

Growing Pains

Problems with Puberty Suppression in Treating Gender Dysphoria

Paul W. Hruz, Lawrence S. Mayer, and Paul R. McHugh

Public controversies about how institutions should treat individuals who identify as a gender that does not correspond to their biological sex have recently been debated in the halls of government, in courtrooms, and on TV talk shows. Should males who identify as women have access to women's restrooms? Which school locker room should girls who identify as boys be permitted, or required, to use? Should teachers be compelled to use a student's preferred pronoun, or even a gender-neutral pronoun such as "ze" instead of "he" or "she"?

Alongside these questions of public concern, however, there are quieter matters of medicine and wellbeing. How should medical and mental health professionals care for patients who identify as the opposite sex, and how should families support loved ones who do so? The stakes are high: as detailed in a recent report in these pages, people who identify as transgender are disproportionately likely to suffer from a variety of mental health problems, including depression, anxiety, suicide attempts, and suicide.¹

Psychiatrists who follow the American Psychiatric Association's *Diagnostic and Statistical Manual* use the term "gender dysphoria" for a condition in which "incongruence between one's experienced/expressed gender and assigned gender" is accompanied by "clinically significant distress or impairment in social, occupational, or other important areas of functioning."² In this context, "experienced/expressed gender" refers to

Paul W. Hruz, M.D., Ph.D. is an associate professor of pediatrics, endocrinology, and diabetes and an associate professor of cell biology and physiology at Washington University School of Medicine in St. Louis. Lawrence S. Mayer, M.B., M.S., Ph.D. is a scholar in residence in the Department of Psychiatry of Johns Hopkins University School of Medicine, a professor of statistics and biostatistics at Arizona State University, and a professor in the Mayo/ASU program in biomedical informatics. Paul R. McHugh, M.D. is University Distinguished Service Professor of Psychiatry at Johns Hopkins University School of Medicine and was for twenty-six years the psychiatrist-in-chief at the Johns Hopkins Hospital. He is the author or coauthor of several books, including, most recently, Try to Remember: Psychiatry's Clash over Meaning, Memory, and Mind (Dana Press, 2008).

SPRING 2017 ~ 3

the gender that the person subjectively identifies as or wishes to be publicly recognized as—what is often referred to as “gender identity”—while “assigned gender” refers in almost all cases to his or her unambiguous biological sex. (In rare cases, a person’s biological sex is difficult to determine; such “intersex” individuals are born with biological features of both sexes. Most transgender individuals are not biologically intersex.³)

There is strikingly little scientific understanding of important questions underlying the debates over gender identity—for instance, there is very little scientific evidence explaining why some people identify as the opposite sex, or why childhood expressions of cross-gender identification persist for some individuals and not for others.⁴ Yet notwithstanding the limited data, physicians and mental health care providers have arrived at a number of methods for treating children, adolescents, and adults with gender dysphoria.

Of particular concern is the management of gender dysphoria in children. Young people with gender dysphoria constitute a singularly vulnerable population, one that experiences high rates of depression, self-harm, and even suicide.⁵ Moreover, children are not fully capable of understanding *what it means* to be a man or a woman. Most children with gender identity problems eventually come to accept the gender associated with their sex and stop identifying as the opposite sex.⁶ There is some evidence, however, that gender dysphoria and cross-gender identification become more persistent if they last into adolescence.⁷

In one prominent treatment approach, called “gender-affirming,” the therapist accepts, rather than challenges, the patient’s self-understanding as being the opposite sex. Gender-affirming models of treatment are sometimes applied even to very young children.⁸ Often, the gender-affirming approach is followed in later youth and adulthood by hormonal and surgical interventions intended to make patients’ appearances align more closely with their gender identity than their biological sex. In order to improve the success of the physical changes, interventions at younger ages are increasingly being recommended.⁹

Gender identity clinics offering gender-affirmative psychotherapy for children and adolescents have opened for business in the United States and several other countries.¹⁰ Though there is little systematically collected data on the number of young people (or even the number of adults) who identify as transgender or who have undergone sex-reassignment surgery,* there is some evidence that the number of people receiving medical and psychotherapeutic care for gender identity issues is on the rise:

4 ~ THE NEW ATLANTIS

- The Gender Identity Development Service in the United Kingdom, which treats only children under the age of 18, reports that it received 94 referrals of children in 2009/2010 and 1,986 referrals of children in 2016/2017—a relative increase of 2,000%.¹¹ The service also reports that it received six referrals for children under the age of 6 in 2009/2010, compared to thirty-two referrals for children under the age of 6 in 2016/2017—a relative increase of 430%.¹²
- In a brief paper by psychologists from a gender clinic in Toronto, the authors reported a large increase in the number of referrals for children (ages 3 to 12) per year between 1988 and 1991, when the number of children referred went from around 40 per year to around 80, a rate that remained steady through 2011.¹³ The authors also reported that between 2004 and 2007, the rate of adolescents (ages 13 to 20) referred to their clinic rose from roughly 20 per year to 60, and then to nearly 100 per year by 2011.¹⁴
- In a paper by clinicians at Children’s Hospital Boston, the authors reported on the number of individuals who presented at the hospital with gender identity issues. Between 1998 and 2006, such patients presented to the hospital’s Endocrine Division at an average rate of 4.5 patients per year, but in the period from 2007 to 2009, after the hospital opened a gender identity clinic, the annual average of patients presenting with gender identity issues rose to 19 patients per year.¹⁵
- In a paper published in 2016, physicians from an Indianapolis pediatric endocrinology clinic reported a “dramatic increase” in referrals for gender dysphoria since 2002, finding that of 38 patients referred between 2002 and 2015, “74% were referred during the last 3 years.”¹⁶ The authors emphasized that their clinic does not specialize in gender dysphoria, and that “the remarkable increase in the number of new patients seen in our clinic over the last 3 years has occurred even though our referral base is unchanged, and our clinic has not specifically advertised its care for transgender patients.”¹⁷

* The most familiar colloquial term used to describe the medical interventions that transform the appearance of transgender individuals may be “sex change” (or, in the case of surgery, “sex-change operation”), but this is not commonly used in the scientific and medical literature today. While no simple terms for these procedures are completely satisfactory—in the context of this article the most accurate description would be “hormonal and surgical interventions to modify secondary sex characteristics”—we employ the commonly used terms *sex reassignment* and *sex-reassignment surgery* or *procedures*, except when quoting a source that uses “gender reassignment” or some other term.

The reasons for these rising rates are unclear. It may be that increased public awareness of gender dysphoria has made parents more willing to seek medical help for their children. (We should remember that it is parents or guardians, not children themselves, who make decisions about medical care.) However, the medical treatments provided for children with apparent symptoms of gender dysphoria, including affirmation of gender expression from the earliest evidence of cross-gender behaviors, may drive some children to persist in identifying as transgender when they might otherwise have, as they grow older, found their gender to be aligned with their sex. Gender identity for children is elastic (that is, it can change over time) and plastic (that is, it can be shaped by forces like parental approval and social conditions).¹⁸ If the increasing use of gender-affirming care does cause children to persist with their identification as the opposite sex, then many children who would otherwise not need ongoing medical treatment would be exposed to hormonal and surgical interventions.

One particular gender-affirming intervention for children and young adolescents with gender dysphoria is puberty suppression (also known as puberty blocking)—a hormone intervention that prevents the normal progression of puberty. Puberty is a turbulent time in any young person's life, and it can be terrifying for those who identify as the opposite sex. For parents of children with gender dysphoria, puberty suppression can appear very attractive. It seems like it might offer a medical solution for the anticipated confusion, anxiety, and distress by holding back the development of the most conspicuous features of their children's biological sex. Puberty suppression seems to offer an intermediate step between the social affirmation that parents can give very young children and the sex-reassignment procedures that their kids can pursue once they've grown. And it seems to offer a way to mitigate the discordance between children's beliefs about their gender and the realities of their bodily development (while acquiescing to, rather than challenging, the children's self-understanding). Puberty suppression can, in short, look like safe passage from stormy seas of childhood expressions of beliefs about gender to the secure harbor of an adulthood lived permanently as the opposite sex.

In light of the growing prominence of gender identity issues in our society, and the appeal that puberty suppression may have for parents raising children who identify as the opposite sex, it is worth examining in detail what puberty suppression is, how it works, and whether it is as safe and prudent as its advocates maintain. As we shall see, the evidence for the safety and efficacy of puberty suppression is thin, based more on the subjective judgments of clinicians than on rigorous empirical evidence. It is,

in this sense, still experimental—yet it is an experiment being conducted in an uncontrolled and unsystematic manner.

What Is Puberty?

Having experienced adolescence and the tumultuous changes it involves, most adults are familiar in a very personal way with puberty. But addressing the questions surrounding puberty-blocking interventions for gender dysphoria requires acquaintance with how puberty is defined and understood in biology and medicine. Some fundamental facts about puberty are still unknown; in the words of one medical textbook, “Initiation of the onset of puberty has long been a mystery.”¹⁹ But on the whole, the main aspects of puberty are well understood.

