psychopathology in Young Adulthood?" *Journal of the American Academy of Child and Adolescent Psychiatry* 43 (2004): 718-27.

Graber JA et al., "Is Psychopathology Associated with the Timing of Pubertal Development?" *Journal of the American Academy of Child and Adolescent Psychiatry* 36 (1997): 1768-76.

Grumbach MM and Styne DM, "Puberty: Ontogeny, Neuroendocrinology, Physiology, and Disorders," in Larsen PR et al., eds., *Williams' Textbook of Endocrinology*, 10th ed. (Philadelphia: Saunders, 2003), pp. 1115-1286.

Grun F and Blumberg B, "Environmental Obesogens: Organotins and Endocrine Disruption Via Nuclear Receptor Signaling," *Endocrinology* 147, supp. 6 (2006): S50-55.

Guillette EA et al., "Altered Breast Development in Young Girls from an Agricultural Environment," *Environmental Health Perspectives* 114 (2006): 471-75.

Hambrick-Dixon PJ, "The Effects of Exposure to Physical Environmental Stressors on African-American Children: A Review and Research Agenda," *Journal of Children & Poverty* 8 (2002): 23-34.

Hamilton AS and Mack TM, "Puberty and Genetic Susceptibility to Breast Cancer in a Case-Control Study in Twins," *New England Journal of Medicine* 348 (2003): 2313-22.

Han SK et al., "Activation of Gonadotropin-releasing Hormone Neurons by Kisspeptin as a Neuroendocrine Switch for the Onset of Puberty," *Journal of Neuroscience* 25 (2005): 11349-56.

Harlan WR et al., "Secondary Sex Characteristics of Girls 12-17 Years of Age: the U.S. Health Examination Survey," *Journal of Pediatrics* 96 (1980): 1074-78.

Hayes LE et al., "Evidence that GABAergic Neurons in the Preoptic Area of the Rat Brain Are Targets of 2,3,4,8-Tetrachlorodibenzo-p-dioxin during Development," *Environmental Health Perspectives* 110, suppl. 3 (2002): 369-76.

Haynie DL and Piquero AR, "Pubertal Development and Physical Victimization in Adolescence," *Journal of Research in Crime and Delinquency* 43 (2006): 3-35.

Herman-Giddens ME, "The Decline in the Age of Menarche in the United States: Should We Be Concerned?" *Journal of Adolescent Health* 40 (2007): 201-03.

Herman-Giddens ME, "Recent Data on Pubertal Milestones in United States Children: The Secular Trend Toward Earlier Development," *International Journal of Andrology* 29 (2006): 241-46.

Herman-Giddens ME et al., "Navigating the Recent Articles on Girls' Puberty in Pediatrics: What Do We Know and Where Do We Go From Here?" *Pediatrics* 113 (2004): 911-16.

Herman-Giddens ME et al., "Secondary Sexual Characteristics and Menses in Young Girls Seen in Office Practice: A Study from the Pediatrics Research in Office Settings," *Pediatrics* 99 (1997): 505-12.

Hileman B, "Causes of Premature Birth Probed," *Chemical and Engineering News* (26 Nov. 2001).

Himes JH, "Examining the Evidence for Recent Secular Changes in the Timing of Puberty in U.S. Children in Light of Increases in the Prevalence of Obesity," *Molecular and Cellular Endocrinology* 254-55 (2006); 13-21.

Hoier S, "Father Absence and Age at Menarche: A Test of Four Evolutionary Models," *Human Nature* 14 (2003): 209-234.

Howdeshell K et al., "Plastic Bisphenol A Speeds Growth and Puberty," *Nature* 401 (1999): 762-64.

Hsieh CC et al., "Age at Menarche, Age at Menopause, Height, and Obesity as Risk Factors for Breast Cancer: Associations and Interactions in an International Case-Control Study," *International Journal of Cancer* 46 (1990): 796-800.

Huang TTK et al., "Dairy Intake, Obesity, and Metabolic Health in Children and Adolescents: Knowledge and Gaps," *Nutrition Reviews* 63 (2005): 71-80.

Hughes SM and Gore AC, "How the Brain Controls Puberty, and Implications for Sex and Ethnic Differences," *Family and Community Health* 30 (2007, Suppl. 1): S112-14.

Hulanicka B et al., "Effect of Familial Distress on Growth and Maturation of Girls: A Longitudinal Study," *American Journal of Human Biology* 13 (2001): 771-76.

