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Environmental Estrogenic Chemicals: Their Impact on Embryonic Development

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In 1991, I attended a meeting at Wingspread (Racine, WI) and participated in writing a consensus statement (known as the Wingspread statement) with 20 other scientists from a wide range of disciplines which began as follows:

> *We are certain of the following*
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> A large number of man-made chemicals that have been released into the environment, as well as a few natural ones, have the potential to disrupt the endocrine system of animals, including humans. Among these are the persistent, bioaccumulative, organohalogen compounds that include some pesticides (fungicides, herbicides and insecticides) and industrial chemicals, other synthetic products, and some metals.
>
> The patterns of effects vary among species and among compounds. Four general points can nonetheless be made: (1) the chemicals of concern may have entirely different effects on the embryo, fetus, or perinatal organism than on the adult; (2) the effects are most often manifested in offspring, not in the exposed parent; (3) the timing of exposure in the developing organism is crucial in determining its character and future potential; and (4) although critical exposure occurs during embryonic development, obvious manifestations may not occur until maturity (for the full text see: Colborn and Clement, 1992).

I will focus here on the impact on embryos of one class of chemical being released by man into the environment, those that can disrupt embryonic development due to their capacity to bind to intracellular estrogen receptors. A chemical is classified as estrogenic if it binds to the estrogen receptor and initiates gene transcription, thus leading to the differentiation and growth of cells. Antiestrogens are chemicals that can either: (1) bind to the estrogen receptor but do not initiate gene transcription, thus blocking estrogen from binding to the receptor and initiating a biological response (for example, tamoxifen), or (2) interfere with the action of endogenous estrogen within cells via other, as yet, unknown mechanisms (for example, dioxin). Estrogenic chemicals can influence embryonic development, since functional estrogen receptors are present in numerous developing tissues (the most potent of

the endogenous estrogenic sex steroids is 17ß-estradiol); endogenous estrogen plays a role in the normal differentiation of many embryonic tissues (vom Saal et al., 1992). Embryo is used here to refer to a developing organism at any time prior to birth or hatching, while fetus only applies after organs have begun to form.

I will present evidence that there is reason for concern about the consequences for wildlife and humans due to exposure of embryos to environmental estrogenic chemicals. While the focus here will be on the impact that exposure during critical periods in development to low levels of environmental chemicals can have on developing tissues in embryos, it is possible that long-term exposure to a low level of these chemicals can also have detrimental effects in adults (Wolff et al., 1992).

Environmental chemicals have been reported to interfere with developmental processes in representative species from many different vertebrates (fish, reptiles, birds and mammals, including humans) by mimicking or antagonizing a variety of endogenous hormones that regulate developmental processes (Colborn and Clement, 1992). We have named environmental chemicals that can alter the functioning of the endocrine system (as well as neurotransmitters that allow communication between neurons and other tissues) endocrine-disrupting chemicals (for a list of known endocrine disruptors see: Colborn et al., 1993). The result of exposure to these chemicals during embryonic development is that various tissues, such as reproductive, thyroid, immune, and nervous tissues, are permanently altered, which I will refer to as embryonic chemical *imprinting*.

It is likely that the processes by which environmental estrogens can lead to abnormalities in estrogen-responsive tissues is due, at least in part, to the fact that natural or synthetic estrogenic chemicals act by regulating gene transcription and subsequent processing of RNA. During embryonic life, the capacity for genes to be transcribed at a later time can be permanently altered or chemically *imprinted*. One potential *imprinting* mechanism is by altering the degree of methylation of nucleotides comprising a gene (Gilbert, 1991; Jost and Saluz, 1993). Since the sequence of nucleotides is not changed by this process, a gene mutation has not occurred, but the functioning of the gene has been altered. Exposure to an endocrine-disrupting chemical during embryonic life can impose a "life sentence" on the embryo and irreversibly compromise the health and well being of an exposed embryo for the rest of its life (Colborn et al., 1993).

