Epigenetics, Evolution, Endocrine Disruption, Health, and Disease

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Endocrine-disrupting chemicals (EDCs) in the environment have been linked to human health and disease. This is particularly evident in compounds that mimic the effects of estrogens. Exposure to EDCs early in life can increase risk levels of compromised physical and mental health. Epigenetic mechanisms have been implicated in this process. Transgenerational consequences of EDC exposure is also discussed in both a proximate (mechanism) and ultimate (evolution) context as well as recent work suggesting how such transmission might become incorporated into the genome and subject to selection. We suggest a perspective for exploring and ultimately coming to understand diseases that may have environmental or endocrine origins. (Endocrinology 147: S4–S10, 2006)

“Genetics proposes, epigenetics disposes.”
—Medawar and Medawar (1)

Endocrine-disrupting chemicals (EDCs) are compounds in the external environment that mimic or block endogenous hormones. In other words, they behave as biological signals and, as such, can be misinterpreted by the organism. To date, the vast majority of known EDCs are those that activate the parts of the endocrine system associated with the steroid/retinoid/thyroid super-family of receptors, most often receptors related to the hormone estrogen that are found in all vertebrates. Also, many other species, such as crustaceans and mollusks, respond to estrogen, and, surprisingly, plants, corals, and at least one fungus make estrogen-like molecules. Environmental contaminants such as the ortho, para isomer of dichlorodiphenyltrichloroethane (DDT), some hydroxylated polychlorinated biphenyls (PCBs), the plasticizer bis-pheno A, and some detergents such as p-nonylphenol, can exhibit estrogenic activity (2).

In this article, we will discuss some aspects of evolution that may help to explain why so many EDCs produce a signal that is interpreted by vertebrate systems as being estrogen. To understand what effect they might have, the individual’s social and biological environment, namely its ecology, must be considered. This ecology includes interactions between and within species; for example, symbiotic signaling, predatory-prey interactions, males and females during mating, mother-embryo interactions, and, in mammals, even embryo-embryo interactions. Environmental signal disruption principles also apply to far less mobile species (e.g. plants, corals, crustaceans, and mollusks).

To understand the process by which these chemicals work we must look to the gene. Like an organism, a gene is not expressed in isolation but rather in the context of other genes and their products, cells, and tissues in a temporal/spatial dimension (3). This might be thought of as the ecology of gene expression. It is well known that EDCs, and very likely endogenous hormones, can act on a gene’s developmental mechanisms, altering phenotype expression. We are now seeing that the mechanism of these phenotypic changes is probably epigenetic; in other words, they cause mitotically heritable changes in gene function without changing the DNA sequence, i.e. without mutation. In fact, EDCs do not act on genes alone but on developmental mechanisms that integrate genetic and epigenetic interactions, resulting in the phenotype.

One mechanism for inducing epigenetic change is through DNA methylation, a process by which methyl groups are added to the base cytosine in DNA, usually suppressing expression of the gene. In most studies, increased DNA methylation is associated with gene silencing and decreased methylation is associated with gene activation. Currently, a handful of papers have implicated EDCs in epigenetic programming and DNA methylation (4–7). These changes, when they occur during certain stages of development, are permanent and can be inherited by offspring (6, 8, 9). This inevitably leads us to consider whether such epigenetic changes can be subject to selection.
Epigenetics

Before the 1940s, the gene as the unit of heritable material was a theoretical concept without a physical identity. In 1942, C. H. Waddington (10) reintroduced the term epigenetics from classical embryology, ascribing to it the manifold ways that gene action and expression give rise to the phenotype (11). In developmental genetics today, however, the definition has become far more narrow and specific, referring principally to DNA-related mechanisms of inheritance such as methylation and chromatin remodeling resulting in the monoallelic silencing of genes in early mammalian development. This relatively recent area of research focuses on processes such as DNA methylation and histone modifications that are heritable in the short term but do not change the DNA or create mutations. Because manipulation of methylation patterns is often lethal, or at the least results in maladaptive traits or monsters, this method of research illuminates normal development by creating abnormalities or anomalies. Furthermore, although mechanisms such as DNA methylation are clearly involved in genomic imprinting, the signal for the imprint is not yet known.

