Published in final edited form as:
J Neurol Sci. 2011 June 15; 305(1-2): 11–21. doi:10.1016/j.jns.2011.03.014.

ENDOCRINE DISRUPTORS AS A THREAT TO NEUROLOGICAL FUNCTION

Bernard Weiss
Department of Environmental Medicine, University of Rochester, School of Medicine and Dentistry, Rochester, New York USA 14642

Abstract

Endocrine disruption is a concept and principle whose origins can be traced to the beginnings of the environmental movement in the 1960s. It began with puzzlement about and the flaring of research on the decline of wildlife, particularly avian species. The proposed causes accented pesticides, especially persistent organochlorines such as DDT. Its scope gradually widened beyond pesticides, and, as endocrine disruption offered an explanation for the wildlife phenomena, it seemed to explain, as well, changes in fertility and disorders of male reproduction such as testicular cancer. Once disturbed gonadal hormone function became the most likely explanation, it provoked other questions. The most challenging arose because of how critical gonadal hormones are to brain function, especially as determinants of brain sexual differentiation. Pursuit of such connections has generated a robust literature embracing a broad swath of chemical classes. How endocrine disrupting chemicals influence the adult and aging brain is a question, so far mostly ignored because of the emphasis on early development, that warrants vigorous investigation. Gonadal hormones are crucial to optimal brain function during maturity and even senescence. They are pivotal to the processes of neurogenesis. They exert protective actions against neurodegenerative disorders such as dementia and support smoothly functioning cognitive activities. The limited research conducted so far on endocrine disruptors, aging, and neurogenesis argues that they should be overlooked no longer.

Keywords

Aging; Alzheimer's disease; Androgens; Antiandrogens; Autism; Bisphenol A; Congenital Adrenal Hyperplasia; Endocrine disruption; Environmental chemicals; Epigenetics; Estrogens; Menopause; Methylmercury; Neurogenesis; Persistent Organic Pollutants; Pesticides; Phthalates; Play behavior; Sexual dimorphism; Testosterone; Thyroid function; Window of opportunity

Trends in reproductive success

Rachel Carson's *Silent Spring* (1) sensitized us to the devastating toll exacted by our willful neglect of how toxic pesticides had endangered the natural world. Some of those, such as DDT, now classified as Persistent Organic Pollutants (POPS), have been withdrawn from

bernard_weiss@urmc.rochester.edu, Tel: 585-275-1736, Fax: 585-256-2591, Bernard Weiss, Ph.D., Professor of Environmental Medicine, University of Rochester Medical Center, 610 Elmwood Avenue, Rochester, NY 14642.

CONFLICT OF INTEREST. None

commerce because of their toxic potency and environmental persistence. Carson's work touched only peripherally on human health. Her gaze was fixed on nature, and birds became its focus. She wrote,

"…On the mornings that had once throbbed with the dawn chorus of scores of bird voices there was now no sound; only silence lay over the fields and woods and marsh."

Carson's theme was pursued and exemplified at the first Rochester Conference on Environmental Toxicity in 1968, whose proceedings appeared in a volume entitled *Chemical Fallout* (2). It discussed both methylmercury and pesticides. It included reports of how eggshell thinning, already noted by Carson, had blighted populations of eagles and other predatory avian species, a phenomenon that featured the role of birds as sentinels of environmental poisoning and the possible role of hormonal imbalances in reproductive declines. Some participants, building on Carson's observations, provided new data about how eggshell thinning was produced by estrogenic pesticides, among them DDT. One of the editors, Berg, discussed an issue that only now is coming to prominence: the relevance of low doses for risk assessment. He wrote, "The control of reproduction by hormones is delicately poised… If organochlorine compounds interfere in small ways with the regulation of hormones, then this model predicts that low doses will do no damage whatever to pest populations while they exterminate the most stable and well-established predator populations."

Another, more subtle, phenomenon, a behavioral one, also emerged. George and Molly Hunt (3) noted what they described as "lesbian gulls," a term denoting the presence of female-female pairings of western gulls on Santa Barbara island, California. Fry (4) later proposed that these pairings resulted from both a reduced male population and anomalies in male reproductive structures and behavior. He attributed these features to DDT and other estrogenic contaminants in the environment.

Carson's message seems to have been diluted by time and by the swarm of debates about issues such as global climate change, political arguments about the "cost" of environmental protection, and the continuing identification of still more toxic chemicals contaminating the environment. Her lyrical description of how such agents diminish the natural world needs to be heard by scientists and a public that thinks of it as an episode that belongs in the distant past. It thinks so because her message has been incorporated into our current world view. The term, "sustainability," heard and seen so frequently in contemporary environmental discussions, is Carson's argument echoing through time.

Implications for human health during this time had received little attention except for speculations about cancer. In a 1992 article that attracted considerable notice, comment, and debate, Carlsen et al (5) asserted that semen quality had decreased progressively during the previous 50 years. Sharpe and Skakkebeak (6) connected these findings to estrogenic chemicals in the environment. They wrote, "We argue that the increasing incidence of reproductive abnormalities in the human male may be related to increased oestrogen exposure in utero, and identify mechanisms by which this exposure could occur."

The British writer P.D. James, probably unaware at the time of the 1992 paper, built a novel around the theme of declining male fertility. *The Children of Men* (7) imagines an England of 2021 as a world in which all human males have become sterile. Human reproduction has come to an end. The final generation is now twenty-five, and civilization is in the throes of extinction. Our species is not at this stage, but many voices have now expressed concerns for patterns of declining fertility in advanced industrial societies that cannot be attributed solely to voluntary birth control.

Since those publications, a growing volume of data continues to verify and expand the theme of reproductive disorders and their connections to environmental exposures. Moller et al (8) pointed to a continual decline from 1940 to 2000 in the proportion of males at birth and in the incidence of testicular cancer. More recently, Andersson et al (9) noted that the continuing adverse trends in male reproductive health suggest that "…we have reached a tipping point." Skakkebaek (10), peering at the total landscape of male reproductive disorders, offered a unifying hypothesis to explain such observations:

"There is evidence that poor semen quality, testicular cancer, undescended testes and hypospadias are symptoms of one underlying entity, testicular dysgenesis syndrome (TDS), which may be increasingly common due to adverse environmental influences. Experimental and epidemiological studies suggest that TDS is the result of disruption of embryonal programming and gonadal development during fetal life. An endocrine disrupter hypothesis to explain the adverse trends has been proposed. It is recommended that future epidemiological studies on trends in male reproductive health should not focus on one symptom alone, but be more comprehensive and take all aspects of TDS into account."

The Endocrine Disruptor Hypothesis

In the early 1990s, scientists from various scientific disciplines puzzled over how to account for declining wildlife populations and developmental anomalies such as reduced gonad size in alligators (11). They came together to formulate, what is now known as the Endocrine Disruptor Hypothesis, in a Wingspread Conference summarized by Colborn (12). Those strands were woven together in a book (see Figure 1), now translated into at least 20 languages, that planted the seeds of endocrine disruptor research and principles (13). It also gave prominence to the idea that the brain, as well as the gonads, could be a target for environmental endocrine disruptors (EEDs).

At the summit of the possible health hazards posed by endocrine disruptors, almost all of the researchers involved agreed that early developmental exposures held the greatest potential for adverse consequences. Sharpe (14) made the argument in graphic terms in his discussion of the hazards to male development:

"The difference between becoming a male rather than a female is about as fundamental as you can get, as it will alter that individual's place in society, transform the shape of his body, reshape his inherent abilities, his thought processes and his behaviors. Whilst it is a constant source of debate and amusement as to whether this "transformation" process represents an improvement or not, when compared with the "set-up" program which would have led to a female, it is becomingly increasingly clear that "making a male" is a rather perilous process."