Ibanez L et al., "Early Puberty-Menarche After Precocious Pubarche: Relation to Prenatal Growth," *Pediatrics* 117 (2006): 117-21.

Ibanez L et al., "Insulin Sensitization Early After Menarche Prevents Progression from Precocious Puberty to Polycystic Ovary Syndrome," *Journal of Pediatrics* 144 (2004): 23-29.

Ibanez L et al., "Premature Adrenarche—Normal Variant or Forerunner of Adult Disease?" *Endocrine Reviews* 21 (2000): 671-96.

Irwin CE, "Pubertal Timing: Is There Any New News?" *Journal of Adolescent Health* 37 (2005): 343-44.

Iwasaki M et al., "Role and Impact of Menstrual and Reproductive Factors on Breast Cancer Risk in Japan," *European Journal of Cancer Prevention* 16 (2007): 116-23.

Jeffrey Chang R and Coffler MS, "Polycystic Ovary Syndrome: Early Detection in the Adolescent," *Clinical Obstetrics and Gynecology* 50 (2007): 178-87.

Johansson T and Ritzen EM, "Very Long-Term Follow-Up of Girls with Early and Late Menarche," *Endocrinology and Development* 8 (2005): 126-36.

Juul A et al., "Pubertal Development in Danish Children: Comparison of Recent European and U.S. Data," *International Journal of Andrology* 29 (2006): 247-55.

Kaplowitz P, "Pubertal Development in Girls: Secular Trends," *Current Opinion in Obstetrics and Gynecology* 18 (2006): 487-91.

Kaplowitz P, *Early Puberty in Girls: The Essential Guide to Coping with This Common Problem* (New York: Ballantine, 2004).

Kaplowitz P, "Earlier Onset of Puberty in Girls: Relation to Increased Body Mass Index and Race," *Pediatrics* 108 (2001): 347-53.

Kaplowitz P and Oberfield SE, "Reexamination of the Age Limit for Defining When Puberty is Precocious in Girls in the United States: Implications for Evaluation and Treatment," Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society, *Pediatrics* 104 (1999): 936-41.

Keith SW et al., "Putative Contributors to the Secular Increase in Obesity: Exploring the Roads Less Traveled," *International Journal of Obesity* 30 (2006): 1585-94.

Kelsey JF et al., "Reproductive Factors and Breast Cancer," *Epidemiologic Review* 15 (1993): 36-47.

Khadilkar VV et al., "Secular Trends in Puberty," *Indian Pediatrics* 43 (2006): 475-78.

Kimbro RT et al., "Racial and Ethnic Differentials in Children's Overweight and Obesity Among 3-Year-Olds," *American Journal of Public Health* 97 (2007): 298-305.

Kimm SY et al., "Decline in Physical Activity in Black Girls and White Girls During Adolescence," *New England Journal of Medicine* 347 (2002): 709-15.

Kolpin DW et al., "Pharmaceuticals, Hormones, and Other Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance," *Environmental Science & Technology* 36 (2002): 1202-11.

Kunz GJ et al., "Virilization of Young Children After Topical Androgen Use by Their Parents," *Pediatrics* 114 (2004): 282-84.

Largo RH and Prader A, "Pubertal Development in Swiss Girls," *Helvetica Paediatrica Acta* 38 (1983): 229-43.

Latini G et al., "In Utero Exposure to Phthalates and Fetal Development," *Current Medicinal Chemistry* 13 (2006): 2527-34.

Latini G et al., "In Utero Exposure to Di-(2-ethylhexyl)-phthalate and Human Pregnancy Duration," *Environmental Health Perspectives* 111 (2003): 1783-85.

Lee DH et al., "Association Between Serum Concentrations of Persistent Organic Pollutants and Insulin Resistance Among Nondiabetic Adults," *Diabetes Care* 30 (2007): 622-28.

Lee DH et al., "A Strong Dose-Response Relation Between Serum Concentrations of Persistent Organic Pollutants and Diabetes. Results from the National Health and Examination Survey 1999-2002," *Diabetes Care* 29 (2006): 1638-44.

Lee JM et al., "Weight Status in Young Girls and the Onset of Puberty," *Pediatrics* 119 (2007): e624-30.

Lee PA et al., "Age of Puberty: Data from the United States," *Acta Pathologica, Microbiologica, et Immunologica Scandinavica* 109 (2001): 81-88.