Might natural hormones or EDCs be one of the signals? Hormones are known to epigenetically imprint genes in nonmammalian vertebrates. Work on epigenetic memory with the vitellogenin gene in frogs (12) shows that hormonal treatments early in life alter the response of hormonally regulated genes to the same or different hormones later in life. The first hormonal experience epigenetically alters the set point for the later hormone response. This process can be determined, in frogs, by methylation (13). The term epigenetic imprinting has also been used to describe a process in which estrogens in development cause persistent alterations in gene expression and reprogram cell fate (5, 14, 15). It has also been used to describe gene silencing observed in the carcinogenic process as well.

Epigenetic imprinting by EDCs or other hormones represents one potential mechanism for Waddington’s concept of genetic assimilation, a direct outgrowth of his research in epigenetics. Based in part on his work with Drosophila, Waddington (10, 16) speculated that environmentally induced changes in phenotype could become incorporated into the genome as evidenced by the persistence of the phenotype even after the original selection pressure is relaxed. It is in this manner that selection might act on developmental pathways leading to adaptive change in the genome in conjunction with genetic mutation. Evidence has emerged in recent years that epigenetically mediated changes in phenotype can be stable over many generations. Indeed, in the annually reproducing plant Linaria vulgaris, an epigenetically determined variant has been maintained for over 250 yr (17). Furthermore, Ruden and colleagues (18) have documented epigenetic change that can be assimilated in Drosophila. As they point out, gene-associated tandem repeat expansions and contractions as well as retrotransposon mobilizations are epigenetically up-regulated during times of environmental and hormonal stress. Because such events can occur at rates up to 100,000 times higher than point mutations, this class of mutation potentially has a much greater effect on morphological evolution than do point mutations (19). This has led Ruden et al. (20) to suggest that the regulation of the CpG methylation status of repetitive sequences in germ cells could increase the rate of morphological variation and thereby the rate of morphological evolution.

 Likewise, Holliday (21, 22) has proposed that teratogens and, indeed, hormones could work through patterns of DNA methylation in the embryo, which may lead to developmental alteration in the offspring with persistent changes in the germ line. With regard to exogenous compounds altering genomically imprinted genes, in vitro incubation of preimplantation mouse blastocysts with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, or dioxin) alters the pattern of DNA methylation in specific genes. H19 and IGF-2, the affected genes, are also embryonically imprinted genes. TCDD, although not a ligand for the estrogen receptors (ERα or -β), has numerous associations with estrogen action at the molecular as well as functional levels, e.g. dioxin receptor (AhR) interacting with the ERα or -β (23, 24) or TCDD-associated endometriosis in treated primates (25).

That epigenetic mechanisms may play a role in endocrine disruption helps explain the transgenerational effects of some hormonally active chemicals. Treatment with diethylstilbestrol (DES) during pregnancy results in vaginal adenocarcinoma in female offspring in humans (26) and mice (27). Female offspring of mice exposed to DES during pregnancy, when mated to control males, produce a second generation of females who, although not exposed to DES themselves, express this same rare genital tract cancer (8). This transgenerational transmission of a specific reproductive tract lesion would be hard to explain without invoking an epigenetic mechanism for heritable change and, given the finding of altered DNA methylation patterns in a specific uterine gene in mice treated developmentally with DES (4), we think a strong case can be made for such a conclusion. Newbold and colleagues (9) next showed that specific, rare genital tract cancers (rete testes cancers) are also expressed and therefore transmitted to the male offspring of females treated in utero with DES. In colloquial terms, this demonstrated the occurrence of reproductive tract tumors in the grandsons and granddaughters of mothers treated with DES. A possible mechanism for how DES exerts its action epigenetically has been proposed recently (28). The transmission of uniquely specific changes in the program of development in mice has implications for similarly exposed humans as well as the biology of hormonally induced disease.