The Unique Effects of Endocrine-Disrupting Chemicals in Embryos

It is difficult in the adult to predict all of the consequences of exposure to an exogenous chemical that can bind to a hormone receptor and either interfere with or mimic the normal action of an endogenous hormone, such as estradiol, but in the embryo it is virtually impossible. The reason for this unpredictability is that the embryo has an endocrine system that is in the process of developing, and the consequences of exposure to endocrine-disrupting chemicals at one time in the maturation of the embryonic endocrine system can be totally different than the consequences of exposure at another time in development. Similarly, the capacity for tissues to respond to hormonal signals (specifically, the expression of metabolizing enzymes and hormone receptors) changes during development, and the effect on a

tissue of exposure to endocrine-disrupting chemicals (that act via binding to these hormone receptors and may or may not be able to be acted on by enzymes) will thus change throughout development (vom Saal et al., 1992). Also, in mammals, the functioning of the endocrine system of the mother changes during pregnancy, and the impact of endocrine-disrupting chemicals on the maternal endocrine system will thus change throughout pregnancy. Many maternal hormones freely pass across the placenta into the embryo, and with regard to environmental chemicals that can mimic the actions of endogenous estrogen, these are small, lipophilic molecules that also freely diffuse across the placenta (Colborn et al., 1993; vom Saal et al., 1995). Finally, the placenta contains cells that can make a wide variety of hormones. The endocrine physiology of the placenta changes throughout embryonic development, and the effects of endocrine-disrupting chemicals on placental physiology will also change during pregnancy (Tulchinsky and Ryan, 1980).

It has been proposed that during embryonic life, there may be unique receptors for hormones that are not present after differentiation of a tissue has occurred (if an endogenous ligand for a receptor has not been identified, it is referred to as an *orphan* receptor). These receptors may mediate developmental events that only occur in the embryo. This is one reason that applying findings to embryos from studies of adults or cells in culture concerning the possible risk of exposure to a particular environmental chemical or mix of chemicals is not appropriate (McLachlan et al., 1992).

Dr. Howard Bern has extensively studied the devastating consequences of exposure of developing animals, including humans, to synthetic estrogens, such as the potent synthetic estrogen, diethylstilbestrol (DES). DES was administered to as many as 5 million pregnant women to block spontaneous abortion prior to being banned in the early 1970's. DES was administered to women in the mistaken belief that it would prevent miscarriage and promote fetal growth. One of the main effects of DES (and environmental chemicals that can bind to estrogen receptors) is the disruption of development of the reproductive system, which does not become functional until after puberty. Detrimental effects on the reproductive system from exposure to DES during embryonic life were thus not observed at birth in either men or women. Delayed expression of consequences of embryonic exposure to chemicals is a significant problem for epidemiologists who are trying to determine how to link abnormalities expressed in adulthood (or even much later in old age; vom Saal et al., 1994) to exposure of parents to chemicals during conception, pregnancy and lactation (Herbst and Bern, 1981; Colborn et al., 1993).

Howard Bern has written of the "fragile fetus" with regard to exposure to environmental endocrine disruptors (Bern, 1992). The litany of pathologies in offspring due to the administration to pregnant women of drugs which do not cause similar pathologies when administered to adults has led physicians to understand that, unless absolutely necessary, they should avoid exposing embryos to any synthetic chemical. For example, the tranquilizer, thalidomide, did not result in damage to organs in adults, but when administered to women during the first two months of pregnancy, thalidomide profoundly interfered with limb formation and other aspects of early embryonic development. But, even though babies were being born without arms and legs, it took epidemiologists many years to link these abnormalities to maternal use of thalidomide during early pregnancy.

Many environmental estrogenic chemicals, such as some metabolites of the estrogenic insecticide, DDT (Bulger and Kupfer, 1983), persist stored in fat cells for decades (the half life - loss of one-half of the DDT - is 57 years). These chemicals are withdrawn from fat cells, along with other stored nutrients, during pregnancy and lactation and transported into the developing embryo and newborn (Colborn et al., 1993). The epidemiologist interested in studying a link between maternal exposure to environmental chemicals and behavioral abnormalities, infertility, autoimmunity, thyroid dysfunction, etc., in offspring is thus typically faced with the challenge of not only determining what maternal exposure might have occurred during a limited period in pregnancy (as was the case with thalidomide and DES), but what chemicals a woman had been exposed to throughout her life prior to pregnancy (for an example see: Jacobson and Jacobson, 1990).