A textbook chapter by William A. Marshall and James M. Tanner (for whom the Tanner scale, a detailed measure of the stages of pubertal development is named) describes puberty as “the morphological and physiological changes that occur in the growing boy or girl as the gonads change from the infantile to the adult state. These changes involve nearly all the organs and structures of the body but they do not begin at the same age nor take the same length of time to reach completion in all individuals. Puberty is not complete until the individual has the physical capacity to conceive and successfully rear children.”²⁰ The authors go on to list the principal manifestations of puberty:

1. The adolescent growth spurt; i.e., an acceleration followed by a deceleration of growth in most skeletal dimensions and in many internal organs.
2. The development of the gonads.
3. The development of the secondary reproductive organs and the secondary sex characters.
4. Changes in body composition, i.e., in the quantity and distribution of fat in association with growth of the skeleton and musculature.
5. Development of the circulatory and respiratory systems leading, particularly in boys, to an increase in strength and endurance.²¹

The ability to physically conceive children is made possible by the maturation of the primary sex characteristics, the organs and structures that are involved directly in reproduction. In boys, these organs and structures include the scrotum, testes, and penis while in girls they include the

ovaries, uterus, and vagina. In addition to these primary sex characteristics, secondary sex characteristics also develop during puberty—the distinctive physical features of the two sexes that are not directly involved in reproduction. Secondary sex characteristics that develop in girls include “the growth of breasts and the widening of the pelvis” and in boys “the appearance of facial hair and the broadening of shoulders,” while other patterns of body hair and changes in voice and skin occur during puberty in both girls and boys.²²

Physicians characterize the progress of puberty by marking the onset of different developmental milestones. The earliest visible event, the initial growth of pubic hair, is known as “pubarche”; it occurs between roughly ages 8 and 13 in girls, and between ages 9.5 and 13.5 in boys.²³ In girls, the onset of breast development, known as “thelarche,” occurs around the same time as pubarche.²⁴ (The “-arche” in the terms for these milestones comes from the Greek for beginning or origin.) “Menarche” is another manifestation of sexual maturation in females, referring to the onset of menstruation, which typically occurs at around 13 years of age and is generally a sign of the ability to conceive.²⁵ Roughly corresponding to menarche in girls is “spermarche” in boys; this refers to the initial presence of viable sperm in semen, which also typically occurs around 13.²⁶

Hormones and Puberty

Having established *what* puberty is, we now turn to *how* puberty happens.

Scientists distinguish three main biological processes involved in puberty: adrenal maturation, gonadal maturation, and somatic growth acceleration.²⁷ We will discuss each of these processes in turn, with a particular focus on gonadal maturation.

“Adrenarche”—the beginning of adrenal maturation—begins between ages 6 and 9 in girls, and ages 7 and 10 in boys. The hormones produced by the adrenal glands during adrenarche are relatively weak forms of androgens (masculinizing hormones) known as dehydroepiandrosterone and dehydroepiandrosterone sulfate. These hormones are responsible for signs of puberty shared by both sexes: oily skin, acne, body odor, and the growth of axillary (underarm) and pubic hair.²⁸

“Gonadarche”—the beginning of the process of gonadal maturation—normally occurs in girls between ages 8 and 13 and in boys between ages 9 and 14.²⁹ The process begins in the brain, where specialized neurons in the hypothalamus secrete gonadotropin-releasing hormone (GnRH).³⁰

This hormone is secreted in a cyclical or “pulsatile” manner³¹—the hypothalamus releases bursts of GnRH, and when the pituitary gland is exposed to these bursts, it responds by secreting two other hormones. These are luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate the growth of the gonads (ovaries in women and testes in men).³² (The “follicles” that the latter hormone stimulates are not hair follicles but ovarian follicles, the structures in the ovaries that contain immature egg cells.) In addition to regulating the maturation of the gonads and the production of sex hormones, these two hormones also play an important role in regulating aspects of human fertility³³—but for present purposes, we will focus on their role in the development of the gonads and the production of sex hormones during puberty.

As the gonadal cells mature under the influence of LH and FSH, they begin to secrete androgens (masculinizing sex hormones like testosterone) and estrogens (feminizing sex hormones).³⁴ These hormones contribute to the further development of the primary sex characteristics (the uterus in girls and the penis and scrotum in boys) and to the development of secondary sex characteristics (including breasts and wider hips in girls, and wider shoulders, breaking voices, and increased muscle mass in boys). The ovaries and testes both secrete androgens as well as estrogens, however the testes secrete more androgens and the ovaries more estrogens.³⁵

The gonads and the adrenal glands are involved in two separate but interrelated pathways (or “axes”) of hormone signaling. These are the hypothalamic-pituitary-gonadal (HPG) axis and the hypothalamic-pituitary-adrenal (HPA) axis.³⁶ Though both play essential roles in puberty, it is, as just noted, the HPG axis that results in the development of the basic reproductive capacity and the external sex characteristics that distinguish the sexes.³⁷

The third significant process that occurs with puberty, the somatic growth spurt, is mediated by increased production and secretion of human growth hormone, which is influenced by sex hormones secreted by the gonads (both testosterone and estrogen). Similar to the way that the secretion of GnRH by the hypothalamus provokes the pituitary gland to secrete FSH and LH, in this case short pulses of a hormone released by the hypothalamus cause the pituitary gland to release human growth hormone.³⁸ This process is augmented by testosterone and estrogen.³⁹ Growth hormone acts directly to stimulate growth in certain tissues, and also stimulates the liver to produce a substance called “insulin-like growth factor 1,” which has growth-stimulating effects on muscle.⁴⁰

The neurological and psychological changes occurring in puberty are less well understood than are the physiological changes. Men and women have distinct neurological features that may account for some of the psychological differences between the sexes, though the extent to which neurological differences account for psychological differences, and the extent to which neurological differences are caused by biological factors like hormones and genes (as opposed to environmental factors like social conditioning), are all matters of debate.⁴¹

Scientists distinguish between two types of effects hormones can have on the brain: organizational effects and activational effects. Organizational effects are the ways in which hormones cause highly stable changes in the basic architecture of different brain regions. Activational effects are the more immediate and temporary effects of hormones on the brain's activity. During puberty, androgens and estrogens primarily have activating effects, but long before then they have organizational effects in the brains of developing infants and fetuses.⁴² (Some researchers speculate that cross-gender identification may be caused by atypical patterns of fetal exposure to sex hormones, but these theories have yet to be scientifically confirmed or even seriously tested.⁴³) However, animal studies have provided some evidence that sex hormones may contribute to organizational effects (or reorganization) of the brain during puberty.⁴⁴ How, whether, and to what extent this process occurs in humans remain poorly understood.⁴⁵

In sum: Puberty involves a myriad of complex, related, and overlapping physical processes, occurring at various points and lasting for various durations. Adrenarche and the secretion of growth hormones contribute to the child's growth and development, while gonadarche crucially leads to the maturation of sex organs that allow for reproduction, as well as the development of the other biological characteristics that distinguish males and females. The description offered here has been very simplified, of course, but it gives sufficient background to understand the workings of puberty suppression, to which we turn next.

The Origins of Puberty-Suppression Techniques

Hormone interventions to suppress puberty were not developed for the purpose of treating children with gender dysphoria—rather, they were first used as a way to normalize puberty for children who undergo puberty too early, a condition known as “precocious puberty.”

For females, precocious puberty is defined by the onset of puberty before age 8, while for males it is defined as the onset of puberty before

age 9.⁴⁶ Premature thelarche (the appearance of breast development) is usually the first clinical sign of precocious puberty in girls. For males, precocious puberty is marked by premature growth in genitalia and pubic hair.⁴⁷ In addition to the psychological and social consequences that a child might be expected to suffer, precocious puberty can also lead to reduced adult height, since the early onset of puberty interferes with later bone growth.⁴⁸

Precocious puberty is divided into two types, central precocious puberty (sometimes labeled “true precocious puberty”) and peripheral precocious puberty (sometimes labeled “precocious pseudopuberty”).⁴⁹ Central precocious puberty is caused by the early activation of the gonadal hormone pathway by GnRH, and is amenable to treatment by physicians. Peripheral precocious puberty, which is caused by secretion of sex hormones by the gonads or adrenal glands independent of signals from the pituitary gland, is less amenable to treatment.⁵⁰ Precocious puberty is rare, especially in boys. A recent Spanish study of central precocious puberty estimated the overall prevalence to be 19 in 100,000 (37 in 100,000 girls affected, and 0.46 in 100,000 boys).⁵¹ A Danish study of precocious puberty (not limited to central precocious puberty) found the prevalence to be between 20 to 23 per 10,000 in girls and less than 5 in 10,000 in boys.⁵²

Treatment for precocious puberty is somewhat counterintuitive. Rather than stopping the production of GnRH, physicians actually provide patients more constant levels of synthetic GnRH (called GnRH analogues or GnRH agonists).⁵³ The additional GnRH “desensitizes” the pituitary, leading to a decrease in the secretion of gonadotropins (LH and FSH), which in turn leads to the decreased maturation of and secretion of sex hormones by the gonads (ovaries and testes). The first publication describing the use of GnRH analogues in children for precocious puberty appeared in 1981.⁵⁴

The process of desensitization of the pituitary gland by synthetic GnRH is not permanent. After a patient stops taking the GnRH analogues, the pituitary will resume its normal response to the pulsatile secretion of GnRH by the hypothalamus, as evidenced by the fact that children treated for precocious puberty using GnRH analogues will resume normal pubertal development, usually about a year after they withdraw from treatment.⁵⁵

