CHAPTER 1

Disrupting Hormonal Signals

In March 2000, I joined an environmental justice field trip that met with women of Washington State's Shoalwater Bay Indian Tribe. One of the poorest tribes in the West, the Shoalwater were losing their tiny reservation to erosion and legal battles, and they were losing their future to a mysterious run of miscarriages. One woman after another described losing her fetus. They spoke to us of their grief, anger, sense of confusion, and fear that something in the water they drank or the fish they ate was killing their babies.[1]

The U.S. Centers for Disease Control and Prevention claims that the miscarriages could simply be random events, or possibly the result of genetic flaws. Or they could stem from diet, poverty, alcohol, or drug abuse, all of which can contribute to miscarriages. Few tribal members are reassured, for women on the reservation have taken meticulous care of their health during their pregnancies, yet they still have high rates of pregnancy loss. Many people in the tribe fear that the culprit could be environmental. Farmers spread pesticides on cranberry bogs near the reservation, foresters spray herbicides on surrounding forests, and oysterers use chemicals in Willapa Bay to control parasites that threaten the oyster industry. Many of these chemicals have the potential to disrupt the actions of hormones that shape fetal development. Yet because fetal development is so complex and because synthetic chemicals are so difficult to monitor, no one can determine exactly what is harming the developing children.

The expectant mothers of the Shoalwater tribe are being exposed to

something, yet no one knows what. Their situation is extreme but not unique. Rich or poor, urban or rural, we are all breathing air that carries toxic dust from fertilizers, drinking water contaminated by plumes of toxins, eating food tainted with chemicals leached from plastic containers. The water that moves inside us is eventually the water that moves through the bodies of the Shoalwater women. It is the water that stagnates over the Superfund site behind my old house, and it is the water where fish swim, connecting one ecosystem to another, one species to another, and one body to another. Toxic chemicals have the potential to cross the boundaries between species and generations, altering the hormone systems that shape our internal ecosystems of health, as well as our relationships with the broader ecosystems around us.[2]

New technologies and methods for the detection of synthetic chemicals, particularly endocrine disruptors, have drawn increasing attention toward the pervasive presence of industrial chemicals in our bodies. In July 2005, the Centers for Disease Control released its *Third National Report on Human Exposure to Environmental Chemicals,* revealing that synthetic chemicals permeate bodies and ecosystems.[3] Many of these chemicals can interfere with the body's hormonal signaling system (called the endocrine system), and many are persistent, resisting the metabolic processes that bind and break down natural hormones.

In the 1980s the researcher Theo Colborn of the Conservation Foundation began documenting wildlife responses to pollutants in the Great Lakes. About one-fifth of U.S. industries and one-half of Canadian industries are located along the Great Lakes or tributary streams, making the region a microcosm for problems with pollutants in industrial society. Colborn found no shortage of wildlife problems in the area, but few consistent patterns. Some studies suggested elevated rates of cancer in certain species, others showed impaired fetal development, while still others found behavioral changes in wildlife.

Little seemed to tie these results together until Colborn learned of research by the biologist Frederick vom Saal showing that developing fetuses could be extraordinarily sensitive to tiny differences in fetal hormones. Vom Saal had noticed that female mice from the same litter showed dramatic differences in size and aggression. Because these mice were genetically identical, something other than genes was determining their differences. A female mouse's position in the womb turned out to

powerfully influence her behavior when she reached adulthood. In the mother's uterus, females positioned next to their developing brothers were exposed to more androgens than those next to their sisters. In maturity, the mice located near their brothers were more aggressive and slower to mature, not because of genetic differences but because of tiny differences in prenatal hormones.[4]

Vom Saal's work made Colborn wonder whether the effects she was seeing in Great Lakes species might be linked to fetal development. If exposure to tiny doses of hormones could lead to significant effects later in life for laboratory animals, might the same be true for wildlife? Could synthetic chemicals be disrupting the endocrine system in developing fetuses? Colborn hypothesized that certain chemicals in the Great Lakes were mimicking estrogen, thus influencing the action of steroid hormones on fetal development, leading to reproductive problems in adulthood.[5]