Sharpe's mechanistic focus was the reproductive tract. His comment about "thought processes and his behaviors" describes the perspectives of another group of scientists. These scientists, spanning a variety of disciplines, became concerned about the potential coupling of endocrine disruption and brain function because of the vital roles played by hormones in brain development and brain function. Gonadal hormones (estrogens and androgens) mold sexual differentiation of the brain. Thyroid hormone is essential for other aspects of brain development such as neuronal migration and differentiation, myelination and synaptogenesis. Figures 2, 3 and 4 list environmental chemicals recognized as actors in estrogenic and anti-estrogenic, anti-androgenic, and anti-thyroid mechanisms and processes.

The lists of chemicals in these figures are far from complete, yet underscore the staggering variety of sources that could interfere with or modify the action of endogenous hormones during the course of brain development. The focus of this article will be on those EEDs that

operate on systems responding to gonadal hormones. Thyroid has been addressed by Zoeller (15) and others.

Sexual Differentiation of the Brain

Many neurobehavioral disorders affect males and females differently. For example, depression occurs much more frequently in females, and autism spectrum disorders and ADHD are far more frequent in males (13, 50). The origins of these differences are not just genetic; more and more we see that adult diseases are the outcome of events and conditions arising early in development, so it is reasonable to investigate the linkages between environmental exposures and neurobehavioral development, especially when those exposures influence endocrine mechanisms that help mold the developing brain. Sex differences, taking root before birth, are planted by the actions of hormones. These actions can be modified during fetal life by exposure of the mother to environmental chemicals that mimic, inhibit, or otherwise distort normal hormonal function.

Sex differences are set in motion at conception by genetic programming (16). Genetic males and females are structurally identical during the first two months of pregnancy, however. This structure, basically female, is often termed the default form. With the formation of the testis, and the onset of testosterone secretion (Figure 5), the male gonads begin to assume their masculine configuration. the proximal androgen is dihydrotestosterone (DHT), converted from testosterone by 5-α reductase. DHT is the predominant determinant of masculinization of the external genitalia in humans and other primates.

Sexual differentiation of the gonads occurs during gestational weeks 8–20, but sexual differentiation of the brain may be proceeding beyond that point (17). DHT is the predominant determinant of masculinization in humans and other primates.

Most of our mechanistic knowledge of brain development comes from experiments in rats and mice. Masculinization of the rodent brain differs from that of the primate brain. In a provocative biological irony, formation of the male rodent brain is governed by estradiol, converted by the enzyme aromatase (CYP 19) from testosterone secreted by the male fetus (Figure 6).

In both primates and rodents, hormones mold sexual differentiation of the brain which, owing to its developmental organization, responds to hormonal signals later in life in a sexually dimorphic fashion. Figure 7 lists some of the ways in which gonadal hormones play a role. Take notice of their scope. They are intimate partners of how animals (not excluding humans) behave and perform.

Human brains are sexually differentiated to an extent not fully appreciated until the possibilities of imaging technology became evident and were exploited; for example, see Goldstein (18). These differences underlie subtle differences in behavior. Some of the subtleties are noted in Figure 8. One that is especially intriguing is the difference in Broca's area and planum temporale, both of which are involved in language processing. Females tend to be more adept than males in two functions: language and fine motor control. Males tend to be more adept in spatial visualization and throwing at a target, perhaps explaining why bars often install dart games that appeal to male patrons (19). The clinical condition labeled as Congenital Adrenal Hyperplasia (CAH) provides a compelling example of how abnormal levels of gonadal steroids during early development are converted into behavioral markers.

CAH is an autosomal recessive disorder that induces elevated adrenal androgens, particularly testosterone, in the fetus. The cause is deficiency in the enzyme 21 hydroxylase.

It occurs in 1 in 14,500 live births. Girls with CAH exhibit male features in the external genitalia, and usually are treated with corticosteroids. Even with treatment, CAH girls, presumably due to elevated prenatal testosterone, display some masculine proclivities in toy choice, rough–and-tumble play patterns, and choice of playmates, choosing boys as often as girls, a departure from normal girl choices (20). CAH can serve as a striking model of the potency of developmental hormonal conditions to influence sexually dimorphic behaviors.

Neurodevelopmental Implications

Animal studies

Morphological differences between male and female brains, as noted above, translate into behavioral differences. EEDs transform these differences in various ways. One is to reduce the magnitude of the difference. For example, female rats show a distinctive preference for saccharin solutions compared to males. Developmental exposure to dioxins or certain estrogenic PCBs induces males to express the female pattern (21). Developmental exposure to dioxins, which are both anti-estrogenic and anti-androgenic, also produces such an effect (22). Measures of complex performance, such as schedule-controlled operant behavior, respond to prenatal dioxin exposure with male rats becoming more female and female rats becoming more male in their response patterns (23).

Vinclozolin is a fungicide used to treat grape vines, strawberries, vegetables, and other produce and is classified as an antiandrogen. At high doses administered to male rats shortly after birth (24) it feminized play behavior (play fighting). Play fighting typically occurs with greater frequency and intensity in juvenile males than in females, a disparity eliminated by vinclozolin. At much lower doses (25), changes in social play as well as sexual behavior were seen in the offspring of treated pregnant dams. The same laboratory (26) also observed learning deficits in such offspring.

Methoxychlor is an organochlorine insecticide developed as a replacement for DDT. It also belongs to the POPS class of contaminants and its use was suspended by the United States Environmental Protection Agency (USEPA) in 2000. It is both estrogenic and anti-antiandrogenic, a natural conjunction at the mechanistic level. Nevertheless, it provides a useful lesson in the expression of anti-androgen toxicity. Methoxychlor produces its most dramatic effects from exposures during prenatal development. At the USEPA laboratories (27) rats were exposed from gestation until puberty. In both males and females, even at what are considered low doses, numerous disorders of reproductive tract morphology and function appeared, including suppression of testicular Leydig cell function (28). Several studies indicate that methoxychlor administered perinatally can modify behavioral sex differences. For example, (29) methoxychlor administered to pregnant mice at environmentally relevant dose levels narrowed male-female differences on a number of behavioral measures.

Bisphenol A (BPA) is a compound that recently has evoked a plethora of media attention and scientific debate. It is produced in such great quantities (est. 2.9 billion kg/year) and appears in so many products (Figure 9) that human exposure is universal. BPA has been found in the serum and follicular fluid of pregnant women as well as in fetal serum and amniotic fluid, indicating placental transfer. It was originally synthesized as an estrogen, then found useful as a plasticizer. However, through a variety of means, it is released from such products and finds its way into the environment, including food products.

For BPA, the lowest dose previously examined for risk assessment purposes was 50 mg/kg/day in studies with rats and mice. These assays did not include neurobehavioral measures. The 50 mg/kg/day dose is the currently accepted Lowest Adverse Effect Level (LOAEL)

and was used to calculate the current EPA Reference Dose (RfD) of 50 μg/kg/day. The LOAEL is the dose that, by convention, is the dose at which adverse effects become statistically greater than those observed in control groups. The RfD is the daily dose to which an individual can be exposed chronically without suffering adverse effects.

The current RfD is still based on those high dose experiments conducted in the 1980s. One class of outcomes not considered in the older studies consists of more recent research examining neurobehavioral measures (30, 31). The latter endpoints elicited noteworthy comments from the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) (31). It expressed "some" concern that pregnant women, fetuses, infants and children may be susceptible to BPA disruption for neural and behavioral endpoints while viewing other endpoints as lacking evidence of adverse effects at environmental levels. The Chapel Hill BPA expert panel also stated "that low doses of BPA during development have persistent effects on brain structure, function and behavior in rats and mice" (32).

"Low dose" is a key phrase in EED literature. Traditional toxicology assumes a direct relationship between dose and toxicity. Such a relationship is uncommon in endocrinology (33). Instead, hormones themselves, and agents such as EEDs that alter their actions, tend to display nonmonotonic dose-response functions. For example, they may take on an inverted U-shape, with toxic effects maximal at very low and very high exposure levels. Nonmonotonic functions were seen in an experiment relating perinatal phthalate exposure to brain aromatase levels in rats (34). A graphic depicting this property appears in Figure 10.

