Adolescent Health and the Environment

Mari S. Golub

California Regional Primate Research Center, University of California Davis, Davis, California, USA

The effects of toxicants depend on the dose and the time in the life span when exposure occurs. The biology of adolescence is distinctive and provides opportunities for unique actions of toxicants both in terms of disruption of function and disruption of maturation. Maturation of a number of organ systems occurs during this period, including not only the reproductive system but also the respiratory, skeletal, immune, and central nervous systems. Adolescence is a time of increased risk for infectious disease and accidental injury, making the effects of toxicants on the immune and central nervous systems particularly harmful. Differences in blood volume, respiratory parameters, metabolic needs, and capacity all contribute to altered pharmacokinetics. Exposures can also change. Increased food intake associated with rapid adolescent growth alters exposure to food contaminants. Voluntary drug consumption increases, including drinking; smoking; substance abuse; and the use of over-the-counter, prescription, and performance-enhancing drugs. At the same time, adolescents are introduced to toxicants in the workplace. Basic research in the toxicology of adolescence needs to take into account the appropriateness of animal models for this distinctive human developmental stage; risk assessment must take into account pharmacokinetic and lifestyle factors. Screening methodologies that would identify toxic effects unique to adolescence would also be valuable. ***Key words*****: adolescence, animal, exposure, health effects, human, postnatal, puberty.** ***Environ Health Perspect*** **108:355–362 (2000). [Online 6 March 2000]**

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Recently there has been concern in the risk assessment community about the potentially greater susceptibility of children to environmental toxicants (*1–3*). In these documents, "children" refers to neonates through 18-year-olds. Although progress has been made in understanding and preventing risk at earlier stages of development, less is known about the later stages and, in particular, the final stage of maturation (adolescence). Adolescence is a fascinating period in terms of both its biology and its unique contributions to competent human adult functioning. The toxicology of adolescence needs to take into account both the biology and the function of this developmental period.

Literature on adolescent toxicology does not yet exist. Further, key words related to adolescent development are infrequently provided by the authors of toxicology studies. Thus, this review attempts to provide more general information about adolescence that may be valuable in considering risks to adolescent health due to exposure to environmental toxicants.

"Adolescence" is a term that has no precise biologic definition. It most often applies to humans, and it usually refers to the period from the appearance of secondary sex characteristics to the attainment of adult height (being "grown-up") at roughly 11–19 years of age (*4,5*). The term "puberty" is usually restricted to sexual maturation and refers to the onset of reproductive function.

Major Health Problems of Adolescence

The mortality rate in adolescence is low as compared to other periods of the life span. In 1996, the major causes of adolescent mortality in the United States, using U.S. health statistics categories, were injury (including accidents, homicide, and suicide), cancer, heart disease, and acquired immunodeficiency syndrome (*6*). Major sources of morbidity are infectious disease, particularly sexually transmitted disease, and substance abuse. This same pattern is seen in developing countries as pediatric care improves, marriage is postponed, and a pattern of urban migration for employment is established in young people. Although morbidity and mortality are relatively low, some types of disease show a peak incidence in the adolescent years. The highest incidence of hepatitis (*7*) and infections of the gastrointestinal tract (*8*) have been noted in the adolescent age range. The highest rate of near-fatal asthma attacks occurs in adolescence (*9*). Midadolescence is the peak time for the onset of eating disorders (*10*). Pathologic sleep conditions such as sleep apnea and delayed sleep phase syndrome have their symptomatic onset in adolescence (*11*). In addition, adolescence is a time of symptomatic emergence for diseases that are largely dormant in childhood, including diabetes, thyroid disorders, coronary artery disease, schizophrenia, and autoimmune disease. Public health focus is typically on reducing injury risk behaviors; promoting reproductive health (safe sex); and preventing pregnancy, substance abuse, and dropping out of school (*12*). Environmental exposures are rarely mentioned as a subject of concern or intervention.

Disorders of timing of maturation are one subject of concern that has been linked to environmental exposures (*13,14*). In particular, precocious puberty and the early appearance of secondary sex characteristics in girls have been attributed to contaminants with estrogenic properties (*15,16*). Delayed puberty and inadequate pubertal growth are thought to have strong environmental as well as genetic determinants, although the effects of chemicals in the environment have not been widely investigated (*17*).