The more researchers looked, the more they found that rivers and streams were laden with chemicals that had the potential to affect reproduction in wildlife. In the effluent of sewage plants, scientists found male carp and walleyes that were not making sperm but were instead producing high quantities of vitellogenin, an egg-yolk protein typically made by females. Other studies in the Great Lakes region found male white perch that had developed intersex characteristics. Students on a biology field trip in Florida noticed that every mosquitofish they found seemed to be a male, for each had a gonopodium—an anal fin that males use for copulation. But many of these apparent males turned out to be pregnant, and the students discovered that many of them were actually females that had developed gonopodia. As the biologist Mike Howell discovered, the problem was that wastes from pulp and paper mills were contaminated with chemicals that acted like testosterone. Around the world female killifish, sailfin mollys, blue-gill sunfish, American eels, and Swedish eelpouts had all become masculinized in streams that contained pulp-mill waste. Other fish species have become feminized by synthetic chemicals that mimic estrogen. In some western U.S. rivers, male Chinook salmon have developed female characteristics, while some male Atlantic cod and winter flounder have reduced testosterone levels, hampering reproduction.[6]

Sexual transformations were not limited to fish. Once researchers began looking, they found signs of reproductive problems in numerous species. Male alligators exposed to DDT in Florida's Lake Apopka devel-

oped penises that were one-half to one-third the typical size, too small to function. Two-thirds of male Florida panthers had cryptorchidism, a hormonally related condition in which the testes do not descend. Prothonotary warblers in Alabama, sea turtles in Georgia, and mink and otters around the Great Lakes all showed reproductive changes.[7] Male porpoises did not have enough testosterone to reproduce, while polar bears on the Arctic island of Svarlbard developed intersex characteristics. In one particularly disturbing example, Gerald A. LeBlanc of North Carolina State University in Raleigh found that more than a hundred species of marine snails were experiencing a condition known as imposex, a pollution-induced masculinization. Affected females could develop a malformed penis that blocked their release of eggs. Engorged by eggs that could not get out, many snails died.[8]

By the 1990s, researchers had noticed that not only wildlife species were showing difficulties with reproductive health; increasing numbers of people were as well. As with panthers, the incidence of cryptorchidism in British men has increased, doubling in two decades. Since 1970, boys in the United States have become increasingly likely to develop severe hypospadias, a birth defect of the penis. Testicular cancer has increased in many industrialized countries; in Denmark it has more than tripled since World War II, while in the United States incidence increased by 51 percent between 1973 and 1995. Similar increases have occurred in other Scandinavian countries and Scotland. Since the 1950s, sperm counts in some regions have declined significantly worldwide. Men in many industrial nations are showing increases in prostate cancer; a 1999 review found that men in the United States in 1994 had a much greater risk of being diagnosed with prostate cancer than their fathers had.[9] Much of the increase in the number of diagnosed cases is probably the result of better screening tests, but researchers are nonetheless concerned that actual incidence may also be increasing for unexplained reasons. Across the United States and Puerto Rico girls appear to be developing breasts at a younger age, and other signs of early puberty have also become apparent.[10] Epidemiological research on women's reproductive health has found an increase in the incidence of infertility, endometriosis, fibroids, breast cancer, and ovarian cancer since synthetic chemical production began to boom in the 1950s.[11]

What, if anything, connects all these problems with reproductive health? Many researchers now believe that these changes stem from dis-

ruptions of hormones by synthetic chemicals, particularly during vulnerable stages of fetal development. Hormones are chemical signals that regulate communication among cells and organs, orchestrating a complex process of fetal development that relies upon precise dosage and timing. Anything that scrambles the messages from hormone-signaling systems can alter patterns of development and health, just as scrambling airplane radio systems can alter flight patterns. The plane might not crash, but the static can disrupt the signals necessary for clear communication. The consequences may sometimes be minor, such as when the plane is in mid-flight at a steady altitude, but at other times — during take-off and landing, for instance — scrambled messages create havoc. Similarly, when synthetic chemicals alter hormone-signaling systems, adults might be resilient to the changes, but fetuses and young children can experience permanent transformations.[12]

Ever since endocrine-disrupting chemicals were first commercially produced in the 1940s, their hormonal mechanisms of action have posed novel challenges for scientists and regulatory agencies seeking to protect public health, because they do not easily fit within traditional risk paradigms. Toxicologists based their paradigms of risk on natural toxins that caused acute poisoning at high doses. As the environmental scientist John Peterson Myers writes, "Traditional toxicants are thought to work by starting a process (or stopping one) by overwhelming the body's defense system. Up to some level of contamination, the body can defend itself against chemical assaults." Chemicals that disrupt hormone systems act in a variety of ways, however, usually by changing signals that direct complex processes with intricate feedback loops.[13]

