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SPECIAL REPORT

Environmental Effects on Reproductive Health: The Endocrine Disruption Hypothesis

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Reproductive health is exquisitely sensitive to characteristics of an individual's environment —including physical, biological, behavioral, cultural and socioeconomic factors. The relative effects of these features may vary in different parts of the world or even within a country. For example, in populations with high rates of sexually transmitted diseases or in areas with inadequate health care resources, untreated infections may pose the greatest threats, increasing women's risk of experiencing premature delivery, fetal loss or prenatal mortality. Furthermore, the infants of women with such diseases risk acquiring the infection during delivery and are vulnerable to other complications during the neonatal period.[1]

In societies where cultural norms favor large families, women may suffer health problems resulting from frequent childbearing. Similarly, malnutrition increases a pregnant woman's susceptibility to poor outcomes.

In some regions, workplace and industrial pollution, as well as substances that are used commercially or in the home, may pose the greatest threats. Exposure to lead, for instance, is associated with fertility impairments in both women and men, as well as with the risk of spontaneous abortion and stillbirth; exposure to mercury in certain forms may cause birth defects and neurological disorders. A number of solvents contribute to the risk of spontaneous abortion and birth defects, and some of these substances may be a factor in hypertensive disorders during pregnancy and male infertility. Epidemiological studies have proven the adverse reproductive health effects of some pesticides, and mounting evidence suggests that other of these products also are harmful to reproductive health.[2]

Both man-made and naturally occurring materials that appear to interfere with hormone synthesis or action are among substances whose effects on reproductive health are strongly suggested, if not clearly established. Recent research pointing to the possible role of so-called endocrine disrupters in a variety of reproductive health problems in wildlife, laboratory animals and humans has engendered considerable controversy in scientific circles. Some scientists question the validity of the findings

on a variety of grounds, while others have used them to outline agendas for further research and relevant policymaking.

As the endocrine disruption debate continues to occupy researchers, it also is gaining attention among the public. During the past several years, articles and opinion pieces about reproductive health problems and endocrine disruption have appeared in newspapers and in popular science, business, news and general interest magazines.[3] Public interest groups have produced monographs reviewing the subject,[4] and the trade publications of industries whose products have been labeled endocrine disrupters have carried articles and editorials seeking a balanced reading of the evidence.[5]

A new round of coverage followed the publication in early 1996 of *Our Stolen Future: Are We Threatening Our Fertility, Intelligence, and Survival? —A Scientific Detective Story*.[6] The book, written for lay readers, chronicles the development of the endocrine disruption hypothesis and considers its implications.

Much of the popular coverage of the issue has reflected great attention to presenting both sides of the question in a manner that will inform but not alarm the public. Some of it, however, has been less successful at establishing a context for the findings, clearly distinguishing facts from hypotheses, and communicating a measured view of the implications both of what has been demonstrated and of areas requiring extensive additional research.

The public has a right and a need to know about issues with a potential for substantial public health ramifications; sensible voices on both sides of this debate acknowledge the need for additional research and risk assessment, clear priorities for dealing with documented risks and dissemination of verifiable information that can help individuals make informed health decisions.

The endocrine disruption hypothesis promises to remain a focus of research —and debate —for some time to come. Therefore, without minimizing the importance of other environmental risk factors for men's and women's reproductive health, this report focuses on what is known about hormone disrupters, areas that are being explored and the potential implications for public health and policy.

HORMONES AND DISRUPTERS

MECHANISMS OF ACTION

The organs of the endocrine system (including the pancreas, pituitary, thyroid and reproductive organs) produce a variety of hormones, each of which triggers a specific biochemical response.* For example, insulin regulates the body's level of blood sugar, thyroid hormones are important for regulating the metabolic rate, and estrogen and testosterone control the development and functioning of the reproductive organs.

