Normal human development represents a continuum of biological events enabling somatic growth, sexual maturation, and reproduction. In the context of clinical pharmacology, the processes of physical and sexual maturation are also responsible for the characteristic changes in drug disposition and action occurring throughout the developmental continuum. As a consequence of recent regulatory initiatives mandating conduct of pediatric clinical trials, evidence continues to accumulate regarding the need for age-dependent adjustments in drug dosing. Characterization of age-associated pharmacokinetic and pharmacodynamic alterations has also facilitated the identification of developmental breakpoints that can be used to stratify children into distinct subpopulations based on definable changes in drug exposure. These changes can be largely attributed to normal developmental alterations in the physiological factors influencing drug absorption, distribution, metabolism, and elimination. There are, however, discrete developmental changes, particularly in drug clearance, that cannot be predicted solely on the basis of physiological alterations (e.g., increased organ mass, acquisition of functional organ capacity). It is therefore possible that developmental changes in drug disposition may be regulated by specific biochemical signaling events occurring during the processes of physical and sexual maturation.

The use of pharmacological techniques to map the ontogeny of hepatic drug-metabolizing enzyme (DME) activity has generated important information that, in combination with pharmacokinetic and pharmacodynamic data, has facilitated the creation of a developmental roadmap that demonstrates distinct, isoform-specific changes in phase I and phase II DME activity. The mechanisms responsible for upregulation and downregulation of DME activity during maturation, however, remain unknown. Relationships between the biochemical signaling events of growth and development and age-dependent changes in drug metabolism have also been largely unexplored. Nevertheless, in the absence of mechanistic data, emerging information regarding the ontogenesis of DME activity provides important insight into the biochemical and/or molecular events that may be involved in initiating and regulating developmental changes in hepatic drug metabolism and clearance.

In general, activities of DMEs are low in the fetus and newborn and increase rapidly over the first years of life to levels in toddlers and older children that may exceed adult capacity (Figure 1). Around the onset of puberty, DME activities...
begin a gradual decline that continues throughout adolescence and concludes with attainment of adult capacity at the completion of pubertal development. This ontogenic pattern closely mirrors that of important hormonal axes involved in growth and sexual maturation, with an apparent inverse relationship between hormone levels and DME activity (Figure 2). The periods of greatest change in DME activity also occur during those developmental periods when hormonal fluctuations are most pronounced (i.e., early infancy and adolescence). These extreme discordant developmental phenotypes therefore provide a framework within which hormonal regulation of DME activities can be considered.

Almost 15 years ago (20–21 January 1994), the Pediatric, Adolescent, and Maternal AIDS Branch of the Center for Research for Mothers and Children and the National Institute of Child Health and Human Development convened a joint workshop, Pharmacokinetics and Pharmacodynamics in Adolescents, which resulted in the development of a research agenda for the study of therapeutic drugs in this patient population. A key component of this agenda included the conduct of studies to characterize the effects of growth and sexual maturation on drug biotransformation. At present, however, information regarding the effects of physical and sexual development on DME activity remains limited to a small number of pharmacokinetic studies describing changes in the clearance of multi-enzymatic substrates during adolescence. Evaluation of these pharmacokinetic changes in the context of the significant hormonal changes occurring during puberty, however, provides a theoretical model for considering biochemical regulation of DME activity. Important information regarding potential influences of growth and sex hormones can also be extrapolated from studies that evaluate changes in DME activities occurring as a consequence of physiological (e.g., pregnancy, menopause, and sex differences), pathological (e.g., growth hormone (GH) deficiency), and/or pharmacological (e.g., oral contraceptives (OCs), hormone replacement therapy) hormonal fluctuations.

**CHANGES IN HEPATIC DRUG CLEARANCE DURING ADOLESCENCE**

Clinical pharmacokinetic studies have consistently demonstrated that the clearances of many heptically metabolized drugs, such as theophylline, carbamazepine, phenytoin, and phenobarbital are increased in young children (ages 2–11 years) compared with those of adults. Consequently, proportionally higher doses are often required to achieve comparable levels of systemic exposure. By the end of adolescence, however, drug dosing requirements are generally similar to those in healthy young adults. The relationship between chronological age and systemic clearance also becomes increasingly nonlinear during adolescence. Adolescence is therefore more than a simple continuum between childhood and adulthood; it is a period of significant change during which maturation of both reproductive and DME functional capacities occur.