Even today, a popular Yale University Web site for poisons teaches that "the dose makes the poison." *All* toxins, this Web site states, are dose dependent: "The toxic effect of a substance increases as the exposure (or dose) to the susceptible biological system increases. For all chemicals there is a dose response curve, or a range of doses that result in a graded effect between the extremes of no effect and 100 percent response (toxic effect). All chemical substances will exhibit a toxic effect given a large enough dose. If the dose is low enough even a highly toxic substance will cease to cause a harmful effect."[14] Endocrine disruptors, however, violate every aspect of this definition of risk. Instead of being dose dependent,

with a threshold below which the chemical is safe, endocrine disruptors typically demonstrate the following properties:

Dose: Their effects are often not dose dependent. Classic natural toxins such as poisonous mushrooms typically show a dose-response curve, with larger doses leading to more harmful effects than smaller doses (often in a linear relation: twice as much toxin leads to twice the effect). In contrast, endocrine disruptors may show greater effects at lower doses, depending on the timing of exposure rather than the dose alone.

Threshold: Natural toxins usually have a threshold of safety, or what is called a "no observable adverse effect level." At some point, for example, a sample of a poisonous mushroom will be so tiny that a person would not be harmed by it. In contrast, endocrine disruptors often lack this threshold. Even a single molecule diluted in a trillion molecules of water may have potential activity. These biological effects occur at doses that are orders of magnitude lower than current dose limits for other toxins.

Age: Effects often do not correlate to the size or weight of the exposed individual, as is usual with traditional toxins. A large person should be able to eat more of a poisonous mushroom than a small person before feeling the harmful effects, but the effects of endocrine disruptors are rarely so predictable. Age rather than size is often the critical factor. Infants and developing fetuses are most at risk, while adults can often show entirely different effects.

Timing: Endocrine disruptors often have effects that are not apparent immediately after exposure. Unlike natural toxins, which usually show effects almost at once, endocrine disruptors may not show effects for decades. A person who was exposed to synthetic endocrine disruptors such as DES in the womb might show no harm at birth but might develop cancer or reproductive problems at puberty.

Researchers detected many of these patterns in the 1930s and 1940s during their initial investigations of diethylstilbestrol. While many scientists believed that these unexpected patterns indicated a need for extra caution, industry advocates dismissed the possibility that the new chemicals might be causing harm because the observed effects violated standard beliefs about toxicology. Yet these unusual effects all derive from the ways hormones typically function.

A review of some basic principles about the body's hormone system (known as the endocrine system) can help us make sense of the ways

synthetic chemicals can act as endocrine disruptors. These principles will frame my argument about why regulators struggled to respond to the risks of many synthetic chemicals. To explore them I shall focus on one group of hormones critical for sexual development in both males and females: the estrogens, which include estradiol, estrone, and estriol.

Estrogens are steroid hormones: that is, they are fat-soluble and derived from cholesterol.[15] Estrogen can be made in several locations within the body, but the ovaries are the most important production site in women of reproductive age. After the ovaries secrete estradiol, the molecules travel through the bloodstream until they encounter cells with specific receptor proteins that fit the hormone. Each hormone has a unique shape that fits the shape of particular receptor proteins at the target cell. Imagine the hormone as a key and the receptor protein as the lock. Only if the key fits can the door be unlocked. After estradiol binds to a matching receptor protein, it triggers a change in the shape of that protein, forming a new molecule called a hormone-receptor complex. The hormone-receptor complex enters the cell's nucleus and binds to its DNA, triggering a cascade of events in the cell, such as signaling the DNA to express particular genes, make particular proteins, or develop particular tissues. One familiar result is the instruction to breast cells to begin replicating during puberty. Even a tiny amount of estradiol that binds with the correct receptor can trigger the signaling cascade, with far-reaching effects such as breast growth.