In order for a hormone to produce an effect, once it has been released into the bloodstream, a carrier protein transports it to a cell wall; there, it binds to a receptor, and the hormone and receptor together bind to a specific region of a cell's DNA to activate particular genes. A hormone and its receptor fit together precisely, much as a key fits in a lock, and this specificity is crucial to the hormone's functioning. Also crucial are the precise levels of hormones produced and the timing of their synthesis

and action.

Several dozen synthetic compounds appear to interfere with hormonal activity in a number of ways. Some of these endocrine disrupters mimic a hormone by binding to its receptor and activating the same response that the natural hormone would or a stronger response, and some stimulate the production of more hormone receptors; all of these substances can amplify the effects of the endogenous hormone. On the other hand, some compounds bind to a receptor and trigger a weaker effect than the naturally occurring hormone would, and some produce no biochemical effect but prevent hormonal action simply by occupying the appropriate hormone's site on the receptor.

Certain endocrine disrupters bind to carrier proteins, thereby reducing the availability of these proteins to transport hormones through the bloodstream. Others alter the level of endogenous hormones by accelerating their breakdown and elimination or by deactivating the enzymes that facilitate their breakdown; some react directly with hormones to alter their structure or affect their synthesis.

SOURCES OF HORMONE DISRUPTERS

Endocrine disrupters, some of which occur naturally (phytoestrogens) and some of which are man-made, are ubiquitous: They can be found in soil, water, air and food, as well as in commonly used industrial and household products. Phytoestrogens are present in grains, legumes, grasses, herbs, nuts and a variety of fruits and vegetables; some fungi also produce compounds that may interfere with hormonal function. Phytoestrogens are weaker than endogenous estrogen (i.e., they do not bind as well to hormone receptors) and are quickly excreted or broken down into other compounds; they do not accumulate in body tissue.

Perhaps the best-known man-made endocrine disrupters are synthetic hormonal drugs, such as birth control pills and diethylstilbestrol (DES); dioxin, a by-product of waste incineration and industrial processes (e.g., the production of some pesticides and the bleaching of paper pulp); and polychlorinated biphenyls (PCBs), which once were widely used in the United States in electrical equipment, adhesives and plasticizers. Other synthetic compounds that disrupt hormone activity are alkyphenols and phthalates, which are widely used in industrial and household products, and some pesticides, fungicides and insecticides.

Man-made endocrine disrupters vary in potency and in the level of exposure required to produce a deleterious effect. Individually, they may not be released into the environment at levels that would pose substantial risks, but the effects of chronic low levels of exposure are of concern.[7] In addition, these substances occur in the environment not individually but in various combinations, and they may interact synergistically: In some experimental systems, a combination even of two weak compounds has proven to be more than 1,000 times as potent as either compound alone.[8]

Furthermore, while some of these man-made substances are ubiquitous simply because they are produced in large quantities, others may be found in regions of the world where they are not produced because they are easily transported through the atmosphere and do not break down readily in the environment. Rather, they

accumulate in soil and sediments, which serve as continued sources of exposure to wildlife; the substances then make their way up the food chain, and unlike phytoestrogens, they can be stored for long periods in the body fat of animals and humans. Consequently, species feeding at the highest levels of the food chain are the most vulnerable to adverse effects of environmental pollutants because in addition to being directly exposed to contaminants, they feed on animals with accumulations of harmful compounds in their body tissue.[9]

Thus, for example, although most uses of PCBs were banned in the United States in the late 1970s, PCB residues remain widespread in the environment, and animals and humans continue to ingest food with small amounts of these chemicals. Women who have, over their lifetime, regularly eaten animals contaminated with PCBs may deliver slightly preterm, and their newborns may suffer from a variety of deficits; if these women nurse, they risk passing the toxicant along through their breast milk, making their infants vulnerable to developmental disorders.[10]

KNOWN EFFECTS

Wildlife studies and research on laboratory animals have identified a broad range of effects of endocrine disrupters on reproductive health. These results are the necessary starting point for considering reproductive health effects in humans, which to date are most clearly established by the DES experience.