It is likely that the transgenerational epigenetic effects seen with the environmental estrogen DES also occur with other EDCs. Rats treated with the estrogenic pesticide methoxychlor or the antiandrogenic fungicide vinclozolin during pregnancy produce male offspring that have decreased sperm capacity and fertility (6). Remarkably, the compromised fertility is passed through the adult male germ line for four generations with high penetrance. The authors demonstrated altered patterns of DNA methylation in the germ cells of generations two and three. Interestingly, individuals initially are fertile, but with age, fertility is reduced. This study is an elegant demonstration of epigenetic alteration in genes apparently important to reproductive function by two kinds of EDCs in an age-dependent manner.
Evolution

According to neo-Darwinian Modern Synthesis, natural selection of heritable variation results in small but cumulative genetic changes. This gene-based theory has served adequately for explaining extant species, but it does not entirely explain observed variation (29, 30). New developments in evolutionary theory, or what some have termed the Second Synthesis, consider the interplay of genes and the environment along with development, especially the emergent nature of development. However, most studies continue to be restricted to narrow windows of embryonic development or, at the most, to a single life-history stage. They do not take into consideration the cumulative nature of critical experiences throughout the life cycle. This requires giving careful thought to an additional dimension, namely the social environment in which the individual lives, which itself has a genetic basis that can evolve.

Morphological evolution results from mutation and selection such that gene-level changes are incorporated into the genome. Another mechanism may also exist, namely the epigenetic regulation of tandem repeat expansions and contractions that occur in the germ line during times of stress (20, 31). An example of epigenetic variation whereby the environment induces stable phenotypic changes without any genetic change is that of ectopic bristle outgrowth from the eye in Drosophila (18). Similar processes may occur in the evolution of other, interdependent complex traits. That is, the individual, with its adapted morphological, physiological, and behavioral traits, can be both a result and a cause of evolutionary change.

The ability of the genotype to produce different phenotypes in response to different environments has been termed plasticity. Commonly, the time of maximal plasticity appears to be during development; however, the individual’s capacity to respond to environmental change or insult with heritable phenotypic variation at a later stage may also be possible. This ability to facilitate change has been termed adaptability (32). It is likely that suites of genes underlie the fundamental plasticity of an organism, particularly during development or life-history transitions. This characteristic of trait variability, whether molecular, cellular, physiological, morphological, or behavioral, represents the leading edge of evolution.

Epigenomic regulation of a network of genes and their products more accurately reflects the evolutionary process, particularly as it relates to the heritability of complex traits (29, 33). In this instance, new traits are constructed as the constituent genes, and their products interact in a temporal, spatial, and conditional (tissue or external environment) context (34). The adaptive responses that emerge in turn set the stage for future variation. In this manner, evolution can be a tandem process involving first development, with its built-in flexible responsiveness to both gene products and environment, followed by selection, which dictates which variants are spread and maintained (35). In this sense, it might be said that the “genome learns from its experience” (36).

How likely is it that EDCs and other environmental signals could actually contribute to the process of evolution? In this present context, it is the persistence of the challenge of EDCs that yields to altered function over generations. For example, phytoestrogens (estrogenic compounds found in leguminous plants) can globally alter the pattern of methylation in mice exposed in utero (7). We have already mentioned that DES treatment of mice during development results in reproductive tract cancers, persistent up-regulation of key estrogen-responsive genes, and altered patterns of gene methylation in the affected genes (4) and that the cancer can be transmitted through two generations. In addition to DES, methoxychlor has been reported to increase global DNA methylation in uterine ribosomal DNA after in utero exposure; the alteration in methylation remains months after treatment (5). Recently, methoxychlor has been reported to alter the expression of Hox genes involved in the developmental patterning of the uterus (15). The finding that male infertility associated with prenatal exposure to the EDCs methoxychlor or vinclozolin in rats extends through four generations and is accompanied by altered methylation patterns in germ-cell DNA (6) suggests that EDCs have at least the potential for long-term change consistent with being a substrate for evolution. These and other studies provide insight into the mechanisms for epigenetic change that can be incorporated into a heritable system with functional significance in development.

A plausible scenario for the way in which EDCs may influence changes that lead to epigenetic inheritance is that EDC exposure might involve their ability to mimic the action of endogenous estrogens or by stressing the embryo by altering Hsp90 (20, 37). This in turn can result in methylation of imprinted genes during embryogenesis such that developmental pathways are affected. Consequent changes in DNA methylation patterns at CpG islands would be persistent and heritable. These CpG sites are often associated with 5’ promoter regions of transcription factors and have a higher probability of undergoing mutation than other regions of the genome. But evidence suggesting that EDCs might reprogram methylation patterns that are then incorporated into the germ line, and hence transmitted to future generations, is still sparse.