Anatomical evidence of alterations in brain sexual differentiation was examined in mice born to dams exposed chronically to 0, 0.025, or 0.25 μg/kg/day BPA during the period from Gestational Day 8 to Postnatal Day 16 (35). The investigators examined the sexually dimorphic population of tyrosine hydroxylase (TH) neurons in the rostral periventricular preoptic area (AVPV). These are important brain regions for estrous cyclicity and estrogen-positive feedback. Female brains contain a high density of TH neurons in the AVPV. The significant sex differences in TH neuron number observed in control offspring were diminished or obliterated in BPA offspring. This effect was due primarily to a decline in TH neuron number in BPA-exposed females. Open field activity also showed significant sex differences in the control offspring (more activity in females) that were not observed in the BPA offspring. Such results underscore the consequences of low-level exposure during development as they are expressed in sexually dimorphic neurochemical and behavioral endpoints. Other behavioral investigations have been conducted to evaluate the effects of low dose BPA exposure. Gestational exposure to 40 μg/kg/day BPA produced statistically significant gender-specific changes in sexual performance (36) and effects on active and passive maternal behavior (37) in rats.

Endocrine disruptors can no longer be discussed without touching on an issue that only recently claimed out attention because of its unexpected implications. In 2005, a research group led by Michael Skinner (38) reported that when they injected vinclozolin or methoxychlor into pregnant rats during a specific period of gestation, 8 to 15 days after fertilization, offspring sperm counts and motiliy, when the rats reached reproductive age, suffered significant reductions, and sperm-producing cells underwent apoptosis. These effects, without further treatment, persisted through the F_4 generation when these males and their male descendents were mated. Since then, the phenomenon has been pursued by many investigators. The mechanism is epigenetic. The genome remains unaltered. Exposure to these EEDs produced a distinctive pattern of DNA methylation in the germ line that apparently is able to transmit transgenerational adult onset disease (39). Especially intriguing from the standpoint of behavior are two associated findings. Crews et al (40)

found transgenerational effects on mate preference. Normal females showed a distinct preference, in a special experimental arrangement, for normal males compared to F_3 males, presumably an effect due to differences in male pheromone secretions. Subsequently, Skinner et al (41) found transgenerational transmission of anxiety behavior via epigenetic mechanisms.

These selected instances represent only a minute sample of what has become a sizable literature relating endocrine disruption to neurobehavioral function in animals. Translating them into implications for human neurobehavioral function requires us to travel along multiple paths because of the immense diversity of normal and abnormal human conditions. One path takes us to an exploration of sex differences in function and the status of EEDs as their determinants. A second is how to translate the confluence of hormones and neurogenesis into a clinical perspective, a connection with momentous implications for aging.

Human studies

Despite a growing number of studies relating EED exposure to neurodevelopmental endpoints, few possess sufficient clarity to relate them specifically to their impact on gonadal steroids. Some pesticide formulations possess estrogenic properties, but are toxic in other ways as well, and sexually dimorphic neurobehavioral endpoints are too seldom addressed specifically. The voluminous literature on another chemical class, the PCBs, which also possess estrogenic properties, also lacks clarity about sexually dimorphic outcomes; the measures selected for assessment are dominated by cognitive assays such as IQ scores. Similar deficiencies are apparent in the literature on heavy metals such as lead and mercury.

The insights that can result from specifically addressing sexually dimorphic behaviors are demonstrated by a recent publication on the class of plasticizers designated as phthalates. These chemicals are ubiquitous in human tissue because they appear in an broad array of products (Figure 11). Although originally labeled as xenoestrogens, they subsequently were found to be antiandrogens. In rodent studies, they have been shown to act by impairing the ability of the testis to secrete testosterone. This toxic property leads to disorders and pathology of the male reproductive tract. These include cryptorchidism, hypospadias, reduced penis size, and decreased anogenital distance.

Because of such effects in animal studies, Swan et al (42) undertook to study a cohort enrolled originally to study fertility. Participants had provided samples of urine taken during pregnancy. Concentrations of various phthalate metabolites, which provide an index of fetal exposure, were later determined by the U.S. Centers for Disease Control and Prevention (CDC). By correlating these values with anogenital distance in male offspring, the authors were able to demonstrate that even low environmental exposure levels were sufficient to feminize these males. Anogenital distance is typically twice as long in males as in females, serving as an index of virilization in both rodents and humans, and phthalate exposure decreased its length, in accordance with metabolite concentration. It also reduced penis size and volume. These findings demonstrated that adverse effects of phthalate exposure could be detected at low environmental levels and generated substantial discussion (43).

If a chemical agent acts as an antiandrogen, and alters reproductive tract development, it implies that the same action could also alter brain development to interfere with its masculinization. It further implies that such an outcome would be detectable as altered masculine behavior. Proceeding from such assumptions, Swan et al (44) asked mothers from the same cohort to complete an inventory of play behavior, the Prescool Activities Inventory or PSAI (45), known to show marked differences between boys and girls. The PSAI is

designed to discriminate play behavior both within and between the sexes and and has been standardized on children in the UK, the Netherlands and the US (46). It consists of 24 items (12 considered ‘feminine’ and 12 ‘masculine’) and asks the respondents about play preferences of the child such as types of toys and physical activities. A total score is computed based on the sum of scores for masculine items (for example, playing with trucks), minus the sum of scores for feminine items (for example, playing with dolls). A higher total (composite) score implies more male-typical play behavior and a lower score implies more female-typical play behavior.

Results are depicted graphically in Figure 12. It conveys a clear message; namely, that masculine development, as reflected by play preferences, has been impeded in this cohort of 74 boys, (accompanied by 71 girls whose scores were not related to phthalates).

Although they evaluated Korean children as old as 8–11 years of age, so that their exposure values during early development were lacking, Kim et al (47) nevertheless were able to show an association between urinary metabolites of DEHP (diethyl hexyl phthalate) and teacher ratings on a validated scale of ADHD symptoms. In addition, using a Korean version of the Continuous Performance Test, they found an association between performance and DBP (di butyl phthalate) metabolites. This classic test measures errors of omission and commission when responding to a computer display requiring either emitting a response or inhibiting a response. Despite the mass of evidence showing that boys are about four times as likely as girls to suffer from ADHD (19), the authors failed to analyze the data by sex.

A study conducted by Engel et al (48) centered on the neonate. These investigators measured performance on the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) of children within 5 days of delivery. They correlated performance with concentrations of metabolites of 7 phthalate esters collected in maternal urine between 25 and 40 weeks’ gestation. They also found sexually dimorphic effects; in this instance, the girls showed a a significant linear decline in adjusted mean Orientation score (attention to visual and auditory stimuli and quality of overall alertness) with increasing urinary concentrations of high molecular weight phthalate metabolites. The girls also displayed a strong linear decline in their adjusted mean Quality of Alertness score (a subscale of the Orientation score). Also, the boys and girls showed opposite patterns of association between low and high molecular weight phthalate metabolite concentrations and motor performance. Such complex patterns suggest that the strong focus on male susceptibility to phthalates needs revision, and that female patterns of adverse effects need further exploration.

A recently published paper suggested that developmental phthalate exposure could be a risk factor for autism spectrum disorders. It grew out of a project in Sweden devoted to factors in the indoor environment potentially associated with asthma and allergies in children (49). In the course of these investigations, the investigators (50) discovered that floor coverings containing phthalates, notably PVC tiles, a common flooring material, showed an association with a medical diagnosis of autism. It is one of the rare instances in which an environmental chemical has shown such an association, and has spurred further studies by the authors to confirm and amplify these unexpected findings.

The message conveyed by the phthalate data should be seen as profound and disturbing. It reflects permanent changes in brain anatomy and function that will shape a lifetime of decisions, predilections, even neurological disorders.

The other plasticizer currently evoking wide interest, and discussed in the section on effects in animals, is bisphenol A. Braun et al (51) conducted the first study demonstrating a connection between human fetal exposure and neurobehavioral outcome. They assessed children’s behavior at two years of age, using a parent questionnaire that explores the child’s

adaptive and problem behaviors in community and home settings. Girls whose mothers had the higher levels of BPA metabolites in urine early in pregnancy tended to become somewhat more aggressive than normal (externalizing behavior). These data are plotted in Figure 13.