ANIMAL STUDIES

In 1991, a multidisciplinary group of scientists concerned about the evidence of endocrine disruption by chemicals in the environment gathered to review the issue. In their consensus statement (dubbed the Wingspread Statement, for the name of the conference site), they summarized the following reproductive health effects of endocrine disrupters on wildlife: "decreased fertility in birds, fish, shellfish, and mammals; decreased hatching success in birds, fish, and turtles; gross birth deformities in birds, fish, and turtles; metabolic abnormalities in birds, fish, and mammals; behavioral abnormalities in birds; demasculinization and feminization of male fish, birds, and mammals; defeminization and masculinization of female fish and birds."[11]

Furthermore, they concluded, while effects vary according to species and substance, a number of generalizations can be made: Endocrine disrupters may have "entirely different effects" on developing organisms than on adults; the timing of exposure is critical to the outcome; and effects may not be obvious until an organism has reached maturity.

Experiments on laboratory animals have corroborated many of these theories. For example, research on rats has identified day 15 of a typical 21-day pregnancy as a critical "window of vulnerability": A low level of exposure to dioxin on that day, when the tissues are actively differentiating and developing, is more likely than exposure on other days to produce a wide range of adverse effects in the reproductive development and behavior of male offspring.[12]

The authors of the Wingspread Statement acknowledged that the implications of their conclusions for humans were uncertain for a number of reasons, including that "information is limited concerning the disposition of these contaminants within

humans....This is compounded by the lack of measurable endpoints (biologic markers of exposure and effect) and the lack of multi-generational exposure studies that simulate ambient concentrations." Nevertheless, they noted, effects documented in wildlife should "be of concern to humans," who are exposed to the same contaminants.

DES

DES is a synthetic estrogen that was prescribed to pregnant women between the late 1940s and early 1970s to prevent miscarriage. In all, 5-10 million Americans were exposed to DES during pregnancy or in utero.[13] With data available both on women who took DES and on their adult children, the experience with this drug serves as a model demonstrating the possible effects on humans of exposure to synthetic estrogens in utero.

Although questions about the consequences of exposure to DES remain, several effects are well established:[14] Women who took DES have a small (less than twofold) but significantly elevated risk of breast cancer. Their daughters are at risk of developing vaginal clear-cell adenocarcinoma, a cancer that typically occurs among women in their 50s but may occur about 30 years earlier among young women exposed to DES in the womb. This effect raises the concern that when young women who were exposed in utero reach the age at which the risk of cancers of the reproductive organs may be expected to increase, they may have an above-average incidence of these cancers.

DES also is associated with abnormal development or dysfunction of reproductive organs and with premature births among women exposed in utero. It may affect the risk of ectopic pregnancy and reduced fertility, but these relationships are less clear.

In males exposed to DES in utero, the drug has been associated with several structural abnormalities of the reproductive tract; it may be a factor in infertility and testicular cancer, although the literature reveals conflicting findings. Additionally, some studies have shown semen quality in DES-exposed men to be lower than that in men not exposed to the drug.[15]

The grandchildren of women who took DES are entering their childbearing years, and their reproductive experiences will provide an opportunity for the evaluation of any third-generation effects on fertility. As yet, no such effects have been documented.

The DES experience illustrated in humans a number of points made by the wildlife studies summarized in the Wingspread Statement. It showed that chemical exposure in utero can have serious, long-term, delayed effects; that substances that have little apparent effect in adults can cause substantial damage to a developing fetus; and that the human body can mistake a synthetic hormone for a natural one.[16]

POSSIBLE EFFECTS

DES is the only synthetic hormone with a proven role in reproductive health disorders. However, a variety of reproductive disorders affecting both women and men that appear to be occurring with increasing frequency are causing some scientists to speculate that endocrine disrupters may be partly responsible for these, too.