Several authors have proposed that early and late puberty are risk factors for later adult disorders, particularly brain dysfunction. Over the years, differences in cognitive ability (*18,19*) and susceptibility to psychopathology (*20–22*) have been attributed to early and late maturers. Influential hypotheses have been advanced concerning the role of delayed or faulty adolescent brain maturation in the etiology of schizophrenia (*22–24*), and some direct evidence has been presented (*25,26*). These hypotheses are prompted by evidence that neural substrates implicated in schizophrenia mature during adolescence (*27*). Other outcomes for which age at puberty may be a risk factor include short stature (*28*), obesity (*29*), breast cancer (*30,31*), and polycystic ovary syndrome (*32*).

Finally, the regression of clinical problems at adolescence bears consideration. A small body of research has also developed to investigate the regression of symptomatology of hyperactivity, attention deficit disorders, and minimal brain dysfunction syndromes at

Address correspondence to M.S. Golub, California Regional Primate Research Center, University of California Davis, Davis, CA 95616 USA. Telephone: (530) 752-5119. Fax: (530) 752-2880. E-mail: msgolub@ucdavis.edu

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the time of puberty (*33,34*). Several interesting hypotheses concerning the role of growth factors (*35*) and steroid hormones have been proposed. Thus, failure of the normal pattern of symptom regression in these disorders could also be a consequence of environmental toxicant exposure.

Factors That Influence Toxicant Exposure and Effects

Exposure to environmental toxicants can be altered as a consequence of introduction into new environments; altered food, water, and air intakes; and physiologic changes that influence toxicokinetics.

Situational changes. Initiation of drinking and smoking and experimentation with recreational drugs are hallmarks of adolescence. The National Institute on Drug Abuse conducts a yearly survey of drug, alcohol, and tobacco use (*36*) with information for students in grades 8, 10, and 12. Data are provided in terms of prevalence; in 1998, the percentage of children who had ever used an illegal drug (including inhalants) was 38, 49, and 56% for grades 8, 10, and 12, respectively. Information on dose and frequency is not provided in this report. The initiation of oral contraception use, the use of anabolic steroids and other performance-enhancing drugs in athletics, and direct access to over-the-counter medications also occur in adolescence. Documentation of the extent of exposure in terms of dose, duration, and age groups affected is rarely available. In addition to potential direct harmful effects, many of these agents can secondarily influence environmental toxicant metabolism by inducing metabolic pathways.

Adolescents, when introduced to the workplace, may be exposed to chemicals in an occupational setting that has safeguards designed for adults. Here in the United States, the legal age for employment as an adult is 18, but younger children can work with some restriction (*37*). Workers 14–17 years of age are limited in the hours that they can work and are excluded from certain hazardous occupations; restrictions differ for children who are 14–15 and 16–17 years of age. Some of the restricted jobs involve the use of power tools, equipment, or motor vehicles, or involve physical danger such as mining, working with explosives, demolition, and roofing; it is not clear to what extent chemical exposure is taken into account in the designation of hazardous jobs for young workers. Separate laws govern agricultural employment (*38*). Children younger than 16 years of age are restricted from handling or applying pesticides labeled danger, poison, or warning, but they can be employed in harvesting after pesticide application. Rules are less restrictive for teenagers who work on family farms and in family businesses. Illegal employment of adolescents must also be taken into account (*39*).

Children younger than 14 years of age also work, according to a recent National Academy of Sciences report (*40*). During the school year, 30.6% of 12-year-olds and 36.9% of 13-year-olds report working. Information on work-related fatalities and nonfatal injuries is provided in the report, but there are no data on exposure to chemical toxicants. Indeed, the report discusses the possibility of long-term health effects of chemical exposures during developmental periods, and points out the absence of information in this area. Systematic research programs on human adolescent exposure to toxicants are needed to fill this gap.

Whether or not they are employed, adolescents are typically involved in various internships and apprenticeships in the workplace and in clubs with occupational themes, such as 4-H. The type of work children engage in at home can also change during adolescence and can involve broader chemical exposure. Information on exposures during these activities is limited.

Physiologic changes influencing pharmacokinetics. Adolescent-specific pharmacokinetic modeling is not commonly encountered in the toxicology literature. A number of compilations of human data on somatic growth, organ weights, and tissue composition extend into adolescent years, providing useful information for this effort (*41–44*). Similar compilations for common animal models would be useful; *Growth at Adolescence,* by Tanner (*45*), is a classic text on adolescent growth and sexual maturation that contains a valuable chapter on animals as well as extensive information on humans.