Hormones, Neurogenesis, and Aging

Although the neurobehavioral consequences of EED exposure early in life present serious societal problems, in some ways their depth and scope may be hugely magnified late in life. In one scenario, the damage inflicted during early development remains silent until, with aging, the compensatory capacity of the brain has eroded and the latent damage emerges as functional impairment ("silent damage" (52)). Under a related scenario, EED exposures during advanced age amplify the normal effects of dwindling hormonal production. In both instances, the cost is an elevated risk of neurological disorders and neurodegenerative diseases such as dementia because both estrogens and androgens serve as sex-specific protective mantles. Magnified hormonal insufficiencies or distortions would exact an even more disastrous economic toll than what is now predicted with an aging population. Cognitive declines, moreover, although they may not be classified as disease, also strain societal resources and stability. In this section, I try to assemble and integrate a variety of data pointing to the potential impact of EEDs on neurobehavioral function, especially cognition, during aging. Cognition refers to processes such as executive function, memory, learning, attention, and similar qualities.

The first question to consider is the mechanistic source of such declines in function. Although some areas of the brain, such as substantia nigra, gradually lose nerve cells, for sites such as the cerebral cortex and hippocampus, such losses are difficult to document. A more apparent loss can be seen in measures such as the complexity of dendritic branching and density of dendritic spines. Hof and Morrisson (53) illustrated the marked differences in dendritic complexity and spinal density from prefrontal cortex between young and old macaque monkeys. They also reviewed some of the data demonstrating the crucial role of estrogen in restoring losses in dendritic spine density evoked by ovariectomy (54)(55). This finding can be linked to a new appreciation of the adaptability of the aging brain.

Some of the more common, less dramatic, accompaniments of aging, such as impaired memory, may arise from a diminished capacity for neurogenesis and synaptogenesis, which grow less potent with time, but are still retained. Their retention is a crucial element in maintaining neurobehavioral function as we age.

Until about 15 years ago, the possibility of neurogenesis (which I will use to also describe synaptogenesis) in the adult brain was mostly dismissed except for regions such as the olfactory bulb. The prevailing dictum, following authorities such as Ramon y Cajal, asserted, in essence, "Use it and lose it." Almost all neuroscientists and clinicians accepted his view that, "…in the adult centers the nerve paths are something fixed, ended and immutable. Everything may die, nothing may be regenerated."

The year 1998 provided the culmination of a stream of research that contradicted that dogma. Kempermann and Gage (56), in discussing a paper showing for the first time the occurrence of neurogenesis in the primate brain, wrote, "A recent paper… describes the generation of new nerve cells in the brains of adult… monkeys…[the] old dogma…that the mature brain cannot produce new nerve cells [is obsolete]." The other publication (57) provided evidence in humans: "Our study demonstrates that cell genesis occurs in human brains throughout life (average age of 64.4 ± 2.9 years)." Additional history is given by Gross (58).

A number of other developments, including new methods for tracing neurogenesis, also came together to overthrow that dogma. Alvarez-Buylla and Lim (59) presented the new view in this way: “It is now becoming clear that pieces of the embryonic developmental puzzle are retained for adult neurogenesis.” Accompanying this revised view are data supporting the idea that continuing to challenge the brain by intellectual activities helps to maintain its vigor (60). The new view has been adopted by the public. Substantial sums are now being spent on methods and instruments, such as computer-based games, allegedly designed to foster brain activity.

The element of neurogenesis that has earned insufficient attention from neuroscientists is the part played by hormones (61). The underlying processes are known to depend, in part, on endocrine mechanisms, particularly the gonadal hormones estrogen and testosterone. Their roles in neurogenesis, in fact, were among the sources of data demonstrating that the process endured beyond early development (62), (63), (64). The earlier papers demonstrated that the reduced density of apical dendrites in the brains of ovariectomized female rats could be restored by administering estradiol. More recently, Tanapat et al (65) showed that estradiol administration to such rats also increased the number of BrdU-labeled cells in the dentate gyrus. In parallel, (66) Leranth et al reported that the administration of testosterone to gonadectomized male rats restored synaptic spine density in the CA1 hippocampal subfield.

Gonadal hormone levels, along with neurogenic capacity, also wane with aging, as seen clearly in women after menopause, but in men as well (67). Depressed androgen levels are an apparent risk factor for impaired cognitive function (68) (69) (70) (71)) and for Alzheimer’s disease (72). One example comes from Yaffe et al (68), who examined the relationship between the levels of free testosterone (low, middle, and high) and scores on three neuropsychological tests. These data are shown in Figure 14.

The current status of knowledge about the relationships among testosterone, aging, and brain function is given in Figure 15.

We now know that supplemental doses can enhance both neurogenesis and synaptogenesis in males (73) and, under most, but not all circumstances, enhance neurobehavioral function in older men.

One phase of the Women’s Health Initiative (WHI) was undertaken to study the effects of hormone replacement therapy in postmenopausal women. When first planned, it foresaw beneficial effects on cognitive function (74) (75), a prediction also supported by research in adult and aging animals (66) (53). For example, in nonhuman primates, estrogen treatment enhanced delayed response performance and increased dendritic spine density in the hippocampus. In humans, these publications demonstrated effects such as:

- Women receiving *monthly* estradiol injections following surgery performed better than women who received placebo injections
- Women who began treatment early after menopause experienced a lower risk of dementia than those who had initiated treatment later
- Women who initiated hormone therapy before age 56 performed better than late initiators and women who had never adopted hormone therapy
- Impairment of memory after ovary removal could be prevented with early estrogen treatment
- On the basis of voxel-based morphometry, HRT appeared to spare gray matter in some cortical regions and maintain hippocampal volume

The WHI memory study seemed to indicate, in conflict with the studies cited above, that, in the form of equine estrogens, hormone replacement therapy exerted adverse consequences on cognitive function rather that enhancing it (76) (77). These effects, their conclusions, and their translation into clinical practice generated a torrent of debate and questions. It is now becoming increasingly apparent that the investigation was flawed. Its population consisted of women between 65 and 79 years of age, a long period since the onset of menopause. Because of the beneficial effects noted above in women who adopted hormone replacement therapy at the advent of menopause, the discrepancies stimulated a reexamination of the WHI study. Many investigators now term this discrepancy a “window of opportunity” effect (61). That is, early adoption is associated with beneficial effects. Delayed adoption incurs adverse effects. MacLennan et al (78) conducted a study, based on several neuropsychological tests, to examine this possibility. In general, early initiators outperformed never users and late initiators. as summarized in Figure 16. These findings support the “window of opportunity” argument.

Because of the overwhelming emphasis on developmental outcomes, we know rather little about how EEDs might alter function in the aging brain. What is clear is that gonadal steroids are crucial to its maintenance. The literature indicates that functional changes induced by gonadal steroids are accompanied by alterations in neuron and synapse numbers, as well as in dendritic and synaptic morphology. This research demonstrates the roles of both estradiol and testosterone in supporting synaptic plasticity in various brain areas.

One group of investigators undertook to investigate how bisphenol A might alter neuro- and synaptogenesis in adult brains, a choice derived from its estrogenic properties. They have now shown that bisphenol A interferes with this process at dose levels presumed free from adverse effects by the USEPA. Three aspects of this action are worthy of attention:

- It inhibits hippocampal synaptogenesis induced by estradiol in ovariectomized rats (79).
- It prevents synaptogenesis induced by testosterone in both control and gonadectomized adult male rats in the hippocampus and prefrontal cortex (80).
- It prevents synaptogenesis, induced by estradiol, in the hippocampus and prefrontal cortex of ovariectomized female monkeys (80).