This brings us to the role of behavioral plasticity in evolutionary change. Animals typically respond to changes in the environment by modifying their behavior, thereby changing their environment. Over generations, consequent modifications in anatomy, physiology, and patterns of gene regulation can arise out of the new environment’s impact on the developmental processes associated with the new behavior. Such actions can be independent of mutational changes in the genotype. The “changes in behavior create the new variants on which natural selection works” (38). This is seen particularly clearly with sexual and reproductive behaviors (39). In nature, individuals (particularly females) actively discriminate and choose among potential mates; successful mating requires a reciprocal synchronicity in behavior and physiology among males and females (40). We know that EDCs influence the behavior of animals both in nature and in the lab (41, 42); might they also influence the embryo’s developing nervous system such that, in adulthood, the individual’s ability to discriminate and choose between possible mates is compromised? Extrapolating from altered behaviors to evolutionary significance is straightforward.


Endocrine Disruption

Endocrine disruption has been shown to be both acute (reversible) and long term, depending on the developmental stage at which the chemical is seen by the organism. Certainly, the acute effects of environmental estrogen in stimulating a target in an adult organism, such as vitellogenin induction by p-nonylphenol or bisphenol A in male fish, frogs, reptiles, or birds (2) shows the power of environmental signaling. However, what is truly compelling are examples of permanent sex reversal such as that seen in turtles exposed early in development to PCBs (43) or the occurrence of pseudohermaphroditic polar bears in EDC-contaminated areas (44). There is a relationship between the developmental features of estrogen disruption and the evolutionary basis for this effect. This is a property of an evolutionarily ancient functional relationship between estrogen and the estrogen receptor.

We are struck by the conservation of certain portions of the ERα across metazoans, specifically the DNA-binding domain and, to a lesser extent, the ligand-binding domain. Moreover, analysis of the evolution of the nuclear receptor gene family suggests that this ancestral receptor is functionally similar to the ER (45), raising the possibility that the signaling motif is evolutionarily ancient. We are further struck by the widespread distribution of the functional signal interpreted as estrogen (46). The fact that animals, fungi, and plants have evolved a similar chemical signal that functions as estrogen suggests independent adaptations with separately evolved genes coding for proteins that serve a common function, namely recognition of a ubiquitous environmental compound. Numerous plants contain molecules that activate the vertebrate ER and induce an estrogenic effect in, for example, mice (2). At least one fungus also produces chemicals that fulfill the criteria to be considered estrogens. In fact, it has been shown that the chemicals in plants recognized by vertebrates as estrogens, the phytoestrogens, function as signaling molecules for transcription factors in rhizobial bacteria (47). The result of this symbiotic signal is the migration of bacteria into the root hair and the formation of root nodules with subsequent nitrogen fixation. Fox and colleagues (48) recently showed that environmental chemicals known to disrupt the vertebrate endocrine system would also disrupt the signaling system between alfalfa and Rhizobium meliloti at environmental levels. When looking at a wide range of pesticides and other environmental agents, this group was able to show that estrogenicity of the environmental agent was correlated with the disruption of the symbiotic signaling system (49); the ecological implications are obvious because this signaling system is the root of nitrogen fixation and opens a wholly new area of endocrine disruption. This suggests that the reason the function that we associate with estrogen may be so widely distributed in the environment and nature is because it is an environmentally ancient signal. Perhaps this is why most EDCs are estrogenic, not because estrogen is simply what has been looked for, but because it is the evolutionarily determined signal that is the most ubiquitous.

Health and Disease

In previous sections, we have examined the possibility that hormones or EDCs may function in evolution as epigenetic factors. Here we explore the epigenetic action of exogenous or environmental estrogens in health and disease. It may be that the processes are similar. The relationship of developmental change and evolution has been covered in an earlier section. We expand on that concept here by looking at the manner in which cell differentiation occurs, what role hormones may play, and what altering that process may do.