BREAST CANCER

Worldwide, the incidence of breast cancer has been rising since the 1940s; it is highest

in developed countries, but is increasing most rapidly in developing societies. Despite major strides in research on the disease —particularly the discovery of a gene that increases a woman's susceptibility to the condition —the cause of breast cancer cannot be identified in about two-thirds of cases. However, a review of known risk factors has led some researchers to question the possible influence of exogenous estrogens.[17]

Established risk factors for breast cancer include several that are related to levels of the naturally synthesized estrogen estradiol. Early onset of menstruation, late menopause, never having given birth and never having breastfed contribute to the risk by elevating a woman's lifetime exposure to estradiol. Another risk factor, being older than 50, probably reflects older women's long-term exposure to this hormone. Additionally, the increased odds of the disease that have been found among women with diets high in animal fat and with high levels of alcohol consumption may be explained by the fact that fat tissue can manufacture estrogen, and alcohol can increase the hormone's production.

These are not the only risk factors for the disease (high-dose exposure to X rays also plays an important role), and the mechanism by which estradiol might participate in the development of breast cancer is not entirely clear. Nevertheless, researchers hypothesize that if an excess of natural estrogen can be harmful, prolonged exposure to man-made estrogens might pose similar threats; laboratory findings indicating that synthetic estrogens can cause breast tumors in animals, they contend, support their hypothesis. Furthermore, they suggest, the accumulation of environmental hormones in fat tissue may help explain the association between breast cancer and high-fat diets.

Studies evaluating the link between environmental hormones and breast cancer risk in humans have yielded inconsistent findings. Results from a large study on hormones, diet and cancer risk implicate DDE, the chief breakdown product of the pesticide DDT.[18] The study involved 14,290 New York City women who attended a mammography screening clinic between 1985 and 1991, many years after DDT use was banned in the United States.

In all, 58 participants had breast cancer diagnosed within six months after entering the study, and these women had higher levels of DDE in their blood than did 171 women in a comparison group. Furthermore, analyses controlling for potentially confounding factors revealed that women with the highest concentrations of DDE were four times as likely as those with the lowest concentrations to have breast cancer. The researchers also examined the influence of PCBs and found no significant associations.

Findings from a large California study, however, challenge these results.[19] A group of 57,040 women who underwent health examinations between 1964 and 1969 were followed up through 1990, and the researchers identified those in whom breast cancer was diagnosed six months or more after their examination. Using blood samples drawn during the examination and kept frozen, the investigators compared the levels of DDE and PCBs in the blood of 150 randomly selected breast cancer patients (50 whites, 50 blacks and 50 Asians) with those in blood samples taken from 150 controls. The results showed no difference between the groups in the blood level of DDE or PCBs.

Analysts comparing these two studies observe that the California study's larger sample makes it more persuasive. Additionally, the California women, whose blood samples

were drawn before the DDT ban, had considerably higher blood levels of the chemical than did those in the New York study.[20] Critics of the California study, however, suggest that its inclusion of Asian women may have skewed the results.[21] Asian women generally have a much lower risk of breast cancer than whites and blacks,[22] and those in the sample had no increased risk of breast cancer despite high levels of potentially harmful chemicals in their blood.

MALE REPRODUCTIVE HEALTH PROBLEMS

Although research results have been inconsistent, a substantial body of evidence suggests that in recent decades, men have grown increasingly vulnerable to reproductive health problems. Perhaps the most extensively publicized finding is the decline in semen quality over the past 50 years reported in a 1992 meta-analysis of 61 studies conducted worldwide.[23] The studies, whose results were published between 1938 and 1990, included a total of 14,947 men without a history of infertility.

According to the analysts, the results show that between 1940 and 1990, the mean sperm count declined by 42% and the mean semen volume declined by 18%. These changes, the analysts contend, cannot be explained by methodological variation or selection bias, but reflect a "true biological phenomenon."