These investigations hardly begin to foreshadow the health and societal threats posed by EEDs over the lifetime. We already know that phthalates diminish testosterone levels in adult men (81) and are associated with increased waist circumference and type 2 diabetes as well (82) while bisphenol A is associated with cardiovascular disease (83). What we can take away from the entire body of evidence on EEDs is their ability to interfere with our ability to function from conception to senescence and even to succeeding generations. The brain is the target, to most of us, presenting the greatest vulnerabilities. The threats to us as individuals and as members of the community are still largely unrecognized.

For clinicians, the quandary is how to respond to and incorporate this array of scientific findings. For example, would hormone supplements help delay the onset of dementia? For women, although some evidence points to positive effects of estrogen supplements during the immediate postmenopausal transition, most clinicians would continue to be cautious. For men, although testosterone supplements might argued as a reasonable preventive approach, some authorities question the usefulness and safety of such a course of treatment (84). Perhaps the best strategy for concerned clinicians is to advise patients to consume a healthy diet (because certain foods, such as high-fat meats) tend to contain higher concentrations of these chemicals), maintain a healthy weight, because fat stores collect chemicals such as dioxins and polychlorinated bibenyls, and because obesity itself, another condition linked to

endocrine disruption, is also a risk factor for cognitive decline. And neurogenesis, we know, is fostered by continuing physical and intellectual activity.

Acknowledgments

FUNDING. Author's support provided in part by research grant RC2 ES018736 and Center grant ES01247 from the National Institute of Environmental Health Sciences. No funding sources had any role in the writing of this article.

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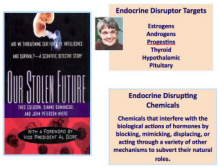

FIGURE 1.

OUR STOLEN FUTURE (13) became the launching point for engaging both the scientific and general publics in reflecting on how the mass of chemicals in the environment might be altering how our own endocrine systems.

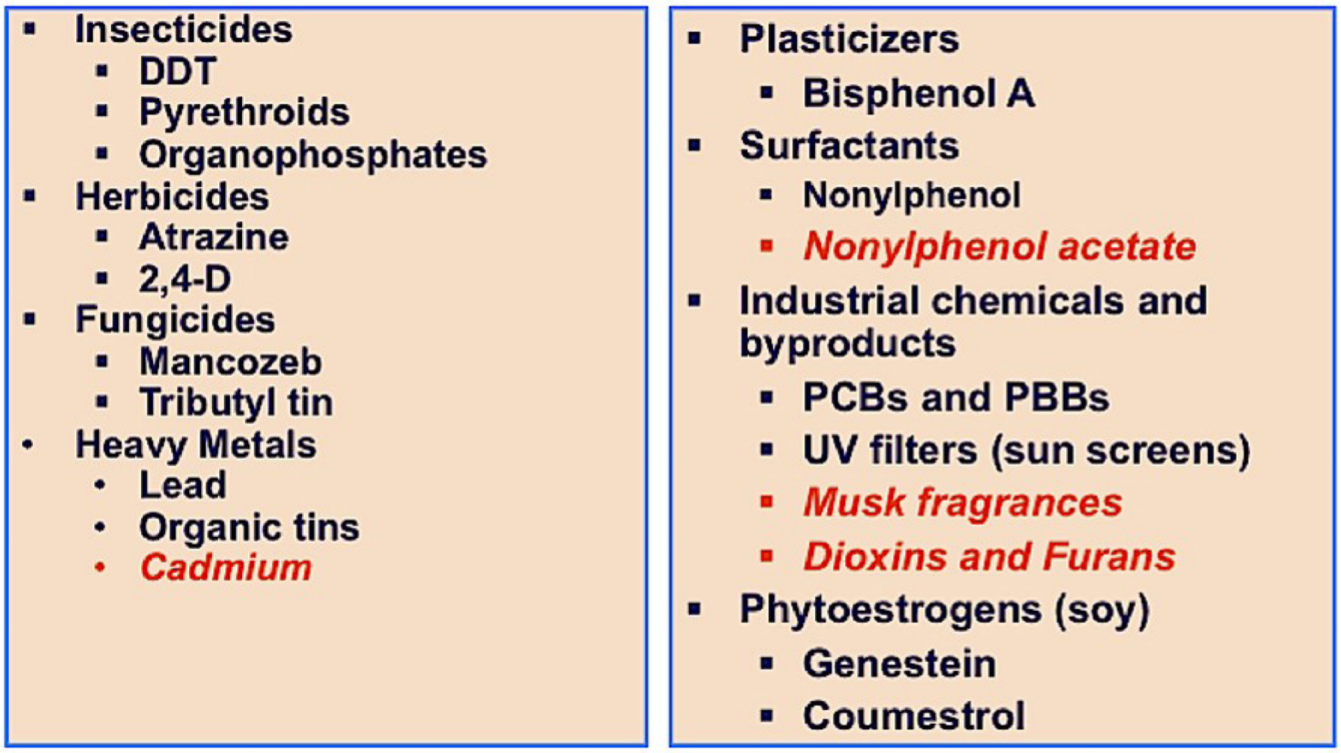

FIGURE 2.
A partial list of environmental estrogens, estrogen mimics, and antiestrogens. It embraces a wide variety of chemical classes.

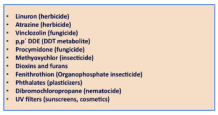

FIGURE 3.

A partial list of environmental chemicals with antiandrogenic actions. Some of these, such as dioxins, can act as both antiestrogens and antiandrogens.

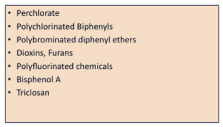

FIGURE 4.
Environmental chemicals identified as interfering with the function of thyroid hormones.

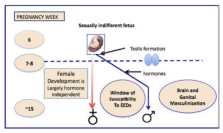

FIGURE 5.

Diagram to display the events and their occurrence in time that characterize human fetal development. The female fetus is considered the default structure, so to speak. In company with the templates erected earlier by genetic programming, sexual differentiation of the brain is thought to begin at about 8 weeks gestation, when the male testis begins to secrete testosterone. The “window of susceptibility to EEDs” begins when this differentiation process is initiated.