There is increasing evidence to suggest that pubertal development per se may play an important role in regulating age-dependent changes in hepatic drug biotransformation. Longitudinal data from repeated, within-subject assessments of carbamazepine pharmacokinetics in children have demonstrated that the most significant intrindividual variations in drug clearance occur during adolescence and puberty (ages 9–13 years). Significant variability in the steady-state clearance of pravastatin (mean ± SD, 11.0 ± 11.91/min) is similarly observed in adolescents between the ages of 10 and 16 years. Comparison of adolescents during various stages of sexual maturation has also demonstrated differences in the clearances of several drugs eliminated primarily via hepatic biotransformation. A pharmacokinetic study in children with sickle cell crisis (N = 24) demonstrated weight-normalized morphine total body clearance values in late or postpubertal children (Tanner stage 4 or 5) that were ~30% lower than those in prepubertal children (Tanner stage 1). Weight-normalized theophylline clearance values in sexually mature adolescents are also reportedly lower (~45%) than those in prepubescent individuals. A Tanner stage–dependent decrease in CYP1A2-mediated caffeine clearance (measured using the caffeine breath test) has been similarly described in healthy adolescents, with the lowest clearance values observed in the most sexually mature individuals (Tanner stages 4–5).

Previous investigations have demonstrated a temporal relationship between changes in somatic growth and drug
clearance, suggesting that the process of growth itself may, either directly or indirectly, regulate age-dependent changes in the elimination of agents cleared via hepatic biotransformation. Alterations in antipyrine clearance during sexual maturation have been attributed to changes in body composition coinciding with the pubertal growth spurt. A highly significant positive correlation \((P < 0.001)\) between Tanner stage and theophylline elimination half-life \((t_{1/2})\) has also been reported in adolescents with asthma and attributed, at least in part, to alterations in distribution volume resulting from changes in body composition during puberty. Sex-based differences in the ontogeny of CYP1A2 (measured via the caffeine breath test) have been similarly described, with lower enzyme activity seen at an earlier stage of sexual maturity in females (Tanner stage 2) than in males (Tanner stages 4–5). The temporal pattern of sex-related divergence in maturation of CYP1A2 activity mirrors that of pubertal growth, which peaks early in puberty in females and in mid- or late puberty in males.

The physical changes in height, weight, and lean body mass occurring during pubertal growth are clearly important factors that influence hepatic drug elimination and clearance during adolescence. However, age-dependent changes in liver size and/or functional capacity may also significantly contribute to observed clearance alterations. When normalized to body weight, liver volume, an estimate of total hepatic parenchymal mass, is greater in young children than in adolescents and adults. The liver-to-body-weight ratio also decreases with increasing age, and there are data to suggest that age-dependent changes in this physiological ratio may be responsible, at least in part, for alterations in drug clearance occurring during adolescence. In a recent pharmacokinetic study of the CYP2C9 substrate, S-warfarin, weight- and body surface area–adjusted oral clearance values in prepubertal children were significantly greater than those in pubertal children or adults. When clearance values were adjusted for estimated liver weight, however, differences between groups were no longer apparent. In contrast, systemic clearance of the nonspecific CYP450 substrate, antipyrine, was unrelated to liver volume and was significantly greater in young children (<5 years) than in adolescents (>15 years) when normalized for both body weight and liver volume, which suggests that changes in the expression and/or activity of DMEs may occur during sexual and physical maturation.

It is likely that changes in hepatic drug clearance during adolescence are mediated by a complex interplay between alterations in body size/composition, liver mass, and constitutive DME expression/activity during pubertal development. For some substrates, it appears that changes in body size or composition alone are responsible for changes in systemic clearance. For others, however, there are alterations that occur independently of or in addition to physical or somatic changes. It is therefore possible that the constitutive expression and/or activity of individual DMEs may change during the course of sexual maturation. Given the temporal relationship with the pubertal growth spurt, it is also plausible that these processes (i.e., somatic growth and DME ontogeny) may be regulated by common hormonal or biochemical mechanisms. Consequently, understanding the normal physical and hormonal events of puberty may help elucidate those developmental factors that initiate and control changes in hepatic drug clearance during adolescence.