In the time since GnRH analogues were first proposed in the early 1980s, they have become fairly well accepted as a treatment of precocious puberty, with one prominent GnRH analogue, Lupron, approved for that

use by the FDA in 1993.⁵⁶ However, there remain some questions concerning the effectiveness of treatment with GnRH analogues. A recent consensus statement of pediatric endocrinologists concluded that GnRH analogues are an effective way to improve the height of girls with onset of puberty at less than 6 years of age, and also recommended the treatment be considered for boys with onset of precocious puberty who have compromised height potential.⁵⁷ Regarding the negative psychological and social outcomes associated with precocious puberty, the authors found that the available data were unconvincing, and that additional studies are needed.⁵⁸

It is worth noting that the use of GnRH analogues has been considered in other contexts as well—for example, in some cases of children with severe learning disabilities, to ease the difficulties that those children and their caregivers may experience with puberty.⁵⁹ Synthetic GnRH to desensitize the pituitary has also been adapted to treat a variety of other conditions related to the secretion of sex hormones in adults, including prostate cancer⁶⁰ and fertility issues.⁶¹ This is because the natural pulsatile release of GnRH continues to play an important role beyond puberty, in that it stimulates the pituitary gland to secrete gonadotropins that trigger the gonads to secrete sex hormones from the testes and ovaries.⁶²

To sum up how puberty suppression works, a thought experiment might be helpful. Imagine two pairs of biologically and psychologically normal identical twins—a pair of boys and a pair of girls—where one child from each pair undergoes puberty suppression and the other twin does not. Doctors begin administering GnRH analogue treatments for the girl at, say, age 8, and for the boy at age 9. Stopping the gonadal hormone pathway of puberty does not stop time, so the puberty-suppressed twins will continue to age and grow—and because adrenal hormones associated with puberty will not be affected, the twins receiving GnRH analogue will even undergo some of the changes associated with puberty, such as the growth of pubic hair. However, there will be major, obvious differences within each set of twins. The suppressed twins' reproductive organs will not mature: the testicles and penis of the boy undergoing puberty suppression will not mature, and the girl undergoing puberty suppression will not menstruate. The boy undergoing puberty suppression will have less muscle mass and narrower shoulders than his twin, while the breasts of the girl undergoing puberty suppression will not develop. The boy and girl undergoing puberty suppression will not have the same adolescent growth spurts as their twins. So all told, by the time the untreated twins reach maturity, look like adults, and are biologically capable of having

children, the twins undergoing puberty suppression will be several inches shorter, will physically look more androgynous and childlike, and will not be biologically capable of having children. This is only a thought experiment, but it illustrates some of the effects that puberty suppression would be expected to have on the development of a growing adolescent's body.

Advocacy and Guidelines

A number of medical associations and advocacy groups have endorsed puberty suppression as a prudent and compassionate way of helping youth with gender dysphoria. In 2009, the Endocrine Society—an international organization of professionals who deal with the body's hormones—published guidelines for the treatment of transsexual persons, recommending “that adolescents who fulfill eligibility and readiness criteria for gender reassignment initially undergo treatment to suppress pubertal development.”⁶³

Two years later, the Endocrine Society partnered with other organizations—the World Professional Association for Transgender Health, the European Society of Endocrinology, the European Society of Pediatric Endocrinology, and the Pediatric Endocrine Society—to circulate another set of guidelines for the treatment of transgender individuals.⁶⁴ Three observations are provided in the guidelines to justify puberty suppression. First, gender dysphoria “rarely desists after the onset of pubertal development” and additionally, “suppression causes no irreversible or harmful changes in physical development and puberty resumes readily if hormonal suppression is stopped.”⁶⁵ Second, the typical physical changes of puberty are “often associated with worsening of gender dysphoria,” which has “been reversed by pubertal suppression.”⁶⁶ Third, the modification of secondary sex characteristics by hormonal treatments “is easier and safer when the sex steroids of the adolescent's genetic sex and their physical effects, for example, virilization of breast growth, are not present.”⁶⁷

The World Professional Association for Transgender Health (WPATH, a membership organization for health care professionals that advocates for transgender health care) also endorses puberty suppression in its *Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People* (2011), if the following criteria are met:

1. The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed);

2. Gender dysphoria emerged or worsened with the onset of puberty;
3. Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment;
4. The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.⁶⁸

The WPATH *Standards of Care* document gives the following two justifications for puberty suppression interventions: “(i) their use gives adolescents more time to explore their gender nonconformity and other developmental issues; and (ii) their use may facilitate transition [to living as the opposite sex] by preventing the development of sex characteristics that are difficult or impossible to reverse if adolescents continue on to pursue sex reassignment.”⁶⁹

In 2016, the Human Rights Campaign, an LGBT advocacy group, partnered with the American Academy of Pediatrics—the nation's most prominent professional organization for pediatricians—and the American College of Osteopathic Pediatricians to publish a guide for families of transgender children. The guide says that “to prevent the consequences of going through a puberty that doesn't match a transgender child's identity, healthcare providers may use fully reversible medications that put puberty on hold.”⁷⁰ Delaying puberty, according to the guide, gives the child and family time “to explore gender-related feelings and options.”⁷¹

Reading these various guidelines gives the impression that there is a well-established scientific consensus about the safety and efficacy of the use of puberty-blocking agents for children with gender dysphoria, and that parents of such children should think of it as a prudent and scientifically proven treatment option. But whether blocking puberty is the best way to treat gender dysphoria in children remains far from settled and it should be considered not a prudent option with demonstrated effectiveness but a drastic and experimental measure.

Experimental medical treatments for children must be subject to especially intense scrutiny, since children cannot provide legal consent to medical treatment of any kind (parents or guardians must consent for their child to receive treatment), to say nothing of consenting to become research

subjects for testing an unproven therapy. In the case of gender dysphoria, however, the safety and efficacy of puberty-suppressing hormones is not well founded on evidence—though hormone interventions used for suppressing puberty in children have undergone clinical trials, these trials were, as discussed above, for other indications, such as delaying precocious puberty. Whether puberty suppression is safe and effective when used for gender dysphoria remains unclear and unsupported by rigorous scientific evidence. This is especially worrying in light of the lack of understanding of the causes of gender dysphoria in children or adults. Conditions like precocious puberty, for instance, have a biological course that is relatively well understood. Hormone interventions that treat that condition are tailored to its causes. In the case of gender dysphoria, however, we simply do not know what causes a child to identify as the opposite sex, so medical interventions, like puberty suppression, cannot directly address it.

Some doctors who use puberty suppression to treat children with gender dysphoria argue that “the etiology does not affect the way adolescents with GD [gender dysphoria] should be treated”⁷²—that is, treating gender dysphoria does not require us first to understand its causes. In an analogy offered by one anonymous psychiatrist interviewed in a study of physicians’ attitudes on the subject, “even if you do not know exactly why or how [a] person has broken his leg,” it is possible to “understand that it is painful and impairs function.”⁷³ Though there are obvious differences between the importance of the etiology of incidental injuries (like a broken leg) and persistent psychological conditions (like gender dysphoria), this comparison is worth considering carefully. It is true that caring for patients is important regardless of the etiology of their conditions. However, even for an injury like a broken bone, a doctor should be interested in (for example) whether the patient has some condition that makes his or her bones more breakable. A bone fracture may be a symptom of an underlying pathology such as osteoporosis, and in such cases, different courses of treatment may be indicated; the bone may need to set for longer, and doctors will generally recommend certain lifestyle changes or extensive courses of treatment to mitigate the underlying condition and to reduce the risk of future injuries.

If we understood the underlying causes of gender dysphoria (or even factors that contribute to the risk and severity of gender dysphoria, as osteoporosis is a risk factor in bone fractures), doctors would be able to make different kinds of recommendations to patients for mitigating the underlying disconnection between the gender identity and the body of a patient, and reducing the severity of the dysphoria experienced by their

patients. All discussions of appropriate treatments for gender dysphoria in adolescents or adults are subject to the qualification that entirely new therapeutic approaches might be discovered as a result of improvements in our currently limited understanding of the etiology and course of gender dysphoria.

Puberty suppression as an intervention for gender dysphoria has been accepted so rapidly by much of the medical community, apparently without scientific scrutiny, that there is reason to be concerned about the welfare of children who are receiving it, as well as reason to question the veracity of some of the claims made to support its use—such as the assertion that it is physiologically and psychologically “reversible.” To better understand the treatment options for children with gender dysphoria, it is worth examining the origins of this approach and the justifications offered for it.

