CHALLENGED CONCEPTIONS:
ENVIRONMENTAL CHEMICALS AND FERTILITY

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Writer:
Jon Luoma

Reviewers:
Alison Carlson, Commonweal/Collaborative on Health and the Environment
Edith T. Eddy, The Compton Foundation, Inc.
Dr. Linda C. Giudice, University of California, San Francisco
Dr. Sarah Janssen, University of California, San Francisco
Dr. John Peterson Myers, Environmental Health Sciences
Dr. Shanna H. Swan, University of Rochester

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Hana Bauguess, Heather Albright, Louis J. Guillette Jr., University of Utah Andrology Department, Alpha Scientists/Thomas Elliott, Environmental Health Science/John Peterson Myers, Fred vom Saal.

Correspondence: Collaborative on Health and the Environment, c/o Commonweal, Fertility/Early Pregnancy Compromise Working Group, PO Box 316, Bolinas, CA 94924

UNDERSTANDING ENVIRONMENTAL CONTAMINANTS AND HUMAN FERTILITY: SCIENCE AND STRATEGY
A WORKSHOP....

In late February 2005, the Stanford University School of Medicine's Women's Health@Stanford Program and the Collaborative on Health and the Environment convened a small multidisciplinary group of experts at the Vallombrosa Retreat Center in Menlo Park, California, to assess what the science tells us about the contribution of environmental contaminants to human infertility and associated health conditions. Workshop organizers chose this focus because critical new discoveries in the field have raised many new scientific questions and heightened interest in the risks of environmental exposures within patient organizations and reproductive medicine/science professional societies. This meeting, titled *Understanding Environmental Contaminants and Human Fertility: Science and Strategy*, marked the first time researchers in reproductive epidemiology, biology, toxicology, and clinical medicine gathered with representatives of relevant professional societies and patient advocacy/support organizations in the United States to review the state of environmental health science as it pertains to infertility. Funding for this workshop was provided by its sponsors, and by The Compton Foundation, Inc. and the Mitchell Kapor Foundation.

This paper, prepared following the workshop, is intended to provide background for lay readers on both the basic scientific information and some of the central issues addressed at Vallombrosa. Funding for this publication was provided by The Compton Foundation.

A copy of the workshop program, this paper, and a companion scientific statement titled *Vallombrosa Consensus Statement on Environmental Contaminants and Human Fertility Compromise* can be found online at **www.healthandenvironment.org/working_groups/fertility** and also at **womenshealth.stanford.edu/environment/fertility.html**.

Women's Health @ STANFORD

Stanford University School of Medicine
300 Pasteur Drive
Stanford, California 94305

Collaborative on Health and the Environment
c/o Commonweal
PO Box 316
Bolinas, California 94924

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Women's Health@Stanford (womenshealth.stanford.edu) is a multidisciplinary program in the Stanford University School of Medicine committed to improving the health and well being of all women, by way of collaborative research, education, advocacy, and clinical care. The program houses the School of Medicine's Center for Research on Reproduction and Women's Health & Genomic Medicine.

The Collaborative on Health and the Environment (CHE; www.healthandenvironment.org) is a US-based network of 1,800 organizations and individuals from 47 states and 18 countries. CHE's mission is to highlight emerging environmental health science and increase the level of scientific, public, and collaborative dialogue concerning links between environmental factors and human health effects. CHE offers monthly teleconferences, regional and national conference forums, and peer-reviewed overview papers on salient topics, and is an umbrella for discussion and working groups focused on specific health challenges.

The Compton Foundation (www.comptonfoundation.org) seeks to foster human and ecological security through its grantmaking in the areas of Peace & Security, Environment & Sustainability, and Population & Reproductive Health. Founded in 1946 as the Compton Trust, the Foundation believes that research and activism should inform each other, and that both perspectives are necessary for productive public debate and effective policy change. The foundation actively encourages creative collaboration between agencies, institutions and/or foundations, and projects that advance human knowledge by connecting theory with practice.

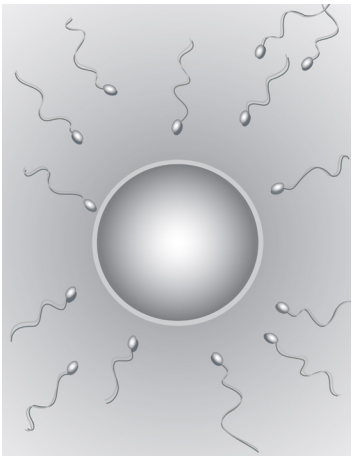
Jon R. Luoma is a nationally-recognized writer who focuses on science and the environment. His work has appeared in national publications including the *New York Times Magazine* and "Science Times," *National Geographic*, *Wildlife Conservation*, *Discover*, and *Audubon,* where he is a longtime contributing editor. His books include *The Hidden Forest*, *Biography of an Ecosystem*, *A Crowded Ark*, and *Troubled Skies, Troubled Waters*.

It's a profound human drive and as basic a liberty as one can name: to bear children. But for at least 10 to15 percent of reproductive age couples in the United States today, conceiving or bearing children proves difficult, sometimes impossible. Technologies in reproductive medicine, such as in vitro fertilization, allow more and more people with fertility problems to overcome them. But the economic costs can be daunting. A single in vitro fertilization cycle totals on average over $12,000 in this country, and often a successful pregnancy is achieved only after repeated attempts. This means costs can easily soar above $40,000 or $50,000—an economic burden far beyond the means of many who struggle with infertility. Still, in 2002, an estimated $2.9 billion was spent on infertility treatments in the United States by patients and health insurers.

The emotional anguish infertility brings cannot be measured in dollars.

"You go through months—years—of hoping, hoping, hoping and then crashing," said one woman who underwent multiple, ultimately unsuccessful in vitro cycles after she and her husband tried for years but were unable to conceive a child naturally. "It would be two weeks of tension waiting to ovulate, then two weeks of praying you don't get your period. Eventually, after all the failed efforts, I was just brought to my knees."

In the majority of cases, doctors can identify an apparent medical condition or risk factor in the male, female, or couple that explains the infertility. However, often the *underlying* causes of those conditions and risk factors are not well understood. In up to 10 percent of cases, no apparent reason at all can be discovered for a couple's infertility—and in a much higher proportion of cases than that, according to the American Society of Reproductive Medicine, "only minor abnormalities are found that are not severe enough to result in infertility. In these cases, the infertility is referred to as unexplained. Couples with unexplained infertility may have problems with egg quality, tubal function, or sperm function that are difficult to diagnose and/or treat. "



Reproductive health is affected by the interaction of multiple factors, among them age, genetics, nutrition, lifestyle behaviors, reproductive tract infections, stress, and pharmaceutical use. In recent years, scientists have increasingly reported evidence that certain pollutants in the environment may also play an important role, contributing at least in some cases to underlying causes of fertility problems. A surprisingly wide range of compounds has been implicated, particularly in studies of laboratory animals and wildlife, although for the most part the science is still inconclusive as it applies to humans.

Physicians, patients, and advocacy organizations supporting those facing fertility challenges may agree that taking a precautionary approach toward potential environmental chemical threats to reproductive health would be better than having to treat disorders after the fact. But because much of the related science is relatively new and complex, doctors, patients, and support groups are left with a host of unanswered questions about what risks exist, what the "threat levels" are, and what precautions are warranted to protect fertility.

LANDMARK WORKSHOP ON HUMAN FERTILITY AND ENVIRONMENTAL CONTAMINANTS

In February 2005, the Stanford University School of Medicine's Women's Health@Stanford program and the national Collaborative on Health and the Environment brought together 40 experts in infertility and reproductive health for a workshop at the Vallombrosa Center in Menlo Park, California. This meeting was the first to convene scientists conducting research on environmental contaminants with infertility doctors; representatives of relevant professional societies; and major infertility patient support, women's health, and reproductive rights advocacy groups from the United States. The primary purpose was to allow participants to begin exchanging information across a wide range of disciplines and interests about links between contaminants and fertility problems, and to encourage scientists and physicians to share expertise with advocacy organizations that seek to address this complex issue accurately and responsibly.

Another goal of the meeting was to begin defining elements of a more coherent and vigorous research agenda. Scientists have made a series of intriguing and sometimes troubling discoveries in recent years. But because important dots remain unconnected, the prevailing theme at Vallombrosa was that a better coordinated, better funded "comprehensive environmental reproductive health" research program must be developed and supported. For if some proportion of infertility cases is environmentally induced, then that proportion is also, in theory, preventable.

This paper, prepared after the completion of the Vallombrosa workshop, is intended to provide background for lay readers on the central issues addressed during the meeting. It includes a general introduction to some of the basic scientific information, and a summary of key concerns expressed by patient advocates and physicians.

ARE FERTILITY PROBLEMS ON THE RISE?

