

That Feminine Touch

Are men suffering from prenatal or childhood exposures to “hormonal” toxicants?

By JANET RALOFF

Second in a two-part series

Sex hormones orchestrate myriad biological activities throughout our lives, beginning with the initial signaling for certain fetal tissues to differentiate into structures that are quintessentially male or female.

But gender — both its physical expression and its characteristic behavior — traces more to the relative concentrations of various sex hormones circulating in the body than to the mere existence of certain dominant ones. For example, women produce some androgens, or male hormones. Indeed, a woman's body synthesizes estrogens from androgens such as testosterone. Similarly, though estradiol is the animal kingdom's primary estrogen, or feminizing hormone, it plays important roles in both men and women.

At no time does an imbalance of sex hormones produce more obvious results than during fetal development. Too much estrogen at the wrong moment can turn an organism with male genes into what to all outward appearances is a female. Similarly, an overabundance of androgens can produce the sex organs of a male in a fetus with the genes to be female.

Our genetic inheritance tends to oversee the production of sex hormones so that these mix-ups don't occur. But increasingly, scientists are finding, we have been seeding our environment with chemicals that can inadvertently alter or mimic the activity of feminizing hormones.

These agents are everywhere. Many — such as pesticides — contaminate our drinking water and foods. We unsuspectingly breathe others in urban air. A mother may even unwittingly pass some hormone-mimicking pollutants on to her child — via the blood she supplies a fetus before birth and the breast milk with which she later feeds her newborn (SN: 4/26/86, p.264).

A growing appreciation of the ubiquity of these “environmental hormones” has increased concern that large and un-

timely exposures to them may send gender-bending signals to males. In fact, some severely affected animal populations — principally birds, fish, and alligators — have already begun to exhibit the emasculating effects of these pollutants (SN: 1/8/94, p.24).

Researchers also have linked coincident declines in fertility in these and other populations to the pollutants' disruption of endocrine function.

Today, data tying similar reproductive abnormalities in humans to hormone-like pollutants remain scanty at best. However, signs are mounting that some males of our species may already have begun to suffer ill effects.

Early in human development, genetic programming must signal if a fetus is to be male. If it is, observes Richard M. Sharpe, a reproductive physiologist at the Medical Research Council's Center for Reproductive Biology in Edinburgh, Scotland, then the genes will “broadcast” certain chemical communications that result in the secretion of male hormones. These signals effectively flip a series of molecular “switches” that turn on male development.

If nothing happens — that is, no switches are flipped — a female will result. Explains Sharpe, feminine development “is what we call the default pathway.”

Today, researchers still seek to identify the precise mechanisms of this female-to-male transformation. However, Sharpe says, animal studies show that if a fetus receives too much estrogen — for example, if its mother has been administered a natural or synthetic estrogen during the critical period when genes attempt to express masculinity — “then you disrupt



Produce sold in U.S. markets often contains trace residues of pesticides, some of which can affect hormone function. Studies show that a single peach, for example, can carry residues of up to six different pesticides (SN: 7/3/93, p.4).

this switch from female to male.”

In humans, the male reproductive tract begins developing between about the seventh and 14th weeks of pregnancy. If external hormones appear sporadically or in low concentrations during this time, the disruptions they cause will not necessarily trigger a complete reversal of an individual's apparent gender. Rather, they may exert subtle changes, ones that play out later in life.

Nor are estrogens the only agents that can elicit gender-bending effects. Any chemical that blocks the activity of certain androgens can also foster feminization by preventing the developmental changes those androgens control. For instance, a male fetus depends on certain androgens to direct the development of its external genitalia.

With the growing ubiquity of pesticides and other pollutants possessing the functional attributes of female hormones, our environment effectively bathes us in a sea of estrogens. This realization has led Sharpe and endocrinologist Niels E. Skakkebaek to propose that estrogenic pollutants may underlie some disturbing trends affecting the male reproductive tract.