Blocking Puberty for Gender Dysphoria

During the 1980s, at about the same time that GnRH-based treatments for precocious puberty were being developed, another use of the technique was being tested: to suppress the normal physiological production of male sex hormones among adult males who identify as females. This form of hormonal sex reassignment was first described in 1981, when Canadian doctors reported their use of GnRH analogues to suppress androgen production in four transsexual males, ages 18 to 29.⁷⁴ GnRH analogues continue to be used as part of sex-reassignment procedures for some adult male-to-female sex reassignment patients.⁷⁵

It was only in the 1990s that GnRH analogues came to be used for the first time to suppress puberty in children who identify as the opposite sex. In 1998, Peggy Cohen-Kettenis and Stephanie van Goozen, psychologists at a Dutch gender clinic, described the case of a 13-year-old female gender-dysphoria patient. GnRH analogue was used to suppress puberty before she received a definitive diagnosis of gender identity disorder at age 16. (Gender identity disorder was then the generally accepted term for what is now more often called gender dysphoria, although the two are not identical.) At age 18, she underwent sex-reassignment surgery.⁷⁶ The clinic’s scientists and physicians went on to develop an influential protocol for using puberty suppression as part of a gender-affirming therapeutic approach to gender dysphoria and gender identity issues in adolescents. A description of the protocol was published in the *European Journal of Endocrinology* in 2006,⁷⁷ with another paper describing “changing insights” into the use

of puberty suppression in adolescents published in the *Journal of Sexual Medicine* in 2008.⁷⁸

The protocol, often referred to as the “Dutch protocol,” calls for puberty suppression to begin at age 12 after a diagnosis of gender identity disorder. The protocol stipulates that the diagnosis should be made by both a psychologist and a psychiatrist, after information is “obtained from both the adolescent and the parents on various aspects of general and psychosexual development of the adolescent, the adolescent’s current functioning and functioning of the family.”⁷⁹ The researchers’ method for suppressing puberty was to inject 3.75 milligrams of the GnRH analogue triptorelin every four weeks.⁸⁰ With this regimen, “there was no progression of the pubertal stage,” and “regression of the first stages of the already developed sex characteristics.” This meant that, in girls, “breast tissue will become weak and may disappear completely,” and in boys, “testicular volume will regress to a lower volume.”⁸¹

Then, starting at age 16, cross-sex hormones are administered while GnRH analogue treatment continues, in order to induce something like the process of puberty that would normally occur for members of the opposite sex. In female-to-male patients, testosterone administration leads to the development of “a low voice, facial and body hair growth, and a more masculine body shape” as well as to clitoral enlargement and further atrophying of breast tissue.⁸² In patients seeking a male-to-female transition, the administration of estrogens will result in “breast development and a female-appearing body shape.” Cross-sex hormone administration for these patients will be prescribed for the rest of their lives.⁸³

Surgery is prescribed for patients once they reach 18 years of age, though “if the patient is not satisfied with, or is ambivalent about, the hormonal effects or surgery, the applicant is not referred for surgery.”⁸⁴ Male-to-female surgery involves the construction of “female-looking external genitals” (which involves the removal of the testes), in addition to breast enlargement if estrogen therapy has not resulted in satisfactory breast growth.⁸⁵ For female-to-male patients, the first surgery is often mastectomy; some female-to-male patients elect not to undergo the phalloplasty (the surgical construction of a penis), since the quality and functionality of such surgically constructed “neopenises” vary.⁸⁶ Removal of the uterus and ovaries are also common surgical procedures for female-to-male patients.⁸⁷ After the surgical removal of the gonads (testes in male-to-female patients or ovaries in female-to-male), the patients then discontinue GnRH analogue treatment, since the signaling pathway from GnRH to the pituitary gland will no longer result in the production

of sex hormones once the gonads are removed.⁸⁸ Some of the surgical operations involved in sex reassignment, such as breast augmentation, are primarily cosmetic; others, such as the removal of gonads, have significant biological effects in that they impair or eliminate the individual's natural reproductive capacities and ability to produce important sex hormones. However, none of the surgeries or hormone treatments currently possible confer the reproductive capacities of the opposite sex.

According to researchers at the Dutch clinic, some of the known effects of puberty suppression on physiologically normal children are what you would expect from alterations made to that critical stage of human development. It has a significant negative effect on the height growth rates of both male-to-female and female-to-male patients.⁸⁹ The female-to-male patients subsequently experienced a growth spurt when androgens were administered, whereas for male-to-female patients, estrogen treatment "may result in a more appropriate 'female' final height."⁹⁰ The development of normal bone-mineral density is another concern for children and adolescents treated with puberty-suppressing hormones. Early reports suggested that the patients may have experienced reduced development of bone-mineral density while on puberty-suppressing treatments, though density increased when cross-sex hormone treatments began.⁹¹ Other more recent reports are mixed; one paper found that, although bone mass did not decline during puberty suppression, the children undergoing puberty suppression fell behind the average rates of bone-density growth for their age,⁹² while another reported that puberty suppression resulted in decreased bone growth in adolescents with gender dysphoria.⁹³

In the United States, the treatment of gender dysphoria is not yet an FDA-approved use for GnRH analogue drugs (although treatments for precocious puberty, prostate cancer, and other conditions are approved).⁹⁴ This means that puberty suppression relies on the "off-label" prescription of GnRH analogue treatments; doctors are permitted to use these drugs in treating children with gender dysphoria, but the lack of FDA approval means that pharmaceutical companies selling the drugs cannot market them for treating gender dysphoria. Off-label status reflects that the use has not been proven in clinical trials to be safe and effective.

Weak Justifications

Modifying biologically normal development in 12-year-olds to treat a psychiatric condition is a serious step, one that the scientists who developed the Dutch protocol attempt to justify with a number of arguments.

First, they argue that blocking puberty may mitigate the psychosocial difficulties experienced by adolescents with gender dysphoria by lessening the growing incongruity between the adolescent patient's gender identity and sex.⁹⁵ They also argue that mitigating the early development of secondary sex characteristics during puberty can make the eventual transition (both medical and social) to living as the opposite sex easier.⁹⁶

For patients and doctors who are committed to the view that the young person's gender dysphoria represents a persistent and real problem that can best be solved by transitioning the patient to living as the opposite sex, puberty suppression can seem like a desirable approach. But most children who identify as the opposite sex will not persist in these feelings and will eventually come to identify as their biological sex: According to the *Diagnostic and Statistical Manual of Mental Disorders*, "In natal [biological] males, persistence [of gender dysphoria] has ranged from 2.2% to 30%. In natal females, persistence has ranged from 12% to 50%."⁹⁷ (As noted earlier, there is some evidence that cross-gender identification becomes more persistent if it lasts into adolescence.⁹⁸) The relatively low levels of persistence pose a challenge for those who would use puberty-suppressing treatments for young children—and for those who recommend encouraging and affirming children in their cross-gender identification. The epidemiologically low persistence rates suggest that puberty suppression would not be wise for all children who experience gender dysphoria, since it would be an unnecessary treatment for those children whose gender dysphoria would not persist if they received no intervention, and it is generally considered best, in clinical practice, to avoid unnecessary medical interventions. And beyond *unnecessary*, the interventions could, in some cases, be *harmful*, if they lead children whose gender dysphoria may have resolved in adolescence to instead persist in a dysphoric condition.

In a 2008 article, the Dutch scientists respond to this concern—the possibility that young adolescents might undergo medical interventions that could ultimately be unnecessary or worse—by arguing that adolescents who continue to identify as the opposite sex and who continue to desire sex reassignment into early puberty rarely come to identify as their biological sex; they also note that none of their own patients who were found eligible for sex reassignment decided against it.⁹⁹ But the fact that none of the patients for whom they recommended sex reassignment decided against the procedure may either indicate that their recommendations were based on a sound diagnosis of persistent gender dysphoria, *or* that their diagnosis—along with the course of treatment that followed

from it, including gender-affirmative psychotherapy and puberty suppression—may have solidified the feelings of cross-gender identification in these patients, leading them to commit more strongly to sex reassignment than they might have if they had received a different diagnosis or a different course of treatment.

The criteria used by the Dutch scientists to ensure that puberty-suppressing drugs are used only in appropriate cases do little to alleviate the concern that such treatments might make feelings of cross-gender identification more persistent:

- i) a presence of gender dysphoria from early childhood on; (ii) an increase of the gender dysphoria after the first pubertal changes; (iii) an absence of psychiatric comorbidity that interferes with the diagnostic work-up or treatment; (iv) adequate psychological and social support during treatment; and (v) a demonstration of knowledge and understanding of the effects of GnRH, cross-sex hormone treatment, surgery, and the social consequences of sex reassignment.¹⁰⁰

It is worth closely examining some of these criteria. The first criterion, that gender dysphoria is present from early childhood on, seems to assume that a patient's identification as the other gender will endure if the patient has felt that way for a long time. But signs of gender dysphoria in children are even more vague and unreliable than signs of gender dysphoria in adolescents and adults; diagnoses of gender dysphoria in children rely more on gender-atypical behaviors (for example, boys playing with dolls or girls preferring to play with boys) than on a committed belief on the part of the patients that they "really are" the opposite sex. While an increasing severity of gender dysphoria around the onset of puberty (the second criterion) may be associated with the long-term persistence of gender dysphoria, it is difficult to separate this from the possibility that the "psychological and social support" for the child's cross-gender feelings, behaviors, and identification (the fourth criterion) may have contributed to the persistence of the child's gender dysphoria. And regarding the fifth and final criterion, it seems difficult to expect that a 12-year-old would have an understanding of the effects of these complex medical interventions and of the "social consequences of sex reassignment" when these are matters that are poorly understood by doctors and scientists themselves. Furthermore, whether children as young as 12 fully understand their gender identity and whether they can be diagnosed reliably as having persistent gender dysphoria are difficult psychological questions that cannot be separated from medical judgments about the appropriateness of puberty suppression.

In the same 2008 paper, the authors write that providing pubertal suppression allows patients to avoid the “alienating experience of developing sex characteristics, which they do not regard as their own” and it “is also proof of solidarity of the health professional with the plight of the applicant.”¹⁰¹ Though it is important for physicians to establish a relationship of trust and compassion with their patients, for physicians to offer “proof of solidarity” to patients by acceding to their wishes, regardless of whether the patients’ wishes are in their best medical interests, is far from the Hippocratic tradition and surrenders the physician’s responsibility to treat patients with their ultimate benefit in mind.

Claims of “Reversibility”

A major selling point for puberty suppression is the claim that the procedure is “fully reversible.”¹⁰² This assertion allows advocates to make puberty suppression seem like a prudent compromise between two extremes: not providing any medical treatment for young patients diagnosed with gender dysphoria, which would seem negligent, and immediately and permanently medically altering the sexual characteristics of children, which would seem reckless.