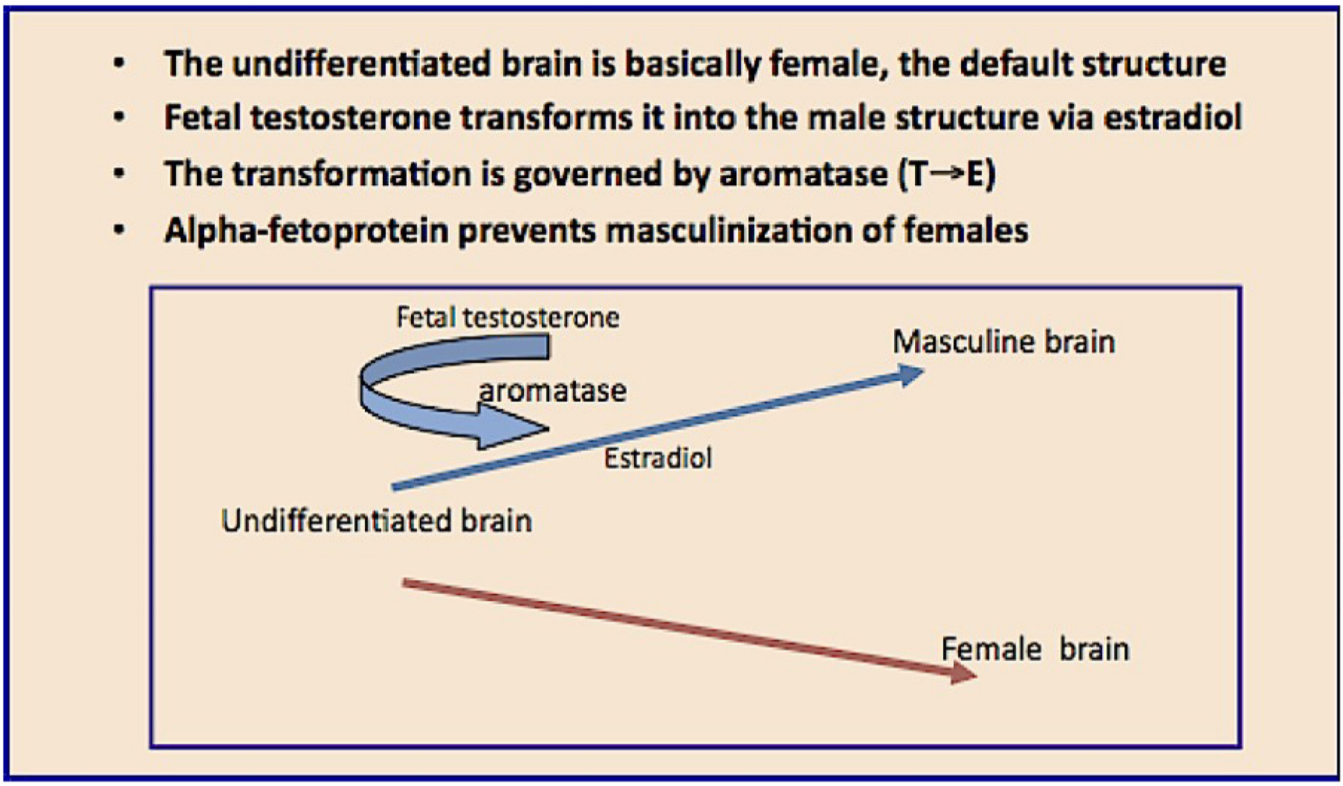

FIGURE 6.

In the rodent brain, which serves as the predominant model in neuroscience research, sexual differentiation is determined by the conversion of testosterone to estradiol. Male rodents deficient in aromatase (CYP 19) exhibit aberrant behaviors such as absence of copulatory activity.

FIGURE 7.
Factors that are sexually dimorphic and depend on the hormonal environment during gestation.

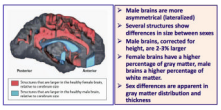

FIGURE 8.

Differences between male and female brains, based on both the rodent and human literature. Left: Detailed structural differences between male and female brains based on MRI (85). Right: List of male-female differences in brain anatomy.

FIGURE 9.
Sources of exposure to the plasticizer Bisphenol A. Produced originally as an estrogen, it subsequently found use in many products.

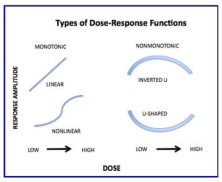

FIGURE 10.

Dose-response functions can take many different forms. The traditional assumption, that virtually all conform to the linear monotonic variety is untenable with endocrine-active drugs. Sex steroids are notorious for departing from the traditional model. However, such departures are common with other substances as well.

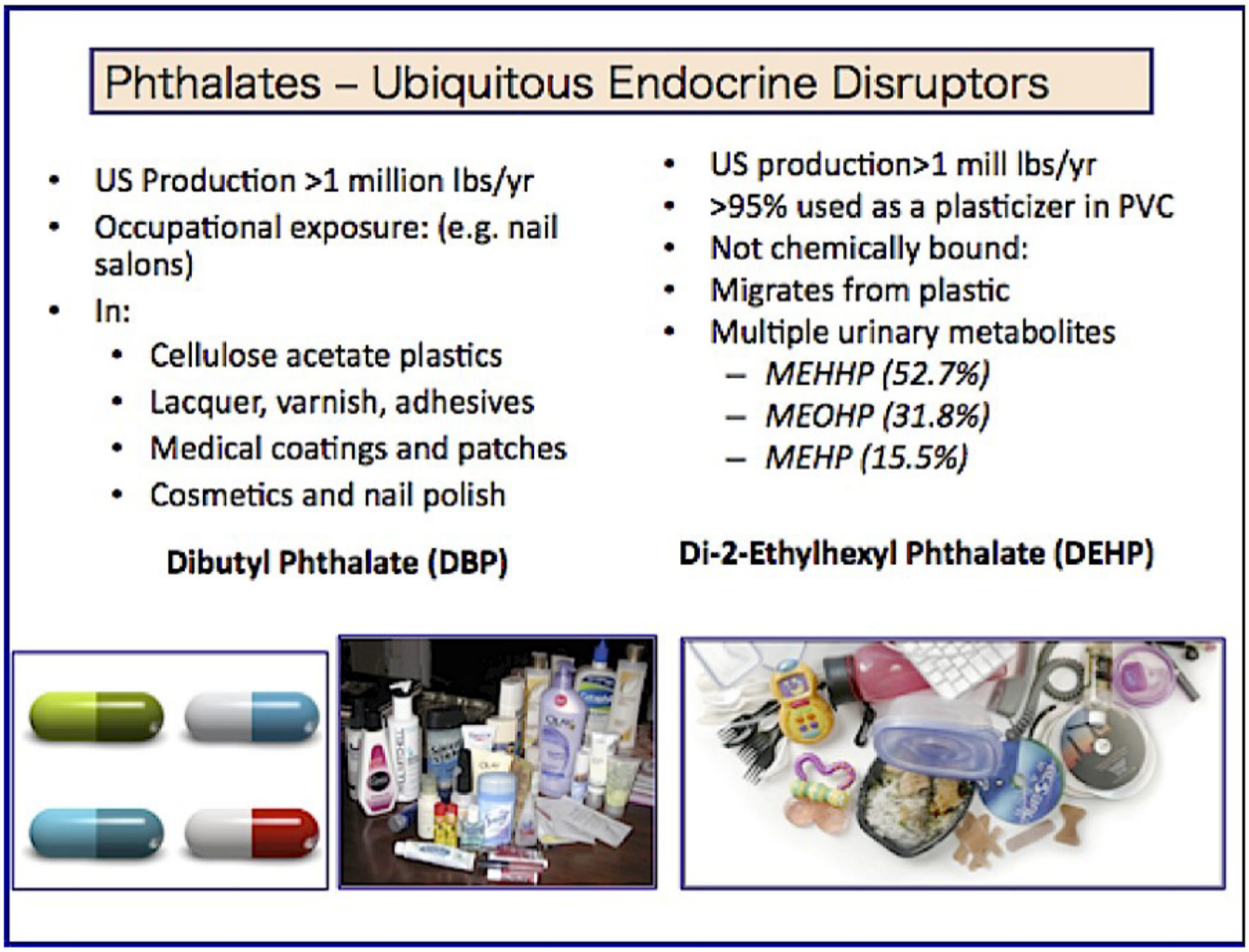

FIGURE 11.

Phthalate esters are used in a startling number of industrial and consumer products. For example, perfumes, hair sprays, soaps, shampoos, nail polish, food packaging, plastic wrap, detergents, adhesives, pesticides (“inert” ingredients), medical tubing, skin moisturizers, raincoats, shower curtains, PVC flooring. The two most common are dibutyl phthalate and di-2-ethylhexyl phthalate.