Do Environmental Antiestrogens Neutralize the Effects of Environmental Estrogens in Wildlife and Humans?

Recently, it has been proposed that estrogenic and antiestrogenic chemicals in the environment might interact as would an acid and a base and thus cancel each other's effects (Stone, 1994). This "acid-base argument" is naive in that it predicts that environmental estrogens and antiestrogens react with each other prior to binding to intracellular receptors. Estrogens do not react chemically with antiestrogens; this has been known for decades. Antiestrogens act as competitors for the binding of estrogens to their receptors within cells (Figure 1). If cells are exposed to a mix of estrogenic and antiestrogenic chemicals with equal activity, the estrogenic and antiestrogenic chemicals will compete equally for receptor binding sites, and one-half of the receptors will be occupied by the estrogenic chemical and one-half by the antiestrogenic chemical. The result is that while the antiestrogenic chemical will reduce the amount of binding of the estrogenic chemical by one-half, an equal mix of estrogenic and antiestrogenic activities will still exhibit a net estrogenic effect. There is thus no possibility of an interaction between estrogenic and antiestrogenic chemicals in the environment which is analogous to the interaction of an acid and a base.

It has also been argued that since there are some chemicals in the environment which mimic estrogen while others antagonize the action of endogenous estrogen, the "overall effects of these compounds may not be highly significant since the two classes of chemicals may be contra-active" (Safe, 1994, p. 31). The only way to "neutralize" the effect of estrogen within a tissue with estrogen receptors is with a competitive excess of antiestrogens; a 100-fold excess is typical in experiments. However, it is well known that most compounds that act as blockers of estrogen in one tissue are also found to have estrogenic activity in some other tissues, and the mechanisms mediating the complex, tissue-specific responses to these chemicals are being actively investigated (Jordan and Murphy, 1990). However, with regard to whether these antiestrogenic chemicals might counteract the effects of chemicals which mimic estrogen, chemicals with estrogenic (or partial estrogenic) activity vastly outnumber the chemicals which are predominantly antiestrogenic. In any event, regardless of the concentrations of estrogenic and antiestrogenic chemicals in

the environment, an embryo exposed to such an abnormal chemical environment will have the normal actions of endogenous estrogen interfered with, and the course of embryonic development will be altered.

What has not generally been appreciated is that the view that environmental chemicals with estrogenic and antiestrogenic activity may have no net effect and thus may pose no threat to human health is based primarily on experiments conducted with cultured breast cancer cells (Safe, 1994). As the Consensus