Levin DE, "So Sexy, So Soon: The Sexualization of Childhood," in Olfman S, ed., *Childhood Lost: How American Culture is Failing Our Kids* (Westport, Conn.: Praeger Publishers, 2005), pp. 137-54.

Lien L et al., "The Relationship Between Age of Menarche and Mental Distress in Norwegian Adolescent Girls and Girls from Different Immigrant Groups in Norway: Results from an Urban City Cross-Sectional Survey," *Social Science & Medicine* 63 (2006): 285-95.

Lindgren G, "Pubertal Stages 1980 of Stockholm Schoolchildren," *Acta Paediatrica* 85 (1996): 1365-1367 (as cited in de Muinck Keizer-Schrama, 2001).

Linn S, *Consuming Kids: Protecting Our Children from the Onslaught of Marketing and Advertising* (New York: Anchor Books, 2005).

Mac Mahon B, "Age at Menarche, United States," *National Health Survey* 133 (1973): 74-1615 (as cited in Parent, 2003).

Macchi MM and Bruce JN, "Human Pineal Physiology and Functional Significance of Melatonin," *Frontiers in Neuroendocrinology* 25 (2004): 177-95.

MacLeod M, "Her Father's Daughter," *New Scientist*, 10 February 2007, pp. 38-41.

Maestripieri D et al., "Father Absence, Menarche and Interest in Infants Among Adolescent Girls," *Developmental Science* 7 (2004): 560-66.

Marshall WA and Tanner JM, "Puberty," in Falkner F and Tanner JM, eds., *Human Growth* (New York: Plenum, 1986), pp. 171-209.

Marshall WA and Tanner JM, "Variations in the Pattern of Pubertal Changes in Girls," *Archives of Disease in Childhood* 44 (1969): 291-303.

Martin KA, *Puberty, Sexuality and the Self: Boys and Girls at Adolescence* (New York: Routledge, 1996).

Martine JA et al., "Preliminary Births for 2004: Infant and Maternal Health," Health E-stats. (Hyattsville, MD: National Center for Health Statistics, U.S. Centers for Disease Control, 2005).

Massart F et al., "How Do Environmental Estrogen Disruptors Induce Precocious Puberty?" *Minerva Pediatrica* 58 (2006): 247-54.

Massart F et al., "High Incidence of Central Precocious Puberty in a Bounded Geographic Area of Northwest Tuscany: An Estrogen Disruptor Epidemic? *Gynecological Endocrinology* 20 (2005): 92-98.

Matchock R and Susman EJ, "Family Composition and Menarcheal Age: Anti-Inbreeding Strategies," *American Journal of Human Biology* 18 (2006): 481-91.

Mayer-Davis EJ et al., "Breast-feeding and Risk for Childhood Obesity: Does Maternal Diabetes or Obesity Status Matter?" *Diabetes Care* 29 (2006): 2231-37.

McDowell MA et al., "Has Age at Menarche Changed? Results from the National Health and Nutrition Examination Survey (NHANES) 1994-2004," *Journal of Adolescent Health* 40 (2007): 227-31.

McLachlan JA et al., "Endocrine Disrupters and Female Reproductive Health," *Best Practice & Research, Clinical Endocrinology & Metabolism* 20 (2006): 63-75.

McMillen IC and JS Robinson, "Developmental Origins of the Metabolic Syndrome: Prediction, Plasticity, and Programming," *Physiological Reviews* 85 (2005): 571-633.

Mendez P et al., "Cross-talk Between Estrogen Receptors and Insulin-like Growth Factor-I Receptor in the Brain: Cellular and Molecular Mechanisms," *Frontiers in Neuroendocrinology* 27 (2006): 391-403.

Midyett LK et al., "Are Pubertal Changes in Girls Before Age 8 Benign?" *Pediatrics* 111 (2003): 47-51.

Mills LJ and Chichester C, "Review of Evidence: Are Endocrine-Disrupting Chemicals in the Aquatic Environment Impacting Fish Populations? *Science of the Total Environment* 343 (2005): 1-34.

Mitchell M et al., "Adipokines: Implications for Female Fertility and Obesity," *Reproduction* 130 (2005): 583-97.

Moffit TE et al., "Childhood Experience and the Onset of Menarche: A Test of a Sociobiological Model," *Child Development* 63 (1992): 47-58.

Muir A, "Precocious Puberty," *Pediatrics in Review* 27 (2006): 373-81.