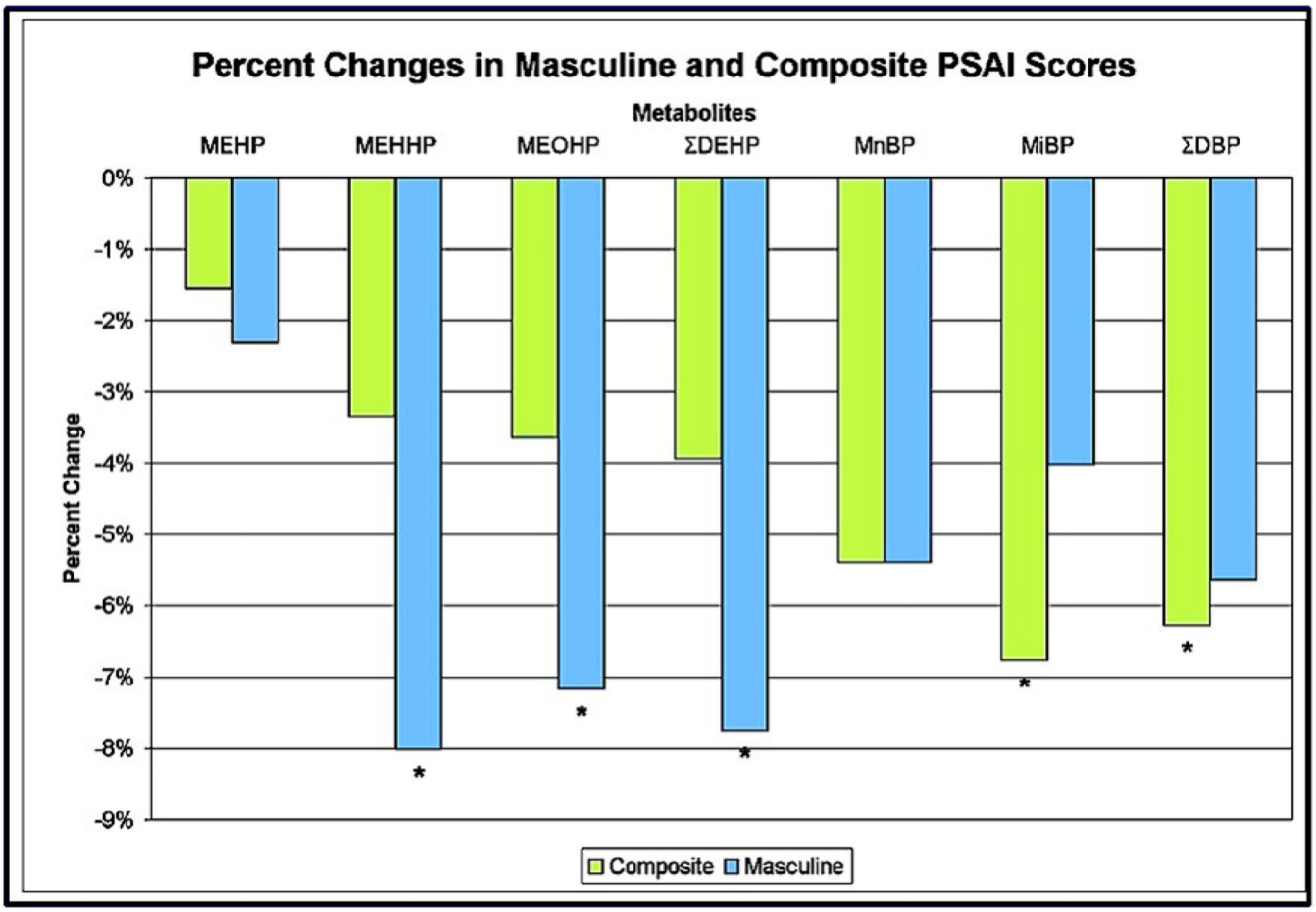

FIGURE 12.

Relationship Between Phthalate Metabolites in Maternal Urine and Masculine Behavior in Male Children (44). Percent change=change in expected score if metabolite concentration is increased from 10th to 90th percentile. The PSAI provides a masculine score (e.g., items such as likes to play with trucks), a feminine score (e.g., likes to play with dolls), and a composite score (feminine minus masculine scores).

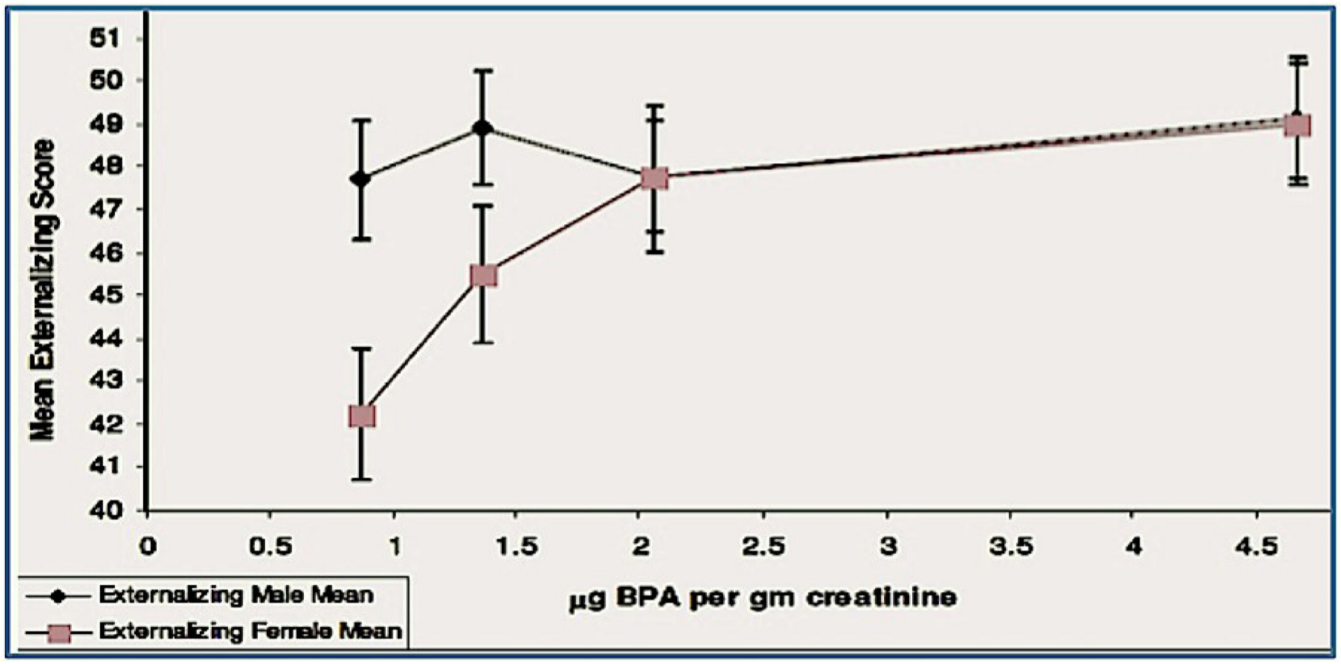

FIGURE 13.

Externalizing scores in children 2 years of age. Based on Braun et al (2009). The chart plots the relationship between concentrations of Bisphenol A in maternal urine at 16 weeks gestation and parent rating scores from the Behavioral Assessment System for Children. *Externalizing Behavior*: Behavior manifested outwardly. Externalizing disorders include aggression, delinquency, hyperactivity. The typical sex difference disappears at the higher levels of exposure.