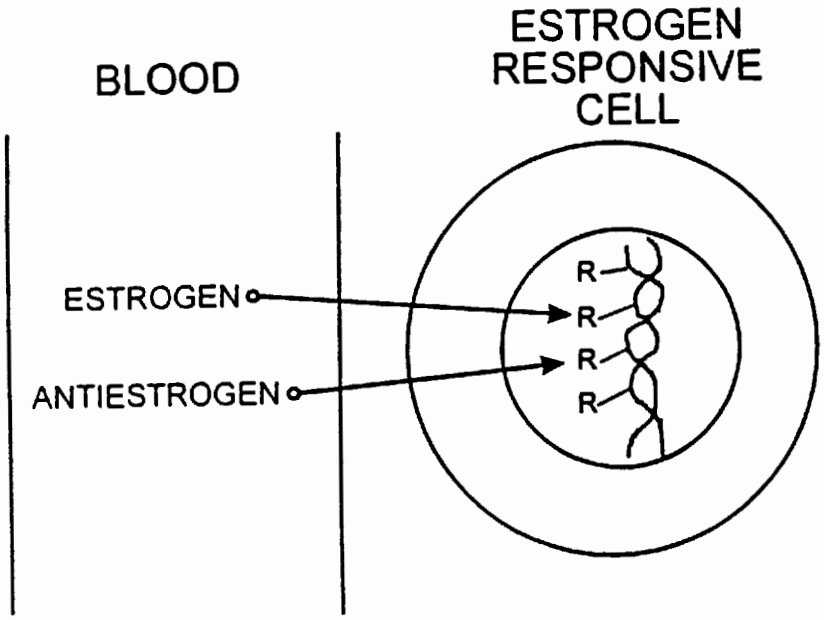

FIGURE 1. Schematic diagram of the competition by estrogenic and antiestrogenic chemicals for binding to estrogen receptors that are located within the nucleus of estrogen-responsive cells. Estrogenic chemicals initiate transcription of RNA (and changes within the cell, such as cell growth) after binding to as few as 1% (or even less) of the available estrogen receptors. Antiestrogenic chemicals bind to the same receptors but do not result in the initiation of transcription of genes associated with the protein receptors. By occupying available receptor binding sites, antiestrogenic chemicals competitively block estrogenic chemicals from binding to receptors, thus reducing the degree to which estrogenic chemicals can initiate transcription of genes. Typically, a 100-fold excess of antiestrogenic chemicals is used to competitively block cells from responding to estrogenic chemicals with equal binding affinity for the receptors.

Statement quoted above brought to the forefront, the main concern is the effects of exposure to low doses of endocrine-disrupting chemicals during embryonic development. With regard to the prediction that environmental estrogens and antiestrogens will cancel each others effects, findings from experiments with a homogeneous population of cultured cells (where such effects may be possible) are not relevant to what would occur in a human embryo whose mother is exposed to endocrine-disrupting chemicals, or, indeed, in any vertebrate or invertebrate during development.

The concept of the "fragile fetus" is now widely recognized based on awareness of the tragic consequences of exposure of embryos to drugs such as thalidomide and DES. Developing embryos, including human embryos, represent a highly complex, constantly changing biological system and are thus quite unlike a homogeneous population of cells maintained in culture. There is no possibility of achieving a stable balance of endocrine-disrupting chemicals in a developing embryo. Whether a synthetic chemical mimics estrogen or acts to block the normal actions of endogenous estrogen, it will still disrupt the delicate synchrony between estrogen production by the maternal ovaries, the placenta and the embryo, and the expression of metabolizing enzymes and receptors for estrogen at specific times during development in tissues throughout the body of the embryo (vom Saal et al., 1992).

How Specific are Responses to Different Environmental Estrogenic Chemicals?

One question of interest is whether all chemicals that can bind to estrogen receptors are biologically equivalent with regard to effects on developing embryos. It is possible that some differences may eventually be found in the response to estrogen normally produced within organisms, estrogenic chemicals made by plants, and estrogenic chemicals made and released into the environment by man, such as pesticides and other industrial chemicals. However, the current evidence is that all of these categories of estrogenic chemicals have similar biological effects *after* binding to estrogen receptors (Katzenellenbogen et al., 1979; White et al., 1994). Other than the chemicals now being made by man, the "natural" estrogens produced within animals and plants are found not only in a wide (from the perspective of evolution) variety of multicellular organisms, but are found even in unicellular organisms (LeRoith et al., 1986). These compounds may have served as regulators of activities within unicellular organisms or perhaps served as what we refer to as pheromones - intraspecific signalling molecules that communicate information between organisms. It thus appears that many of these chemicals, including estrogens, may have been around throughout the evolution from unicellular organisms to plants and both invertebrate and vertebrate animals. One would thus expect co-evolution in those cases where different organisms typically came in contact with each other (for example, in the food chain, where one organism might consume another organism), and that there would be adaptation by the feeding organism to exposure to the substances being consumed (such as estrogenic compounds in plants). The co-evolution of animals with plants which contain estrogenic chemicals (referred to as phytoestrogens) is an interesting example, although in some cases consuming these chemicals can interfere with reproduction in animals (Hughes, 1988).