**ENDOCRINOLOGY OF GROWTH AND SEXUAL MATURATION**

Physical and sexual maturation represent a series of coordinated, hormonally regulated events that begin during fetal life, continue throughout childhood, and conclude during adolescence with the onset and completion of puberty. Alterations in the hormonal milieu underlying pubertal development are therefore not discrete, sudden events but rather represent the culmination of progressive and longitudinal changes occurring during youth. The process of sexual maturation is under endocrine control of the hypothalamic–pituitary–gonadal (HPG) axis, a negative feedback system that mediates its effects through actions of the pituitary gonadotropins (i.e., follicle-stimulating hormone and luteinizing hormone) and gonadal sex steroids (i.e., estradiol and testosterone). The hypothalamic hormone, gonadotropin hormone–releasing hormone (GnRH, also known as luteinizing hormone–releasing hormone), controls the pituitary release of the gonadotropins, which, in turn, regulate sex steroid secretion from the ovaries and testes (Figure 3).

In the fetus, the HPG axis is fully functional and plays an important role in the process of sex differentiation. The HPG axis is also responsible for the postnatal rise in gonadal sex steroid levels occurring ~2 months of age. In both the fetus and the infant, serum gonadotropin and sex steroid levels are equal to or even greater than those in pubertal adolescents. In the months and years after birth, however, there is a progressive decrease in HPG axis activity. By the age of 2 years, the HPG axis enters into a quiescent period commonly referred to as the “juvenile pause,” during which circulating plasma levels of gonadotropins and sex steroids are low. This period of relative inactivity continues until around the age of 10 years, when there is a reactivation of the HPG axis at the onset of puberty.

The earliest hormonal changes of adolescence occur between the ages of 7 and 8 years, when circulating levels of the adrenal androgens, dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S), increase. The increase in adrenal androgen secretion signals the onset of adrenarche, the phase of development during which maturation of the hypothalamic–pituitary–adrenal axis occurs (Figure 3). Adrenal androgen secretion continues to increase throughout adrenarche and into puberty, when plasma DHEA and DHEA-S levels demonstrate a second peak around the ages of 12–13 years. Increased secretion of other adrenal androgens (e.g., \(\Delta_4\)-androstenedione) also occurs during the immediate prepubertal period (ages 8–10 years). Although related to HPG maturation and function, adrenarche is a distinct process that appears to be independently regulated by a pituitary-stimulating factor that, to date, remains unidentified. It is also unknown whether the changes in adrenal androgen levels that occur during adrenarche have any effect on the subsequent maturation of the HPG axis.

The onset of puberty is characterized by reactivation of the HPG axis, which, in turn, leads to an increase in the pulsatile release of GnRH, gonadotropins, and sex steroids.
Although the exact mechanisms involved remain unknown, it is postulated that alterations in the balance of inhibitory (e.g., γ-aminobutyric acid) and excitatory (e.g., glutamate) neurotransmitters may contribute to disinhibition and reactivation of the HPG axis.23 During the very early stages of puberty, there are distinct hormonal alterations that occur in the absence of any physical signs of sexual maturation.26 Release of high-amplitude gonadotropin pulses is apparent predominantly during sleep and is accompanied by a concomitant increase in circulating early morning sex steroid levels. Continuation of the increased adrenal androgen secretion initiated during adrenarche is also observed. These early hormonal changes precede the appearance of physical alterations by at least 2 years.27 As pubertal development progresses, however, physical signs of sexual maturation, such as increased testicular volume in males and breast budding in females, become perceptible as pulsatile gonadotropin release continues.

Physical and hormonal changes reflective of sexual maturation continue during mid-puberty, and in females peak height velocity is usually reached during this phase.26 Sleep augmentation of gonadotropin release persists, and higher peak levels are attained. Gonadotropin and sex steroid levels are also increased during the waking period. In late puberty, sleep augmentation of gonadotropin release is maximal and may even exceed that observed in adults. Circulating gonadotropin and sex steroid levels also remain elevated above those observed during the prepubertal period. In females, menarche is achieved, and in males, peak height velocity occurs. At the completion of puberty, physical changes in both sexes are complete, and hormonal levels decrease to those observed in healthy adults. Sleep augmentation of gonadotropin and sex steroid release disappears, and reproductive capacity is complete.