Estrogen receptors are abundant in our bodies: in breast cells, the uterus, the ovaries, bone cells, hair cells, blood vessels, liver, kidneys, eyes, and even the prostate. Some hormone receptors for estrogens are unique, allowing only a single configuration of a molecule to fit. Other receptors are less specific, and many different chemicals can bind to them. A synthetic chemical that binds to an estrogen receptor might trigger cellular processes, effectively acting as an estrogen in the body. Other synthetic chemicals might bind to an estrogen receptor with antagonistic effects, blocking the binding of the body's own (endogenous) hormones. The PCBs in the Fox River, for example, can function as anti-estrogens by binding to a particular estrogen receptor and then preventing that receptor from binding to the body's endogenous estrogens.

While hormones are critical for life, too much of a given hormone can lead to havoc. Depending on timing, excess estrogens might stimulate the replication of cancer cells, signal tumors in a woman's uterus to grow, and

transform patterns of sexual development. Because the levels of a particular hormone needed by a body can change from moment to moment, a complex suite of interconnected feedback systems governs hormone activity. This may regulate hormone synthesis within glands, control hormone release into the bloodstream, affect hormone uptake by target receptors, and alter the ways hormones bind to proteins so they can be broken down and removed from the body.[16]

Negative feedback systems function like a thermostat, maintaining homeostasis, or internal balance. When temperatures go up, the thermostat shuts the furnace off, and when the temperature drops low enough, the thermostat signals the furnace to turn back on. Similarly, when levels of the body's estrogens drop below a certain amount, an organ called the hypothalamus secretes gonadotropin-releasing hormone, which travels to another organ in the body (the anterior pituitary gland), which then secretes yet another hormone called follicle-stimulating hormone, which makes its way back to the ovaries and stimulates more estrogen production. Blood estrogen levels eventually rise high enough that the hypothalamus stops secreting its gonadotropin-releasing hormone, thus stopping the secretion of follicle-stimulating hormone from the pituitary gland, and that in turn stops the production of estrogen from the ovaries. Feedback systems potentially enable small amounts of hormones to create larger effects than high doses, because high doses can shut down hormone synthesis.[17]

Estrogen levels in the body are also regulated by serum-binding proteins known as sex-hormone-binding globulin. This protein binds with estrogen and other steroid hormones circulating in the bloodstream. Bound estrogens are unable to enter target cells, making these estrogens biologically inactive. When blood estrogen levels drop low enough, serum-binding proteins may release their estrogens, allowing them to become biologically active once again. Biologically active estrogen levels are thus determined not by estrogen production alone but also by the level of serum-binding proteins in the blood. Binding-protein levels depend on a complex balance of other chemicals known as enhancing and inhibiting factors. Hormones such as insulin may act as inhibiting factors, decreasing the level of serum-binding protein in the blood, and thereby increasing biologically active estrogen levels. Synthetic chemicals may do the same thing.

The complexities of the feedback, receptor, and binding-protein systems allow for rapid fine-tuning of estrogen levels in the body, but they

also mean that synthetic chemicals can interfere with numerous different pathways.[18] Endocrine-disrupting chemicals may interfere with hormone signaling by altering the metabolism of steroid hormones or by inhibiting their synthesis. Synthetic chemicals may bind with serum-binding proteins so that those proteins cannot bind with the body's own endogenous estrogens, increasing their biological activity. Alternatively, synthetic chemicals may be much weaker estrogens than the body's own estrogens but be unable to bind with serum-binding proteins, making them biologically quite potent. This proved to be one of the major ways that DES and other synthetic endocrine disruptors affected the body. At certain times during pregnancy, estrogen levels increase dramatically, but the production of sex-hormone-binding globulin also increases, thereby protecting the fetus from the mother's high levels of circulating estrogens. DES is a weaker estrogen than the body's own estrogens, but it is less likely to be bound by serum-binding proteins, leaving the fetus vulnerable to the chemical's effects.[19]

Receptors and serum-binding proteins also influence the difference between natural and synthetic hormones. Beginning in the 1940s the livestock industry relied on what I call the "natural" argument to claim that their use of synthetic hormones in livestock was safe. When regulators and scientists raised concerns about synthetic estrogens, producers would point out that the body has high levels of its own natural estrogens and yet not everyone dies of cancer, so small amounts of a synthetic estrogen must also be safe. Because natural plant compounds in the human diet can also act as estrogens, industry advocates offered complex calculations purporting to show that natural estrogens were thousands of times more abundant than synthetic estrogens. If the body could survive high levels of natural estrogens, they argued, synthetic estrogens must also be safe, and regulatory staff were often persuaded. Many plants do indeed contain natural estrogenic compounds (called phytoestrogens), and when eaten in large concentrations, these may affect human reproduction. Like the body's own estrogens, however, phytoestrogens are quickly bound up by serum-binding proteins in the blood, and the body tends to flush them out rapidly. Synthetic chemicals, on the other hand, may be weaker estrogens, but because they avoid the chemical defenses of the woman's body, they can accumulate in body fat to toxic levels, persisting until pregnancy.