The presence of naturally occurring phytoestrogens in our food has generated the hypothesis that the addition of synthetic estrogenic chemicals to the food, such as estrogenic pesticides and industrial chemicals, is unlikely to have any physiological impact (Safe, 1994). However, this proposal is premature, since there remain many unanswered questions concerning the possibility of unique biological responses (for example, the capacity to convert a chemical to a harmless metabolite) which could occur in response to estrogenic chemicals synthesized within organisms that have co-existed for millions of years versus those (potentially difficult for animals to metabolize) made and released into the environment by man in the last few decades. A major difference between some synthetic chemicals, such as DDT and alkylphenols (White et al., 1994), and estrogenic compounds synthesized in plants and animals, is that only synthetic estrogens exhibit the property of resistance to metabolism and long-term storage in fat, and these chemicals thus bioaccumulate. Persistent, synthetic estrogenic chemicals can dramatically increase in concentration as they move up the food chain (Norstrom et al., 1988). The estrogens synthesized normally in animals and plants are rapidly metabolized when consumed by an animal.

How Sensitive are Embryos to Estrogenic Chemicals?

An important issue relates to the sensitivity of developing organisms to environmental chemicals that can bind to estrogen receptors. I will thus briefly review recent findings from my laboratory that show the remarkable sensitivity of fetuses to very small differences in circulating estradiol, as well as synthetic estrogenic chemicals, during fetal life. In collaboration with scientists from the University of Parma, Italy, we recently examined the effects in male house mice (*Mus domesticus*) of exposure during embryonic life to DES, and two estrogenic insecticides: o,p'DDT (which is the estrogenic component of DDT and comprises about 25% of commercial DDT) and methoxychlor (vom Saal et al., 1995).

We fed pregnant mice a wide range of doses of these chemicals during the period of prenatal organ differentiation (between days 11-17 of pregnancy; pregnancy lasts 19 days, and development of reproductive organs begins on day 11 in mouse embryos). The lowest dose of DES administered (1 ng/mother/day = 20 ng/kg maternal body weight/day = 20 parts-per-trillion) resulted in a significant increase in territorial marking behavior (depositing urine marks around the periphery of a novel environment) by male offspring after they reached adulthood. This is a behavior which is indicative of the dominance status of a male, since only dominant males extensively mark their territorial boundaries. The lowest dose of both o,p'DDT and methoxychlor (1 µg/mother/day = 20 µg/kg maternal body weight/day = 20 parts-per-billion) that we fed to pregnant females resulted in a similar significant increase in this behavior in male offspring. Further studies will determine whether lower doses of these chemicals can also significantly alter behavior in offspring in mice (we are also examining male and female offspring for other physiological changes).

It is not uncommon to find parts-per-million amounts (µg/g tissue) of environmental chemicals in fish (for example, lake trout) which are at the top of the

food chain in some of the Great Lakes (Miller et al., 1992). Somewhat lower levels of chemicals, such as DDT, that are persistent and are stored for decades in tissues, are found in a wide range of foods consumed by the general public (Yess et al., 1993).

Our findings show that developing mice are very sensitive to small amounts of these chemicals in terms of permanent effects on brain development and thus behaviors exhibited during later life. It is not unexpected that DES at 20 parts-per-billion would result in changes in brain development in male mouse fetuses. In male mouse fetuses the serum level of total estradiol is about 100 pg/ml (0.1 parts-per-billion) during this time in development (vom Saal, 1989). In mouse fetuses, the amount of free, biologically active estradiol (not bound to plasma proteins that block estradiol from leaving the blood and entering cells) is only 0.2% of the total amount of estradiol in the blood. The concentration of free estradiol during sexual differentiation in male mouse fetuses is thus 0.2 pg/ml or 0.2 parts-per-trillion (vom Saal et al., 1994, p. 1237). The free concentration of estradiol in blood provides the reference level for assessing how sensitive developing tissues are to stimulation by estradiol; blood levels of total and free estradiol in rat fetuses are similar to those of mice (vom Saal et al., 1992).