Some claims of reversibility:

- The Dutch scientists who developed the protocol for puberty suppression describe it as “fully reversible.”¹⁰³
- Pediatric endocrinologist Daniel Metzger says that “the effect of the puberty-blocking drugs is reversible.”¹⁰⁴
- Norman Spack, a physician at Boston’s Children Hospital who treats gender dysphoria, describes puberty-suppressing drugs as “totally reversible.”¹⁰⁵
- In a review of the research on puberty-blocking drugs for an LGBT advocacy group, Laura E. Kuper, a researcher focused on transgender health, describes puberty blocking as “fully reversible.”¹⁰⁶
- Transgender journalist Mitch Kellaway, writing for the website Advocate.com about how “blocking puberty is beneficial for transgender youth,” describes puberty blocking as “fully reversible.”¹⁰⁷
- In another Advocate.com story about puberty blocking, transgender activist Andrea James writes that “the treatment is reversible.”¹⁰⁸

- Bioethicist Arthur Caplan has described puberty blocking as reversible, saying that “if it’s decided to stop the treatment, puberty will resume.”¹⁰⁹
- Pediatric endocrinologists Christopher P. Houk and Peter A. Lee write that puberty suppression in children with gender dysphoria is “reversible.”¹¹⁰

A twist on the theme of reversibility appears in the guide for supporting and caring for transgender children published in 2016 by the Human Rights Campaign. The document highlights how “extremely distressing” the development of secondary sex characteristics can be for transgender youth, and even notes that “some of these physical changes, such as breast development, are *irreversible* or require surgery to undo” (emphasis added).¹¹¹ Similar language is used by the scientists who developed the Dutch protocol, who write that “the child who will live permanently in the desired gender role as an adult may be spared the torment of (full) pubescent development of the ‘wrong’ secondary sex characteristics”¹¹² and elsewhere write that puberty suppression is important because the development of secondary sex characteristics that cause a transgender person to look “like a man (woman) when living as a woman (man)...is obviously an enormous and lifelong disadvantage.”¹¹³ This turns the normal language of reversibility on its head, speaking of the natural process of biological development as an irreversible series of problems that medicine should seek to prevent, while presenting the intervention—puberty suppression—as benign and reversible.

One common argument based on the idea that puberty suppression is a reversible and prudent first step is that it can, as the Dutch scientists put it, “give adolescents, together with the attending health professional, more time to explore their gender identity, without the distress of the developing secondary sex characteristics. The precision of the diagnosis may thus be improved.”¹¹⁴ There is much that is strange about this argument. It presumes that natural sex characteristics interfere with the “exploration” of gender identity, when one would expect that the development of natural sex characteristics might contribute to the natural consolidation of one’s gender identity. It also presumes that interfering with the development of natural sex characteristics can allow for a more accurate diagnosis of the gender identity of the child. But it seems equally plausible that the interference with normal pubertal development will influence the gender identity of the child by reducing

the prospects for developing a gender identity corresponding to his or her biological sex.

Given its potential importance in the lives of the affected children, it is worth carefully examining these claims about reversibility. In developmental biology, it makes little sense to describe anything as “reversible.” If a child does not develop certain characteristics at age 12 because of a medical intervention, then his or her developing those characteristics at age 18 is not a “reversal,” since the sequence of development has already been disrupted. This is especially important since there is a complex relationship between physiological and psychosocial development during adolescence. Gender identity is shaped during puberty and adolescence as young people’s bodies become more sexually differentiated and mature. Given how little we understand about gender identity and how it is formed and consolidated, we should be cautious about interfering with the normal process of sexual maturation.

Rather than claiming that puberty suppression is reversible, researchers and clinicians should focus on the question of whether the physiological and psychosocial development that occurs during puberty can resume in something resembling a normal way after puberty-suppressing treatments are withdrawn. In children with precocious puberty, this does appear to be the case. Puberty-suppressing hormones are typically withdrawn around the average age for the normal onset of gonadarche, at about age 12, and normal hormone levels and pubertal development gradually resume. For one common method of treating precocious puberty, girls reached menarche approximately a year after their hormone treatments ended, at an average age of approximately 13, essentially the same average age as the general population.¹¹⁵

However, the evidence for the safety and efficacy of puberty suppression in boys is less robust, chiefly since precocious puberty is much more rare in boys. Although the risks are speculative and based on limited evidence, boys who undergo puberty suppression may be at greater risk for the development of testicular microcalcifications, which may be associated with an increased risk of testicular cancer, and puberty suppression in boys may also be associated with obesity.¹¹⁶

Most critically, unlike children affected by precocious puberty, adolescents with gender dysphoria do not have any physiological disorders of puberty that are being corrected by the puberty-suppressing drugs. The fact that children with suppressed precocious puberty between ages 8 and 12 resume puberty at age 13 does not mean that adolescents suffering from gender dysphoria whose puberty is suppressed beginning at

age 12 will simply resume normal pubertal development down the road if they choose to withdraw from the puberty-suppressing treatment and choose not to undergo other sex-reassignment procedures. Another troubling question that has been largely uninvestigated is what psychological consequences there might be for children with gender dysphoria whose puberty has been suppressed and who later come to identify as their biological sex.

Though there is very little scientific evidence relating to the effects of puberty suppression on children with gender dysphoria—and there certainly have been no controlled clinical trials comparing the outcomes of puberty suppression to the outcomes of alternative therapeutic approaches—there are reasons to suspect that the treatments could have negative consequences for neurological development. Scientists at the University of Glasgow recently used puberty-suppressing treatments on sheep, and found that the spatial memory of male sheep was impaired by puberty suppression using GnRH analogues,¹¹⁷ and that adult sheep that were treated with GnRH analogues near puberty continued to show signs of impaired spatial memory.¹¹⁸ In a 2015 study of adolescents treated with puberty suppression, the authors claimed that “there are no detrimental effects of [GnRH analogues] on [executive functioning],”¹¹⁹ but the results of their study were more ambiguous and more suggestive of harm than that summary indicates.¹²⁰ (It is also worth noting that the study was conducted on a small number of subjects, which makes the detection of significant differences difficult.)

In addition to the reasons to suspect that puberty suppression may have side effects on physiological and psychological development, the evidence that something like normal puberty will resume for these patients after puberty-suppressing drugs are removed is very weak. This is because there are virtually no published reports, even case studies, of adolescents withdrawing from puberty-suppressing drugs and then resuming the normal pubertal development typical for their sex. Rather than resuming biologically normal puberty, these adolescents generally go from suppressed puberty to medically conditioned cross-sex puberty, when they are administered cross-sex hormones at approximately age 16. During this time, as per the Dutch protocol, puberty-suppressing GnRH analogues continue to be administered to prevent the initiation of gonadarche; the sex hormones that are normally secreted by the maturing gonads are not produced, and physicians administer sex hormones normally produced by the gonads of the opposite sex. This means that adolescents undergoing cross-sex hormone treatment circumvent the most fundamental form of

sexual maturation—the maturation of their reproductive organs. Patients undergoing sex reassignment discontinue GnRH treatment after having their gonads removed, since the secretion of sex hormones that the treatment is ultimately intended to prevent will no longer be possible.

Today's medical technology does not make it possible for a patient to actually grow the sex organs of the opposite sex. Instead, doctors focus on preventing the maturation of primary sex characteristics and manipulating secondary sex characteristics through the administration of hormones. Infertility is therefore one of the major side effects of the course of treatment that runs from puberty suppression through cross-sex hormones to surgical sex reassignment.

After the surgical removal of ovaries or testes, which the Dutch protocol recommends for young adults with gender dysphoria at around age 18, the possibility of normal pubertal development becomes impossible, since it is these organs that normally produce the androgens and estrogens responsible for the development of secondary sex characteristics. Even though the secretion of GnRH by the hypothalamus may continue to stimulate the pituitary to secrete gonadotropins, if the gonads themselves are physically removed from the body, these hormonal signals become virtual “dead letters.”

Because the major studies of puberty suppression have not reported results of patients who have withdrawn from treatment and then resumed the puberty typical of their sex, we also do not know how normally the primary and secondary sex characteristics will develop in adolescents whose puberty has been artificially suppressed beginning at age 12. And so the claim that puberty suppression for adolescents with gender dysphoria is “reversible” is based on speculation, not rigorous analysis of scientific data.

The lack of data on gender dysphoria patients who have withdrawn from puberty-suppressing regimens and resumed normal development raises again the very important question of whether these treatments contribute to the persistence of gender dysphoria in patients who might otherwise have resolved their feelings of being the opposite sex. As noted above, most children who are diagnosed with gender dysphoria will eventually stop identifying as the opposite sex. The fact that cross-gender identification apparently persists for virtually *all* who undergo puberty suppression could indicate that these treatments increase the likelihood that the patients' cross-gender identification will persist.

As philosopher Ian Hacking has argued, many psychological conditions are subject to what he calls a “looping effect,” wherein the classification of

people as belonging to certain “kinds” can change how those people think of themselves and how they behave.¹²¹ Children and adolescents who are experiencing confusion about gender roles, their sexuality and behavior, and the changes caused by puberty may be especially likely to take up the way of life provided for by a “kind” like “transgender” as a way to make sense of their confusing circumstances, especially when they are subjected to the pressure of being labeled as such by adults in positions of authority, including parents, teachers, psychologists, and physicians.