The effects of estrogenic chemicals such as DES puzzled researchers in the 1940s and 1950s because they differed dramatically among individuals, depending on the age of the individual and the timing of the exposure. These findings made little sense when interpreted through a standard toxicological paradigm, but they are less surprising when we consider how the endocrine system functions at different life stages. In adults, hormones mainly regulate ongoing physiological processes such as metabolism. Synthetic chemicals can lead to temporary endocrine changes, but adults are often able to recover from these disturbances. During fetal development, however, hormonal changes can have permanent, irreversible effects. Because a woman accumulates toxic chemicals over her entire lifetime of exposure, she can transfer much of her contaminant burden to her developing fetus during pregnancy, the time of greatest sensitivity.

Hormones orchestrate the complex dance of fetal development, telling various genes to turn on and off, and directing cellular replication and morphogenesis, the processes that transform simple collections of cells into complex organs. An embryo must develop from just two cells into an organism with trillions of cells and many organs, and hormonal signals guide the fetus through these developmental paths. Synthetic chemicals can disrupt critical steps, leading to effects that may become apparent only decades later, when the child reaches adulthood.

Early in life the endocrine system develops set points that control the number of hormone receptors and their sensitivity to changing hormonal signals throughout adulthood. When synthetic chemicals influence these hormonal set points in the fetus, the impacts are felt for a lifetime. Sexual development is particularly sensitive to these effects: for example, in the male fetus specialized cells known as Sertoli cells direct the development and descent of the testes, regulate the development of germ cells, and orchestrate the progress of cells that will secrete the hormones responsible for masculinization. Turning on too many estrogen receptors in the developing fetus can reduce the multiplication of Sertoli cells and fix their numbers at very low levels. This can affect descent of the testes and the development of urethral structures, setting into motion events that could lead to cancer decades later. Research on the developing prostate shows that exposure to synthetic estrogens such as diethylstilbestrol in the womb can lead to prostate problems later in life.[20]

Researchers in the 1940s and 1950s learned that exposing pregnant lab

animals to synthetic chemicals such as DES could result in reproductive problems that emerged only at adulthood. Why, then, didn't they suspect that people might suffer similar effects? Some scientists were indeed concerned about the potential effects of synthetic chemicals on human reproduction. Yet after World War II, as genetic models of development began to dominate, few researchers remained interested in environmental influences on development. Genes rather than the environment were believed to set the blueprint for development.

Since the 1990s, an explosion of research in the field of epigenetics has transformed conceptual models of gene-environment effects on the developing fetus. Every cell in the body contains the individual's entire genetic code. But brain cells must use only the genes needed by the brain, while kidney cells should activate only the genes needed for renal function. Epigenetic processes direct how these different parts of the genome are activated or silenced during development. Cells commonly control gene behavior by attaching small molecules known as methyl groups to specific sections of DNA. The attachment and detachment of methyl groups is particularly important in the fetal development of the reproductive system, and hormones play key roles in these epigenetic processes.[21]

Exposure of the fetus to toxic chemicals can permanently reprogram tissue in a way that determines whether tumors will develop in adulthood. Many cells have tumor-suppressor genes that keep tumors from becoming malignant. Chemical exposure can lead to epigenetic changes that silence these genes, even when their DNA sequence is unchanged. Likewise, cells also contain tumor-promoter genes, which are normally suppressed. Exposure to synthetic chemicals can block the suppression of these genes, thereby allowing them to promote the growth of tumors. In animals bred to contain genes that make them particularly susceptible to fibroid tumors, those genes are normally suppressed, but exposure to toxic chemicals such as DES will turn those genes on in the fetus, and tumors will develop years later. Without the initial toxic exposure, however, such a genetic susceptibility may not lead to cancer in adulthood.