To understand the role of estrogens in development, there is hardly a more powerful model than that of the outcomes observed in humans and mice developmentally exposed to the synthetic estrogen DES. Female offspring of humans (26) or mice (27) exposed prenatally to DES have a risk for vaginal clear cell adenocarcinoma. The mechanisms underlying these developmentally induced lesions have been sought for three decades. There was the suggestion by clinical investigators that DES had altered the normal differentiation of the epithelial cells of the fetal cervix and vagina such that they responded abnormally to estrogen at puberty, because no cancers had been seen in prepubescent girls. Similarly, ovariectomy of developmentally DES-treated mice prevented the subsequent expression of uterine adenocarcinomas.

Epigenetic change in the molecular program of cell differentiation in the affected tissues may be a common mechanism. The clear cell cancers of the vagina in DES-exposed women displayed genetic instability consistent with epigenetic imprints in the absence of any expected mutation in classical oncogenes or tumor suppressor genes (50). Using a well validated mouse model for DES genital tract tumors, Li and colleagues (4) discovered that one of the estrogen-inducible genes in the mouse uterus, lactotransferrin, that had been shown earlier to be persistently up-regulated by developmental DES exposure, had an altered pattern of CpG methylation in the promoter region of the gene upstream from the estrogen response element. Subsequent work demonstrated that other developmentally up-regulated genes such as fos and jun also had persistent changes in the pattern of methylation of the gene after DES exposure during development (51, 52). These experiments raise the possibility that DES (and other environmental estrogens) alter the program of differentiation of estrogen target cells in the reproductive tract through an epigenetic mechanism.

Other studies support this hypothesis. In addition to cervicovaginal adenocarcinomas in female mice and humans exposed prenatally to DES and uterine adenocarcinoma in mice, it has been shown that developmental exposure to DES results in excess risk of uterine leiomyomas (fibroids) in mice (27), rats (53), and women (54). It was also recently reported that sea lions in areas contaminated with EDCs have a higher prevalence of uterine fibroids (55). The Eker rat carries a germ-line mutation in a tumor suppressor gene and is predisposed to uterine leiomyoma. Cook and colleagues (53) used this model system to demonstrate a DES-induced alteration in developmental imprinting as analyzed by tumor suppressor gene penetrance, concluding that developmental programming by estrogen works in concert with preexisting genetic change. In a population of 819 black and 504 white
women, fibroid status was determined by ultrasound screening or surgical record review, whereas prenatal DES exposure was determined by interview. DES-exposed women had a significantly greater risk for uterine fibroids and tended to have larger tumors. The authors conclude that their study, as well as animal studies, indicate a role for prenatal estrogen in the etiology of uterine leiomyoma in women (54).

In addition to the research linking EDCs, epigenetics, and reproductive disease at the molecular level, a growing body of information suggests that epigenetic effects might extend to gender differences in brain and behavior. Over 70 yr of research with animal models has demonstrated that sex hormones organize the brain perinatally such that the individual’s sexuality is modified to determine how the individual’s perception and learning abilities respond to nonsexual stimuli. Not only does the nature and amount of hormone affect individual development, but also the timing of this hormone exposure is important. However, although the principle of critical periods of hormone sensitivity is well established in animal studies, the data on human behavior are only now being collected (56). It is well known that conditions such as congenital adrenal hyperplasia, resulting in elevated androgens, are associated with disorders such as androgen excess and sexual ambiguity. Congenital adrenal hyperplasia is a disorder characterized by the presence of genetic information that results in increased production of androgens in utero. This increase in androgen levels leads to the masculinization of the external genitalia, resulting in a phenotype that is typically consistent with a male identity. However, it is important to note that the degree of masculinization and the resulting sex of rearing can vary depending on the severity of the disorder and the level of prenatal androgens.

For many psychiatric disorders, there are significant gender differences in relative risk level and severity. In females, the incidence of eating disorders, major depressive disorder, obsessive-compulsive disorder, posttraumatic stress disorder (PTSD), anxiety and panic disorders, seasonal affective disorder, and Alzheimer’s disease and dementia are 2-fold higher or greater than in men. Males are at higher risk for early-onset disorders such as autism and schizophrenia. That these disorders may be modulated by hormones is suggested by the fact that the sex differences manifest after puberty or, in the case of schizophrenia in women, increasing symptoms are experienced during pregnancy and postpartum.