According to the US National Center for Health Statistics, its periodic National Survey of Family Growth shows that in 2002 about 7.3 million women reported that they had experienced impaired fecundity (the biologic capacity of men and women for reproduction), compared with 6.1 million women in 1995, and 4.9 million in 1988. Scientists also report that certain physical and medical conditions that contribute to infertility appear to be increasing, ranging from testicular cancer and poor semen quality in men to endometriosis in women. And data show that visits to doctors for infertility consultations and treatment are also on the rise.

But the National Survey of Family Growth also suggests the possibility that biological fertility challenges themselves may be on the rise, among all women of reproductive age but most significantly among younger adults. The study found the most dramatic increase in self-reported problems conceiving and/or carrying a pregnancy to term in women under age 25.

Yet several factors can confound these statistics. Greater availability of infertility services and newer technologies that make problems more treatable account for some fraction of the increase in doctor visits. Some of the increased reporting of fertility problems during the 1990s surely stems from the sheer number of people in an aging, and consequently less fertile, baby boom generation, coinciding with a trend of more couples waiting until they are older before trying to have children. But the National

Survey of Family Growth also suggests the possibility that biological fertility challenges themselves may be on the rise, among all women of reproductive age but most significantly among younger adults. The study found the most dramatic increase in self-reported problems conceiving and/or carrying a pregnancy to term in women under age 25—a 42 percent increase between 1982 and 1995, as compared with a 12 percent increase in women age 25 to 34, and six percent in women 35 and older. Data from the most recent round of the survey suggest that this pattern is continuing.

DO ENVIRONMENTAL CONTAMINANTS PLAY A ROLE?

A modern "chemical revolution" that began in earnest in the last half of the twentieth century has released thousands of man-made synthetic compounds into the environment. To date some 80,000 have been registered for use in the United States, including components of products ranging from pesticides to plastics, from detergents to cosmetics. Today, many of these synthetic compounds—never part of the environment our ancestors lived and evolved in—can be measured in drinking water, soils, foods, the air, and even in our own bodies. And yet, in contrast to regulation imposed on pharmaceutical manufacturers, there is no requirement that chemical industry manufacturers test their products (other than new kinds of pesticides and some food additives) for effects on human health before commercial introduction. It falls to federal and state agencies to do this testing after products are already on the market and in the environment, and then only if specific concern about the health risks of a chemical is raised. The result is that more than 85 percent of the 80,000 synthetic chemicals registered have never been assessed for their effects on human health.

Many of these compounds may be harmless, but a significant number of those that have been tested are now known to be reproductive toxicants. What especially concerns environmentalists, health groups, and reproductive specialists is that in some notorious cases, the very features that make synthetic compounds attractive to modern industry also make them particularly difficult environmental problems. Consider polychlorinated biphenyls (PCBs), which were used for decades in a wide range of products (including electrical transformers, adhesives, and paints) particularly because they tend to be chemically stable, or persistent. Although banned in the late 1970s because of suspected links to cancer, PCBs persist in lake and river sediments and elsewhere in the environment, and continue to work their way into and concentrate up food chains in ecosystems. This means PCBs end up in people, where they also persist, or bioaccumulate, because they tend to bind to fatty tissue and aren't easily broken down. Other examples of notably persistent contaminants include the pesticide DDT; a class of industrial byproducts called dioxins; certain flame retardants; and perfluorinated compounds, which are used to create nonstick cookware coatings and in fabrics and carpets for their stain and water-resistant qualities.

All of us now carry in our bodily tissues and fluids a virtual stew of heavy metals and hundreds of synthetic chemicals—both persistent ones, which can have a "half-life" in the body of several years, as well as nonpersistent compounds, which may pass through the body in a matter of hours.

In fact, all of us now carry in our bodily tissues and fluids a virtual stew of heavy

metals and hundreds of synthetic chemicals—both persistent ones, which can have a "half-life" in the body of several years, as well as nonpersistent compounds, which may pass through the body in a matter of hours. The July 2005 biannual *National Report on Human Exposure to Environmental Chemicals* by the US Centers for Disease Control (CDC) provides exposure data for 148 chemicals and their breakdown products in a representative cross section of 2400 Americans. The report tells us, for instance, that over 90 percent of Americans have a mixture of pesticides in their bodies; and virtually everyone is exposed to the phthalates, which are a class of widely-used nonpersistent compounds that soften plastic and hold scents and colors. Phthalates are found in products ranging from food packaging to detergents, from vinyl flooring and plastic toys to medical tubing, as well as in a wide variety of cosmetics, shampoos, and fragrances. Another CDC study shows that 95 percent of us carry traces of bisphenol A, a component of polycarbonate plastic and in such products as eyeglass lenses, food container linings, dental sealants, and some plastic water and baby bottles.

Chemical "body burden" studies led by the Mount Sinai School of Medicine and the Environmental Working Group found 167 different contaminants in the blood and urine of nine adult volunteers and an average of 200 contaminants in umbilical cord blood samples from each of 10 babies (dispelling the old belief that babies in the womb are protected from most toxic chemicals by the placenta). In addition to pesticides, plastics and industrial chemicals, other compounds detected in these studies include solvents of all kinds, and waste byproducts from burning coal, fuel, and garbage.

No one can say exactly what the "trace" levels of contaminants now seen in people mean for individual health. The presence of a synthetic chemical in the body does not predict disease, nor will it necessarily reveal how exposure occurred.

However, science long ago proved that some chemicals encountered in the workplace can directly harm an individual's reproductive capacity. In one of the most striking cases, researchers determined nearly three decades ago that men could become sterile if exposed to sufficiently high doses of an agricultural fumigant called dibromochloropropane. The current list of substances regulated due to occupational risks to reproductive health is a short one: The US Occupational Health and Safety Administration regulates only dibromochloropropane and a few other compounds such as lead and ethylene oxide, along with nonionizing radiation, based on their clear and well-documented high-dose effects on the reproductive systems of human adults. Yet, more recent studies suggest that a greater range of agents in the environment could be harmful to human reproductive systems or function, and not necessarily only at high doses, but in some cases, perhaps even at more moderate or "environmentally relevant" exposure levels. *(Tables 1 and 2 below show a sampling of chemicals of concern, associated fertility related effects in animals and/or humans, and representative references for sources of more specific information. The tables differentiate between adult exposures and effects and developmental/fetal exposures and effects.)*

To date some 80,000 have been registered for use in the United States, including components of products ranging from pesticides to plastics, from detergents to cosmetics.

Chemical Exposures During Adulthood and Fertility/Fecundity Related Impacts

A sampling of compounds, effects, and representative references or sources of further information

Exposure (sources)	Potential female effects	Potential male effects
Bisphenol A (BPA) monomer used to make polycarbonate plastic, resins	**oocyte (egg) chromosome abnormalities,** (A) [1] **recurrent miscarriage** (H) [2]	**decreased semen quality*** (A) [3,4]
Chlorinated hydrocarbons dioxins/furans, PCBs, some pesticides (organochlorines) and wood preservative (pentachlorophenol)	**menstrual irregularities** (H, A) [5,6,8] **hormonal changes** (H, A) [5,7,8] **reduced fertility‡** (A) [5,8] **endometriosis** (H, A) [5,9,10] **fetal loss^** (H, A) [8,11,13]	**decreased semen quality*** (H) [8,11,14] **hormonal changes** (H, A) [7,15]
Disinfection by-products drinking water treatment	**fetal loss^** (H) (conflicting) [16,17,58] **menstrual irregularities** (H) [18]	
Ethylene oxide chemical sterilant used in dental and medical practices	**fetal loss^** (H, A) [5,19]	**decreased semen quality*** (H) [19] **miscarriage in female partner** (H) [19]
Glycol ethers paints, varnishes, thinners, printing inks, electronics	**fetal loss^** (H) [20,21] **reduced fertility‡** (H) [21,22]	**decreased semen quality*** (H) [15,20]
Heavy Metals lead, mercury, manganese, cadmium	**fetal loss^** (H, A) [5,23,24] **reduced fertility‡** (H) [25,26] **hormonal changes** (A) [5] **menstrual irregularities** (H) [5]	**abnormal sperm** (H) [15,27] **reduced fertility‡** (H, A) [5,7,15,24] **hormonal changes** (H) [7,15,28]
Pesticides broad category that includes many classes of insecticides, fungicides, herbicides, rodenticides, and fumigants	**menstrual irregularities** (H) [6] **reduced fertility‡** (H, A) [19,29-31] **fetal loss^** (H, A) (conflicting studies) [7,32-36]	**decreased semen quality*** (H, A) [7, 20, 37, 38] **reduced fertility‡** (H, A) (conflicting data) [7,39-42] **miscarriage in female partner** (H) [33,43-45] **sperm chromosome abnormalities** (H) [46,47] **hormonal changes** (H) [7,15,48]
Phthalates plasticizers added to soften plastics like PVC; also found in cosmetics, toys, pharmaceuticals, and medical devices	**fetal loss^** (A) [5] **estrous cycle, ovulatory irregularities** (A) [5] **reduced fertility‡** (A) [49]	**decreased semen quality*** (H) [50]
Solvents benzene, toluene, xylene, styrene, 1-bromopropane, 2-bromopropane, perchloroethylene, trichloroethylene, and others	**reduced fertility‡** (H) [16,19,51-53] **fetal loss^** (H, A) [5,7,19,54] **hormonal changes** (H, A) [5,15] **menstrual irregularities** (H) [5,7,19]	**decreased semen quality*** (H) [15,19,24,52]; **reduced fertility‡** (H) [53,55]; **miscarriage in female partner** (H) [19]; **hormonal changes** (H) [56];
Cigarette smoke includes active and/or passive smoking	**reduced fertility‡** (H) [16,19] **miscarriage** (H) [16] **early menopause** (H) [16] **hormonal changes** (H) [16]	**reduced fertility‡** (H) [19] **decreased semen quality** (H) [16] **hormonal changes** (H) [57]