Last week, the pair chronicled these trends and their possible molecular underpinnings at “Estrogens in the Environment,” a federally sponsored international conference in Washington, D.C.

For instance, many industrialized countries have witnessed recently a sharp rise in testicular cancer, notes Skakkebaek, chief of the University Department of Growth and Reproduction at Rigshospitalet in Copenhagen, Denmark. Some of the first data heralding this increase emerged in his country, which has maintained a national cancer registry since 1943.

There, the incidence of testicular cancer has more than tripled over the past 50 years, he observes. And the frightening thing, he says, is that the rate of increase continues to grow. Moreover, he notes, strong data demonstrate similar increases in Scotland, the United States, and other Scandinavian countries.

Sperm counts also have fallen in the last two generations. Skakkebaek and his co-workers conducted a meta-analysis of previously published studies on semen quality. The international data, from studies involving 14,947 men, indicate that the average density of sperm has fallen from 113 million per milliliter (ml) of semen in 1940 to just 66 million per ml in 1990.

In the January 1992 *BRITISH MEDICAL JOURNAL*, Skakkebaek's team noted that because the volume of semen available in these men at any given time has also dropped an average of 19 percent, the 50-year drop in sperm count has been more

precipitous than sperm density alone would indicate.

Another worrisome trend is the apparent increase in the incidence of undescended testicles in newborn males — a condition known as cryptorchidism. Though formed near the kidneys, both testicles should migrate down into the scrotum by birth. Few countries maintain registries on this condition, but Skakkebaek noted that two British studies have documented a near doubling of the number of boys born with at least one undescended testicle — from about 1.6 percent in the 1950s to 2.9 percent in the late 1970s.

Though undescended testicles usually complete their migration within a year or two after birth, some never do. Men with undescended testicles are unable to make sperm. Moreover, even individuals who were temporarily cryptorchid during infancy face an increased risk of fertility problems in adulthood, Sharpe notes.

Then there are hypospadias, congenital abnormalities of the urinary tract. During fetal development, the penis initially possesses an open groove down its entire length. Before birth, that opening should fuse closed to form an internal channel known as the urethra. Boys born with only partial fusion of that groove need surgery to correct the problem.

Birth registries in England and Wales

document that hypospadias more than doubled between 1964 and 1983.

At least some of these trends may be related, Skakkebaek says. His own studies have identified an apparent link not only between undescended testicles at birth and testicular cancer in adulthood, but also between semen quality (such as low sperm counts or abnormal sperm) and testicular cancer.

Moreover, he points out, all these changes "could be the consequences of fetal events." Testicular cancer, undescended testicles, hypospadias, and poor-quality semen have been reported in the male offspring of women who during pregnancy received treatment with diethylstilbestrol (DES), a potent synthetic estrogen, he notes.

"We got more fuel for this estrogen hypothesis in late 1991," Skakkebaek recalls. It was then that he learned of work at the National Institute of Environmental Health Sciences in Research Triangle Park, N.C. This research showed that certain environmental contaminants can emulate the reproductive effects of estrogen and DES in male animals.

The previously unexplained male reproductive trends suddenly started to make sense, Sharpe says. It became clear "that a surprising number of chemicals that we've managed to pollute our environment with are estrogenic," he says.

Manliness: The Sertoli cell connection

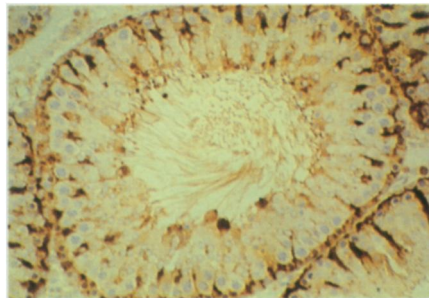
Early exposure to hormone-like pollutants may confuse or tinker with male development in a host of ways. One of the most obvious is by limiting the generation of Sertoli cells, says Richard M. Sharpe of the MRC's Center for Reproductive Biology in Edinburgh. In fact, he notes, production of these cells "is the very first change that happens when a fetus takes the male developmental pathway."