Development is no longer envisioned as an inevitable chain of events dictated by genes alone. Rather, developmental biologists now describe a complex symphony between cells, genes, organs, individuals, and environment, all influencing one another's melodies and harmonies. Genes may form the sheet music, but without the hormonal conductor to select

which music to play and coordinate the musicians, cacophony would break out. Researchers in 2004, for example, exposed young mice to DES and observed epigenetic changes in the DNA that could cause the onset of cancerous growths in adulthood. Even quite low doses of DES altered methylation patterns and increased uterine tumor incidence, and these changes could pass from one generation to the next.[22]

Not all individuals respond in the same way to particular chemical exposures, making it difficult for epidemiological researchers to detect subtle effects. Experimental research on rats and mice, for example, shows that strains differ tremendously in their genetic susceptibility to endocrine disruptors. Although DES harms the rat thyroid, for example, strains differ in their sensitivity to DES-induced thyroid problems. In people, complex gene-environment interactions shape the likelihood of a woman getting breast cancer. Women with mutations in the BRCA1 and BRCA2 tumor-suppressor genes are more likely to get breast cancer, an indication of a genetic influence. But environmental factors influence whether these BRCA1 and BRCA2 genetic mutations will lead to cancer. For women born before 1940, before the boom in synthetic chemicals, having the BRCA1 and BRCA2 mutation has led to little increased risk of cancer. But for women born after 1940, having those mutations has meant a substantially increased cancer risk. These results suggest that environmental exposures can increase cancer risk even for women with an inherited cancer-susceptibility gene.[23]

As the women of the Shoalwater tribe have learned, the complex nature of hormone systems makes trying to connect any particular chemical exposure to particular reproductive problems extremely difficult. Pregnant women exposed to pesticides are more likely to have miscarriages, but this correlation is not firm proof that a pesticide caused the miscarriage. The case of PCBs illustrates some of the difficulties researchers encounter when they try to link chemical exposure to reproductive failure. PCBs are industrial chemicals that disrupt thyroid hormone function. The Environmental Protection Agency (EPA) banned their production in 1979, but Great Lakes fish still carry PCBs in their fat, and people who eat those fish accumulate the chemicals. Thyroid malfunction can lead to miscarriage, and because PCBs alter thyroid function, researchers suspect that PCBs might contribute to miscarriages. In lab studies, PCBs have been shown to

change rates of thyroid-hormone synthesis, increase the metabolic clearance of some thyroid hormones, and cause miscarriages in rodents. Outside the lab, women who eat a lot of Great Lakes fish accumulate more PCBs than women who eat no Great Lakes fish. Yet it is not clear that eating such fish endangers women's fetuses. Women with a history of miscarriages do show higher PCB levels in their blood than women who have not had miscarriages, suggesting that PCBs may have been a contributing factor. But other studies have found that women who eat more fish from the Great Lakes do not have higher rates of miscarriages than women who eat less Great Lakes fish. Such findings, however, do not necessarily prove that low-level PCB exposure is safe. The PCBs in the fish may have had little effect on pregnancy; alternatively, the fish oils also present in the fish might have helped protect the developing fetus. Or perhaps the control women who were eating less Great Lakes fish were exposed to other synthetic chemicals that increased their miscarriage rates. Epidemiological correlations suggest paths for future research, but they rarely offer firm proof of either safety or harm.[24]

Laboratory studies show that other endocrine-disrupting chemicals can also lead to miscarriages. In rodents, experimental treatment with DES and bisphenol A (a chemical found in many plastics) both increase miscarriage rates. If the pregnant rodent manages to carry the offspring to term, the female offspring also show higher rates of miscarriages when they reach adulthood. A single chemical exposure, therefore, may affect three generations: the exposed mother, the developing daughter, and that daughter's potential offspring.[25]

In 2005 epidemiological studies on people showed that women with a history of recurrent miscarriage had higher levels of bisphenol A in their blood than women who had been able to carry their pregnancies to term. Yet the combination of epidemiological studies on people and experimental studies on laboratory animals does not provide proof that synthetic chemicals would cause the same effects in people that they do in other animals. Miscarriage, birth defects, and infertility have numerous potential causes for they are all part of a complex ecology of health. This complexity stems from the nature of endocrine systems, yet it has made political pressure against regulatory action difficult for federal agencies to withstand.