(H) evidence from human studies. (A) evidence from animal studies. (H,A) evidence from human and animal studies.
* decreased semen quality could include low semen volume, abnormal sperm shapes or motility, decreased sperm counts.
‡ - reduced fertility could include infertility and increased time to pregnancy (reduced fecundity).
Δ - menstrual irregularities could include short or long menstrual cycles, missed periods, abnormal bleeding, anovulation.
^ - fetal loss (typ. in animal studies) is used as shorthand also for early pregnancy loss, miscarriage, or stillbirth (human).

References: See page 26

TABLE 2

Chemical Exposures During Development and Fertility/Fecundity Related Impacts

A sampling of compounds, effects, and representative references or sources for further information

Exposure (sources)	Potential female effects	Potential male effects
Bisphenol A (BPA) monomer used to make polycarbonate plastic, resins	**altered puberty onset** (A) [1] **obesity** (A) [1]	**altered prostate development** (A) [2,3] **decreased semen quality*** (A) [4,5] **hormonal changes** (A) [5]
Chlorinated hydrocarbons dioxins/furans, PCBs	**malformations of the reproductive tract^** (A) [6] **altered estrous cycle** (A) [7] **reduced fertility‡** (A) [7] **hormonal changes** (H, A) (conflicting) [8,9] **altered sex ratio** (H,A) [10–12] **altered puberty onset** (H) [13,14]	**malformations of the reproductive tract^** (H,A) (conflicting) [12,15,16] **decreased semen quality*** (H,A) [6,17] **altered sex ratio** (H,A) [10,12,18, 19] **altered puberty onset** (H) [14]
Organochlorine pesticides DDT/DDE, linuron, others	**delayed time to pregnancy** (H) [20]	**malformations of reproductive tract^** (A) [11,21,22]
Pesticides broad category that includes many classes of insecticides, fungicides, herbicides, rodenticides, and fumigants	**altered sex ratio** (H,A) [19,23] **altered puberty onset** (A) [24]	**altered sex ratio** (H,A) [19,23] **altered puberty onset** (A) [25,26] **malformations of reproductive tract^** (H,A) [27–29] **reduced fertility** (A) [30,31]
Cigarette smoke maternal smoking		**decreased semen quality*** (H) [32,33]
DES	**malformations of reproductive tract^** (H,A) [7,34] **altered hormone response** (A) [34] **menstrual irregularities** (H,A) [7,11] **reduced fertility‡** (H,A) [7,11] **uterine fibroids** (A) [7] **miscarriage** (H) [11]	**malformations of reproductive tract^** (H,A) [34] **altered hormone response** (A) [34]
Heavy Metals lead, mercury, manganese, cadmium	**hormonal changes** (A) [7] **altered puberty onset** (H) [13,35]	
Phthalates plasticizers added to soften plastics; also found in cosmetics, toys, pharmaceuticals, and medical devices		**shortened anogenital distance** (H) [36] **malformations of reproductive tract** (A) [37] **hormonal changes** (A) [37] **decreased semen quality*** (A) [37]
Perfluorinated compounds (PFOS, PFOA) used to make fabrics stain-resistant/water-repellant; in coating of cooking pans, floor polish, insecticides	**hormonal changes** (A) [38]	**hormonal changes** (A) [38]
Polybrominated Diphenyl Ethers (PBDEs) flame retardants found in furniture foam, mattresses, textiles, and electronics		**decreased semen quality*** (A) [39]
Octylphenol/nonylphenol surfactants	**hormonal changes** (A) [7] **altered puberty onset** (A) [40]	**hormonal changes** (A) [5,41] **decreased semen quality***(A) [5,42] **decreased testes size** (A) [41,42]

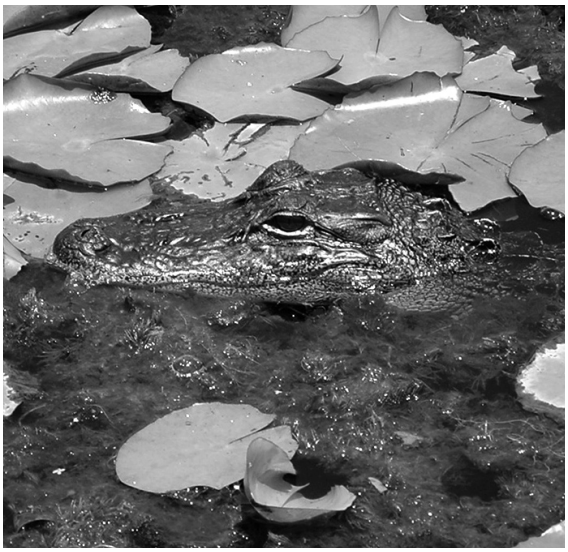
References: See page 28

(H) evidence from human studies. (A) evidence from animal studies. (H,A) evidence from human and animal studies.
* decreased semen quality could include low semen volume, abnormal sperm shapes or motility, decreased sperm counts.
‡ - reduced fertility could include both infertility and increased time to pregnancy (reduced fecundity).
Δ - menstrual irregularities could include short or long menstrual cycles, missed periods, abnormal bleeding, anovulation.
^ malformations of the reproductive tract: In males, could include shortened ano-genital distance in animals or hypospadias (humans), undescended testicles (cryptorchidism), small testicles (hypoplasia), and structural abnormalities of the epididymis. In females, could include small ovaries, reduced number of follicles (eggs), and structural abnormalities of the oviducts, uterus, cervix, and/or vagina.

Just as worrisome as the persistence of some "bad actor" chemicals is emerging evidence that a few nonpersistent compounds, including bisphenol A, can alter the reproductive system of laboratory animals even at extremely low exposure levels. This could be especially relevant because some of these compounds are now chronically present in our environment and lives, with the potential for constant exposure making them functionally equivalent to persistent. Much of this evidence indicates that those most likely to be at risk from exposure to both persistent and nonpersistent but ubiquitous pollutants would be fetuses still developing in the womb and infants, not adults. Scientists are indeed finding it critical to study and distinguish between adult and in utero (or fetal) effects, because the latter can result from much lower doses, depending upon the timing of exposure in the womb. The difficulty in studying effects from fetal or early life exposures, however, is that reproductive health damage that occurs during these early stages of human development may only manifest once an affected individual reaches reproductive age and attempts to conceive a child.

WHAT DO ALLIGATORS AND MICE HAVE TO DO WITH EACH OTHER, AND HUMAN FERTILITY?

Reproductive problems affecting large reptiles living in and around a lake in Florida might seem far removed from people struggling with their own infertility. But studies of wild alligators have indeed been one vital key to understanding important emerging science linking contaminants to human fertility compromise.



In the 1980s, scientists at the University of Florida began finding alligators they described as "reproductively incompetent" in nearby Lake Apopka. The reptiles' afflictions were puzzling. The most obvious symptom: extremely low reproductive rates compared to alligators in other lakes. Closer examination revealed that many young female alligators from the lake had ovarian problems—ovarian follicles that should have produced a single egg instead were producing multiple eggs. Eggs from these "polyovular follicles" could sometimes be fertilized, but embryos typically died soon after. Some of the eggs had multiple nuclei instead of the normal single nucleus. The phalluses (penises) of male alligators were abnormally small, and blood samples showed that juvenile males had markedly lower levels of the male hormone testosterone—one third the level in normal juvenile male alligators—and unusually high levels of estrogen (technically, the female hormone estradiol). The females, too, carried abnormally high levels of estradiol in their blood. Where, the researchers wondered, could all this estrogen be coming from?

In time, the Florida scientists, led by zoologist Louis J. Guillette Jr., began to piece together a probable answer to the puzzle. It turned out the alligators' mothers had been exposed to pesticide contamination in the lake, including from a large 1980 spill of the

insecticide dicofol from a nearby chemical plant that had since closed. The Florida scientists were also learning that researchers elsewhere had proven that some pesticides can behave like synthetic forms of estrogen, and wreak havoc with the animal reproductive systems. In fact, Guillette and his colleagues were able to produce similar abnormalities in baby alligators newly hatched from otherwise clean eggs by painting the eggs with various pesticides. They then duplicated those effects by painting clean eggs with synthetic estrogen. This established solid scientific evidence that the pesticides could behave much like hormones.