Named for the 19th century Italian physiologist who first described them, Sertoli cells reside within the testicles. In the fetus, these cells direct the development and descent of the testes, control the development of germ cells, and control the cells that secrete the hormones responsible for masculinization. Sertoli cells continue to play an important role in adulthood, when they nourish the early germ cells as they mature into sperm.

Throughout each sperm's 10-week maturation, Sharpe notes, "the Sertoli cells look after its every need."

As such, he says, "I would argue that the Sertoli cell is the most important cell in the male body."

Production of Sertoli cells continues beyond birth, although "for how many years, we're not quite sure," Sharpe says. Because each cell can nurture



Michael Miller

Circular cross section of seminiferous tubule from rat testis. Wedged shoulder to shoulder along the outer edge and down toward the center of the tubule are Sertoli cells (stained brown). In adults, these cells nurture maturing sperm.

only a fixed number of sperm at one time, the fewer Sertoli cells that ultimately form, the smaller the testes will be — and the lower a man's production of sperm.

What's more, the number of Sertoli cells an individual produces can be limited by reducing his secretion of follicle-stimulating hormone (FSH). And, at least in young animals, FSH is "exquisitely sensitive to inhibition by exogenously administered estrogen," Sharpe and Niels Skakkebaek noted last year in the May 29 *LANCET*.

Mullerian inhibiting substance (MIS), another hormone, is produced by Sertoli cells. This hormone's primary role is to cause a regression of fetal structures known as Mullerian ducts. Because the failure of these ducts to regress has been associated with undescended testes, abnormalities in MIS production may play a role in cryptorchidism. Disturbance of MIS production could, therefore, impair normal testicular descent or other aspects of male reproductive development, Sharpe and Skakkebaek argue.

Though studies have shown that over the past five decades sperm counts have been falling — and cryptorchidism rising — Sharpe notes that "we have no data on what Sertoli cell [counts] were in men 50 years ago. So we have no way of proving that these changes are due to a drop in Sertoli cell number." However, he told *SCIENCE NEWS*, "that would be your prime suspicion."

At a meeting in Washington, D.C., last week, Sharpe said his laboratory is initiating a research program to identify the full cascade of physiological events that normally fixes an individual's maleness. In addition, his team will be looking to establish what factors can interfere with that process and when — and how that may ultimately play out in terms of reproductive success.

— J.A. Raloff

Among these, he notes, are "a lot of the chemicals that we started making in large quantities from the 1940s and '50s onwards, and which are very resistant to degradation," including polychlorinated biphenyls (PCBs), DDT, and the breakdown product of certain detergents.

"I'm not trying to be alarmist," Sharpe told *SCIENCE NEWS*, but when it comes to the male reproductive risks posed by hormone-like pollutants, "the data show there's reasonable cause for concern."

A paper in the October ENVIRONMENTAL HEALTH PERSPECTIVES (EHP) lists 45 environmental contaminants or classes of agents that have been reported to cause changes in reproductive and hormone systems. They include eight herbicides, eight fungicides, 17 insecticides, two nematocides, and a miscellaneous category that includes metals, toxic industrial by-products, and commercial chemicals, such as styrenes.

Though releases of many substances on this list, including the toxic pesticides DDT, heptachlor, and kepone, have been banned or severely restricted in the United States, such compounds continue to pollute the environment.

Indeed, a pair of papers in the January ENVIRONMENTAL SCIENCE AND TECHNOLOGY (ES&T) reports on diverse occurrences of such organochlorine pesticides — from

residues in seals in Siberia's Lake Baikal to those in sediments in a bay that provides fish for Portland, Maine. These compounds even show up long distances from where they were used. For example, detectable levels of such pesticides appeared in an Antarctic penguin, a third ES&T paper reports.