What We Don’t Know Can Hurt Us

The use of puberty suppression and cross-sex hormones for minors is a radical step that presumes a great deal of knowledge and competence on the part of the children assenting to these procedures, on the part of the parents or guardians being asked to give legal consent to them, and on the part of the scientists and physicians who are developing and administering them. We frequently hear from neuroscientists that the adolescent brain is too immature to make reliably rational decisions,¹²² but we are supposed to expect emotionally troubled adolescents to make decisions about their gender identities and about serious medical treatments at the age of 12 or younger. And we are supposed to expect parents and physicians to evaluate the risks and benefits of puberty suppression, despite the state of ignorance in the scientific community about the nature of gender identity.

The claim that puberty-blocking treatments are fully reversible makes them appear less drastic, but this claim is not supported by scientific evidence. It remains unknown whether or not ordinary sex-typical puberty will resume following the suppression of puberty in patients with gender dysphoria. It is also unclear whether children would be able to develop normal reproductive functions if they were to withdraw from puberty suppression. It likewise remains unclear whether bone and muscle development will proceed normally for these children if they resume puberty as their biological sex. Furthermore, we do not fully understand the psychological consequences of using puberty suppression to treat young people with gender dysphoria.

More research is needed to resolve these unanswered questions. At the same time, research into how and why gender dysphoria occurs, persists, and desists must also continue, as it could elucidate new ways to help people cope with gender dysphoria with less permanent and drastic treatments than sex reassignment.

In light of the many uncertainties and unknowns, it would be appropriate to describe the use of puberty-blocking treatments for gender dysphoria as experimental. And yet it is not being treated as such by the medical community. Over the course of decades, experimental medicine has developed many norms, standards, and protocols, including human subjects protections, the use of institutional review boards, and carefully controlled clinical trials, as well as long-term follow-up studies. These longstanding practices are meant to make experimental medicine more rigorous and to serve the interests of patients, physicians, and the community. But when it comes to the use of puberty-blocking treatments for gender dysphoria, these standards and protocols seem to be almost entirely absent—a fact that ill serves patients, physicians, the community, and the search for truth. Physicians should be cautious about embracing experimental therapies in general, but especially those intended for children, and should particularly avoid any experimental therapy that has virtually no scientific evidence of effectiveness or safety. Regardless of the good intentions of the physicians and parents, to expose young people to such treatments is to endanger them.

While there is much that is not known with certainty about gender dysphoria, there is clear evidence that patients who identify as the opposite sex often suffer a great deal. They have higher rates of anxiety, depression, and even suicide than the general population. Something must be done to help these patients, but as scientists struggle to better understand what gender dysphoria is and what causes it, it would not seem prudent to embrace hormonal treatments and sex reassignment as the foremost therapeutic tools for treating this condition.

Notes

1. Lawrence S. Mayer and Paul R. McHugh, “Part Two: Sexuality, Mental Health Outcomes, and Social Stress,” in *Sexuality and Gender: Findings from the Biological, Psychological, and Social Sciences*, *The New Atlantis* 50 (Fall 2016): 73–75, <http://www.thenewatlantis.com/publications/part-two-sexuality-mental-health-outcomes-and-social-stress-sexuality-and-gender>.
2. American Psychiatric Association, “Gender Dysphoria,” *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [hereafter *DSM-5*] (Arlington, Va.: American Psychiatric Publishing, 2013), 452, <http://dx.doi.org/10.1176/appi.books.9780890425596.dsm14>.
3. Estimates for the prevalence of intersex conditions vary widely; reputable studies indicate that true genital ambiguity occurs in roughly 1 in 5,000 births, while others

claim that as many as 1 in 300 children are intersex in some sense. Amy C. Rothkopf and Rita Marie John, "Understanding Disorders of Sexual Development," *Journal of Pediatric Nursing* 29, no. 5 (2014): e23–e34, <http://dx.doi.org/10.1016/j.pedn.2014.04.002>.

4. For an overview of this subject, see Lawrence S. Mayer and Paul R. McHugh, "Part Three: Gender Identity," in *Sexuality and Gender, The New Atlantis* 50 (Fall 2016): 86–143, <http://www.thenewatlantis.com/publications/part-three-gender-identity-sexuality-and-gender>.

5. Maureen D. Connolly *et al.*, "The Mental Health of Transgender Youth: Advances in Understanding," *Journal of Adolescent Health* 59, no. 5 (2016), 489–495, <http://dx.doi.org/10.1016/j.jadohealth.2016.06.012>.

6. American Psychiatric Association, "Gender Dysphoria," *DSM-5*, 455.

7. Bernadette Wren, "Early Physical Intervention for Young People with Atypical Gender Identity Development," *Clinical Child Psychology and Psychiatry* 5, no. 2 (2000): 222–223, <http://dx.doi.org/10.1177/1359104500005002007>; Thomas D. Steensma *et al.*, "Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study," *Clinical Child Psychology and Psychiatry* 16, no. 4 (2011): 499–516, <http://dx.doi.org/10.1177/1359104510378303>.

8. See, for example, Darryl B. Hill *et al.*, "An Affirmative Intervention for Families With Gender Variant Children: Parental Ratings of Child Mental Health and Gender," *Journal of Sex & Marital Therapy* 36, no. 1 (2010): 12, <http://dx.doi.org/10.1080/00926230903375560>. See also such press accounts as Petula Dvorak, "Transgender at five," *Washington Post*, May 19, 2012, http://www.washingtonpost.com/local/transgender-at-five/2012/05/19/gIQABfFkbU_story.html.

9. See, for example, Peggy T. Cohen-Kettenis and Stephanie van Goozen, "Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent," *European Child and Adolescent Psychiatry* 7, no. 4 (1998): 246, <http://dx.doi.org/10.1007/s007870050073>.

10. Sam Hsieh and Jennifer Leininger, "Resource List: Clinical Care Programs for Gender-Nonconforming Children and Adolescents," *Pediatric Annals* 43, no. 6 (2014): 238–244, <http://dx.doi.org/10.3928/00904481-20140522-11>.

11. "GIDS referrals figures for 2016/17," Gender Identity Development Service, GIDS. NHS.uk (undated), http://gids.nhs.uk/sites/default/files/content_uploads/referral-figures-2016-17.pdf.

12. *Ibid.*

13. Hayley Wood *et al.*, "Patterns of Referral to a Gender Identity Service for Children and Adolescents (1976–2011): Age, Sex Ratio, and Sexual Orientation," *Journal of Marital and Family Therapy* 39 (2013): 2, <http://dx.doi.org/10.1080/0092623X.2012.675022>.

14. *Ibid.*

15. Norman P. Spack *et al.*, "Children and Adolescents With Gender Identity Disorder Referred to a Pediatric Medical Center," *Pediatrics* 129, no. 3 (2012): 420, <http://dx.doi.org/10.1542/peds.2011-0907>.

16. Melinda Chen, John Fuqua, and Erica A. Eugster, "Characteristics of Referrals for Gender Dysphoria Over a 13-Year Period," *Journal of Adolescent Health* 58, no. 3 (2016): 369, <http://dx.doi.org/10.1016/j.jadohealth.2015.11.010>.
17. *Ibid.*, 370.
18. Kay Bussey, "Gender Identity Development," in *Handbook of Identity Theory and Research*, eds. Seth J. Schwartz, Koen Luyckx, and Vivian L. Vignoles (New York: Springer, 2011): 608, http://dx.doi.org/10.1007/978-1-4419-7988-9_25.
19. Arthur C. Guyton and John E. Hall, *Textbook of Medical Physiology*, Eleventh Edition (Philadelphia, Penn.: Elsevier, 2005), 1008.
20. William A. Marshall and James M. Tanner, "Puberty," in *Human Growth: A Comprehensive Treatise*, Second Edition, Volume 2, eds. Frank Falkner and James M. Tanner (New York: Springer, 1986), 171.
21. *Ibid.*, 171–172.
22. Robert V. Kail and John C. Cavanaugh, *Human Development: A Life-Span View*, Seventh Edition (Boston, Mass.: Cengage Learning, 2016), 276.
23. Jamie Stang and Mary Story, "Adolescent Growth and Development," in *Guidelines for Adolescent Nutrition Services*, eds. Jamie Stang and Mary Story (Minneapolis, Minn.: University of Minnesota, 2005), 4.
24. *Ibid.*, 3.
25. Marshall and Tanner, "Puberty," 191–192.
26. *Ibid.*, 185.
27. Margaret E. Wierman and William F. Crowley, Jr., "Neuroendocrine Control of the Onset of Puberty," in *Human Growth*, Volume 2, 225.
28. Sharon E. Oberfield, Aviva B. Sopher, and Adrienne T. Gerken, "Approach to the Girl with Early Onset of Pubic Hair," *Journal of Clinical Endocrinology and Metabolism* 96, no. 6 (2011): 1610–1622, <http://dx.doi.org/10.1210/jc.2011-0225>.
29. Selma Feldman Witchel and Tony M. Plant, "Puberty: Gonadarche and Adrenarche," in *Yen and Jaffe's Reproductive Endocrinology*, Sixth Edition, eds. Jerome F. Strauss III and Robert L. Barbieri (Philadelphia, Penn.: Elsevier, 2009), 395.
30. Allan E. Herbison, "Control of puberty onset and fertility by gonadotropin-releasing hormone neurons," *Nature Reviews Endocrinology* 12 (2016): 452, <http://dx.doi.org/10.1038/nrendo.2016.70>.
31. *Ibid.*, 453.
32. *Ibid.*, 454.
33. *Ibid.*, 452.
34. Michael A. Preece, "Prepubertal and Pubertal Endocrinology," in *Human Growth: A Comprehensive Treatise*, Volume 2, 212.

