## Box 2.5 Are Hormone Mimics Affecting Our Health?

The March 1996 publication of *Our Stolen Future* brought into full public view a debate that had been simmering in the scientific literature for several years. In this widely publicized book, zoologist Theo Colborn of the World Wildlife Fund and two coauthors hypothesize that some industrial chemicals commonly found in the environment could be wreaking havoc with human health by disrupting the body's hormonal system. Specifically, the authors suggest that these substances—dubbed "endocrine disruptors" because they interact with the endocrine, or hormone system—may be playing a role in a range of problems, from reproductive and developmental abnormalities to neurological and immunological defects to cancer (1). Evidence suggests that, at high exposures, some of these substances, which include DDT and PCBs and some pesticides, can cause reproductive and developmental problems in wildlife. The question is whether these substances can exert similar effects on humans at the relatively low doses typically found in the environment.

A lack of definitive evidence of adverse health effects in humans, yet abundant suggestive evidence associating these chemicals with problems in animals, has provided tinder for a volatile debate. Colborn and others believe that the weight of evidence in animals and people provides warning that these contaminants are threatening our fertility, intelligence, and basic survival (2). Others, such as Stephen Safe of Texas A&M University, believe these concerns are overstated, claiming they are based on findings that are contradictory at best or not relevant to the human situation (3)(4). Although many of these chemicals have been banned by developed countries because of other documented adverse effects, their widespread dispersal and persistence in the environment makes them potential health menaces for a long time to come.

So far, at least 45 chemical compounds have been proposed to be endocrine disruptors. Many are long-lived organic compounds that can persist in the environment for decades and bioaccumulate in body tissue. The list includes: certain herbicides, fungicides, and insecticides (e.g., atrazine and chlordane); industrial chemicals and byproducts such as polychlorinated biphenyls (PCBs) and dioxin; and a number of compounds found in plastics, such as phthalates and styrenes, that are used to package foods and beverages (5).

### The Endocrine System

The problems attributed to endocrine disruptors are thought to arise mainly from the ability of these compounds to mimic or interfere with the normal functioning of sex hormones such as estrogen, testosterone, and progesterone, or thyroid hormones integral to the development of the brain and other organs and tissues. Natural sex hormones play a crucial role in governing normal development. Estrogen, for example, not only helps orchestrate the sexual development of the human embryo and fetus, but it is also needed for the normal development of the brain, bone, muscles, immune system, and other organs or tissues (6). Prenatal and/or lifetime exposures to sex hormones are also hypothesized to influence the risk of developing various cancers (7).

These hormones travel in the blood and exert their effects by binding to molecules in cells known as hormone receptors. This in turn activates genes in the nucleus of the cell to produce a range of biological responses. Under normal conditions, the body carefully controls the amount of active hormones to ensure that the system runs smoothly. For instance, the body produces specific proteins that can latch onto the hormones and regulate their access to cells. The body also protects itself from excessive amounts of potent hormones by putting the reins on hormone production or by damping cells' sensitivity to hormones. Endocrine disruptors can work as both hormone mimics and hormone blockers, in both cases with a potential to disrupt normal cellular activity. Scientists are still a long way from knowing at what levels of exposure these effects can be seen (8)(9).

### Clues from Wildlife

The first evidence of the effects of endocrine disruptors on reproduction was prompted by dramatic findings in wildlife. During the 1970s and 1980s, PCBs, DDT, dioxin, and other endocrine disruptors were linked with reproductive abnormalities including reduced penis size and hampered fertility of Florida alligators, and abnormal mating behavior and reproductive organs in Western gulls in the United States (10).

These findings prompted researchers to look at the possible role of these substances in human health problems as well. Results have been conflicting, with some studies suggesting harm while others do not. Sorting out these scientific questions is complicated because many of these substances, such as DDT, are known to have adverse effects on both animals and humans, whether or not they disrupt the endocrine system. In other words, their adverse health effects could be unrelated to the compound's influence on hormones. Complicating matters further, many of the recent epidemiologic studies have been preliminary, or "ecological," in nature. That means that a study may find that a rise in cancer, for instance, coincides with a rise in the use of a suspect chemical—but there may be no evidence that people exposed to the chemical develop cancer. As one researcher points out, data can show that the stork population has declined and that the number of births has declined, but that doesn't mean storks bring babies.