Muira T, ed., *Seasonality of Birth* (The Hague: SPB Academic Publishing, 1987), pp. 25-31 and 33-44.

Mul D et al., "Pubertal development in the Netherlands 1965-1997," *Pediatric Research* 50 (2001): 479-86.

Munoz-de-Toro M et al., "Perinatal Exposure to Bisphenol-A Alters Peripubertal Mammary Gland Development in Mice," *Endocrinology* 146 (2005): 4138-47.

Murcia GJ et al., "Puberty and Melatonin," *Anales Espanoles de Pediatria* 57 (2002): 121-26.

Myers M, testimony before the U.S. House Committee on Government Reform, oversight hearing on "Ova-pollution in the Potomac: Egg-Bearing Male Bass and Implications for Human and Ecological Health," October 4, 2006.

National Association for Sports and Physical Education, *2006 Shape of the Nation Report: Status of Physical Education in the USA.*

National Environmental Justice Advisory Council, Cumulative Risks/Impacts Work Group, "Ensuring Risk Reduction in Communities with Multiple Stressors: Environmental Justice and Cumulative Risks/Impacts," report to the U.S. EPA, December 2004.

National Research Council, Committee on Human Biomonitoring for Environmental Toxicants, *Human Biomonitoring for Environmental Chemicals* (Washington DC: National Academies Press, 2006).

Neville KA and Walker JL, "Precocious Pubarche is Associated with SGA, Prematurity, Weight Gain, and Obesity," *Archives of Disease in Childhood* 90 (2005): 258-61.

Novotny R et al., "Formula Feeding in Infancy is Associated with Adolescent Body Fat and Earlier Menarche," *Cellular and Molecular Biology* 49 (2003): 1289-93.

Ogden CL et al., "Prevalence and Trends in Overweight Among U.S. Children and Adolescents, 1999-2000," *JAMA* 288 (2002): 1728-32.

Ojeda SR et al., "Minireview: The Neuroendocrine Regulation of Puberty: Is the Time Ripe for a Systems Biology Approach?" *Endocrinology* 147 (2006): 1166-74.

Okobia MN and Bunker CH, "Epidemiological Risk Factors for Breast Cancer—A Review," *Nigerian Journal of Clinical Practice* 9 (2005): 35-42.

Ong KK et al., "Lessons from Large Population Studies on Timing and Tempo of Puberty (Secular Trends and Relation to Body Size): The European Trend," *Molecular and Cellular Endocrinology* 254-55 (2006): 8-12.

Oranksy I, "What's in Your Milk?" *The Scientist* 21 (2007): 34.

Ouyang F et al., "Serum DDT, Age of Menarche, and Abnormal Menstrual Cycle Length," *Occupational and Environmental Medicine* 62 (2005): 878-84.

Palmert MR et al., "Unsustained or Slowly Progressive Puberty in Young Girls: Initial Presentation and Long-Term Follow-up of 20 Untreated Patients," *The Journal of Clinical Endocrinology and Metabolism* 84 (1999): 415-23.

Pandi-Perumal SR et al., "Melatonin: Nature's Most Versatile Biological Signal?" *The FEBS Journal* (Federation of European Biochemical Societies) 273 (2006): 2813-38.

Papathanasiou A and Hadjiathanasiou C, "Precocious Puberty," *Pediatric Endocrinology Reviews* 3 (2006, suppl. 1): 182-87.

Parent AS et al., "The Timing of Normal Puberty and the Age Limits of Sexual Precocity: Variations Around the World, Secular Trends, and Changes after Migration," *Endocrine Reviews* 24 (2003): 668-693.

Partsch CJ and Sippell WG, "Pathogenesis and Epidemiology of Precocious Puberty: Effects of Exogenous Oestrogens," *Human Reproductive Update* 7 (2001): 392-302.

Pelley J, "U.S. EPA Trims the Public's Right to Know," *Environmental Science & Technology Online News*, February 14, 2007.

Pew Environmental Health Commission, *Healthy From the Start: Why America Needs a Better System to Track and Understand Birth Defects and the Environment* (Baltimore: Johns Hopkins School of Public Health, 2000).

Pinyerd B and Zipf WB, "Puberty—Timing is Everything!" *Journal of Pediatric Nursing* 20 (2005): 75-82.

Porta M, "Persistent Organic Pollutants and the Burden of Diabetes," *The Lancet* 368 (2006): 558-59.