The researchers in Florida soon became part of a growing network of scientists who had collected various pieces of evidence that a wide range of pesticides and other environmental contaminants are capable not only of mimicking estrogen, but of disrupting the hormonal, or endocrine, system in animals in a number of ways. Studies with lab animals showed certain contaminants such as the fungicide vinclozolin, used widely in vineyards but also on other crops, can act as anti-androgens, blocking the action of male hormones or preventing their production in the first place. Others appeared to be anti-estrogens. Still others appeared to interfere with enzymes involved in the formation or metabolism of hormones. This array of hormonally active compounds came to be called "endocrine disruptors."

Relationships between contaminants and disruption of the hormonal system have now been seen in a remarkably wide range of species, from seagulls to polar bears, seals to salmon, and mollusks to frogs. With both seagulls and salmon, contaminants have been linked to the development of intersex reproductive systems that include vestiges of both male and female sex organs. In some of the earliest research on hormonal disruption in animals, researchers were able to prove that the pesticide DDT could cause the intersex effect in seagulls by dosing clean gull eggs with the compound as embryos developed.

Relationships between contaminants and disruption of the hormonal system have now been seen in a remarkably wide range of species, from seagulls to polar bears, seals to salmon, and mollusks to frogs.

Hormones such as testosterone and estrogen, whether in the body of an alligator, a gull, a salmon, or a human, send biological signals to cells that alter how genes behave. While the details vary, typically hormones bind chemically with a cellular structure called a "receptor," move together with the receptor into the cell nucleus, and then bind with DNA in a way that turns the gene on to produce its natural chemical product. Those products are part of the cell's chemical "machinery" that makes life possible. Sometimes they send signals to other genes, sometimes they become part of the cell's structure, building muscle or converting stem cells to more specialized tissues. This process of turning genes on (and off) goes on throughout life in a never-ending symphony, with each gene an instrument that follows its own conductor.

An exquisitely tiny amount of these signaling molecules can trigger a dramatic response between cells in our bodies. One scientist has compared this effect to the thundering wall of sound a music amplifier can produce from a tiny initial electrical pulse.

In the female reproductive cycle, multiple hormonal messengers serve as a complex

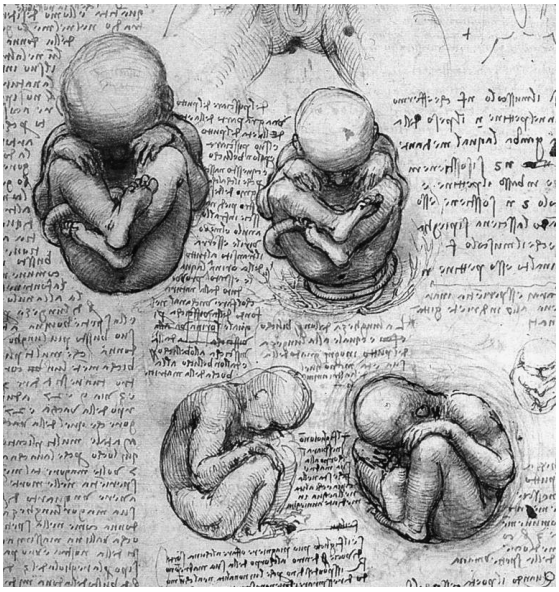
signaling and feedback system, with one hormone switching on a sequence of genes that control ovulation, then another hormone switching off production of the first one to keep ovulation correctly modulated. If an egg is successfully fertilized, hormones signal the entire ovulatory and menstrual cycle to shut down while a pregnancy proceeds. If not, a different pattern of hormonal signals triggers a new ovulation cycle. Birth control pills work by interfering with the normal levels of hormones that direct a woman's cycle, so that ovulation doesn't occur.

FETAL ORIGINS OF ADULT DISEASE—THE DES EXAMPLE

Hormones also play vitally important roles during fetal development, orchestrating in intricate detail aspects of development ranging from the formation of the sex organs to the structure of the brain. A key idea proposed by scientists working with endocrine disruptors is that some of these compounds can do their most serious damage during the critical months that a fetus is in the womb.

The human experience with a compound called diethylstilbestrol (DES), a synthetic estrogen, provides important clues about how this might work. Over a period of more than 30 years beginning in the late 1930s, DES was administered to more than five million pregnant women, and perhaps as many as 10 million. Doctors believed the synthetic estrogen would help prevent miscarriages and premature births.

That assumption proved to be wrong. Still, the drug at least seemed safe (for humans, anyway; rodent studies had shown it to be carcinogenic as early as the 1930s). Through years of prescribed use, mothers who took the artificial hormone showed no serious health effects. But in 1971, scientists came to a stunning conclusion: although there still was no evidence of health problems in the exposed mothers, a significant number of their *daughters* were experiencing reproductive health problems. Those maladies usually appeared only after the daughters were well into their own child-bearing years, long after they had been exposed to the substance in the womb.



Views of the Fetus in the Womb, Leonardo da Vinci, c.1510-12

Symptoms among DES daughters included a higher risk of an otherwise exceedingly rare vaginal and cervical cancer called clear cell adenocarcinoma, as well as abnormalities of the uterus and other parts of the reproductive tract. DES daughters also clearly suffer from an unusually high rate of infertility problems— at least double that in the unexposed population. Additionally, DES daughters suffer more ectopic (tubal) pregnancies, which occur when a fertilized egg lodges in the fallopian tube instead of the uterus. And when DES daughters do conceive, 40 percent or more are unable to achieve a full-term live birth. Laboratory scientists have observed many of these kinds of results in mice they have exposed to DES experimentally.

After researchers began examining DES sons, they discovered that male offspring

of DES mothers tended to develop non-cancerous growths on their testicles called epididymal cysts. Similar effects had already been observed in male mice whose mothers had been exposed to DES in laboratory experiments. Some research also suggests that DES sons have experienced higher rates of other reproductive system abnormalities including undescended testicles (cryptorchidism), and another condition (hypospadias) in which the opening of the penis appears along its shaft rather than at the tip, as well as smaller than normal penis size. Follow up studies have not confirmed whether this is a clear trend.

The entire DES experience turned out to be an unwitting experiment that involved dosing developing fetuses with a poorly understood compound, an experiment that effectively exposed them to far higher doses of hormones than they would ever naturally experience in the womb. Thus DES became a model that helps scientists understand how some endocrine disruptors might harm human health. While doses of DES ingested by pregnant women were much greater than those that would result from exposure to environmental estrogens, many of the mechanisms underlying their effects appear to be similar.

There have been a handful of similar unwitting experiments on humans. Researchers in Taiwan have been able to study children whose mothers had been accidentally exposed to high levels of PCBs while pregnant. Their exposure, in 1979, came from cooking oil that had become accidentally contaminated with the pollutant. The scientists found a surprisingly wide range of disorders in these children. Their afflictions included an echo of the Florida alligators— boys with atypically small penises—along with unusually high rates of learning disabilities and anomalies of their skin and nails.

The most important message to take away from the story of alligators, mice, pesticides, and DES? At low doses, endocrine disrupting contaminants may cause little or no damage to an adult, but for a fetus, hormonal disruptions in the womb can silently set the stage for later problems. When health damage finally appears, it may affect multiple targets in the reproductive system or elsewhere. In recent years, scientists have made considerable progress in identifying dozens of additional compounds that are hormonally active.

So what can be learned from alligators or mice? Plenty. We certainly rely on the results of animal studies to guide us in evaluating the safety of pharmaceuticals and food additives.

Again, although we learned a great deal from the DES and PCB "experiments" where humans were unwittingly exposed, most of the research that has identified reproductive harm from endocrine disruptors has been done in animals. So what can be learned from alligators or mice? Plenty. We certainly rely on the results of animal studies to guide us in evaluating the safety of pharmaceuticals and food additives. Once one understands the similarities and differences among reproductive processes across different types of animals, one can often predict effects in humans based on the animal data. The key here is to understand that the chemical structures of hormones and their receptors are very similar among vertebrates, including humans. A chemical that binds with an estrogen receptor in mice is almost certainly going to bind with an estrogen receptor in people. Strain and species differences do exist, especially in labo-

ratory animals that have been bred for specific research purposes, but large differences would be the exception rather than the rule. This means that the developmental processes that are under the control of hormones, and affected by endocrine disruptors in mice, are likely also going to be affected in people. The specific result may vary—more sensitive, less sensitive, a different endpoint, or outcome—but what the alligator and mice studies tell us, along with research in birds and fish, is that endocrine disruptors that have large effects in one group of vertebrates are highly likely to have large effects in other vertebrates. There is no scientific reason to believe that people will somehow be exempt from these potential effects.