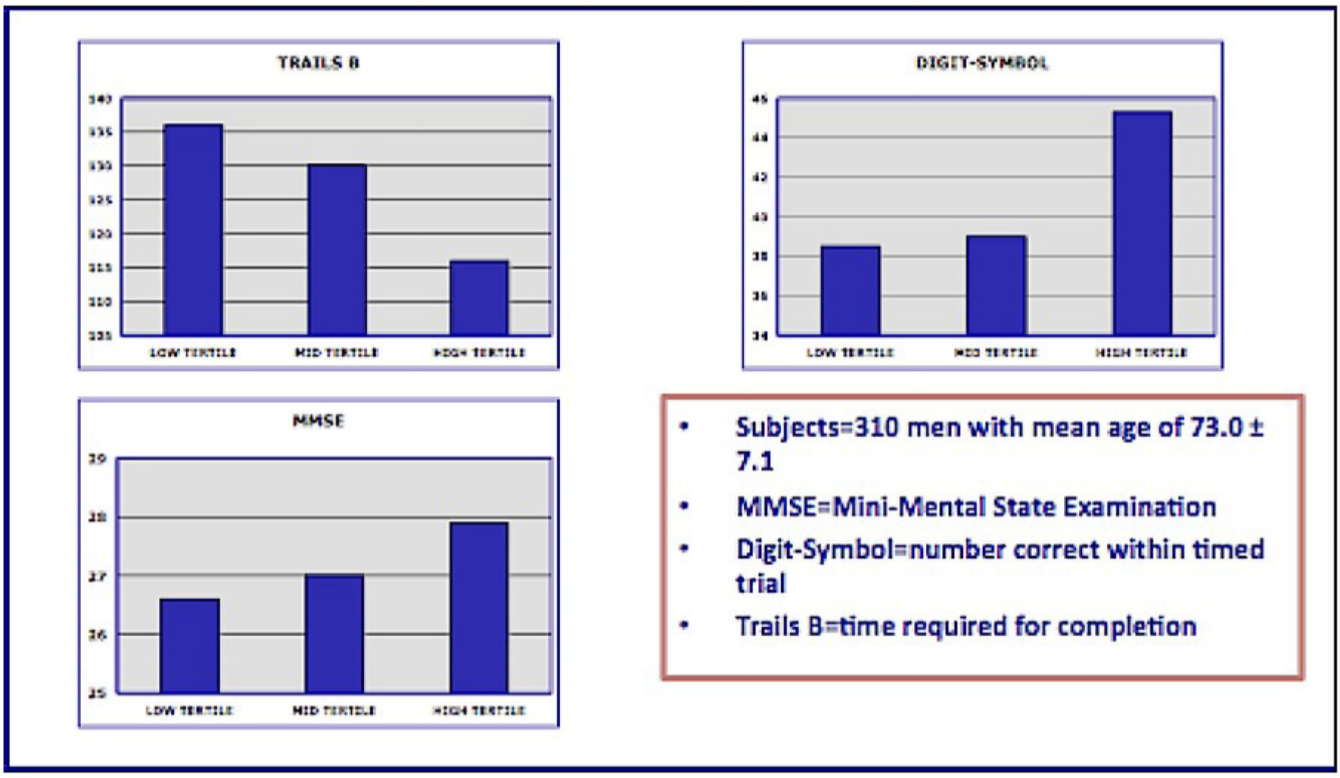

FIGURE 14.
Performance of men on three neuropsychological tests plotted against testosterone concentration (low, medium, high). The higher the concentration, the better the performance. Based on Yaffe et al (2002).

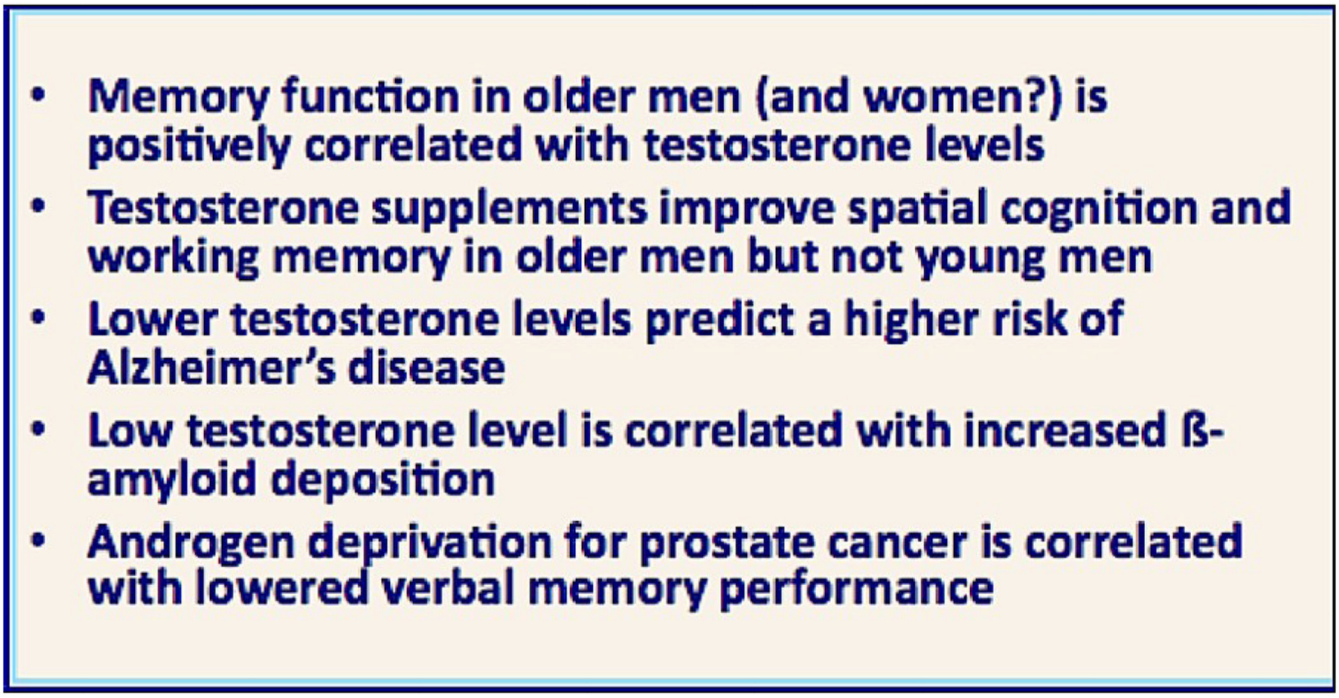

FIGURE 15.
Summary of findings from the current literature relating testosterone to cognitive function in men.

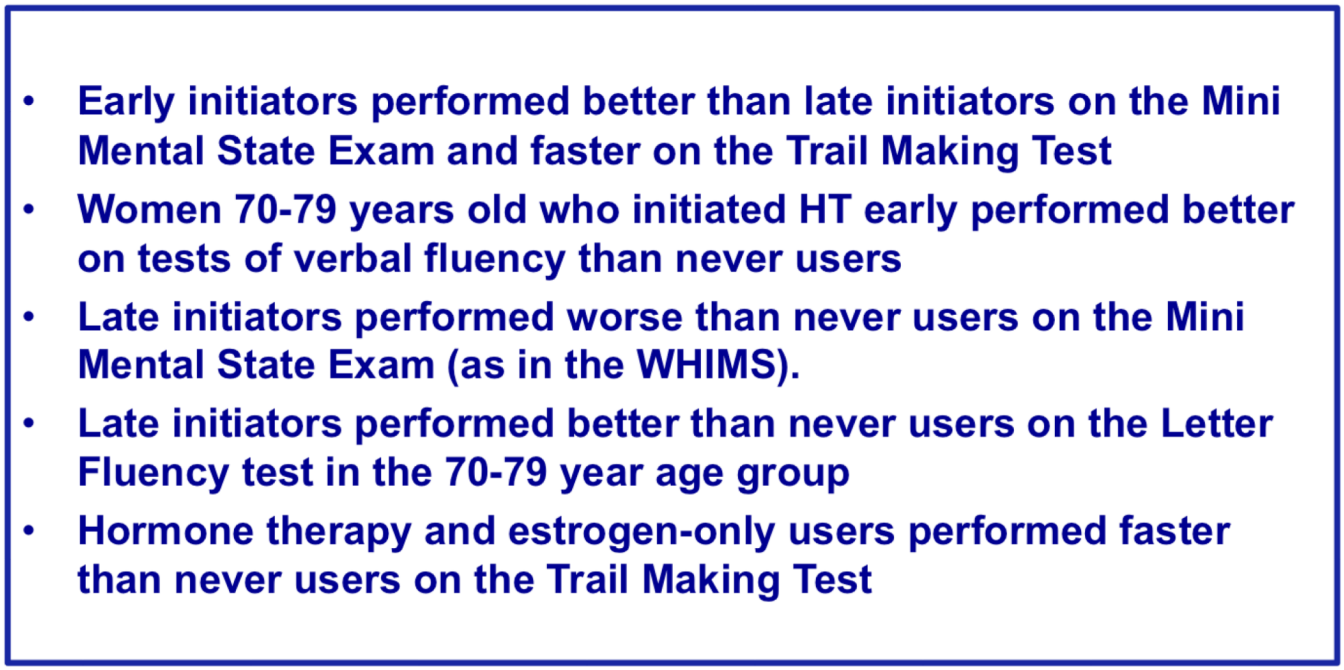

FIGURE 16.
Summary of findings from the REMEMBER study (78), which was designed to investigate the timing of initiation, and duration, of hormone therapy.
current literature relating estrogen treatment to cognitive function in women. The literature indicating beneficial effects from hormone replacement therapy in younger women and adverse effects in older women is characterized as a “window of opportunity” phenomenon.