Putnam R, *The Natural History of Deer* (Ithaca, NY: Cornell University Press, 1988).

Remer T and Manz F, "Role of Nutritional Status in the Regulation of Adrenarche," *Journal of Clinical Endocrinology & Metabolism* 84 (1999): 3936-3944.

Remillard RB and Bunce NJ, "Linking Dioxins to Diabetes: Epidemiology and Biologic Plausibility," *Environmental Health Perspectives* 110 (2002): 853-58.

Revel FG et al., "Kisspeptin Mediates the Photoperiodic Control of Reproduction in Hamsters," *Current Biology* 16 (2006): 1730-35.

Reynolds EL and Wines JV, "Individual Differences in Physical Changes Associated with Adolescence in Girls," *American Journal of Diseases of Children* 82 (1948): 529-47.

Ritz B and Yu F, "The Effect of Ambient Carbon Monoxide on Low Birth Weight Among Children Born in Southern California between 1989 and 1993," *Environmental Health Perspectives* 107 (1999): 17-25.

Roberts DF, "Media and Youth: Access, Exposure, and Privatization," *Journal of Adolescent Health* 27, suppl. 2 (2000): 8-14.

Roede MJ and van Wieringen JC, "Growth diagrams 1980. Netherlands third nation-wide survey," *Tijdschrift Sociale Gezondheidszorg* 63 (1985): 11-32 (as cited in de Muinck Keizer-Schrama, 2001).

Rogan WJ and Ragan NB, "Evidence of Effects of Environmental Chemicals on the Endocrine System in Children," *Pediatrics* 112 (2003): 247-52.

Romans SE et al., "Age of Menarche: The Role of Some Psychosocial Factors," *Psychological Medicine* 33 (2003): 933-39.

Rosenfield RL et al., "Current Age of Onset of Puberty," *Pediatrics* 106 (2000): 622-23.

Rosner B et al., "Reproductive Risk Factors in a Prospective Study of Breast Cancer: The Nurses' Health Study," *American Journal of Epidemiology* 139 (1994): 819-35.

Salardi S et al., "Outcome of Premature Thelarche: Relation to Puberty and Final Height," *Archives of Disease in Childhood* 79 (1998): 173-74.

Salti R et al., "Age-dependent Association of Exposure to Television Screen with Children's Urinary Melatonin Excretion?" *Neuro Endocrinology Letters* (27): 2006: 73-80.

Schack-Nielsen L and Michaelsen KF, "Advances in Our Understanding of the Biology of Human Milk and its Effects on the Offspring," *Journal of Nutrition* 137 (2007): 503S-510S.

Scharfman HE, "Preface: Special Issue on Estrogen, Growth Factors and Brain Function," *Frontiers in Neuroendocrinology* 27 (2006): 361-62.

Schettler T, "Toward an Ecological View: Complex Systems, Health, and Disease," *San Francisco Medicine* (journal of the San Francisco Medical Society) 79 (2006): 12-15.

Selevan SG et al., "Blood Lead Concentration and Delayed Puberty in Girls," *The New England Journal of Medicine* 348 (2003): 1527-36.

Shantakumar S et al, "Reproductive Factors and Breast Cancer Risk Among Older Women," *Breast Cancer Research and Treatment* 102 (2007): 365-74.

Shuttleworth FK, "The Adolescent Period: A Graphic and Pictorial Atlas," *Monographs of the Society for Research in Child Development*, vol. 3, no. 3, 1938.

Shuttleworth FK, "Sexual Maturation and the Physical Growth of Girls Age Six to Nineteen," *Monographs of the Society for Research in Child Development*, vol. 2, no. 5, 1937.

Sisk CL and Zehr JL, "Pubertal Hormones Organize the Adolescent Brain and Behavior," *Frontiers in Neuroendocrinology* 26 (2005): 163-174.

Sloboda DM et al., "Age at Menarche: Influences of Prenatal and Postnatal Growth," *Journal of Clinical Endocrinology and Metabolism* 92 (2007): 46-50.

Slyper AH, "The Pubertal Timing Controversy in the USA, and a Review of Possible Causative Factors for the Advance in Timing of Onset of Puberty," *Clinical Endocrinology* 65 (2006): 1-8.

Stahlhut RW et al., "Concentrations of Urinary Phthalate Metabolites are Associated with Increased Waist Circumference and Insulin Resistance in Adult Males," *Environmental Health Perspectives*, March 14, 2007 [epub ahead of print].