ENVIRONMENT, DISEASE, AND GENES: NEW CLUES, AND SHOCKWAVES

As noted above, some contaminants interfere with signaling by acting like hormones themselves, for example, binding with the hormone receptor and thereby stimulating genes that respond to that hormone. But newly developing science is revealing yet another mechanism of impact, another layer of the system that controls how genes behave. This newer evidence suggests that even when a specific gene is present, and even when the proper hormone signal is being sent, certain chemicals can actually act like a protective screen, preventing the hormone from reaching the switch that normally turns a gene on. The gene may be there, but because the signal can't get to its switch, the gene remains in the switched-off state and therefore it can't produce the proteins that would normally catalyze a given response in a cell.

One mechanism cells use to control whether genes are switched on or off is called DNA methylation. In this case, molecules called methyl groups are attached to the DNA in locations that prevent the signal molecule from reaching the switch. These methyl groups naturally control whether a gene can be turned on when its signal arrives, in other words, whether the gene will be "expressed." If access is blocked, the hormone signal has no effect. Different types of cells within a single person have different methylation patterns. That's how cells in all tissue types—eye tissue or muscle tissue or fat tissue—can share the exact same set of genes but differ widely in what they do. While methylation occurs naturally, scientific research has proven that DNA methylation is also influenced by the environment. In fact, some scientists suggest that one purpose of DNA methylation is to fine tune an individual's genetic makeup to the environment into which it will be born

DES daughters also clearly suffer from an unusually high rate of infertility problems—at least double that in the unexposed population.

In the 1980s, David Barker, an epidemiologist at the University of Southampton, in England, identified a puzzling trend that had appeared in government health data: adults who had been born during the years of the Great Depression in some of Great Britain's most impoverished areas were afflicted with strikingly high rates of obesity, cardiovascular disorders, and diabetes. After ruling out other causes, Barker suggested that while they were fetuses, these individuals' genes might somehow have been programmed in ways that prepared them for a similarly nutrition-deprived world.

When they instead grew up in a world of relative food abundance, genetic alterations they had experienced in the womb—changes that might have saved their lives had they been born into near starvation—instead caused them to overeat, or for their cells to over-conserve fats or salts. A strategy that might have helped them survive in a hungry world instead triggered an entire matrix of health problems. Barker's hypothesis was greeted with skepticism. But later studies lent credence to his observations. Studies of the sons of malnourished Dutch women who were pregnant during the so-called Dutch Hunger Winter in 1944–45, under Nazi occupation, showed that these males at age 19 were far more likely to be obese than their peers. Studies from other nations, including Finland and India, and research with laboratory animals, also appear to support the Barker hypothesis.

If this hypothesis is correct, how might such mechanisms have evolved in humans? Over evolutionary time, the ability of a fetus to make adjustments in response to famines could have conferred survival advantages. But a fetus cannot change its genes. Signals of stress from the mother, however, *could* alter the *sensitivity* of genes to the signals that control what genes actually do (gene expression). Emerging evidence shows that some environmental chemicals can similarly alter this control system. When a male mouse fetus is exposed in the womb to extremely low levels of the polycarbonate plastic component bisphenol A, the prostate gland of that mouse is hypersensitized to hormone signaling when it becomes an adult. This pattern of fetal exposure followed by altered sensitivity to hormonal signals is emerging as a common thread in research, providing clues about how the phenomena Barker observed might actually be produced at the level of genes and molecules.

Signals of stress from the mother, however, could alter the sensitivity of genes to the signals that control what genes actually do (gene expression). Emerging evidence shows that some environmental chemicals can similarly alter this control system.

Participants at the Vallombrosa Workshop learned that compelling new data about multigenerational effects of changes in gene expression were about to be published. In early June of this year, researchers based at Washington State University revealed in the journal Science a study of gene expression in laboratory mice that, as another journal later commented, sent "shock waves" through the scientific community. In this study, researchers dosed pregnant laboratory rats with the fungicide vinclozolin and a pesticide called methoxychlor—both known endocrine disruptors. Nearly all (90 percent) of the exposed females' male offspring had reproductive system problems, including high rates of sperm death. But then the researchers bred the first-generation offspring and found unexpected results: their male offspring, which had never been exposed to the compounds, had similar reproductive system abnormalities. As they continued to breed the lab animals, they discovered that the poor fertility traits were passed through at least three generations of males that had never been exposed to the contaminants. The damage the contaminants caused, in other words, was a trait that could be inherited even though the DNA *sequence* itself had not been affected. They concluded that the exposure to endocrine disruptors was altering DNA methylation (that second layer of control), changing whether or not genes could be turned on when signals arrived.

Scientists found these results especially surprising because they run counter to accepted notions of how disease can be inherited. In this study, the original, exposed male rats did not pass down "bad genes" in the classic sense—that is, with an altered DNA sequence. Instead they passed down genes that had been reprogrammed to behave differently. This preliminary work suggests it is plausible that an individual could experience disease (reproductive or otherwise) that was triggered by a pollutant exposure his or her great-grandmother experienced. But many questions remain to be answered about these discoveries before we learn their relevance to humans. It is important to note that this initial study was done with high levels of exposure—much higher than most people would experience. Scientists do not know whether this sort of reprogramming would occur at lower levels of exposure. And, researchers are only beginning to ask questions about how such phenomena might affect human fertility in a broader sense. However, discoveries such as this one suggest that scientists need to broaden their concept of what genetically-based diseases really are.

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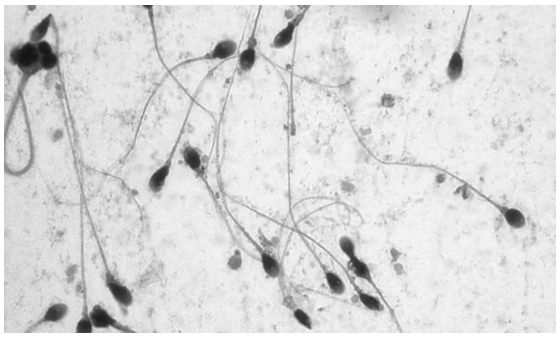
CONTAMINANTS AND MALE INFERTILITY: TESTICULAR DYSGENESIS SYNDROME

Several researchers have suggested that contaminants in the environment might cause a matrix of reproductive problems in men. One formulation of this is a proposed "testicular dysgenesis syndrome." According to this hypothesis, disruption of cellular processes in the fetal testis leads to multiple physical disorders, including at least two that appear at birth: cryptorchism (undescended testicles) and hypospadias (the opening of the penis is along the shaft, rather than at the tip). Other problems may not become evident until later in life: reduced sperm counts, reduced sperm quality (meaning large numbers of deformed sperm or sperm that do not move normally) and testicular cancer. Linkages among the disorders suggest a common cause. Past research has shown that babies born with undescended testicles face a higher risk of contracting testicular cancer later in life. They also appear to be at higher risk for fertility problems as adults.



A widely cited 1992 Danish study analyzed dozens of sperm count studies going back to the 1930s, and concluded that sperm counts had declined by about 50 percent throughout the western industrialized world over a period of five decades. This analysis was controversial. Critics noted that since the previous studies were not conducted in rigorously consistent ways, multiple factors could have confounded the results. (Some of the studies, for instance, had relied on samples from men visiting infertility clinics.)

In 2000, a new review by scientists in the US of 101 studies, including several published since the 1992 Danish work, supported the Danish study's conclusion. Using a more sophisticated statistical analysis, the review also revealed that trends were different in different regions around the world. At the same time, however, the scientists cautioned

that because data in the older studies had in many cases been gathered differently from the way they had in more recent studies, scientific uncertainty remains. This conclusion has stimulated a new generation of research that standardizes data collection in a network of research laboratories around the world, and is also paying special attention to geographic variability in sperm counts and other measures of reproductive function.

Why, for example, are men from Missouri likely to have lower sperm counts than men from Minnesota? Some tantalizing results are suggesting answers. In a rigorously controlled 2003 study conducted at university hospitals, researchers showed striking regional differences in sperm counts in samples from men in New York, Minneapolis, Los Angeles, and Columbia, Missouri. Most notably, men in the more rural Missouri sample had about half as many moving sperm as men in urban centers, most strikingly in Minneapolis, Minnesota.

A follow up study of samples of men from these same locations showed a possible link to the higher levels of agricultural pesticides to which rural men are exposed. The Missouri men showed far higher levels of three widely use pesticides—alachlor, atrazine, and diazinon—in their urine. Men showing the highest levels of these compounds were more likely to have poorer sperm quality. The most striking correlation was with the heavily used weed killer alachlor. Among Missouri men, the chance of low sperm counts was 30 times greater for those with the highest levels of the contaminant in their urine compared with those with the lowest levels.

Interestingly, studies have shown increasing rates of testicular cancer in some countries but not in nearby ones. Testis cancer rates in Sweden are twice as high as in nearby Finland. Rates in nearby Denmark are twice as high as rates in Sweden, and four times as high as in Finland. Furthermore, one detailed study showed that men who had emigrated from Finland to Sweden continued to show dramatically lower rates, lending support to the idea that the cancer's origin had been in the womb. One plausible explanation: at the time the men were fetuses, Danish women, living in a nation with a large modern agricultural industry, might well have been exposed to higher levels of endocrine disrupting pesticides than were mothers in colder, more northern Finland, where farming was less intense.