Results of French and Scottish studies support these findings.[24] Semen samples collected from 1,351 healthy men at a sperm bank in Paris between 1973 and 1992 revealed significant declines over that period in sperm count and the proportions of motile and normal sperm, although semen volume remained unchanged. These results were independent of any effects caused by aging and were inversely associated with year of birth: Men born in any given year had a lower sperm count and smaller proportions of motile and normal sperm than those born a year earlier. In the Scottish study, among 577 semen donors, sperm concentration, sperm count and the number of motile sperm declined among successive birth cohorts from 1951 to 1973.

On the other hand, a review by the Danish Environmental Protection Agency of studies of environmental effects on men's reproductive health points out that the decline in semen quality is not a universal trend.[25] According to research cited in the review, sperm concentration in the semen of Finnish men was unchanged from 1958 to 1992 and is higher than that among other European men. Furthermore, a recent study involving 1,283 men in three regions of the United States found an increase in sperm concentration (with substantial differences among the regions) between 1970 and 1994, and no change in sperm motility or volume.[26]

The Danish review also brings together data from a number of countries indicating that the incidence of testicular cancer has been rising by a rate of 2-4% annually among men younger than 50, the age-group most commonly affected by this disease; overall, the incidence has at least doubled and perhaps quadrupled over the past five decades. Additionally, data on genital abnormalities, although difficult to compare across countries, suggest that the occurrence of cryptorchidism (undescended testicles) and hypospadias (a urethral malformation) is on the rise. All of these conditions show wide geographic variation.

The concurrent emergence of all of these apparent trends has led some analysts to speculate that a common cause underlies these conditions. Given the short period of

time in which these dramatic changes seem to have occurred, researchers suggest that the cause is more likely environmental than genetic.[27] Furthermore, development of the sex organs takes place largely during fetal development, and the DES experience demonstrates that exposure to an exogenous hormone can interfere with that process. These facts, coupled with findings in wildlife and laboratory animals, have caused some researchers to question whether exposure to environmental hormones may be harmful to men's reproductive health.[28]

THE DEBATE

The hypothesis that chemicals in the environment can interfere with the development and action of hormones has sparked debate among scientists both because of the inconsistency of findings and because of certain features of the substances in question. Critics of the hypothesis argue that phytoestrogens and man-made estrogens are weaker than endogenous estrogens; that exposure to estrogenic substances occurring naturally in food outweighs exposure to environmental pollutants; and that chemicals that mimic estrogen and those that block its action cancel each others' effects, much as acids and bases neutralize each other. These critics also discount evidence from animal studies, which are based on higher levels of exposure to contaminants than humans are likely to encounter in their environment, and challenge the relevance of wildlife studies conducted in "hyperpolluted" settings.[29]

Those who advance the endocrine disruption hypothesis counter that while many exogenous hormones are less potent than those produced within the body, they are present in body tissues in much higher concentrations than are natural products. Furthermore, as mentioned earlier, many synthetic endocrine disrupters may be stored in body tissue for long periods, whereas phytoestrogens are rapidly broken down or flushed out. Thus, the transfer of these substances to a developing fetus or a nursing infant is a function of the mother's lifetime exposure.[30] In addition, some man-made chemicals that bind with a hormone receptor may not bind to proteins that limit the passage of endogenous hormones from the bloodstream into cells. Such chemicals (DES is known to be one) may therefore freely enter cells when natural hormones cannot.[31]

Refuting the argument that the effects of estrogenic and antiestrogenic compounds in the environment cancel each other out, supporters of the endocrine disruption hypothesis contend that these substances cannot interact in a way that is analogous to the interaction of an acid and a base. They add that studies suggesting otherwise have been based on homogeneous cell cultures and therefore are not relevant to the complex, constantly changing biological system of a developing fetus.[32]

Supporters of the hypothesis also note that as the dose of exposure to an endocrine disrupter increases, the magnitude of the effect may initially increase but then diminish. Thus, findings based on exposure to high doses of endocrine disrupters may not reflect effects of the same substances at lower doses.[33] In addition, they point out, most studies have focused only on chemicals' estrogenicity and have not examined other potential hormonal effects; for instance, while DDE has limited ability to bind with estrogen receptors, it is a strong androgen antagonist.[34]