Male mouse fetuses that differ by 25 pg/ml serum in total circulating estradiol (0.05 pg/ml free estradiol) differ in the number of prostatic androgen receptors and prostate size as adults: elevated estradiol during fetal life is associated with an enlarged prostate in adulthood and an increase in prostatic androgen receptors (vom Saal, 1989; Nonneman et al., 1992). The very high level of sensitivity to estradiol (and other estrogenic chemicals) of estrogen-responsive cells in mice (and other animals) indicated by these findings is supported by studies examining the response to estradiol and phytoestrogens of estrogen-responsive MCF-7 cells in culture (Welshons et al., 1990).

The importance of these findings is that most synthetic estrogenic chemicals, such as o,p'DDT, that bind to estrogen receptors do so with a lower affinity (are thus less potent) than the most potent endogenous estrogen, 17ß-estradiol, which is similar to DES in potency. The reference concentration of estradiol in the blood required to elicit a biological response is thus critical with regard to the amount of an estrogenic chemical that would also be predicted to produce an effect similar to that seen in response to estradiol. A critical question is whether it is appropriate to use the total or free concentration of estradiol in blood as the reference for assessing the concentration of an estrogenic environmental chemical that would be predicted to produce an effect similar to estradiol. The basis for this question is that it is known that synthetic estrogens, such as DES and o,p'DDT, as well as some phytoestrogens, do not bind to plasma estrogen-binding glycoproteins, and the percent of the total amount of these chemicals that is biologically active (free) will thus be greater than is the case for estradiol (vom Saal et al., 1992). We have developed an assay system that allows us to directly examine this question (vom Saal et al., 1995).

The estrogenic potency of o,p'DDT (in both in vitro and in vivo assays) is approximately 10^4 lower than estradiol (vom Saal et al., 1995). I will be conservative and use the total, rather than free, concentration of estradiol in blood during sexual

differentiation as the reference. In human fetuses the concentration of total estradiol in blood is 10^{-9} g/ml (1 part per billion; Reyes et al., 1974); approximately 1% of total estradiol is biologically active (not bound to plasma proteins; Siiteri et al., 1982). If developing human fetuses or newborns are exposed to o,p'DDT, a blood concentration of 10^{-5} g/ml (10 parts-per-million) o,p'DDT would be predicted to produce effects similar to estradiol. Human breast milk has been reported to contain an average of 0.25 mg/ml o,p'DDT (0.25 parts-per-million); an average infant consuming 700 ml of breast milk per day would thus receive 175 mg o,p'DDT/day. Women in Guatemala have greater than 100 mg/ml o,p'DDT in breast milk, and an infant consuming 700 ml of this milk would thus receive 70,000 mg o,p'DDT/day (Thomas and Colborn, 1992, Table 2).

Functional Changes due to Exposure to Endocrine-Disrupting Chemicals During Embryonic Life.

Scientists interested in relating the effects of exposure to environmental chemicals to changes in organ function and behavior rather than to gene mutations and the induction of cancers have faced a significant problem. Over the last two decades, toxicologists studying the chemicals we are now describing as endocrine disruptors have primarily regarded them as potentially genotoxic, and the regulation of these chemicals has involved a focus on their potential to damage DNA and cause cancer rather than on disruption of the endocrine control of organ development. This also means that the models have been wrong with regard to how to test for these chemicals, since the assumption that high-dose effects would be predictive of a low-dose response, an assumption of a linear-response function often made in cancer testing paradigms (Wilson, 1991), is invalid with regard to chemicals that interact with receptors for hormones or neurotransmitters.

There are a number of reasons why the response of tissues to estrogen and other hormones is never linear throughout a wide range of doses. First, only a very small proportion (< 1%) of the total pool of estrogen receptors needs to be occupied by estradiol to stimulate cell growth. When receptors become saturated, an additional increase in the concentration of estrogen does not lead to a further increase in response. In fact, exactly the opposite can occur, that is, the magnitude of response can begin to decrease. This can result from a process known as "receptor down-regulation" where prolonged exposure to a high concentration of a hormone can result in the loss of active receptors (Gorski and Gannon, 1976).