Why, for example, are men from Missouri likely to have lower sperm counts than men from Minnesota? Some tantalizing results are suggesting answers.

There are other clues from human studies related to testicular dysgenesis syndrome. In 2003, Swedish researchers reported a strong association between testicular cancer risk and the levels of PCBs and a range of chemically related compounds (organochlorines) in male subjects' *mothers'* blood, even though the cancer was detected and the measurements taken two or more decades after birth. There was only a minimal correlation between levels of the organochlorines in the man's own blood and his risk for testicular cancer. These results thus also suggest that testicular cancer has roots in fetal development. Additionally, studies comparing sexually mature males in Taiwan who had been accidentally exposed in the womb to high levels of PCBs in 1979 showed significant problems with abnormal sperm when compared with unexposed males.

In May 2005, shortly after the Vallombrosa workshop, Shanna H. Swan, one of the scientists who had organized the meeting, and a group of coauthors published the results of a new study of the effect of phthalates on male reproductive health. This study found an association between phthalate levels in human mothers' urine and an anatomical variation in the genital area of their newborn sons that appears to be the result of the anti-androgenic effects of phthalates.

The impetus for this study was provided by research with animals, which had shown that when pregnant rodents are exposed to phthalates, their male offspring were born with shortened perineums (the area between the genitals and the anus). Usually this anogenital distance is about twice as long in male rodents as in females. A shortened distance is associated with reduced testosterone availability in the rodent womb.

Only two studies have looked at this measure in human infants, but both indicate that human boys also tend on average to have longer anogenital distance than girls. Swan's study confirmed the prediction from animal results that prenatal exposure to phthalates would be associated with shortened anogenital distance in humans as well, and found the effect was most striking in boys whose mothers carried the strongest mixtures of phthalates. Together with animal data, these results suggest that phthalates act as anti-androgens in humans also, interfering with the hormones needed for normal sexual development, and that the contaminants had partially, if subtly, "undermasculinized" the boys whose mothers carried larger body burdens. Although this anatomical measure may seem inconsequential in and of itself, previous research has shown that when testosterone levels are lowered enough to cause reductions in perineum size in animals, other effects tend to appear later in life, including reduced fertility and changes in sexual behaviors. The researchers noted that they observed the effect at levels of phthalates equivalent to those seen in about one in four American women.

CONTAMINANTS AND FEMALE INFERTILITY

While research focused on the effects of contaminants in the womb has lead to important breakthroughs in recent years, other studies continue to highlight that contaminants can cause harm later in childhood and in adulthood. In addition to the evidence that high occupational exposures to some compounds can lead to sterility in men, one scientist at Vallombrosa noted that at least six studies have shown links between PCBs, lead, and other compounds and early onset of puberty in girls. Other investigations have demonstrated correlations between adult reproductive system effects and exposures to a range of pesticides; chemicals in cigarette smoke; fuel, hobby and industrial solvents, such as benzene and dry cleaning fluids; and water disinfection byproducts. Although the effects sometimes are as striking as increased risk of pregnancy loss (or damaged sperm and poor fertility in men), often they are more subtle: ovarian and menstrual cycle alterations, for example, or delays in the amount of time it takes to conceive. Scientists still know little, however, about the long-term effects of what one Vallombrosa

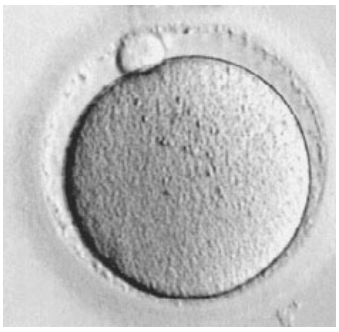
Scientists still know little, however, about the long-term effects of what one Vallombrosa scientist termed "subtle hits" of this kind to the reproductive system...

scientist termed "subtle hits" of this kind to the reproductive system, including multiple hits over time and from different mixtures of these compounds.

Some clues about potential links between adult exposure to contaminants and factors affecting female infertility come from studies of rhesus monkeys exposed to dioxins—ubiquitous chemical residues of various industrial processes. (Dioxins were prominent trace components of the notorious defoliant Agent Orange, but they can form from practices as common as the bleaching of paper and the incineration of certain plastics.) Following exposure, the monkeys developed severe cases of endometriosis. Endometriosis is a chronic disease where tissue similar to that which ordinarily lines the uterus grows abnormally in other locations, including on the ovaries and fallopian tubes, in the pelvic cavity, and in more rare cases, such distant organs as the lungs or heart. Although it sometimes occurs without symptoms, many of the more than five million women in the United States and Canada with the disease suffer from serious physical pain. *About 40 percent of women diagnosed with endometriosis also suffer from infertility.*

The Endometriosis Association, which participated in the workshop, maintains a research registry of patients that suggests that the disease is becoming increasingly common in younger women.

In the studies of rhesus monkeys, adults exposed to dioxins spontaneously developed endometriosis, in some cases progressing to such a severe stage that the animals died. Later research with another species of monkey showed that dioxins promoted the proliferation of endometrial cells implanted in the animals, with higher dioxin doses clearly promoting more severe cases of the disease.



Another area of research that has evoked great interest involves a serendipitous finding reported in 2003 by a team of scientists at Case Western Reserve University. They were studying oocytes (eggs) in mice when they observed suddenly soaring rates of chromosome abnormalities. Such abnormalities lead to a condition called aneuploidy —the loss or gain of chromosomes in a cell as a result of an error in cell division. In humans, aneuploidy can cause early miscarriages and birth defects such as Down Syndrome. The astonishing increase in the number of mouse eggs with chromosome problems in the Case Western lab was eventually traced to the use of a harsh detergent to wash the animals' polycarbonate plastic cages and water bottles. Follow-up experiments established that the detergent damaged the plastic, causing bisphenol A to leach from the bottles and cages—and that it was the exposure to this endocrine disrupting chemical that triggered the dramatic increase in aneuploidy. Although the researchers pointed out that this study does not prove bisphenol A causes aneuploidy in humans, the team was studying eggs in mice specifically because previous work has established that there is significant "conservation" between the two species in the cellular mechanisms involved in the cell division process

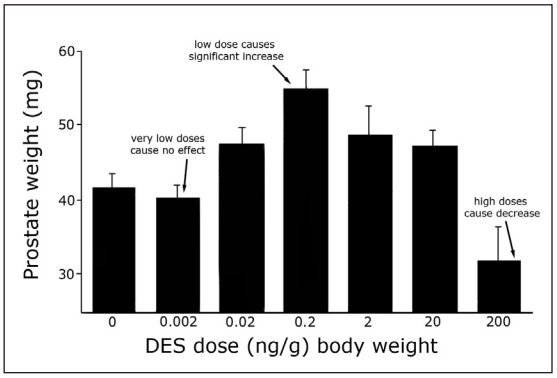
DOES THE DOSE MAKE THE POISON?

The Renaissance-era physician Paracelsus wrote that "All substances are poisons…The right dose differentiates a poison and a remedy." That very idea—that there is a predictable relationship between the dose of a potentially toxic substance and the health effects it causes—lies at the heart of the traditional approach to environmental risk assessment and regulation. Regulators have operated on the assumption that it is possible to identify a level below which exposure to a given substance poses no risk, allowing them to set a "no observable effects" exposure threshold. Typically, scientists do such an analysis by starting with high-dose testing and working down to a dose level where the effects being observed disappear. Although this holds true for many compounds, newer research, particularly on endocrine disrupting compounds, has revealed that some chemicals and health responses do not behave according to this seemingly logical assumption. Some chemicals have effects at very low doses that can't be predicted from the results of high-dose studies. This means that standard toxicity testing that relies on testing high doses could miss important effects.

Some chemicals have effects at very low doses that can't be predicted from the results of high-dose studies.

Scientists at the University of Missouri, for instance, have found that when male mice are exposed in the womb to bisphenol A or the drug DES, low doses cause enlargement of the prostate gland once the mice mature. Intermediate doses caused no apparent effects, and higher doses actually caused the prostate to be *smaller*.

How can this happen? Scientists believe that at low doses these compounds can stimulate the expression of genes involved in controlling prostate size. At higher doses, in contrast, they become toxic and damage the prostate outright. The bottom line: although the dose-makes-the-poison rationale seems logical, new science casts serious doubts at least on the way the principal has been used to develop health standards, particularly when it comes to the dose it takes to alter the hormonal or genetic signaling systems in a still-developing fetus.