Finally, those who hold to the endocrine disruption hypothesis agree that evidence

from wildlife and laboratory animal studies does not prove their case in humans unequivocally. However, they state emphatically that humans and other vertebrates are similar enough so that even though specific effects may differ across species, wildlife can serve as "sentinels" of human risk, and wildlife studies can be used in conjunction with toxicological research to determine the effects of hormone disrupters on men's and women's reproductive health.[35]

IMPLICATIONS

The findings and uncertainties regarding endocrine disruption and reproductive health have suggested a wide-ranging agenda for researchers and policymakers.[36] The chief priority is to identify substances that may have deleterious effects, their mode of delivery and mechanism of action, the developmental stage at which they have their effect and the minimum concentration at which they pose risks. A broad range of outcomes needs to be investigated, including functional deficits in offspring and reproductive health traits other than the ability to conceive and bear children (e.g., menstrual function); changes in these outcomes over time and at different levels of exposure also must be assessed.

Other high priorities are defining normal variability in reproductive health characteristics so that trends can be identified reliably and hypotheses about their causes tested, determining how endocrine disrupters interact and developing risk assessment methods that take these interactions into account. This information can be used as a basis for considering regulatory measures aimed at limiting exposure to substances with known or suspected toxic effects.

All of this will entail epidemiological studies examining specific effects among various subgroups of the population; such studies can also shed light on how susceptibility varies geographically or with demographic, genetic or overall health factors. A complete understanding of the effects of endocrine disrupters will also involve wildlife, laboratory animal and in vitro studies, whose applicability to humans should be clearly demonstrable.

Scientists, government agencies, funders and industry have begun to work together to study endocrine disruption; such continued collaboration will be essential. In addition to conducting and funding studies, government entities can contribute to the research effort by incorporating relevant measures in national-level surveys, encouraging uniform registration of birth outcomes and requiring manufacturers to disclose the names of all chemicals used in their products so that these may be tested.*

Since research on endocrine disruption requires a multidisciplinary approach, funders can enhance their role by assuring that panels reviewing research proposals or results include experts from all appropriate fields. Industries that produce known or suspected endocrine disrupters have launched their own studies, whose results they have shared both with each other and in broader forums;[37] they can also participate in efforts to quantify and assess the effects of occupational exposure to potentially harmful chemicals.

The extent to which substances in the home, the workplace and the general environment jeopardize the reproductive health of men and women is unclear; but it need not, and must not, remain so. Through an extensive, demanding research effort,

government, industry and others can provide the scientific knowledge on which policies and practices may be based that will safeguard reproductive well-being.

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*For more detailed information about the mechanisms of the endocrine system and endocrine disrupters and for information about specific endocrine disrupters, see the following sources, which served as the basis for this section: T. Schettler et al., 1996, op. cit. (see reference 2); Center for Bioenvironmental Research, Tulane and Xavier Universities, "Environmental Concepts Made Easy," Aug. 1996, <http://www.tmc.tulane.edu/ecme/EEHome>, accessed Aug. 1996; and World Wildlife Fund Canada, "Net Surfers' Guide to Endocrine Disruptors," <http://www.wwfcanada.org/hormone-disruptors>, accessed Aug. 1996.Dore Hollander is senior editor of *Family Planning Perspectives*. For their comments on an early draft of this special report, the author thanks Michael Burnhill, Planned Parenthood Federation of America, New York; William R. Kelce, Reproductive Toxicology Division, U.S. Environmental Protection Agency, Research Triangle Park, N.C.; and Ted Schettler, Greater Boston Physicians for Social Responsibility. The preparation of this report was supported through a grant from the John Merck Fund.

†The U.S. government reportedly spends $20-$30 million annually on research directly focused on endocrine disruption; the total may be as much as $500 million if research that indirectly involves endocrine disruption is included. (See: J. Johnson, reference 37.)