Some information is available on changes in hepatic metabolic pathways during adolescence, but implications for effects on toxicant activation/deactivation are not defined (*46,47*). The major changes involve cholesterol and steroid hormone-metabolizing enzymes in liver and reproductive organs (*48–50*). Because pubertal changes in these enzyme systems are sex dependent, they represent one of the systems potentially disrupted by toxicants with endocrine effects. It is not known whether exposure to exogenous substrates for these enzyme systems can influence their maturational time course and adult function.

Lung function parameters undergo a growth spurt similar to the sudden increase in adolescent height and weight (*51*). As is the case for other growth parameters, the growth spurt occurs earlier in girls (12 years of age) than in boys (14 years of age) and culminates in sex-differentiated levels of function seen in adults. The lung function growth spurt lags somewhat behind the body size growth spurt, indicating that exposures by inhalation could be reduced on a milligram-per-kilogram body weight basis at some stages of adolescence.

Growth and nutrition. The striking increases in food intake that occur in connection with adolescent growth are well known in humans and have been documented in animals, although this area has not been the subject of extensive scholarly activity. Increased food intake results in increased intake of food contaminants by humans and of increased doses of toxicants administered in the diet to laboratory animals. Acceleration of food intake does not necessarily correspond to growth and may precede or follow the adolescent growth spurt, resulting in altered intake of food contaminants on a body weight basis. In a recent 4-week study in mice, we found that food intake decreased by one-half between 42 and 70 days of age (puberty/adolescence), whereas body weight increased by 50% at the same time (*52*). As a result, the delivered dose of toxicant, which was a fixed concentration of the diet, was 211 mg/kg/day during the first week of the study and 138 mg/kg/day during the fourth week (a 35% change).

Energy utilization, as indexed by oxygen uptake, also shows distinct changes in the peripubertal years (*53*). These changes are not eliminated by simple body mass corrections. Extrapolations of toxicant impacts based on metabolic rate may need to be modified for adolescents.

Water intake at various ages has been studied in connection with risk assessment for water contaminants (*1*). Neither the amount of fluid intake nor the proportion derived from drinking water changed substantially from childhood to adolescence. A large change in sources of fluid intake was reported in postadolescents (> 20 years of age) because of increased coffee/tea consumption. The age for this transition may occur earlier in some cultural contexts and may change with contemporary trends.

Protein-calorie malnutrition and micronutrient deficiencies can appear during periods of rapid growth in early adolescence because of poor-quality diets (*54–56*). Such deficiencies could influence toxicant action in several ways. For example, antioxidant defense via glutathione is diminished in protein deficiencies and vitamin and trace element deficiencies promote oxidative damage due to reduced antioxidant enzyme activity. Essential trace element deficiencies trigger compensatory changes in expression of the metal-binding proteins transferrin and metallothionein. In addition to their physiologic roles in iron and zinc metabolism, transferrin binds aluminum and manganese and

metallothionein binds cadmium, copper, mercury, and nickel. Thus the uptake, distribution, and intracellular disposition of these toxic metals could be enhanced.

Nutritional deficiencies are of particular concern when pregnancy occurs during the growth phase of adolescent development (*57*). Toxicants that interfere with nutrient uptake or utilization could further exacerbate this situation. Nutritional deficiencies in teenaged mothers have been implicated in the greater incidence of gastroschisis in their offspring (*58*).

Adolescent Maturation in Humans and Laboratory Animals

The growth spurt. A period of rapid growth occurs at different ages in boys and girls and is closely associated with pubertal events (*45,59*). Longitudinal data are important for quantitation of the growth spurt as a rate or velocity (*60*). Height growth is the most general manifestation, and distinct contributions from long bone and trunk growth have been demonstrated (*59*). Peak growth velocity may be a valuable end point for use in toxicologic studies.

The skull also enlarges in adolescence, showing a peak in growth velocity of longitudinal head circumference at 11 years of age in girls and 15 years of age in boys (*61*). Craniofacial growth and ossification and the final stages of dental eruption occur within limited age-defined time spans; the jaw and chin are the last facial elements to reach mature proportions (*62*).

Some believe that the adolescent growth spurt is characteristic of all primate species, whereas others believe that it is uniquely human (*63,64*). Whatever the case may be, pubertal growth patterns in most mammalian species do not show the rate discontinuities seen in humans and in nonhuman primates. As is the case for other developmental stages, the short life span of the rodent makes it difficult to detect changes in the rate of maturation. In particular, the extended juvenile period between weaning and sexual maturity in humans is not prominent, and the discontinuous growth pattern that leads to an adolescent growth spurt has not been clearly demonstrated.