The process of somatic growth is under the neuroendocrine control of the GH/insulin-like growth factor 1 (IGF-1) axis.28 The hypothalamic hormone, GH-releasing hormone, serves as a stimulatory signal for the pituitary release of GH, which, in turn, mediates its growth-promoting effects by inducing peptide growth factors such as IGF-1. GH secretion is highly pulsatile and demonstrates significant circadian variation, with the majority of secretory bursts occurring at night. Integrated plasma GH levels also vary significantly with age, with the highest levels noted at birth and during pubertal growth. During puberty there is an activation of the GH/IGF-1 axis that is attributed, at least in part, to stimulatory influences of the sex steroids.29 Specifically, sex steroids cause an increase in the secretion amplitude of the GH pulse, resulting in increased circulating GH levels; pulse
frequency, in contrast, is not affected. Sex-based differences in GH secretion patterns also become apparent during puberty and mirror those of the differences in growth velocity. In females, circulating GH levels rise significantly during early puberty and peak during mid-puberty. A delayed increase in GH secretion occurs in males, with peak levels observed during late puberty. Upon completion of sexual maturation, levels of GH and IGF-1 fall to those observed in pre-pubertal adolescents and adults.

**PHYSICAL CHANGES OF ADOLESCENCE AND PUBERTY AND ASSESSMENT OF SEXUAL MATURATION**

The hormonal alterations of puberty are accompanied by profound physical changes in both males and females. The hallmark physical changes of puberty include rapid somatic growth, alterations in body composition, and appearance of secondary sex characteristics. In males, one of the earliest physical signs of increased gonadotropin secretion is an increase in testicular volume, which occurs as a consequence of growth of the seminiferous tubules. Pubic hair begins to appear at the same time or shortly after testicular growth and is accompanied by penile growth and enlargement of the seminal vesicles and prostate and bulbourethral glands. Appearance of axillary, perineal, and facial hair typically begins within 18–24 months of pubic hair development. In both sexes, growth of pubic or axillary hair and development of acne and body odor are associated with increasing levels of gonadal and adrenal steroids. Enlargement of the larynx and deepening of the voice in males occur later in puberty, following genital and pubic hair development. Peak height velocity or the pubertal "growth spurt" also occurs during late puberty, around the age of 14 years and is accompanied by a significant increase in lean body mass and a reduction in body fat.

The first physical sign of puberty in females is either the initiation of breast development (also known as breast budding) or pubic hair development. The relative order of appearance of breast and pubic hair changes exhibits significant interindividual and interethnic variability, with pubic hair development occurring before breast budding in most black females and after breast budding in most white females. These early changes are accompanied by less obvious physical changes, including enlargement of the ovaries, uterus, labia, and clitoris, and thickening of the endometrium and vaginal mucosa. In general, menses begins ~2 years following the onset of breast development and coincides with the attainment of peak height velocity at ~12 years of age. Accumulation of body fat also occurs during the somatic growth spurt in females.

The traditional view of relationships among chronologic age, hormonal alterations, and physical/sexual development milestones in males and females is illustrated in Figure 4. It should be recognized, however, that there is significant interindividual variability with respect to the onset and progression of pubertal changes among individuals of both sexes. Timing of puberty is also influenced by a wide range of environmental and genetic factors. Further, a population trend toward an earlier onset of breast development and menarche in females has been observed over the past century, potentially as the result of environmental exposure to endocrine-disrupting chemicals, particularly estrogen mimics and antiandrogens. Previous information regarding relationships between chronologic age and physical/sexual development milestones may therefore be inadequate for characterizing pubertal onset and progression in today’s adolescent population.

Sexual maturity is most frequently characterized by the direct physical assessment of secondary sexual characteristics. In males, genital and pubic hair development are typically used as surrogates of sexual maturation, whereas in females, development of breasts and pubic hair are most commonly used. The status of breast, genital, and pubic hair development is typically assessed using progressive sexual maturity rating scales. Although introduced almost 50 years ago, the staging system developed by Tanner et al. remains the most commonly used clinical tool for assessing sexual maturity in adolescents. The five Tanner stages range from stage 1 (prepubertal) to stage 5 (postpubertal or adult) and delineate the growth of pubic hair in both boys and girls, breast development in girls, and genital development in boys. Standards for pubic hair, breast, and genital development are depicted in the classic photographs of Marshall and Tanner (Figure 5). Although somewhat subjective, Tanner staging is well characterized as a method
to assess levels of sexual maturity and to predict timing of growth spurts. However, Tanner staging results are somewhat unreliable, given that, in many instances, clinical assessments are usually estimated rather than derived from detailed physical examination. The utility of Tanner staging is also limited because it requires direct physical examination and is rather invasive.