The womb is an environment of its own, yet one that is linked to the

outside world. The chemicals that a woman has been exposed to throughout her life, not just what she consumes while she is pregnant, reach her fetus, connecting one generation to the next. Pregnant women hope that if they don't take drugs like DES, their children will be fine. But chemical contamination affects most women: 30 percent of pregnant women in one study had detectable levels of PCBs, DDT, and the pesticide lindane in their amniotic fluid, often at concentrations high enough to cause problems in lab animals.[26] What do these exposures actually mean for people? No one knows for certain, but a consensus is emerging that some synthetic chemicals—even at very low, background levels—can disrupt the signaling systems that shape fetal development.

Are low-level exposures to endocrine-disrupting chemicals a serious problem for people? Some of the central claims of the endocrine-disruption hypothesis are now agreed upon by all scientists, even within the chemical industry. Everyone agrees that wildlife exposed to certain synthetic chemicals show responses similar to those induced by steroid hormones. They agree that lab studies show that synthetic chemicals can bind with and activate hormone receptors, resulting in gene expression. They agree that exposing pregnant mice to extremely low concentrations of certain synthetic chemicals results in offspring with reproductive problems. They agree that some synthetic chemicals can make breast cancer cells multiply in cultures. They agree that persistent organic chemicals build up in human tissue and are passed to the developing fetus and the breast-feeding infant. They agree that many male fish and alligators exposed to industrial effluents show signs of feminization, a result also shown in the lab when eggs are exposed to some synthetic chemicals.[27]

But scientists still disagree on a fundamental issue: What do these animal and lab studies mean for people? Do people who do not experience occupational exposures have anything to worry about? Can endocrine disruptors explain any of the apparent increases in infertility, reproductive cancers, birth defects, reduced sperm counts, or lowered ages of puberty? Or are endocrine disruptors present at such low levels that they are a trivial concern?

In August 1999, the National Research Council of the National Academy of Sciences released its consensus report on endocrine disruption, commissioned in 1995 by the EPA and Congress. After four years of review and debates, the team finally managed to agree that endocrine

disruptors at high concentrations do affect human and wildlife health, yet they could not agree on the extent of the harm caused by levels common in the environment. Moreover, the team argued that their disagreements were owing not only to gaps in scientific knowledge, but also to major epistemological differences on how to interpret the data and draw conclusions. The consensus report stated: "Much of the division among committee members appears to stem from different views of how we come to know what we know. How we understand the natural world and how we decide among conflicting hypotheses about the natural world is the province of epistemology. Committee members seemed to differ on some basic epistemological issues, which led to different interpretations and conclusions on the issues of hormonally active agents in the environment."[28]

The chemical industry's response to this report was to focus on the conclusion that no scientific certainty on human health effects had been established. Without certainty, the industry argued, endocrine disruption was not an issue for public health concern. As Myers writes, "This is a classic argument from industry spokespeople: that the absence of data proves safety. In reality, all it proves is ignorance." So, in the absence of firm proof, what should society do? Many in industry argue that we should do nothing until we have that proof. Others believe that such a course would be unethical, for as the Greater Boston Physicians for Social Responsibility stated, "We are engaged in a large global experiment. It involves widespread exposure of all species of plants and animals in diverse ecosystems to multiple manmade chemicals. . . . The limits of science and rigorous requirements for establishing causal proof often conspire with a perverse requirement for proving harm, rather than safety, to shape public policies which fail to ensure protection of public health and the environment."[29]

Epidemiological evidence is accumulating that supports the hypothesis that endocrine disruptors may be harming reproductive health, while experimental studies have found similar effects in laboratory animals. But researchers cannot ethically do these experiments on human fetuses to test whether the correlations between endocrine disruptors and reproductive disorders are real. Instead, regulatory agencies need to rely on the weight of the evidence from animal models and epidemiological studies, rather than experimental proof, to form policy.[30]

How can animal models be extrapolated to human effects? How can we

understand the risks of low-dose, chronic exposures to synthetic chemicals? How can we understand effects on complex, interconnected systems? And politically, how can the government protect public health and the environment in the absence of complete proof? To understand the federal government's attempts to control the risks of synthetic chemicals, we need to explore early twentieth century debates about regulating the risks posed by natural toxins.