The development of sex-differentiated morphology of body size and composition is an important aspect of adolescent growth. Laboratory animals differ widely in the emergence of sex-differentiated morphology at puberty. Body size and external genitalia are the most widely used markers. Nonhuman primates, such as rhesus monkeys, show strong body size differentiation, but less morphologic differentiation of body proportions and composition than humans.

Puberty; the onset of reproductive function. In humans, normative data for pubertal development are typically reported in terms of the Tanner (*60*) stages, which are based on the appearance and extent of breast and penile development and pubic and axial hair. The Tanner study examined British schoolchildren; norms have also been developed within some other national and ethnic populations. Variations in patterning within normal populations have also been analyzed (*65,66*). Age at menarche (the onset of menses), thelarche (the onset of breast development), and adrenarche (the appearance of axial hair) are sometimes used as discrete landmarks of pubertal maturation in girls. For boys, the age at first ejaculation or at the first voice break are infrequently used as landmarks. In addition, continuous quantitative measures of penis length or nipple growth are sometimes used (*67,68*). Various indices of pubertal development are generally correlated in human populations, but both the sequence of events and the rate of development can vary, and it is not known whether environmental toxicants would be likely to affect all aspects of puberty in a similar manner.

In laboratory rodents, the age at vaginal opening and preputial separation are standard landmarks of puberty. These measures are now recommended for inclusion in safety testing studies conducted according to U.S. Environmental Protection Agency (EPA) guidelines (*69*). A broader context for estimating the impact of environmental chemicals, particularly pesticides, on puberty should become available as more studies including these end points are conducted. However, the relationship of vaginal opening and preputial separation to human landmarks like menarche is not known. In nonhuman primates, the age at menarche is often used for females (nonhuman primates, like humans, have menstrual cycles). Nipple size and anogenital distance have been used as quantitative indices in female monkeys, and testis length has been used in male monkeys.

The transmitters, growth factors, and hormonal influences involved in functional maturation of the hypothalamic–pituitary–gonadal axis and the onset of puberty are gradually becoming known. Control of the onset of puberty has been widely studied in humans, rhesus monkeys, and sheep. These studies allow the elaboration of mechanism hypotheses for investigating the effects of toxicants on puberty. These hypotheses are vital for understanding the biologic plausibility of effects of environmental contaminants on puberty biomarkers and for generalization across doses and species.

The changes in the tract during adolescence are pervasive and profound. After the onset of cyclic gonadotrophin release in boys, sperm cycles are established, leading to expanded size and complexity of testes. In girls, the uterus increases in size and becomes anteverted, the uterine cavity is established, and epithelial secretory activities are initiated. External genitalia increase in size in both sexes, and the vaginal epithelium thickens and undergoes changes in pH and glycogen content. Quantitative information on age- and maturation-dependent changes in internal reproductive organs is generally not available but may increase with the widespread use of noninvasive imaging technologies (*13*).

Anisimov (*70*) suggested that high rates of cell proliferation during periods of rapid growth could differentially predispose organs to genotoxic carcinogens. Thus, cellular proliferation in the male and female reproductive tracts that occurs during adolescence could increase susceptibility to toxicant-induced reproductive tract cancers. A similar hypothesis has been advanced for xenoestrogens and breast cancer (*71*). Experiments designed to directly test this hypothesis have not yet been conducted.

In humans, there is a distinctive but highly variable stage of adolescent sterility, during which menstrual and hormonal cycles gradually mature into the adult form (*72*). During this time, polycystic ovary syndrome is often encountered in young women. Similarly, in boys, ejaculate parameters do not reach adult values until sometime after puberty. Testicular varicocele, a vascular disorder, can appear in young postpubertal males (*73*). Both polycystic ovaries and varicocele have ties to later infertility. By disrupting the establishment of complex interactions that result in mature ovulation and sperm production, toxicants can influence the incidence of these disorders.

Adverse pregnancy outcomes are more common in teenage pregnancies, and some birth defects are associated with young maternal age (*74*). Developmental toxicants might be expected to differ in their impact on pregnancy during adolescence as compared to adulthood, but I could not locate any empirical information on this issue.