GROWTH AND SEX HORMONES AS BIOCHEMICAL REGULATORS OF DMEs

Hormones are important in regulating expression and activity of DMEs, and alterations in the clearances of multienzymatic drug substrates have been observed in patients with various endocrinopathies31,32 and conditions associated with hormonal dysregulation.33–36 Changes in DME activities have also been described during periods of physiological37,38 and pharmacological39,40 hormonal fluctuations. At present, the effects of developmental alterations in sex and GHs on DMEs has not been similarly characterized. Given the striking similarities in the functional ontogenesis of DMEs and the HPG and GH/IGF-1 axes, however, a rational hypothesis regarding the role of hormones in the developmental regulation of DME activity can be formulated.

The ontogenic pattern of the HPG axis is temporally similar to but functionally opposite of that observed for DMEs (Figures 1 and 2). For both systems, the most significant functional variability occurs during early infancy and adolescence. DME functional capacity appears to be greatest, however, during the period of quiescence in HPG axis activity occurring between the ages of 2 and 10 years.5,21 In contrast, reactivation of the HPG axis coincides with the pharmacokinetic alterations (i.e., reduced clearance) occurring at the onset of puberty and adolescence. It therefore appears that the HPG axis and/or its associated hormonal mediators (GnRH, luteinizing hormone, follicle-stimulating hormone, estradiol, and testosterone) may be important in the developmental regulation of DME activity. Similar parallels are also observed between DME activity and GH levels, with the lowest DME functional capacity noted during periods of increased GH secretion (i.e., birth and adolescence). Existence of a temporal relationship between changes in drug clearance and the pubertal growth spurt provides further evidence that alterations in DME activity may be mediated by growth and/or sex hormones.

Data from animal and in vitro models have consistently demonstrated an effect of sex steroids on DME expression and activity. Androgenic steroids (e.g., testosterone, DHEA) have been shown to increase activities of hepatic mixed-function oxidases in rodents,41 possibly through an increase in constitutive expression of hepatic enzyme protein.42 Marked variation in CYP3A4-mediated drug biotransformation has also been demonstrated following exposure of human liver microsomes to various endogenous androgens.43 Estrogens, in contrast, have been shown to decrease hepatic microsomal activity and drug clearance in rodents through a reduction in the amount of microsomal DME protein.44,45 The reported effects of progestogens on DME activity are variable and inconsistent, with some investigations reporting an inhibitory effect,46 and others reporting an inductive effect.44

Additional data from animal and in vitro models provide convincing evidence that GH and/or its downstream biological mediators are also important regulators of sex-specific DME expression and activity.47 In rat liver, expression of CYP2C11 is sexually dimorphic, with higher levels observed in males than in females. This dimorphism is thought to be maintained by the
differential secretion pattern of GH in animals of different sexes. Sexual dimorphism in GH secretory patterns is also present in humans. In males, GH exhibits a pulsatile GH secretory pattern, which results in higher peaks and lower interdose concentrations. In females, the GH secretion profile is continuous, thereby providing lower peaks, with continuous hormone exposure. Sex-specific patterns of GH secretion are maintained through the influences of estrogenic and androgenic sex steroids.