Adapted from: vom Saal, F, et al. 1997.
Prostate enlargement in mice due to fetal exposure to low doses of estradiol or diethylstilbestrol and opposite effects at high doses. PNAS USA 94:2056-61

WHAT'S NEXT

Science has begun to demonstrate clear links between some environmental contaminants and fertility problems, and experts continue to work at filling gaps in scientific understanding. Solving the uncertainties, however, will be challenging—first because infertility is distinguished by complexities that resist easy understanding. There are degrees of infertility, and variability depending upon mate. It can be caused by female, male, or couple-dependent factors—or some combination of those factors simultaneously. And like other health problems, infertility can be the result of multiple interacting influences (including genetics, environment, nutrition, infections, and/or lifestyle).

Adding to the complexity where environmental compounds are concerned is the reality of mixtures of chemicals. To date, most research has focused on single com-

pounds. Yet some early studies, and common sense, suggest it is important to assess the combined effects of various ingredients in the synthetic chemical cocktail to which virtually all of us are exposed. Combined, small amounts of many chemicals could add up to have large effects. And the effects may be more than simply additive. Early studies suggest that some substances might amplify the effects of others, with, say, compound A making cells more sensitive to compound B. Considering that mixtures of compounds are present in all of us, from newborns to adults, understanding more about chemicals' combined effects will be a critical area for future research. Science still has a long way to go in developing accurate methods to assess the effects of most combinations of chemicals.

Yet another challenge in this research arena is the possibility of long latencies of effect—even decades later—following early life exposures. Epidemiological studies are almost never designed and funded long enough to include the evaluation of effects so long after the exposures occurred. The bottom line is that reproductive epidemiologists need to develop a whole new generation of research tools and designs.

Counterbalancing these complexities is the promise of an array of emerging tools and analytic methods that Vallombrosa workshop scientists say will allow investigators to make considerable progress in understanding the effects of chemicals on health. David Keefe, a physician and scientist based until recently at Brown University, showed computerized imagery from a polarized light microscope that has allowed his research team the first-ever opportunity to look deep inside a human egg without damaging it. Keefe and his colleagues' ability to look at the spindle, which holds the chromosomes, is aiding research into how structures called telomeres, which protect the ends of the chromosomes (picture the little plastic caps on the ends of shoelaces), can be damaged by arsenic in a woman's body—specifically, in the ovarian follicle fluid surrounding her eggs.

Other important tools involve fields of inquiry such as toxicogenetics, which focuses on how genetic variations contribute to individual sensitivities to chemicals, and proteomics, the study of how proteins work and interact with each other inside cells—as well as such closely related areas of study as genomics (the analysis of altered patterns of gene expression) and metabolomics (cell metabolism and chemical breakdown). Combined with the development of increasingly sensitive biomonitoring tools to measure more and more compounds at ever lower levels, it is quite possible that huge leaps will be made over the next decades in terms of more specific understanding of environmental reproductive health.

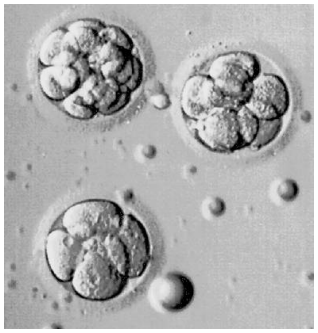
An example of the kind of epidemiological research design that Vallombrosa participants agreed is critical is the National Children's Study, currently in its initial stages. Sponsored by the National Institutes of Health, the Environmental Protection Agency, and other federal entities, the study will assess the effects of environment on the health of more than 100,000 children across the United States, following them from before birth until age 21. While full results won't be available for decades, some insights will

emerge as the children are born and as they develop.

Which leaves everyone involved with a lingering question: what to do while the science moves ahead? Viewpoints at the workshop varied. Physicians pointed out that while patients are eager for information about contaminants and environmental risk factors, doctors can be reluctant to "get ahead of the science"—that is, unwilling to make recommendations based on speculation or early and incomplete research. Other participants made countervailing note of the "precautionary principle"—the notion that health professionals, or in a broader scope, government regulators, should promote precautionary action in the face of "weight of credible evidence" of serious toxicity (from, say, animal studies), even if all the scientific "i's" haven't yet been dotted, nor "t's" crossed. It seems clear that this is a debate that medical and regulatory communities still need to resolve.

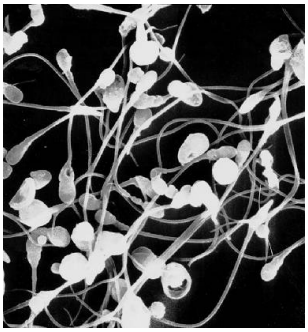
Issues around communication and education emerged as a powerful theme. Despite scientists' and clinical researchers' hard work investigating the impacts of environmental chemicals on health, so far there's been limited information transfer to infertility patients and reproductive health advocacy groups—and some measure of uncertainty about the most effective ways to communicate information accumulated so far to physicians and the general public. One clinician emphasized that medical students are taught little, if anything, about even well-established environmental chemical threats to reproduction, and thus they enter their profession with limited ability to ask the right questions about environmental exposures their patients may face, and limited perspective on the full range of potential culprits as they conduct diagnostic workups and determine infertility treatment strategies. Patient advocates stressed that they need translational models and lay-friendly materials in order to share information with their constituencies.

Among scientists at the workshop, the need for effective communication of another kind—between scientific disciplines—was stressed as a critical aspect of an expanded and more coherent environmental reproductive health research program. For example, researchers attempting to study links between environmental exposures and health problems in human populations are often limited to conducting either retrospective (historical) statistical studies of groups to trace trends, or to waiting patiently for the results of long-term prospective studies like the National Children's Study that follow their subjects over periods of many years. Better interdisciplinary communication and collaboration with scientists conducting actual experiments on lab animals could give those studying humans a better sense of what endpoints, or potential effects, to look for. (Some of this is happening already: Shanna Swan's team decided to look for effects of phthalates on newborn boys based on the results of other scientists' studies of laboratory mice.) Conversely, with better interdisciplinary coordination, lab researchers could gain insights from epidemiologists about endpoints to look for in their work.



There was general affirmation at Vallombrosa that despite the financial barriers, infertility treatment remains a hopeful and increasingly successful alternative for many

would-be parents—but that at the same time there ought to be a commensurate focus on *prevention* of fertility compromise where that is at all possible.



The Vallombrosa discussions are only a starting point. Piece-by-piece, science is yielding answers. That in turn offers hope—because the good news is that on broad public policy scales, prevention strategies based on solid science and medicine work when there is political will to develop and implement such strategies. Think about dramatic past improvements in so many areas of public health, from vaccine programs that have eliminated smallpox to water treatment programs that have conquered cholera in the developed world. Experience in the United States and elsewhere in recent decades has shown that when a community or society makes a decision to ban or reduce exposures to toxic compounds—lead, and more recently, flame retardants in Sweden are both good examples—dramatic progress comes quite rapidly in terms of reduced human body burdens of those chemicals. In certain cases, effective prevention might rely on individual initiative (quitting smoking, not eating fish from contaminated waters) based on advice from physicians and public health authorities. But since it is impossible to simply avoid contaminants that are ubiquitous, or otherwise described as "ambiently pervasive in the environment," action at the personal level ultimately may not be adequate. More complete upstream testing of chemicals and, when necessary, proper regulation may be the only approach that truly protects reproductive health.

Biomonitoring, or the testing of human biospecimens such as blood, urine, hair, adipose tissue, bone, etc., for the presence and level of toxic chemicals is a public health tool that has been used primarily by epidemiologists and health researchers for decades to identify trends in chemical use; to determine if some populations or communities might be more highly exposed than others; to establish exposure levels for average Americans; and to determine whether regulations limiting exposures are effective. Biomonitoring data are also used to examine possible linkages between chemical exposures and health outcomes. But in order to generate data that is useful for this purpose, studies need to test large populations as is standard in epidemiological studies.

Individuals learning about environmental health are increasingly interested in being biomonitored. However, it is important to look carefully at the reasons for individual testing. What will it tell you? Here are some factors to consider:

- Biomonitoring a single individual is difficult, because laboratories are not set up to conduct single-sample testing, and there are few laboratories that have the capacity to test for the low levels of the chemicals most of us have concerns about.
- Individual testing needs to be prescribed by a physician. Since most physicians are unfamiliar with biomonitoring protocols and have little training in the significance of biomonitoring data, finding a physician to order biomonitoring tests can be a challenge. Unless there is a compelling medical complaint or diagnosis (e.g., someone is showing clinical symptoms of mercury poisoning), a private physician would not have a reason to order tests.
- Lab tests are expensive. At this time, a robust set of tests that would provide a good snapshot of exposure costs about $5,000. Without a medical reason to biomonitor, insurance companies will not cover the costs.
- Sometimes biomonitoring can help pinpoint a problem, but in general the presence of a chemical in the body cannot predict disease, nor will it necessarily reveal how exposure occurred. After receiving the raw data of their results, individuals need help understanding and interpreting their body burden numbers.