### Human Health Effects

Some of the strongest evidence on the reproductive effects of endocrine disruptors in humans comes from long-term studies of the potent synthetic estrogen diethylstilbestrol (DES), which was given to thousands of women in the 1950s and 1960s to prevent miscarriage. Studies tracking DES-exposed sons and daughters since the 1970s have found a significant number of abnormalities in the structure and function of reproductive organs (11). Some studies have documented that men exposed to DES prenatally are significantly more likely to have smaller testicles and penises, undescended testicles, and poor semen quality (12). Other studies contradict those findings. In addition, because the men were exposed prenatally to much larger quantities of an estrogen-like substance than they would be likely to encounter in normal environmental settings, these findings cannot be easily extrapolated to the general population.

Nevertheless, some researchers have suggested that endocrine disruptors may be associated with a decline in sperm counts in the general population. This hypothesis emerged when Danish, French, Belgian, and British researchers noted as much as a 50 percent decline in sperm counts over the past 20 to 60 years—roughly the same time during which the use of these endocrine disruptors became widespread (13). Studies in the United States, France, and Finland, however, have not seen a decline in sperm counts; some have even reported an increase (14)(15). That leaves researchers uncertain about, first, whether a decline in sperm counts has actually occurred in some parts of the world; and second, if it has, whether such a decline can be attributed to the influence of endocrine disruptors.

Similar uncertainties abound over whether exposure to endocrine disruptors could be affecting the ratio of male-to-female births in humans. Animal studies suggest that exposure to certain pesticides can affect the sex ratio of gulls, alligators, and turtles, resulting in a decline in male births (16)(17). In humans, some studies have suggested a minor decline in the proportion of male births in the Netherlands from 1950 to 1994 and in Denmark from 1951 to 1995 (18)(19). Many other factors are known to affect the proportion of female births, in-

## Box 2.5 continued

cluding the age of parents, the time in their cycles during which women conceive, or the introduction of hormonally induced ovulation in the 1980s (20).

Concern that endocrine disruptors might cause cancer has arisen in part from the clear role of DES in cancers in female reproductive organs. In addition, a number of epidemiologic studies have shown that elevated lifetime exposure to the body's own estrogens, (from, say, early onset of menses or late menopause) increases a woman's risk of developing breast cancer (21). Could exposure to endocrine disruptors also boost the risk of developing such cancers? (See the Guest Commentary by Devra Davis.) Trend data suggest that the incidence of hormonally mediated cancers, which include breast, testicular, and prostate cancer, are on the rise in some parts of the world (22).

Some of the increase in breast and prostate cancer is thought to stem from better screening techniques, earlier diagnosis, and the effect of an aging population. Some researchers have posited that environmental and occupational exposure to endocrine disruptors may also explain some of the rise. Indeed, some studies have found that farmers exposed to certain pesticides and herbicides have an increased risk of developing prostate cancer or testicular cancer. Other studies have not found such a link, although in some cases other chemicals were examined (23)(24).

Another potentially serious effect of exposure to endocrine disruptors is neurological impairment. Much of the concern stems from a study conducted in the Great Lakes region of the United States, which found that children exposed to PCBs prenatally suffered small but significant intellectual impairment. The most highly exposed children were three times as likely to have lowered IQ scores and were twice as likely to be at least two years behind in reading comprehension. The exposed children were also more likely to have problems with attention span and memory. What's more, the levels of PCBs that these children were exposed to were only slightly higher than those found in the general population (25).

As for a possible mechanism, laboratory studies have suggested that exposure to PCBs prenatally or through breast milk can lower blood levels of thyroid hormones needed to stimulate the growth and maturation of brain cells (26). However, the mechanism has yet to be determined, and it is also possible that PCBs are impairing intelligence through a mechanism unrelated to endocrine disruption (27).

Natural hormones also have a hand in shaping the prenatal development of the immune system and influencing its actions in children and adults (28), sparking concern that endocrine disruptors might affect the immune system to some degree and put people more at risk of developing infections.

The role of endocrine disruptors in causing these and other effects is now under active investigation worldwide. At this stage, the general consensus among most experts is that many more studies need to be done to assess whether the synthetic chemicals that have helped shape agriculture and industry are also shaping the health fates of individuals, or even the population at large. At the international level, the World Health Organization and the Organisation for Economic Co-Operation and Development (OECD) are undertaking an international inventory of research. National governments, other international organizations, and even private companies are funding and/or conducting research to fill in the current knowledge gaps (29)(30). In the interim, countries are struggling with whether and how to regulate these substances as scientific understanding evolves.

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