Skeletal maturation. A period of rapid bone growth mineralization coincides with the adolescent growth spurt. The role of steroid and growth hormones has been documented. Recent studies indicate that peak bone mineralization rate occurs 12–18 months after peak height growth rate (*75*), and corresponds to the time of menarche in girls (*76*). Bone mineralization continues into the next decade, and peak mineralization is reached in the mid to late 20s in women (*77*). Diminished bone mass accrual during adolescence is a risk factor for the

development of osteoporosis later in life (*78*). The adolescent period of rapid mineralization could be a target of toxicants that influence bone (e.g., cadmium and lead). Skeletal maturation is also reflected in epiphyseal closure of the long bones and of some areas of the axial skeleton, such as the iliac epiphysis. Clinical tools have been developed to quantify skeletal maturation in humans using radiographs (*79*) and, more recently, magnetic resonance imaging (MRI) (*80*) and DEXA (*81*). Evaluation of skeletal maturation using these noninvasive techniques could also provide useful biomarkers for adolescent development in larger laboratory animals. In contrast to primate species, rodents do not experience epiphyseal closure at the end of adolescence and continue to add body length throughout the life span. The evaluation of skeletal maturation in rodents usually involves biochemical measurement.

Thymic involution and reproductive tract immunity. Adequate immune defense is extremely important in the adolescent years, when many pathogens are first encountered through an expansion of environmental contacts and the initiation of sexual activity (*7*). Thus, exposure to toxicants that impair immune function can be particularly harmful because of the already high risk of infectious disease.

During adolescence, sex-dependent differences in immune response are established; females have generally more responsive immune systems and are more sensitive to immunotoxicants (*82*). Steroid hormones under the regulation of GnRH are considered responsible for immune system alterations in adolescence. The thymus is an estrogen target tissue. Estrogen receptors are found on lymphocyte precursors as well as on stromal cells. Gonadal hormones appear to provide a tonic inhibitory function on the thymus; gonadectomy in adulthood leads to an increase in thymic tissue, whereas estrogen can produce thymic involution. In addition, GnRH may have effects on immune function around the time of puberty that are not mediated by gonadal steroids.

The major maturational landmark in the immune system during adolescence is thymic involution, characterized by a dramatic decrease in thymic tissue mass, primarily involving the perivascular space (*83*), a decrease in the production of new thymocytes, and an increase in the $CD4^+/CD8^+$ ratio (*84*). Although direct observation of changes in thymus size and composition requires tissue sampling, peripheral markers are available. Studies in humans, generally bracketing adolescence (6–19 years of age), have shown major changes in peripheral lymphocyte subpopulations as determined with cell-surface markers (*85*). Also, during adolescence, changes in the reproductive tract occur in preparation for the establishment of vaginal mucosal immunity. Maturational changes in gut mucosal immunity may also occur, as reflected in a peak number of Peyer's patches in the adolescent years (*8*).

Immunotoxicants that induce thymic involution, such as diethylstilbestrol and tetrachlorodibenzo-*p*-dioxin, might be anticipated to interfere with adolescent maturational changes in the immune system that involve the thymus. However, studies specifically targeting adolescence as a vulnerable developmental stage are not available.

Brain and behavior. Adolescence is a time of rapid advance in cognitive skills and intense acquisition of new information that sets the stage for a productive adult life. Therefore, suboptimal brain function can have long-term consequences. The high risk of injury and of conduct disorder during adolescence also points to the importance of identifying toxicant exposures that can impair brain function. In addition, maturation processes could be disrupted, leading to permanent effects on central nervous system (CNS) structure and function. Because of the importance of behavior in health risks of adolescence, this review emphasizes adolescent brain development.

Increased capacity for complex and abstract thought develops in adolescence, and parallels have been drawn between the timing of the final stages of Piagetian cognitive development (formal operations) and electroencephalography (EEG) coherence parameters (*86*). Correlations between hormone levels and behavioral characteristics of adolescents (impulsivity, etc.) are characterized in the psychology literature (*87*). In general, however, well-defined relationships between cognitive development and brain maturation parameters have not been established.

The maturation of the cerebral cortex is the final event in brain development. Two concepts are currently important in guiding research in late cortical morphologic maturation: pruning and connectivity.

Pruning refers to the decrease in synaptic density from the peak levels reached in early childhood (9–18 months of age in children) and was first described by Huttenlocker (*88*) using histologic methods. Recent MRI studies showing decreases in cortical gray matter volume are consistent with this concept, as are studies showing decreases in cortical glucose metabolism (*89*). In rhesus monkeys, pruning during late brain maturation has been confirmed by Goldman-Rakic and collaborators (*90–93*) through their studies on cortical synaptogenesis from embryogenesis to adulthood. During the juvenile and adolescent stages, decreases in synaptic density continue in the cortex, culminating in late adolescence in adult morphology (*88*).