Clinical data from studies that evaluate the influence of physiological, pathological, and/or pharmacological fluctuations in growth and sex hormone levels on DME activity provide additional insight into those factors that might be important in the developmental regulation of hepatic drug biotransformation. The menstrual cycle represents a normal physiological process that, much like pubertal development, is regulated by changes in the secretion of gonadotropins and sex steroids. Although pharmacokinetic (i.e., clearance) differences have been described during the menstrual cycle, the majority of clinical data suggest that activities of individual DME isozymes (phases I and II) are unaltered during this physiological process.48 However, use of OCs to manipulate gonadotropin secretion pharmacologically during the menstrual cycle results in clinically apparent and isoform-specific alterations in drug clearance. Pharmacokinetic studies have demonstrated decreased clearances of the CYP1A2 substrates caffeine (55% reduction) and theophylline (29% reduction) following administration of combined OCs.49,50 Pharmacological phenotyping studies using specific “probe” substrates have also described decreased activities of CYP2C1940 and CYP2B651 during combined OC therapy. In contrast, similar studies revealed no effect of combined OCs on CYP3A4 or CYP2D6.52 Despite in vitro evidence that both the estrogenic and progestogenic components of the combined OCs can reduce DME activity,53 in vivo data suggest that it is the estrogenic component that mediates the observed effects.39 The estrogenic component of OCs has also been shown to increase phase II drug metabolism by conjugation and glucuronidation.54,55

Menopause is another physiological process that is associated with marked changes in sex hormone levels that occur, at least in part, as a result of normal developmental alterations in HPG axis function.56 Alterations in ovarian follicle number and function, however, are responsible for most of the hormonal changes observed during the menopausal period. After menopause, circulating levels of the gonadotropins follicle-stimulating hormone and luteinizing hormone are reduced by up to ten- and fivefold, respectively. Circulating estradiol levels are also >90% lower than those observed before menopause. In contrast, circulating androgen levels demonstrate little change during menopause. Pharmacokinetic studies have demonstrated that the clearances of the CYP3A substrates alfentanil, prednisolone, and tirilazad are lower in postmenopausal women compared to premenopausal women.57–60 In women receiving estrogen replacement therapy, reductions in prednisolone clearance were found to be even more pronounced.57 although this finding was not confirmed in a later study.59 Subsequent pharmacological phenotyping studies using the substrates midazolam, erythromycin, and endogenous cortisol also failed to demonstrate a significant effect of menopausal status (with or without hormone replacement therapy) on activities of intestinal and hepatic CYP3A.59,61,62 In contrast, a significant reduction in CYP1A2 activity, as measured using the plasma paraxanthine/caffeine metabolic ratio, has been described in postmenopausal women receiving estrogen replacement therapy compared to those who were untreated.63 Reduced CYP2B6 activity has also been noted following exogenous administration of estrogen and progesterone hormones to healthy, premenopausal women.51 Conversely, increased CYP3A activity (measured using prednisolone clearance and the erythromycin breath test) has been described following intravenous medroxyprogesterone supplementation in postmenopausal women, suggesting that both estrogen and progesterone replacement may affect DME activity.64 The effect of menopausal status on activities of phase II DMEs has not been characterized to date.

Fluctuations in female sex steroid levels may also be responsible for the observed alterations in DME activity occurring throughout pregnancy. Both estrogen and progesterone are essential for maintaining pregnancy and for normal pregnancy development. Placental human chorionic gonadotropin, which is measurable in the blood within 48 h of implantation, is responsible for stimulating increased production and secretion of estradiol and progesterone by the corpus luteum.65 Levels of both estradiol and progesterone increase until around the 6th to 10th week of gestation when progesterone levels plateau or, in some individuals, even decrease, followed by a continuous rise until term. This occurs as a result of the demise of the corpus luteum and the onset of placental progesterone production, which occurs around the 8th or 9th week of gestation. Around the 6th–7th week of gestation, there is also an additional increase in estradiol levels, occurring as a result of the placental take-over of estradiol production and secretion. Following the onset of placental hormone production, estradiol and progesterone levels continue to rise during the second and third trimesters, until term.

Several studies have demonstrated isoform-specific alterations in the activities of phase I and phase II DMEs during pregnancy.66 Specifically, increases in the activities of CYP3A4, CYP2D6, CYP2C9, CYP2A6, UGT1A1, and UGT2B7 have been described in multiple clinical investigations of pregnant women. In contrast, activities of CYP1A2 and CYP2C19 are generally lower during pregnancy. It is postulated, based on information from animal and in vitro models, that the observed increases in the activities of CYP3A4, CYP2C9, and CYP2A6 occur consequent to progesterone-mediated activation of the pregnane X receptor (Figure 6). This hypothesis is consistent with data that demonstrated a direct correlation between increased endogenous progesterone levels and CYP3A activity during the mid–luteal phase of the menstrual cycle.37 Reduced activities of CYP2C19 and CYP1A2 are thought to be mediated by the high levels of estrogen that are present throughout gestation.