Stein ZA et al., *Famine and Human Development: The Dutch Hunger Winter of 1944-45* (New York: Oxford Univ. Press, 1975).

Steingraber S, "A Hormonal Message: Why are Girls Reaching Puberty Ever Earlier?" *Orion* 25 (May-June 2006), pp. 70-71.

Steingraber S, *Having Faith: An Ecologist's Journey to Motherhood* (Cambridge, MA: Perseus Book Group, 2001).

Stoll BA, "Western Diet, Early Puberty, and Breast Cancer Risk," *Breast Cancer Research and Treatment* 49 (1998): 187-93.

Strauss RS et al., "Psychosocial Correlates of Physical Activity in Healthy Children," *Archives of Pediatric & Adolescent Medicine* 155 (2001): 897-902.

Striegel-Moore RH et al., "Exploring the Relationship between Timing of Menarche and Eating Disorder Symptoms in Black and White Adolescent Girls," *International Journal of Eating Disorders* 30 (2001): 421-33.

Strom BL et al., "Exposure to Soy-Based Formula in Infancy and Endocrinological and Reproductive Outcomes in Young Adulthood," *JAMA* 286 (2001): 807-14.

Sun SS et al., "Is Sexual Maturity Occurring Earlier Among U.S. Children?" *Journal of Adolescent Health* 37 (2005): 345-55.

Tabb MM and Blumberg B, "New Modes of Action for Endocrine-disrupting Chemicals, *Molecular Epidemiology* 20 (2006): 475-82.

Tahirovic HF, "Menarchal Age and the Stress of War: An Example from Bosnia," *European Journal of Pediatrics* 157 (1998): 978-80.

Tanner JM and Eveleth PB, "Variability between Populations in Growth and Development at Puberty," in Berenberg SR, ed., *Puberty, Biologic and Psychosocial Components* (Leiden, Netherlands: H.E. Stenfert Kroese, 1975), pp. 256-73.

Tarullo AR and Gunnar MR, "Child Maltreatment and the Developing HPA Axis," *Hormones and Behavior* 50 (2006): 632-39.

Teilmann G et al., "Prevalence and Incidence of Precocious Pubertal Development in Denmark: An Epidemiologic Study Based on National Registries," *Pediatrics* 116 (2005): 1323-28.

Tena-Sempere M, "KiSS-1 and Reproduction: Focus on its Role in the Metabolic Regulation of Fertility," *Neuroendocrinology* 83 (2006): 275-81.

Terasawa E, "Role of GABA in the Mechanism of the Onset of Puberty in Non-Human Primates," *International Review of Neurobiology* 71 (2005): 113-129.

Tiwary C, "Premature Sexual Development in Children Following Use of Estrogen- or Placenta-Containing Hair Products," *Clinical Pediatrics* 37 (1998): 733-40.

Tremblay L and Frigon JY, "Precocious Puberty in Adolescent Girls: A Biomarker of Later Psychosocial Adjustment Problems," *Child Psychiatry and Human Development* 36 (2005): 73-94.

Trivers KF et al., "Association between Reproductive Factors and Breast Cancer Survival in Younger Women," *Breast Cancer Research and Treatment* 103 (2007): 93-102.

Tuohy PG, "Soy Infant Formula and Phytoestrogens," *Journal of Paediatric and Child Health* 39 (2003): 401-05.

Vandeloo MJ et al., "Effects of Lifestyle on the Onset of Puberty as a Determinant for Breast Cancer," *European Journal of Cancer Prevention* 16 (2007): 17-25.

Vandenberg LN et al., "The Mammary Gland Response to Estradiol: Monotonic at the Cellular Level, Non-Monotonic at the Tissue-Level of Organization?" *Journal of Steroid Biochemistry & Molecular Biology* 101 (2006): 263-74.

Vandenbergh JG, "Pheromonal Regulation of Puberty," in Vandenbergh JG, ed., *Pheromones and Reproduction in Mammals* (Orlando: Academic Press, 1983), pp. 95-149.

Vasiliu O et al., "In Utero Exposure to Organochlorines and Age at Menarche," *Human Reproduction* 19 (2004): 1506-12.

Veening MA et al., "Pubertal Development in Children Born Small for Gestational Age," *Journal of Pediatric Endocrinology & Metabolism* 17 (2004): 1497-1505.