35. Rex A. Hess, "Estrogen in the adult male reproductive tract: A review," *Reproductive Biology and Endocrinology* 1, (2003), <https://dx.doi.org/10.1186%2F1477-7827-1-52>; Henry G. Burger, "Androgen production in women," *Fertility and Sterility* 77 (2002): 3–5, [http://dx.doi.org/10.1016/S0015-0282\(02\)02985-0](http://dx.doi.org/10.1016/S0015-0282(02)02985-0).
36. Russell D. Romeo, "Neuroendocrine and Behavioral Development during Puberty: A Tale of Two Axes," *Vitamins and Hormones* 71 (2005): 1–25, [http://dx.doi.org/10.1016/S0083-6729\(05\)71001-3](http://dx.doi.org/10.1016/S0083-6729(05)71001-3).
37. Wierman and Crowley, "Neuroendocrine Control of the Onset of Puberty," 225.
38. Preece, "Prepubertal and Pubertal Endocrinology," 218–219.
39. Udo J. Meinhardt and Ken K. Y. Ho, "Modulation of growth hormone action by sex steroids," *Clinical Endocrinology* 65, no. 4 (2006): 414, <http://dx.doi.org/10.1111/j.1365-2265.2006.02676.x>.
40. *Ibid.*
41. For one recent review of the science of neurological sex differences, see Amber N. V. Ruigrok *et al.*, "A meta-analysis of sex differences in human brain structure," *Neuroscience Biobehavioral Review* 39 (2014): 34–50, <http://dx.doi.org/10.1016/j.neubiorev.2013.12.004>.
42. For an overview of the distinction between the organizational and activating effects of hormones and its importance for sexual differentiation, see Arthur P. Arnold, "The organizational-activational hypothesis as the foundation for a unified theory of sexual differentiation of all mammalian tissues," *Hormones and Behavior* 55, no. 5 (2009): 570–578, <http://dx.doi.org/10.1016/j.yhbeh.2009.03.011>.
43. Lawrence S. Mayer and Paul R. McHugh, "Part Two: Sexuality, Mental Health Outcomes, and Social Stress," in *Sexuality and Gender, The New Atlantis* 50 (Fall 2016): 102.
44. Sarah-Jayne Blakemore, Stephanie Burnett, and Ronald E. Dahl, "The Role of Puberty in the Developing Adolescent Brain," *Human Brain Mapping* 31 (2010): 926, <http://dx.doi.org/10.1002/hbm.21052>.
45. *Ibid.*, 927.
46. Karen Oerter Klein, "Precocious Puberty: Who Has It? Who Should Be Treated?," *Journal of Clinical Endocrinology and Metabolism* 84, no. 2 (1999): 411, <http://doi.org/10.1210/jcem.84.2.5533>. See also: Frank M. Biro *et al.*, "Onset of Breast Development in a Longitudinal Cohort," *Pediatrics* 132, no. 6 (2013): 1019–1027, <http://dx.doi.org/10.1542/peds.2012-3773>; Carl-Joachim Partsch and Wolfgang G. Sippell, "Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens," *Human Reproduction Update* 7, no. 3 (2001): 293, <http://dx.doi.org/10.1111/j.1600-0463.2001.tb05760.x>.
47. Anne-Simone Parent *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, no. 5 (2011): 675, <http://dx.doi.org/10.1210/er.2002-0019>.
-

48. Jean-Claude Carel *et al.*, "Precocious puberty and statural growth," *Human Reproduction Update* 10, no. 2 (2004): 135, <http://dx.doi.org/10.1093/humupd/dmh012>.
49. Partsch and Sippell, "Pathogenesis and epidemiology of precocious puberty," 294–295.
50. *Ibid.*
51. Leandro Soriano-Guillén *et al.*, "Central Precocious Puberty in Children Living in Spain: Incidence, Prevalence, and Influence of Adoption and Immigration," *Journal of Clinical Endocrinology and Metabolism* 95, no. 9 (2011): 4307, <http://dx.doi.org/10.1210/jc.2010-1025>. In some cases, peripheral precocious puberty is caused by an underlying condition, such as a tumor, that can be treated.
52. Grete Teilmann *et al.*, "Prevalence and Incidence of Precocious Pubertal Development in Denmark: An Epidemiologic Study Based on National Registries," *Pediatrics* 116, no. 6 (2005): 1323, <http://dx.doi.org/10.1542/peds.2005-0012>.
53. William F. Crowley, Jr. *et al.*, "Therapeutic use of pituitary desensitization with a long-acting LHRH agonist: a potential new treatment for idiopathic precocious puberty," *Journal of Clinical Endocrinology and Metabolism* 52, no. 2 (1981): 370–372, <http://dx.doi.org/10.1210/jcem-52-2-370>. (LHRH refers to "lutening hormone releasing hormone," another term for GnRH.)
54. Crowley *et al.*, "Therapeutic use of pituitary desensitization with a long-acting LHRH agonist," 370–372.
55. Marisa M. Fisher, Deborah Lemay, and Erica A. Eugster, "Resumption of Puberty in Girls and Boys Following Removal of the Histrelin Implant," *The Journal of Pediatrics* 164, no. 4 (2014): 3, <http://dx.doi.org/10.1016/j.jpeds.2013.12.009>.
56. "Full Prescribing Information" for Lupron Depot-Ped, FDA.gov (undated), https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020263s036lbl.pdf.
57. Jean-Claude Carel *et al.*, "Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children," *Pediatrics* 123, no. 4 (2009): e753, <http://dx.doi.org/10.1542/peds.2008-1783>.
58. *Ibid.*
59. Assunta Albanese and Neil W. Hopper, "Suppression of menstruation in adolescents with severe learning disabilities," *Archives of Disease in Childhood* 92, no. 7 (2007): 629, <https://dx.doi.org/10.1136%2Fadc.2007.115709>. (The use of GnRH analogues for children with severe learning disabilities is distinct from the approach to puberty blocking in the famous case of an American girl born in 1997 with severe brain impairment. Her family and doctors undertook a series of drastic measures, sometimes called the "Ashley Treatment": in addition to administering estrogen to induce the kind of growth-limiting effect of early puberty that GnRH treatment is meant to prevent, her doctors also performed a hysterectomy and surgically prevented her breasts from growing. The Ashley Treatment aims at attenuating growth, whereas when GnRH analogues are used for patients with precocious puberty the aim is to maximize adult height. Daniel F. Gunther and Douglas S. Diekema, "Attenuating Growth in Children With

Profound Developmental Disability: A New Approach to an Old Dilemma,” *Archives of Pediatric and Adolescent Medicine* 160, no. 10 [2006]: 1014, <http://dx.doi.org/10.1001/archpedi.160.10.1013>. See also PillowAngel.org, a website operated by the parents of the woman known as Ashley X.)

60. Frans Erdkamp *et al.*, “GnRH agonists and antagonists in prostate cancer,” *Generics and Biosimilars Initiative Journal* 3, no. 3 (2014): 133, <http://dx.doi.org/10.5639/gabij.2014.0303.031>.

61. Charalampos S. Siristatidis *et al.*, “Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproduction,” *Cochrane Database of Systematic Reviews* 11 (2015), <http://dx.doi.org/10.1002/14651858.CD006919.pub4>.

62. On the role of GnRH beyond puberty, see, for example, Naomi E. Rance, “Menopause and the human hypothalamus: Evidence for the role of kisspeptin/neurokinin B neurons in the regulation of estrogen negative feedback,” *Peptides* 30, no. 1 (2009): 111, <http://dx.doi.org/10.1016/j.peptides.2008.05.016>; Alvin M. Matsumoto, “Fundamental Aspects of Hypogonadism in the Aging Male,” *Reviews in Urology* 5, suppl. 1 (2003): S3, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1502324/>.

63. Wylie C. Hembree *et al.*, “Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline,” *The Journal of Clinical Endocrinology and Metabolism* 94, no. 9 (2009): 3133, <http://dx.doi.org/10.1210/jc.2009-0345>.

64. Wylie C. Hembree, “Guidelines for Pubertal Suspension and Gender Reassignment for Transgender Adolescents,” *Child and Adolescent Psychiatric Clinics of North America* 20, no. 2 (2011): 725–732, <http://dx.doi.org/10.1016/j.chc.2011.08.004>. Note: At the time these guidelines were published, the Pediatric Endocrine Society was still operating under its former name, the Lawson Wilkins Pediatric Endocrine Society.

65. *Ibid.*, 725.

66. *Ibid.*

67. *Ibid.*

68. World Professional Association for Transgender Health, “Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People,” Version 7 (2011): 19, http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=4655.

69. Hembree *et al.*, “Endocrine Treatment of Transsexual Persons,” 3132–3154.

70. Gabe Murchison *et al.*, “Supporting and Caring for Transgender Children,” *Human Rights Campaign* (2016): 11, <http://hrc-assets.s3-website-us-east-1.amazonaws.com/files/documents/SupportingCaringforTransChildren.pdf>.

71. *Ibid.*

72. Lieke Josephina Jeanne Johanna Vrouenraets *et al.*, “Early Medical Treatment of Children and Adolescents With Gender Dysphoria: An Empirical Ethical Study,” *Journal of Adolescent Health* 57, no. 4 (2015): 369, <http://dx.doi.org/10.1016/j.jadohealth.2015.04.004>.