Might these gender differences in disease susceptibility, time of onset of symptoms, and drug response in mental health disorders be maintained in populations exposed to various EDCs, but overall risk levels increased? Alternatively, it is possible that the difference may be abolished, with male risk levels equivalent to that of females. This is an important question that deserves study. There are several reports indicating that both men and women exposed to DES in utero are more prone to depression compared with their unexposed siblings (65–67). Similarly, autism, a disorder more prevalent in males, has increased significantly in recent decades. New research suggests a relationship between high levels of fetal testosterone and autism (68). Aromatase inhibitors increase fetal testosterone, and some classes of endocrine disruptors are known to function as aromatase inhibitors such as the pesticide Roundup as well as some fungicides.

Thus, research indicates that factors such as stress, drugs, and hormones acting during embryogenesis can not only shape the subsequent behavioral phenotype of the individual but also modify the way the individual responds to adult experiences. The clinical significance of this work resides squarely within the concept identified as the fetal basis of adult disease, demonstrating, for example, that malnutrition in the mother during early pregnancy increases the risk in the child of schizophrenia in adulthood (69–73). These disorders are often precipitated by stress, which itself alters the endocrine state. Some of these disorders may be modulated by hormones is suggested by the fact that the sex differences manifest after puberty or, in the case of schizophrenia in women, increasing symptoms are experienced during pregnancy and postpartum.

Building on a long history of research in developmental psychobiology, Meaney (75) has demonstrated that the nature and amount of care a pup receives from the mother modulates its reaction to stress later in life largely through effects on the glucocorticoid receptor (GR) in the hippocampus. This maternal effect can cross generations but is heritable only insofar as its manifestation depends upon the pup’s experience in the first week of life. Recently, this group has documented that being reared by a high-quality mother results in the expression of NGFI-A, a nerve growth factor-inducible protein, that binds to the first exon of the GR gene, resulting in increased expression of GR (76). High-quality maternal care during this critical period results in the demethylation of NGFI-A and the acetylation of histones. Just as cross-fostering can reverse these molecular and behavioral changes, infusion of methionine, a histone deacetylase inhibitor, into the hippocampus can also reverse these events (77). Is there a counterpart in humans? Caspi and colleagues (78, 79) have demonstrated how the rearing environment can overcome the influence of genotype in the etiology of violent behavior.

Summary and Recommendations

Human health and disease is a complex interaction between the individual’s genes and its environment factored over time. An interaction between an estrogen, for example,
and its receptor that may be normal and healthy in the adult may be catastrophic early in development as evidenced by the prenatal DES story. In the context of epigenetic programming and gene imprinting, we can now understand at a mechanistic level apparently irreversible changes in cell function that can lead to disease as a result of exogenous hormone exposures. We may even begin to understand how that same process may occur with endogenous hormones. Given that the process of gene imprinting is a normal one seen in cell differentiation and genomic allelic silencing, one may speculate that for estrogens or estrogenic chemicals, the distinction between physiology and pathology are blurred. It would seem to be important, then, to determine the epigenetic imprints associated with hormones in normal healthy cells and organs and compare these to the same patterns in diseased or dysfunctional ones. Similarly, endocrine changes underlie all major life-history transitions (e.g. puberty and reproduction). As individuals respond to these changes in internal state, they behave differently, thereby changing their environment. These altered behaviors can not only result from chromatin restructuring but also, at the same time, lay the foundation for perpetuating the environment that reinforces them. Given that patterns of imprints are usually the result of a network of signaling pathways that are often developmentally active, we again can see the role for evolutionary, developmental, and psychological thinking in human health (Fig. 1).

Thus, after many years of investigation, we are beginning to understand the mechanisms by which estrogens and other hormones, especially during development, can alter the genetic program of target cells without altering the sequence of DNA itself. This suggests a path to follow in exploring and ultimately coming to understand diseases of many organs and systems that may have environmental or endocrine origins.

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Fig. 1. The fetus is particularly vulnerable to changes in the external and internal environments, which interact to influence fetal development and have both immediate and life-long consequences. Such environmentally induced changes can occur at all levels of biological organization, from the molecular to the organism’s behavior and place in society, and tend to be amplified in their consequences as they ascend through these levels. Ultimately, these influences may be epigenetic in nature, inducing mitotically heritable alternations in gene expression without changing the DNA.
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