Others of the listed organochlorines remain in widespread use. For instance, 2,4-D is the largest-selling broadleaf herbicide in North America, with some 60 million pounds of it and its chemical analogs applied annually in the United States alone. While this agent has not been shown to be directly estrogenic, work by Ana Soto, an endocrinologist at Tufts University School of Medicine in Boston and a coauthor of the EHP paper, has shown that nonylphenols are.

These compounds can leach out of some plastics (SN: 7/3/93, p.12) or form during the natural environmental degradation of certain surfactants known as nonylphenol polyethoxylates (SN: 1/8/94, p.24). Soto notes that an estimated 360 million pounds of these surfactants are sold in the United States each year for use in products ranging from dishwashing liquids to toiletries and pesticides.

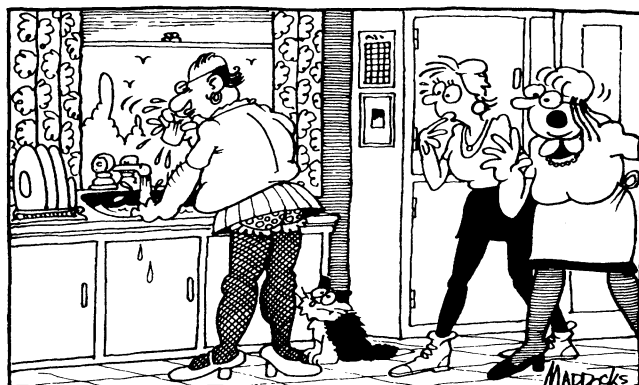
Most of the agents of greatest immediate concern, however, are no longer allowed to enter the environment in large and relatively uncontrolled quantities. And this may contribute to a false sense of security about the threat these agents pose, argues another coauthor of the EHP paper, zoologist Theo Colborn of the World Wildlife Fund in Washington, D.C.

"My big concern now is that by lowering levels [of these pollutants] in the environment, the substances may be present in such small amounts that we cannot even trace them," Colborn told *SCIENCE NEWS*. "They may be there, and we won't even know it."

Soto shares that concern. "Most compounds with estrogenic effects are not present in the environment at levels that alone would produce an effect," she notes. However, unpublished studies by Soto now indicate that if humans are exposed to enough such chemicals, or if enough of them accumulate in the body, they can combine to cause undesirable effects.

For instance, Soto reported at the meeting last week, by taking 10 estrogenic chemicals and combining each of them at one-tenth of their effective dose, "you now have an effective dose."

Moreover, because chemical structure offers few clues to what may prove estrogenic, environmental hormones can be identified only by methodically testing,



"I've warned your dad about the female hormones in the water supply — but he won't listen."

Express News Papers/Archive Photos

one by one, the most widely used chemicals, she says.

Her lab, one of the few that does such testing, has just unmasked the estrogenic alter ego of three widely used pesticides: dieldrin, toxaphene, and endosulfan. Dieldrin and toxaphene are no longer legal in the United States, but "endosulfan remains the nation's most widely used pesticide," Soto says.


Nor are all environmental agents that affect reproduction estrogenic. For instance, benomyl, a systemic fungicide that's used on everything from rice and tomatoes to apples and grapes, "really affects the testes," Soto says; it causes the premature release of cells that would have become sperm. However, Soto notes, benomyl's not an estrogen. Other agents, like dioxin, may actually inhibit estrogen, she notes. Yet in rodents, dioxin feminizes — both physically and behaviorally — males exposed prenatally (SN: 5/30/92, p.359).

Society's preoccupation with cancer has led to regulations requiring that any new chemical be withheld from the marketplace until it passes screening tests that indicate it will not foster malignancies. No rules yet require a similar test of a new or existing chemical's ability to mimic or affect reproductive hormones.