Verner Louis, Ph.D., wildlife biologist, Virginia Department of Fish and Game, Richmond, VA; personal interview, September 18, 2006.

vom Saal FS, "Perinatal Programming of Obesity: Interaction of Nutrition and Environmental Exposures," presentation to the American Association for the Advancement of Science annual meeting, San Francisco, February 16, 2007.

vom Saal FS and Hughes C, "An Extensive New Literature Concerning Low-Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment," *Environmental Health Perspectives* 113 (2005): 926-33.

Wang RY et al., "Effects of Environmental Agents on the Attainment of Puberty: Considerations When Assessing Exposure to Environmental Chemicals in the National Children's Study," *Environmental Health Perspectives* 113 (2005): 1100-07).

Warner M et al., "Serum Dioxin Concentrations and Age at Menarche," *Environmental Health Perspectives* 112 (2004): 1289-92.

Warner M et al,, "Serum Dioxin Concentrations and Breast Cancer Risk in the Seveso Women's Health Study," *Environmental Health Perspectives* 110 (2002): 625-28.

Warner M and Eskenazi B, "TCDD and Puberty: Warner and Eskenazi Respond" [letter], *Environmental Health Perspectives* 113 (2005): A18.

Wattigney WA et al, "Secular trend of earlier onset of menarche with increasing obesity in black and white girls: the Bogalusa Heart Study," *Ethnicity and Disease* 9 (1999): 181-9 (as cited in Parent, 2003).

Whitlock, KE et al., "Development of GnRH Cells: Setting the Stage for Puberty," *Molecular and Cellular Endocrinology* 254-55 (2006): 39-50.

Whitten, PL, "Chemical Revolution to Sexual Revolution: Historical Changes in Human Reproductive Development," in Colborn T and Clement C, eds., *Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection* (Princeton, NJ: Princeton Scientific Publishing, 1992), pp. 311-34.

Windham GC et al., "Age at Menarche in Relation to Maternal Use of Tobacco, Alcohol, Coffee, and Tea During Pregnancy," *American Journal of Epidemiology* 159 (2004): 862-71.

Wolff M et al., "Pilot Study of Urinary Biomarkers of Phytoestrogens, Phthalates, and Phenols in Girls," *Environmental Health Perspectives* 115 (2007): 116-121.

Wolff M et al., "TCDD and Puberty in Girls" [letter], *Environmental Health Perspectives* 113 (2005): A17.

Worthman CW, "Evolutionary Perspectives on the Onset of Puberty," in Trevathan WR, ed., *Evolutionary Medicine* (New York: Oxford, 1999).

Wu T et al., "Blood Lead Levels and Sexual Maturation in U.S. Girls: The Third National Health and Nutrition Examination Survey, 1988-94," *Environmental Health Perspectives* 111 (2003): 737-41.

Wu T et al., "Ethnic Differences in the Presence of Secondary Sex Characteristics and Menarche Among U.S. Girls: the Third National Health and Nutrition Examination Survey, 1988-1994," *Pediatrics* 110 (2002): 752-57.

Wyart C et al., "Smelling a Single Component of Male Sweat Alters Levels of Cortisol in Women," *The Journal of Neuroscience* 27 (2007): 1261-65.

Wyshak G and Frisch RE, "Evidence for a Secular Trend in Age of Menarche," *New England Journal of Medicine* 306 (1982): 1033-35.

Xue F et al., "Maternal Fish Consumption, Mercury Levels and Risk of Preterm Delivery," *Environmental Health Perspectives* 115 (2007): 42-47.

Yun AJ et al., "Pineal Attrition, Loss of Cognitive Plasticity, and Onset of Puberty During the Teen Years: Is it a Modern Maladaption Exposed by Evolutionary Displacement?" *Medical Hypotheses* 63 (2004): 939-50.

Zabin LS et al., "Childhood Sexual Abuse and Early Menarche: The Direction of Their Relationship and its Implications," *Journal of Adolescent Health* 36 (2005): 393-400.

Zuckerman D, "When Little Girls Become Women: Early Onset of Puberty in Girls," *The Ribbon* 6 (2001): 6-8.

Zukauskaite S et al., "Onset of Breast and Pubic Hair Development in 1231 Preadolescent Lithuanian Schoolgirls," *Archives of Disease in Childhood* 90 (2005): 932-36.

BREAST CANCER FUND

PREVENTION STARTS HERE.

www.BreastCancerFund.org

NEW LEAF
PAPER