Sex-based differences in the disposition and action of pharmacological agents have been repeatedly described and attributed to underlying differences in sex hormone and GH levels and/or secretion patterns between males and females. Because
The nature and extent of sex hormone–induced changes in DME activity are significantly influenced by androgens or progesterone (CYP3A). It appears to be estrogen mediated, whereas other DMEs are more androgen dependent. Differences in DME activity in an isoform-specific manner (endogenous and exogenously administered) can significantly influence DME activity in an isoform-specific manner. Regulation of constitutive expression and/or activity of certain DMEs (CYP1A2, CYP2B6, CYP2C19, and CYP2E1) have been described during periods when estrogen levels remain persistently elevated for a relatively prolonged period (e.g., pregnancy) or when changes in the normal “baseline” hormone levels occur (e.g., puberty, exogenous hormone administration). This suggests that it is the process of hormonal signaling/secretion itself and not the actual circulating level that is important in DME regulation because changes in activity are most apparent when the normal HPG signaling and feedback processes are altered.

GH is known to regulate sex-specific DME expression, and altered clearance of multienzymatic substrates following GH replacement has been demonstrated. Previous investigations in children with GH deficiency of various etiologies have reported alterations in amobarbital (39–69% decrease) and antipyrine (4–11% decrease) clearance and in theophylline (30–62% decrease) and amobarbital (42–200% increase) elimination half-life following GH replacement. Observed alterations appear to be substrate specific in both directions (i.e., increase or decrease), and the extent (50–200%) of these alterations may cause clinically relevant changes in systemic drug exposure. Using the caffeine breath test, a single study also noted a significant reduction (~20%) in CYP1A2 activity following 4 weeks of pituitary-derived GH administration. However, using urinary caffeine phenotyping, two subsequent investigations, including one performed by our research group, failed to demonstrate clinically relevant effects on CYP1A and xanthine oxidase following up to 6 months of recombinant human GH treatment.

Our study also did not find evidence of a recombinant human GH–mediated effect on activities of N-acetyltransferase 2 or xanthine oxidase following up to 6 months of recombinant human GH treatment. Baseline pharmacokinetic alterations have also been described in adults and children with GH deficiency following up to 11 years following 30 days of recombinant human GH treatment. Baseline pharmacokinetic alterations have also been described in adults and children with GH deficiency, suggesting that the state of relative GH deficiency itself alters DME activity. Recently, our group demonstrated age-adjusted CYP1A2 and XO ratios in GH-deficient children that were significantly lower than those in healthy controls, suggesting that activities of these DME isoforms may be reduced by GH dysregulation.

It appears that differential regulation of constitutive DME activity is mediated by the GH pulse pattern created by the influences of endogenous estrogens and androgens. Given that the GH pulse pattern during replacement therapy is determined by the administration schedule, it is possible that DME responsiveness to GH-mediated effects differs between states of physiological variation and pharmacological replacement. In animal models and in children with GH deficiency, exogenous GH administration also does not restore DME activity to the levels observed in adults.
observed in normal controls, suggesting that GH may serve as an “incomplete” control peptide in the modulation of hepatic DME activity.75,76 However, GH may very well serve as a final common mediator through which gonadal steroids and other modifiers of pituitary function alter the expression and/or activity of DMEs during pubertal development. Consequently, it is reasonable to speculate that alterations in sex hormones and GH during physical and sexual maturation are responsible for the observed changes in DME occurring during adolescence. Given the known relationships between sex hormones and GH, it is also logical to theorize that observed changes in DME activity during development occur as a result of a complex interaction between the HPG and GH/IGF-1 axes. To elucidate the underlying biochemical alterations responsible for the developmental regulation of DME activity, it is necessary to perform a systematic and simultaneous evaluation of the HPG and GH/IGF-1 axes, their associated hormones/biochemical mediators, and DME activity throughout the course of pubertal development (Table 2).