73. *Ibid.*

74. George Tolis *et al.*, "Suppression of androgen production by D-tryptophan-6-luteinizing hormone-releasing hormone in man," *Journal of Clinical Investigation* 68, no. 3 (1981): 819–822, <http://dx.doi.org/10.1172%2FJCI110320>.
75. Hembree *et al.*, "Endocrine Treatment of Transsexual Persons," 3144.
76. Cohen-Kettenis and van Goozen, "Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent," 246. See also Peggy T. Cohen-Kettenis, Thomas D. Steensma, and Annelou L. C. de Vries, "Treatment of Adolescents With Gender Dysphoria in the Netherlands," *Child Adolescent Psychiatric Clinics of North America* 20, (2011): 689–700, <http://dx.doi.org/10.1016/j.chc.2011.08.001>.
77. Henriette A. Delemarre-van de Waal and Peggy T. Cohen-Kettenis, "Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects," *European Journal of Endocrinology* 155 (2006): S131–137, <http://dx.doi.org/10.1530/eje.1.02231>.
78. Peggy T. Cohen-Kettenis, Henriette A. Delemarre-van de Waal, and Louis J. G. Gooren, "The Treatment of Adolescent Transsexuals: Changing Insights," *Journal of Sexual Medicine* 5, no. 8 (2008): 1892–1897, <http://dx.doi.org/10.1111/j.1743-6109.2008.00870.x>.
79. Delemarre-van de Waal and Cohen-Kettenis, "Clinical management of gender identity disorder in adolescents," S132.
80. *Ibid.*, S135.
81. *Ibid.*, S133.
82. *Ibid.*
83. *Ibid.*
84. *Ibid.*, S134.
85. *Ibid.*
86. *Ibid.*
87. *Ibid.*
88. *Ibid.*
89. *Ibid.*, S135.
90. *Ibid.*, S136–S137.
91. *Ibid.*, S136.
92. Denise Vink, Joost Rotteveel, and Daniel Klink, "Bone Mineral Density in Adolescents with Gender Dysphoria During Prolonged Gonadotropin Releasing Hormone Analog Treatment," *World Professional Association for Transgender Health* (symposium presentation, 2016), <http://wpath2016.conferencespot.org/62620-wpathv2-1.3138789/t001-1.3140111/f004-1.3140315/0706-000371-1.3140317>.
93. Mariska C. Vlot *et al.*, "Effect of pubertal suppression and cross-sex hormone therapy

on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents,” *Bone* 95 (2017): 11–19, <http://dx.doi.org/10.1016/j.bone.2016.11.008>.

94. For example, the drug Lupron is approved for treating both precocious puberty and prostate cancer, http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020263s033lbl.pdf and <http://www.fda.gov/Drugs/DrugSafety/ucm209842.htm#table>.

95. Delemarre-van de Waal and Cohen-Kettenis, “Clinical management of gender identity disorder in adolescents,” S131.

96. *Ibid.*, S131–132.

97. *DSM-5*, 455. Note: Although the quotation comes from the *DSM-5* entry for “gender dysphoria” and implies that the listed persistence rates apply to that precise diagnosis, the diagnosis of gender dysphoria was formalized by the *DSM-5*, so some of the studies from which the persistence rates were drawn may have employed earlier diagnostic criteria.

98. Wren, “Early Physical Intervention for Young People with Atypical Gender Identity Development,” 222–223; Steensma *et al.*, “Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study,” 499–516. See also Peggy T. Cohen-Kettenis and Stephanie H. M. Van Goozen, “Sex Reassignment of Adolescent Transsexuals: A Follow-up Study,” *Journal of the American Academy of Child and Adolescent Psychiatry* 36, no. 2 (1997): 266, <http://dx.doi.org/10.1097/00004583-199702000-00017>; Kenneth Zucker *et al.*, “Puberty-Blocking Hormonal Therapy for Adolescents with Gender Identity Disorder: A Descriptive Clinical Study,” *Journal of Gay & Lesbian Mental Health* 15, no. 1 (2010): 68, <http://dx.doi.org/10.1080/19359705.2011.530574>.

99. Cohen-Kettenis, Delemarre-van de Waal, and Gooren, “The Treatment of Adolescent Transsexuals: Changing Insights,” 1895.

100. *Ibid.*, 1894.

101. *Ibid.*

102. Delemarre-van de Waal and Cohen-Kettenis, “Clinical management of gender identity disorder in adolescents,” S133.

103. *Ibid.*

104. Canadian Pediatric Endocrine Group, “Pubertal blockade safe for pediatric patients with gender identity disorder,” *Endocrine Today*, March 2012, <http://www.healio.com/endocrinology/pediatric-endocrinology/news/print/endocrine-today/%7B69c4c36a-37c3-4053-a856-22a27f8df62c%7D/pubertal-blockade-safe-for-pediatric-patients-with-gender-identity-disorder>.

105. Jenny Fernandez, “Norman Spack: Saving transgender lives,” April 24, 2015, <https://thriving.childrenshospital.org/norman-spack-saving-transgender-lives/>.

106. Laura Kuper, “Puberty Blocking Medications: Clinical Research Review,” IMPACT LGBT Health and Development Program (2014), <http://impactprogram.org/wp-content/uploads/2014/12/Kuper-2014-Puberty-Blockers-Clinical-Research-Review.pdf>.

107. Mitch Kellaway, “Blocking Puberty Is Beneficial for Transgender Youth,” Advocate.com, September 14, 2014, <http://www.advocate.com/politics/transgender/2014/09/14/>

study-blocking-puberty-beneficial-transgender-youth.

108. Andrea James, "Life Without Puberty," Advocate.com, January 25, 2008, <http://www.advocate.com/news/2008/01/25/life-without-puberty>.
109. Freda R. Savana, "Looking at suppressing puberty for transgender kids," *Doylestown Intelligencer*, March 6, 2016, http://www.theintell.com/news/local/looking-at-suppressing-puberty-for-transgender-kids/article_9082cab8-c47c-11e5-8186-afa80da85677.html.
110. Christopher P. Houk and Peter A. Lee, "The Diagnosis and Care of Transsexual Children and Adolescents: A Pediatric Endocrinologists' Perspective," *Journal of Pediatric Endocrinology and Metabolism* 19, no. 2 (2006): 108, <http://dx.doi.org/10.1515/JPEM.2006.19.2.103>.
111. Murchison *et al.*, "Supporting and Caring for Transgender Children," 11.
112. Cohen-Kettenis, Delemarre-van de Waal, and Gooren, "The Treatment of Adolescent Transsexuals: Changing Insights," 1894.
113. Delemarre-van de Waal and Cohen-Kettenis, "Clinical management of gender identity disorder in adolescents," S131.
114. Cohen-Kettenis, Delemarre-van de Waal, and Gooren, "The Treatment of Adolescent Transsexuals: Changing Insights," 1894.
115. Marisa M. Fisher, Deborah Lemay, and Erica A. Eugster, "Resumption of Puberty in Girls and Boys Following Removal of the Histrelin Implant," *The Journal of Pediatrics* 164, no. 4 (2014): 3, <http://dx.doi.org/10.1016/j.jpeds.2013.12.009>.
116. Silvano Bertelloni and Dick Mul, "Treatment of central precocious puberty by GnRH analogs: long-term outcome in men," *Asian Journal of Andrology* 10, no. 4 (2008): 531, <http://dx.doi.org/10.1111/j.1745-7262.2008.00409.x>.
117. Denise Hough *et al.*, "Spatial memory is impaired by peripubertal GnRH agonist treatment and testosterone replacement in sheep," *Psychoneuroendocrinology* 75 (2017): 173, <http://dx.doi.org/10.1016/j.psyneuen.2016.10.016>.
118. Denise Hough *et al.*, "A reduction in long-term spatial memory persists after discontinuation of peripubertal GnRH agonist treatment in sheep," *Psychoneuroendocrinology* 77 (2017): 1, <http://dx.doi.org/10.1016/j.psyneuen.2016.11.029>.
119. Annemieke S. Staphorsius *et al.*, "Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria," *Psychoneuroendocrinology* 56 (2015): 197, <http://dx.doi.org/10.1016/j.psyneuen.2015.03.007>.
120. *Ibid.* Male subjects whose puberty had been suppressed had lower accuracy scores than any of the groups tested (including female gender dysphoria patients, male gender dysphoria patients whose puberty had not been suppressed, and control groups of boys and girls who did not have gender dysphoria). However, the differences between the groups' scores were not all statistically significant: the scores of the male subjects who had undergone puberty suppression *were* statistically significantly different from the control boys and girls, as well as from the female gender dysphoria patients whose puberty was not suppressed, but *were not* statistically significantly different from males

with gender dysphoria who had not undergone puberty suppression, or from females with gender dysphoria who had undergone puberty suppression.

121. Ian Hacking, “The looping effect of human kinds,” in *Causal Cognition*, eds. Dan Sperber, David Premack, and Ann James Premack (1996): 369, <http://dx.doi.org/10.1093/acprof:oso/9780198524021.003.0012>.

122. See, for example, B. J. Casey, Rebecca M. Jones, and Todd A. Hare, “The Adolescent Brain,” *Annals of the New York Academy of Sciences* 1124 (2008): 111, <http://dx.doi.org/10.1196/annals.1440.010>.