Connectivity refers to increased myelination of major intracortical commissures during adolescence, as observed in children by Yakovlev and Lecours (*94*) and Benes (*95*) using histologic methods. MRIs of human adolescent brains and, in particular, the corpus callosum, are generally supportive of increased myelination as a major maturational process in the cortex (*96*), as are magnetic resonance spectroscopy imaging studies showing increased phospholipid metabolism. Several adolescent changes in electrophysiologic measures [increases in EEG coherence (*97*), decreases in delta sleep time (*98*), and decreases in EEG latencies (*99*)] have been attributed to increased intracortical connectivity. Clear temporal relationships between morphologic and functional measures of late brain maturation have not been identified.

Recently, MRI scans that image and quantitate brain composition in terms of white and gray matter have provided a surrogate measure for increased myelination (white matter) and potentially of decreased neuropil (gray matter). Normative data are becoming available, and several studies have specifically targeted adolescence (*100,101*).

Because of intensive myelination, it might be anticipated that myelin toxicants would have greater effects during adolescence. However, studies of age-dependent effects of myelin toxicants have typically targeted earlier postnatal periods.

Sex-differentiated morphology of the brain is thought to be established during fetal life and infancy and develop into full expression at the time of puberty (*102*). Presumably hormonal factors controlling other secondary sex characteristics also orchestrate the change in the brain during adolescence, but the mechanisms are not completely understood (*103,104*). Most of these changes are limited to sexually dimorphic regions of the hypothalamus. Other differences are found in corpus callosum (*105*) and in the cell-packing density of the granular layer of the cortex (*104*). More recently, the effects of estrogen on brain morphology continuing into adulthood have been described. As research expands, progress should be made in understanding the distinct contribution of the adolescent period to sex-differentiated brain structure and function and mechanisms by which this contribution could be disrupted by toxicants that affect the endocrine and nervous systems.

Studies of synaptic pruning in sensory systems have uncovered the importance of *n*-methyl-D-aspartate (NMDA) receptors in differential strengthening of synapses in late maturing cortex; NMDA leads to excess pruning, whereas NMDA antagonists

promote synaptic density (*106,107*). There is also some suggestion that NMDA receptors are maximally sensitive during adolescence (*108*), as first suggested by the finding that pseudopsychotic effects of ketamine are not present in children, but emerge after puberty. Noradrenergic systems have also been implicated in synaptic pruning and cortical connectivity (*109–112*) in infancy. Studies in adolescence are not available.

In 1983, Spear and Brake (*113*) brought attention to changes in dopaminergic systems during adolescence in a thorough review. The authors provided a characterization of periadolescent (30- to 40-day-old) rats in terms of their spontaneous behavior (in isolation and in social settings), their performance in structured learning situations, and their behavioral response to CNS active drugs. Their research characterized 28- to 38-day-old rats as exhibiting an increase in spontaneous motor activity and social behavior. In structured learning situations, both improved and poorer performance was identified, depending on the task. An integrative interpretation offered by the authors was that periadolescent rats excelled in simple situations where increased activity was an advantage, but showed deficits in more complex tasks where increased activity could be a disadvantage. Spear and Brake (*113*) also pointed out some interesting effects on stimulus and reward efficacy. Studies from their laboratories showed a reduced behavioral response to direct and indirect dopamine agonists and an increased response to dopamine antagonists. Similar effects were not noted for cholinergic and serotonergic drugs. The authors proposed that the onset of dopamine autoreceptor function in the mesolimbic dopamine system during adolescence might underlie these characteristics of adolescence in rats.

Dopamine receptor density, like that of other neurotransmitters, changes through late brain development in concert with synaptic overproduction and pruning (*114*). This theme has been further developed in more recent studies by Andersen et al. (*115–117*) and Teicher and et al. (*118,119*), who found transient overexpression of dopamine receptors in the two major subcortical dopamine systems (striatum and nucleus accumbens) around the time of puberty in rats. Others have reported confirmatory findings. Adolescent rats differ from adults in their response to CNS active drugs including, but not limited to, dopamine active agents (*113,120–122*). Age-related changes in dopamine receptor subtypes in cortical areas have also been shown in monkeys (*93,123*), although few time points in the adolescent period have been studied, and information on subcortical areas is limited to adults. Recently reported human data (*124*) also showed a transient overexpression of D2 receptors in cortex through late adolescence.