The result of that omission, Soto charges, is that the economic cost-benefit analyses that today play an important role in determining which toxic chemicals remain on the market — and for how long — fail to capture the cost of exposing wildlife and its stewards to hormone-mimicking toxic chemicals.

"We have just begun to open the door of discovery concerning the noncancer health effects of the synthetic chemicals that in the last 50 years have become an integral part of our life," says Colborn. The take-home message from these new studies, she believes, is that "we need to take these effects as seriously as, if not more seriously than, cancer."

Indeed, argues Soto: "What is the economic cost of having a generation that cannot reproduce?" □

NEW ADDRESS? 

Whenever you write us about your subscription, please enclose a *SCIENCE NEWS* address label to ensure prompt service.

To: SCIENCE NEWS
Subscription Office
231 W. Center St.
P.O. Box 1925
Marion, Ohio 43305

Change of address: If you're moving please let us know four to six weeks before changing your address.

To subscribe, mail this form to the address shown above.

Subscription rates:
 1 year \$39.50 2 years \$68.00
 Payment enclosed Bill me later

NEW ADDRESS:

name (please print) _____
 address _____
 city state zip code _____
 (foreign postage \$6.00 additional per year.)

Attach **OLD** label or print **OLD** address

name (please print) _____
 address _____
 city state zip code _____

The role of chlorine — and its future

Zoologist Theo Colborn of the World Wildlife Fund and her co-workers have compiled a list of 42 chemicals or classes of chemicals that have been reported to affect the reproductive or hormone system. Twenty-three of the compounds — 55 percent — contain chlorine as an essential ingredient. Two others rely on a different halogen, or element in chlorine's chemical class: one on fluorine, the other on bromine.

Because many halogenated compounds are lipophilic (dissolve in fat) and resist breakdown, they tend to persist in the environment — often decades after their use has been banned — and to accumulate in body fat.

As a result, animals exposed to these ubiquitous contaminants frequently become walking, flying, or swimming reservoirs of toxic pollution. Indeed, at least 50 of the papers presented last October at the Ecological Effects of Arctic Airborne Contaminants meeting in Reykjavik, Iceland, dealt with the accumulation of such organochlorines in water and soil and throughout the food chain — from lichens, mosses, fish, and waterfowl to caribou, whales, and newborn harp seals.

Referring to such chlorinated chemicals, Tom Muir, a senior economist with Environment Canada in Burlington, Ontario, argues that “no other class of industrial — or natural — chemicals is known that exhibits so many detrimental properties at the same time. Put simply, the characteristics of chlorinated organic substances that give them useful technical properties are the same ones that make them persistent and/or toxic.”

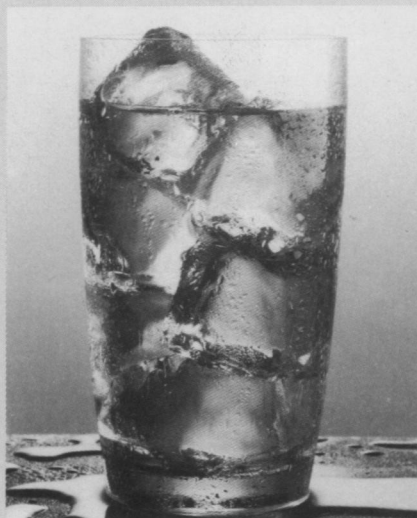
In a 67-page report — *Chlorine, Human Health, and the Environment* — released last October, Greenpeace USA argued that “no further organochlorine pollution should be permitted.” Said Joe Thornton, the author, this “means phasing out the substance that is their root — chlorine, since whenever chlorine is used, organochlorines result.”