**ADOLESCENT PHARMACOLOGY AND THE CURRENT STATE OF THE ART**

Guidelines for drug dosing in newborns, infants, children, and adolescents are currently extrapolated from clinical studies in which subjects are stratified into age groups based on predefined “break points” at which changes in drug clearance and/or exposure are likely to occur. Implicit in this approach is the assumption that individuals within each age category are similar with respect to those developmental characteristics known to influence drug disposition. Given the substantial variability in the timing and progression of normal developmental events, however, the practice of stratifying children by chronologic age may result in grouping of individuals at different stages of physical and/or sexual maturation. This may be particularly true during periods of rapid growth and development, such as adolescence. The process of pubertal development itself is also highly variable with respect to onset, duration, and final outcome and is significantly influenced by genetic, environmental, and ethnic factors. It is therefore difficult to predict pubertal status based on chronologic age alone. In addition, the epidemiology of puberty in the United States, and worldwide, has changed, with a trend toward earlier onset and increased rates of growth noted over the past few decades. Stratification of individuals based on chronologic age alone may therefore result in developmental misclassification.

Despite the significant influence of physical and sexual maturation on drug disposition, many pharmacokinetic and/or
pharmacodynamic studies do not account for physical maturation or pubertal status. This can have important clinical implications because changes in drug disposition or clearance occurring during pubertal development may significantly alter drug exposure. Many of the drugs used to treat common chronic illnesses of adolescence (such as asthma, diabetes, epilepsy, and depression) are cleared by DME pathways that can be altered by the hormonal changes of adolescence and puberty. Consequently, doses used before the onset of puberty may become inappropriately high or low and may cause either toxicity or therapeutic failure. Disease exacerbations occurring during adolescence may also be inappropriately attributed to noncompliance rather than to developmental alterations in drug distribution and/or clearance. Given that puberty-associated hormonal changes are a potentially important source of pharmacokinetic variability in adolescents, they should be accounted for in the development of dosing guidelines for this patient population.

Although it was developed more than 50 years ago and is somewhat subjective, Tanner staging remains the most widely used and clinically accepted measure of sexual maturation. It is well characterized as a method for assessing the level of sexual maturity and predicting timing of growth spurts. Because it requires direct physical examination, however, it is somewhat limited for repeated clinical use, particularly during the conduct of a clinical pharmacokinetic study. Perhaps more important, Tanner staging represents the physical consequences of the underlying hormonal changes occurring during pubertal development and consequently frequently lags behind endocrine alterations. Significant changes in sex hormone and GH levels (i.e., gona-darche) also occur ~2 years before any physical alterations are apparent; adrenarche occurs even earlier, at ~7–8 years of age. Tanner staging may therefore not provide an accurate reflection of the biochemical changes thought to be important in the regulation of DME activity.

The concept of developmental age, introduced in 1994 as part of the Pharmacokinetics and Pharmacodynamics in Adolescents joint workshop, encompasses the idea that developmental changes in drug pharmacokinetics and pharmacodynamics might be better understood within the context of the underlying mechanisms that are responsible for their occurrence. Proponents of the concept of developmental age argue that, for those processes that change with development, use of chronologic age as a surrogate or indicator may be very misleading. For example, in children of the same chronologic age, the hormonal milieu may be substantially different depending on the stage of pubertal development. For those processes affected by hormonal fluctuations, such as DME activity, a biomarker that more accurately reflects the underlying hormonal changes should therefore be used.

FUTURE DIRECTIONS: REVIVING THE RESEARCH AGENDA FOR THE STUDY OF DRUGS IN ADOLESCENTS

The research agenda for the study of drugs in adolescents was proposed almost 15 years ago but has yet to be put into action. Although the study of pharmacological agents in newborns has increased almost exponentially over the past decade, few studies have assessed the effects of pubertal development on drug disposition and action in the adolescent. Despite an increasing amount of information regarding changes in DME activity during the course of normal growth and development, the mechanisms responsible for upregulation and downregulation of DME activity during maturation also remain unknown. Similarly, relationships between the biochemical signaling events of growth and development and age-dependent changes in drug metabolism are still largely unexplored. The effects of physical and sexual maturation on the expression and action of important drug transporters and receptors also remain uncharacterized. Although a rational hypothesis regarding the regulation of DME activity during development can be developed, systemic evaluations throughout the course of pubertal development will be required to fully understand the mechanisms responsible for the observed alterations. The research agenda proposed during the 1994 Pharmacokinetics and Pharmacodynamics in Adolescents joint workshop provides an excellent framework on which these types of studies can be based.

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CONFLICT OF INTEREST

The author declared no conflict of interest.

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