The extrapolation of findings on dopamine receptors from rats to humans may be difficult. There is evidence that autoreceptor regulation of dopamine systems varies by species. Whereas human and nonhuman primates express autoreceptors in nigral striatal pathways, rats express them in striatum but also in ventral tegmental projections to the limbic system (*125*).

No information was found concerning changes in central or peripheral cholinergic systems in adolescence. Such information could be valuable in forming hypotheses about pesticides that influence cholinesterase activity.

The general maturational trend in EEG in adolescence is toward less slow-wave activity (*99*) and greater coherence (*25*) and complexity (*126*). The event-related potential (ERP), the brain electrical response to discrete meaningful sensory stimuli, is one of the best-characterized brain function parameters that changes during adolescence.

The ERP has sex-dependent characteristics that emerge during adolescence (*127,128*). Females generally show larger amplitude and shorter latency visual, auditory, and olfactory ERPs (*129*). The largest sex differences are for olfactory ERP amplitude (*130*), corresponding to the superior performance of women in olfactory tasks. The most significant sex differences occur at 15–20 years of age, and involve later ERP components and novel and task-relevant stimuli (*129–131*). Courchesne (*132*) has argued that changes in amplitude and latency of various ERP components correspond to developmental changes in myelination and synapse density. In particular, the amplitude of the Nc component declines markedly from 10–15 years of age, corresponding to synaptic pruning in the frontal cortex. Girls with Turner's syndrome, a genetic disorder characterized by hypogonadism, fail to show the normal developmental changes in frequency and duration of Nc from 9–14 to 15–20 years of age (*133*).

A decrease in central processing time (the speed with which mental functions are performed) is related to lowered latency of ERPs. Response time during cognitive testing, a marker of central processing time, decreases systematically during adolescence in humans (*134*). The slope of linear decline changed exponentially from 6 to 17 years of age. Although there is no distinct discontinuous change in adolescence, disruption of the predicted rate of change could reflect abnormal brain maturation.

A dramatic transition to later bedtimes is a prominent feature of human adolescence (*135*). Changes in sleep EEG have also been documented in humans (*97,99,136*). The biologic (as opposed to psychologic or sociologic) basis of this phenomenon is supported by a similar finding in rhesus monkeys living in indoor cages with no changes in the physical or social environment during adolescence (*137*). Lengthening of the nocturnal activity period in rodents at puberty may be a related observation (*138*). There is also inconsistent information concerning changes in melatonin production at puberty (*135*).

Some Animal Studies of Adolescent Toxicology

Although pubertal/adolescent rodents are widely used in toxicology research, exposures usually begin, and many times end, before the pubertal/adolescent period. When chronic exposures begin during adolescence, end points are often not measured until late in the life span. Studies directed at adolescence most frequently assess the reproductive system, CNS, and growth.

Reproductive toxicity. Pubertal end points were included in studies of methoxychlor (MXC), a model environmental estrogen, but exposures were not limited to the periadolescent period. One study administered MXC before puberty and through mating trials in adulthood (*139*); early vaginal opening and impaired fertility were reported. Early vaginal opening was again found in a second study, when MXC was administered beginning in the fetal period and continuing through sexual maturation (*140*). Fertility was impaired in adulthood, although MXC administration was discontinued before mating trials.

Although exposures for the uterotrophic assay (*141*) are limited to the adolescent period, the intent is not to study puberty-specific actions of estrogenic agents, but to take advantage of the low endogenous estrogen levels in immature animals to simplify the assay. Nonetheless, the uterotrophic assay does point out the greater susceptibility of estrogen-dependent tissues to exogenous estrogenic influences before the onset of ovarian steroid production and negative feedback via the hypothalamus.

Vaginal opening and preputial separation, indices of pubertal acceleration/delay, are now commonly studied as part of EPA guideline multigeneration studies (*69*). Data gathered in this way do not provide information about the unique response of adolescents to toxicants because the exposures occur throughout development and are not limited to the pubertal period. One study was located using several estrogenic agents and evaluating vaginal opening (*142*), but most studies of this type begin exposure at or before weaning.

Cadmium effects on testes present an example of a male reproductive toxicant for

which pubertal exposures have been compared to adult exposures. The pubertal male rat was generally less sensitive than the adult, presumably because effects were mediated though effects on hypothalamic luteinizing hormone regulation, which was not yet mature in the pubertal males (*143,144*).