Several other groups have issued similar, less-publicized recommendations. At its annual meeting in October 1992, the International Joint Commission (IJC) suggested that its patrons “sunset” — or begin commercially phasing out — persistent toxic chemicals. A federally appointed U.S.-Canadian board, IJC was established in 1909 to advise the U.S. and Canadian governments on how best to implement treaties and laws for preserving water quality in areas along their joint border. Though nonbinding, the commission's recommendations are taken seriously by both governments, notes Marty Bratzel in IJC's Windsor, Ontario, office.

While IJC has addressed a broad spectrum of persistent toxic agents, its recommendation specifically urges that the U.S. and Canadian governments “develop timetables to sunset the use of chlorine and chlorine-containing compounds as industrial feedstocks, and that the means of reducing or eliminating other uses be examined.”

At a September 1992 meeting of the Paris Commission for the Prevention of Marine Pollution, ministers of 15 European nations also agreed that releases of halogenated organics and persistent toxic chemicals should be cut — “with the aim of their elimination.”

And last Oct. 27, at its annual meeting, the American Public Health Association's governing council passed a resolution on these organics. It concluded



Provided by Chlorine Chemistry Council

According to a document issued by the Washington, D.C.-based Chlorine Institute, more than half of all commercially produced chemicals may rely on chlorine. Moreover, it says, the \$70 billion U.S. chlorine industry provides materials used in disinfecting 98 percent of U.S. drinking-water systems and in producing about 85 percent of all prescription drugs.

that “there should be a rebuttable presumption that chlorine-containing organic chemicals pose a significant risk. Therefore, before introducing new chemicals into commerce, using existing chemicals in new applications, or continuing to use these chemicals in the manufacturing processes or products beyond some future date, industry should either:

- demonstrate that the risk is not significant for a particular compound, use, or manufacturing process, or
- demonstrate that there are no substitutions, product reformulations, or changes in manufacturing processes that will result in a lower risk, or

- ensure that substitutes for existing products or changes in manufacturing processes will result in a lower risk.”

Not surprisingly, the chemical industry has responded. Publicly it argues that such sweeping recommendations are not justified or go too far. Internally, however, many companies have begun evaluating what they can do to begin cutting their chlorine use and pollution.

Last October, in fact, Philip H. Brodsky, director of corporate research and environmental technology at Monsanto Co. in St. Louis, made new efforts to develop chlorine-cleanup and chlorine-substitution technologies the focus of his presentation before journalists at the Council for the Advancement of Science Writing.

And what of the scientists whose work Greenpeace cited to support a chlorine ban? Says Mary S. Wolff of the Mt. Sinai School of Medicine in New York City, whose team last year linked concentrations of DDT in the blood to a woman's risk of breast cancer (SN: 4/24/93, p.262): “I don't think any scientist would be against a ban on chlorinated organics.” But does she support a ban on all chlorinated compounds? “No.”

Calling for a chlorine ban “is an extremist position, and like most extremist positions, ridiculous,” charges endocrinologist H. Leon Bradlow of Cornell University's Strang Cancer Prevention Center in New York City. He acknowledges that all toxic chemicals should be used judiciously and only when suitable nontoxic substitutes aren't available. However, he quips: “I think methylene chloride [an animal carcinogen] is a dandy solvent and would hate not to be able to use it.”

Reproductive biologist Ana Soto of Tufts University Medical School also considers a chlorine ban an overly simplistic approach to regulation. Moreover, she notes, such a ban would not affect unchlorinated compounds such as nonylphenol — a substance whose estrogenicity she discovered when it leached out of plastics, destroying four months of endocrine research.

Soto also notes that, unlike chlorinated pesticides, some nonylphenol-containing products — such as spermicides used with contraceptive diaphragms and in many condoms — have been designed expressly for intimate contact with human reproductive tissue.

Adds toxicologist Devra Lee Davis with the Department of Health and Human Services in Washington, D.C., “We're not well served by blanket solutions to complicated problems.” However, she asserts, “I'm glad I live in a democratic country where discussions, like those that Greenpeace has been leading on this chlorine issue, can be aired before the public.” — J.A. Raloff