Another reason that there is not a linear response to estradiol (and other estrogenic chemicals) is that they can also bind to receptors for other steroids. For example, at higher than normal concentrations, estradiol binds to receptors for testosterone (Fox, 1975), and many actions of testosterone, which could potentially be mimicked by the binding of estrogen to the testosterone receptor, are antagonistic to responses initiated by estradiol binding to estrogen receptors (vom Saal et al., 1992). Alternatively, the binding of a synthetic chemical to receptors for testosterone could act to block testosterone from binding to the receptor, thus interfering with the normal actions of testosterone in the developing embryo.

The binding of estradiol to testosterone receptors requires levels of estradiol normally not encountered without addition of supplemental estrogen. Normally then, the concentration of endogenous estradiol is not high enough for this potential for binding to other receptors to have a significant physiological impact on the embryo. The presence of environmental estrogenic chemicals in embryos could result in high enough levels of estrogenic chemicals being achieved to result in "cross-talk" with other receptor systems. As discussed above, if one only conducts experiments with estrogen-responsive cells in culture, these types of responses will not be observed, and it is naive to propose that environmental estrogens are safe based on a simple model system that does not reflect the complexity of a developing embryo.

An important aspect of these findings is that exposure to a high dose of an endocrine-disrupting chemical may not be predictive of effects at lower doses. In studies involving the endocrine system, it is not uncommon to find an inverted-U dose-response function where there is initially an increase in response as the dose of chemical administered increases from zero, but then as the dose increases beyond the maximum response point, the magnitude of the response begins to decrease (for an example with diethylstilbestrol during embryonic life see: vom Saal et al., 1995). Thus, using the high-dose paradigm and focusing mainly on the potential for gene mutations or other gross abnormalities, many endocrine-disrupting chemicals have been deemed safe and are being released into the environment, although they can interfere with normal embryonic development (Colborn et al., 1993).

The Relevance of Findings in Wildlife for Human Health.

A critical issue is whether effects of endocrine-disrupting chemicals in wildlife are only theoretically relevant to humans, and many arguments have been waged over the validity of animal models for predicting human risk (Ziegler, 1993). Estrogens and other steroids are regulators during embryonic life of growth and differentiation, and during subsequent life, of the functioning of a variety of organs in every class of vertebrate, and damage to reproductive organs has been reported in fish, reptiles, birds and mammals exposed to environmental endocrine-disrupting chemicals during embryonic development (Colborn and Clement, 1992; Colborn et al., 1993).

With regard to estrogenic endocrine-disrupting chemicals and their potential for disrupting embryonic development, the similarity between vertebrates, with regard to the mechanism of action of estrogenic chemicals that act via binding to estrogen receptors, argues strongly for the continued use of animal models to assess human risk (Katzenellenbogen et al., 1979; Pakdel et al., 1989; White et al., 1994). Within the field of comparative endocrinology, the finding of highly conserved molecules, such as estradiol and the estrogen-receptor complex, has led to the general assumption that it is the specific uses to which hormones and their receptors have been put that has changed throughout the evolution of multicellular organisms, not the hormones and receptors themselves (LeRoith et al., 1986).

There may be individuals who, in practice, hold the view that humans are somehow fundamentally different from other vertebrates with whom we share a common evolutionary history, and that endocrine disruption somehow applies to animals but not to humans. However, if man-made estrogenic chemicals interfere

with a major system which is fundamentally similar in so many different vertebrates, it is unreasonable to propose that humans will not also be similarly affected.

The chemical revolution which began in the 1940s was initially heralded as a boon to mankind: reduced death due to diseases carried by insects, increased crop yield, new industrial products such as plastics, to mention a few. The short term benefits of the chemical revolution are clear. What is just beginning to be understood are the long-term consequences for the health of future generations of the massive release of these chemicals into the environment. Wildlife populations are already showing impairment of reproduction and other abnormalities due to exposure of embryos to environmental endocrine-disrupting chemicals (Fox, 1992; Colborn et al., 1993). The implications of these findings for the health of future generations of humans are just beginning to be realized.

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