Concern about teenage drinking has made alcohol one of the agents most studied for its effects on adolescence. Recent *in vivo* studies in pubertal female rats suggest that single or short-term oral alcohol administration blocks vaginal opening that is induced by *N*-methyl-DL-aspartic acid (*145*); baseline gonadotropin levels were not altered. Anderson et al. (*146*) evaluated the effects of alcohol on male reproductive tract development. Mice were allowed *ad libitum* access to a liquid diet containing 5% ethanol beginning at weaning through the pubertal period (49 days of age). Effects on the reproductive tract relative to controls included lower weight of testes and accessory organs; reduced sperm count, sperm motility, and sperm fertilization ability; and increased incidence of abnormal sperm. These effects were attributed to delayed reproductive tract maturation, because most parameters normalized when treatment was extended an additional 2 weeks.

CNS end points. Alcohol is also one of the most-studied agents in terms of CNS effects in adolescence. Some indication of differential susceptibility to the sedative effects of alcohol in adolescence comes from studies in rats. The duration of absence of the righting reflex and depression of locomotor activity (*147*) and reduction in core body (*148*) were less affected in adolescents than adults after intraperitoneal (ip) ethanol administration. Development of tolerance to these effects has also been studied in adolescent rats and mice. In general, tolerance to motor effects and reduction of body temperature were greater in adolescents than in adults (*148*). In studies of behavioral function, presession ip administration of ethanol impaired the acquisition of a spatial maze task in 30-day-old male rats. *In vitro* administration studies also demonstrated differential effects of ethanol on electrical activity in brain slices. In studies of hippocampal brain slices from rats, NMDA-mediated electrical responses were more influenced by the addition of ethanol to the media in slices from adolescents than in slices from adults.

In addition, induction of long-term potentiation, an electrical surrogate for memory formation, was affected by the addition of ethanol to the incubation medium of slices from 15- to 25-day-old rats, but not 70- to 100-day-old rats. This effect was thought to be related to differential expression of NMDA receptor subtypes during this period. In a behavioral study, no differences were found in alcohol effects on visual or olfactory tasks in 35- to 38- as compared to 60- to 70-day-old rats (*149*); additionally, no differences in alcohol effects were found on nonspatial learning and memory tasks. However, ethanol effects were detected on a spatial task in adolescent but not in adult rats.

Surprisingly, apart from recent abstracts, literature searches did not locate animal studies on nicotine effects in adolescence. In humans, literature on smoking in adolescence has been directed mainly at respiratory parameters (*150–152*).

Because of the participation of teenagers in agricultural activities, there is concern about special sensitivity to pesticides during this period. Age-dependent effects of pesticides have been studied, both in terms of mortality and neurotoxicity, usually by comparing newborn or weanling rats to older and younger rats (*1*). To date, no general pattern of altered sensitivity has been described (*153*).

Metal toxicants and the growth spurt. Lead is one of the most widely studied developmental toxicants, and weanling rats are a common model. Both reproductive maturation and pubertal growth have recently been studied in lead-exposed rats; however, although they included the pubertal period, exposures were initiated earlier in development (*154,155*). In an interesting series of experiments, Hammond et al. (*156–159*) investigated the mechanism by which pubertal growth retardation was induced by lead administration in weanling female rats. They concluded that a centrally mediated effect on appetite and food intake was responsible.

Recommendations

Basic concepts and data concerning adolescence as a vulnerable period for environmental influences are extremely scattered and difficult to locate. This review represents an attempt to introduce relevant literature on adolescence to those interested in environmental health issues. Additionally, the following recommendations are put forward for consideration:

- Identify adolescence as a distinct developmental period in children's health research. Determine priorities for data needs in the area of adolescent toxicology.
- Identify end point methodologies that are appropriate for inclusion in animal toxicology studies conducted in the adolescent period.
- Establish *in vivo* and *in vitro* models for determining hazards unique to adolescence.
- Identify exposure periods in test species for the study of toxicology in adolescence. Establish guidelines for consistently including or excluding postweaning sexually immature animals in standard toxicology study designs.
- Consider adolescent development when establishing workplace exposure standards.
- Bracket the adolescent period when collecting age-dependent exposure data in survey studies.
- Examine the potential contribution of immunotoxicants and neurotoxicants to the high incidence of infection and injury in adolescents.

Human and animal research in the area of adolescent toxicology will help to safeguard adolescents as they complete their developmental time course and enter adulthood.

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