The bottom line is that getting individual testing can be expensive, complicated, and is not likely to answer specific individual health questions. That said, *individual data can be useful*. Although it may not be predictive of future health or health problems (perhaps at this point simply because toxicologists don't fully understand the role of chemical exposures in the incidence of disease), knowing one's chemical body burden might seem particularly relevant for those planning or already attempting to conceive. Individuals with concerns about a particular disease, disease propensity, or specific unexplained symptoms might well want to learn more about their body burdens so that they can make better consumer and behavior choices to try to reduce worrisome exposures. For example, someone with diffuse and otherwise unexplained symptoms such as stomach upset, hair loss, and fainting spells—or someone with heart disease—may be concerned about how much mercury his or her body carries, since some studies link mercury to these problems. A change of diet can usually lower levels of mercury, if biomonitoring data indicates that an individual's levels are high.

Thus, even given the barriers, a concerned individual may decide to ask his or her physician about biomonitoring. Perhaps as demand increases, barriers to individual testing will decrease. Just as we are able to use a thermometer to measure our body's response to infection, we might some day be able to monitor our body's chemical "temperature," and be able to make better choices about the food we eat, water we drink, and products we use.

BIBLIOGRAPHY

A bibliography for the Vallombrosa workshop and this paper is posted online at both:
womenshealth.stanford.edu/environment/fertility.html
www.healthandenvironment.org/working_groups/fertility
At these Web sites you will also find links to the workshop program and participant list.

COMPANION SCIENTIFIC CONSENSUS STATEMENT

The *Vallombrosa Consensus Statement on Environmental Contaminants and Human Fertility Compromise* can be accessed via links on these three sites:
womenshealth.stanford.edu/environment/fertility.html
www.healthandenvironment.org/working_groups/fertility
www.ourstolenfuture.org/consensus/2005/2005-1030vallombrosa.htm

RESOURCES FOR FURTHER INFORMATION

BOOKS

1. Our Stolen Future: ***Are we threatening our fertility, intelligence, and survival? A scientific discovery story.*** Theo Colborn, Diane Dumanoski, and John Peterson Myers. Foreword by Vice President Al Gore. Plume Publishing. 1996. ISBN: 0452274141

2. Generations at Risk: ***Reproductive Health and the Environment***. Ted Schettler, Gina Solomon, Maria Valenti, and Annette Huddle. MIT Press, 1999. ISBN: 0262692473

GOVERNMENTAL ORGANIZATIONS

1. US Centers for Disease Control (CDC)

a. Produces the National Report on Human Exposure to Environmental Chemicals—an ongoing assessment of the US population's exposure to environmental chemicals using biomonitoring. www.cdc.gov/exposurereport/ Updated 7/26/05.
b. Agency for Toxic Substances Disease Registry (ATSDR) www.atsdr.cdc.gov The principal federal public health agency charged with responsibility for evaluating the human health effects of exposure to hazardous substances. Publishes tox profiles online.
c. The National Center for Environmental Health (NCEH) www.cdc.gov/nceh/ehhe/
d. The National Institute for Occupational Safety and Health (NIOSH) www.cdc.gov/niosh/homepage.html Information on chemical safety, workplace health hazard evaluations, and reproductive health and occupational exposures.
e. National Center for Health Statistics www.cdc.gov/nchs/ and the National Survey of Family Growth (NSFG) www.cdc.gov/nchs/nsfg.htm

2. The National Institutes of Health (NIH)

a. The National Institute of Environmental Health Sciences www.niehs.nih.gov/ Has many links to environmental health information, including reproductive health.
b. Medline Plus, Reproductive health informationwww.nlm.nih.gov/medlineplus/reproductivehealth.html

c. The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) cerhr.niehs.nih.gov/
d. The National Institute of Child Health and Human Development (NICHD) www.nichd.nih.gov/ has a Reproductive Sciences Branch and a Contraception and Reproductive Health Branch
e. The National Library of Medicine www.nlm.nih.gov/ Has links to databases including PubMed, ToxNet, and TOXMAP— an interactive Web site from the National Library of Medicine that shows the amount and location of reported toxic chemicals released into the environment on maps of the United States. Data is derived from the US Environmental Protection Agency's Toxics Release Inventory (TRI).

3. The US Environmental Protection Agency (EPA)
a. Toxics Release Inventory Data (TRI) www.epa.gov/tri/tridata/tri03/index.htm Provides information on releases of toxic chemicals into the environment as reported annually by industrial facilities around the United States.
b. Integrated Risk Information System (IRIS) www.epa.gov/iris/ A database of human health effects that may result from exposure to various substances found in the environment.

4. The World Health Organization (WHO) Has information on reproductive health.

5. California Department of Health Services. www.dhs.ca.gov/
a. Environmental Health Investigation Branch www.ehib.org/cma/index.jsp Conducts a number of studies of reproductive outcomes in relation to community concerns as well as initiating research on suspected toxicants. www.ehib.org/cma/topic.jsp?topic_key=10
b. Occupational Health Branch, www.dhs.ca.gov/ohb/ published the booklet: **"Workplace Chemical Hazards to Reproductive Health.** A Resource for Worker Health and Safety Training and Patient Education. State of California, Department of Health Services, Department of Industrial Relations. Second printing 1999." Available from Hazard Evaluation System and Information Service (HESIS), Occupational Health Branch, California Department of Health Services. Order form available on-line: www.dhs.ca.gov/ohb/HESIS/hesispub.htm

6. California Environmental Protection Agency www.calepa.ca.gov/ Maintains list of reproductive toxins (Prop 65) www.oehha.ca.gov/prop65.html

NON-GOVERNMENTAL ORGANIZATIONS

1. The Collaborative on Health and the Environment (CHE) www.healthandenvironment.org/ This site tracks emerging scientific evidence on links between diseases, disorders and disabilities and possible environmental causes. Has produced a number of peer-reviewed overview papers on environmental causes of disease, including infertility.
a. CHE also has an infertility working group: www.healthandenvironment.org/working_groups/fertility
b. CHE has produced a large database showing the associations between contaminants and human disease: database.healthandenvironment.org

2. Environmental Working Group www.ewg.org Has conducted numerous environmental investigations and produced environmental health issue reports.

3. Children's Environmental Health Coalition www.checnet.org Has a lay-friendly chemicals and effects database and links to many resources and fact sheets for parents. www.checnet.org/healthehouse/education/index.asp

4. Physicians for Social Responsibility, Environment and Health Section www.psr.org/home.cfm?id=environment, Toxics and Health www.psr.org/home.cfm?id=toxics

5. Pesticide Action Network, North America (PANNA) www.panna.org/ Maintains a pesticides database www.pesticideinfo.org/Index.html

6. The Natural Resources Defense Council (NRDC) www.nrdc.org/health/default.asp Has information on toxic chemicals and health.

7. The World Wildlife Fund (WWF) worldwildlife.org/toxics/

PATIENT ADVOCACY ORGANIZATIONS

1. The American Fertility Association theafa.org/

2. Endometriosis Association www.endometriosisassn.org/

3. InterNational Council on Infertility Information Dissemination (INCIID) www.inciid.org/

4. RESOLVE, Inc.: The National Infertility Association www.resolve.org

SCIENTIFIC SOCIETIES

1. American Society for Reproductive Medicine (ASRM) www.asrm.org Affiliated societies include Society for Reproductive Endocrinology & Infertility (SREI); Society for Assisted Reproductive Technology (SART); and Society for Male Reproduction and Urology (SMRU).

2. The Society for the Study of Reproduction ssr.org/

3. The Endocrine Society www.endo-society.org/ has links to both male and female reproductive information.

OTHER USEFUL WEBSITES:

1. Environmental Health Sciences, a nonprofit organization founded in 2002 to help increase public understanding of emerging scientific links between environmental exposures and human health. EHS publishes these informative Web sites:

> www.EnvironmentalHealthNews.org—daily publication with links to news stories from around the world, new science, and new reports on emerging scientific links between environmental exposures and human health.
>
> www.OurStolenFuture.org—web home for the authors of *Our Stolen Future*, which provides regular updates about the cutting edge of science related to endocrine disruption. Also contains information about ongoing policy debates, as well as new suggestions about what you can do as a consumer and citizen to minimize risks related to hormonally-disruptive contaminants.

2. The National Pesticide Information Center npic.orst.edu/—a cooperative effort of Oregon State University and the US Environmental Protection Agency (EPA), provides on-line information about pesticide safety and toxicity. The organization also runs a toll-free hotline for pesticide questions (1-800-858-7378)

3. e.hormone e.hormone.tulane.edu—hosted and run by the Center for Bioenvironmental Research at Tulane/Xavier Universities provides background and up-to-date information about endocrine disruption and other environmental signaling.

4. EM-COM www.emcom.ca—information resource about endocrine disrupting substances directed by a group of faculty at six Canadian universities

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Women's Health @ Stanford
Stanford University School of Medicine
300 Pasteur Drive
Stanford, California 94305

Collaborative on Health and the Environment
c/o Commonweal
PO Box 316
Bolinas, California 94924