Shift in the Sexes

Are Endocrine Disruptors Changing Birth Ratios?

According to demographic data compiled by the United Nations, an average of 105 boys are born for every 100 girls. The male proportion of births, equal to 0.515, varies slightly between years and populations, but these factors do not fully explain consistently shifting ratios in several industrialized countries over recent decades. A new study examines birth and fetal death sex ratios in Japan and the United States and reveals significant male-to-female shifts in both nations [***EHP* 115:941–946; Davis et al.**].

The research team calculated birth and fetal death sex ratios in Japan based on 1949–1999 data from the Japanese Vital Statistics Bureau. The proportion of male births varied yearly before 1970 but declined steadily since then, from 0.5172 to 0.5135. Between 1960 and 1999, the male proportion of fetal deaths increased from 56% to 67.7%. The male fetal death rate is approximately four times higher in Japan than in the United States.

For U.S. calculations, the researchers drew 1983–1995 fetal death data and 1970–2002 birth data from the National Center for Health Statistics. The proportion of male births dropped in the United States, from 0.5134 in 1970 to 0.5117 in 2002. There are significant racial differences, however: between 1970 and 2002 the proportion of non-Hispanic white male births fell from 0.5143 to 0.5122, whereas the proportion of black male births rose slightly from 0.5076 to 0.5079. The male proportion of black fetal deaths also increased, rising from 53.5% to 54.5%; among whites, the male proportion of fetal deaths rose by less than 0.5%.

Why birth sex ratios differ so much between white and black women is unknown, but hormonal differences due to race and to incidence of obesity may be involved. A possible explanation for the increased ratio among black births may stem from improved prenatal and obstetric care in general, reducing the overall number of fetal deaths.

The researchers speculate that parental exposures to endocrine-disrupting chemicals, including metalloestrogens such as methylmercury, might be factors undermining the conception and survival of male children. They suggest particular scrutiny of Japanese body burden of mercury and other metalloestrogens to understand this difference. Additionally, future investigations of declining sex ratios should consider the types and timing of prenatal and parental exposures to endocrine-disrupting chemicals. The researchers hypothesize that paternal exposures prior to conception might affect expression of the *SRY* gene on the Y chromosome. **–Julia R. Barrett**

Phthalates and Metabolism

Exposure Correlates with Obesity and Diabetes in Men

The prevalence of obesity, insulin resistance, and diabetes has increased considerably in the past few decades. Many plausible contributing factors have been identified for this increase, among them low testosterone levels in men. Research has found that exposure to certain synthetic chemicals adversely affects testicular function in animals and possibly in humans. A new analysis looked for—and found—that exposure to one class of these chemicals, phthalates, correlated with two metabolic abnormalities in men: abdominal obesity and insulin resistance [***EHP* 115:876–882; Stahlhut et al.**].

Phthalates are commonly used in products such as cosmetics, soaps, pesticides, lubricants, plastics, and paints. They are widespread; indeed, more than 75% of the U.S. population carries detectable levels of several phthalate metabolites. Studies have also found associations between some phthalate metabolites and antiandrogenic effects in humans, including both infant and adult males.

The authors used 1999–2002 data from the CDC National Health and Nutrition Examination Survey (NHANES) to look for a connection between phthalate exposure and metabolic disease in adult men. They compared urine concentrations of six phthalate metabolites to the participants' waist circumference and measures of insulin resistance. The analysis controlled for a variety of potential confounders, including age, ethnicity, fat and calorie consumption, physical activity, and smoking status.

Four phthalate metabolites were significantly associated with greater waist circumference and three with increased insulin resistance. When the authors further controlled their models for measures of participants' kidney and liver function, the associations decreased somewhat but remained significant for all but one metabolite.

The authors caution that this first look at phthalates, obesity, and insulin resistance is limited by the study's cross-sectional design and the single measurement of urine phthalate metabolites (an imperfect measure of long-term exposure). In addition, although the study was based on the hypothesis that phthalates cause metabolic abnormalities by decreasing androgen levels or function, the authors couldn't examine this mechanism, because the NHANES data do not contain measures of sex hormones in men. They note that other mechanisms could also be involved in a relationship between phthalates and metabolic disease.

If phthalates are eventually shown conclusively to contribute to obesity or diabetes in men, it's still not clear how these chemicals would affect the opposite sex, since low testosterone has been associated with a lower (not higher) prevalence of metabolic disease in women. If further longitudinal studies confirm that phthalate exposure contributes to obesity, diabetes, and related disorders, actions to reduce phthalate exposure could effectively lessen the chemicals' contribution to metabolic disorders, because phthalates are quickly metabolized and excreted by the body. **–Melissa Lee Phillips**

Top to bottom: Brent Bossom, Paul Cowan/ShutterStock

Childhood Leukemia in Germany

Cluster Identified near Nuclear Power Plant

Childhood leukemia clusters have been observed at a number of sites near European nuclear facilities. With the identification of the largest cluster to date, a new German study underscores the need to clarify the association [***EHP* 115:947–952; Hoffmann et al.**].

Between February 1990 and May 1991, five cases of leukemia were diagnosed in children living within 5 kilometers of the Krümmel nuclear power plant in Geesthacht and a neighboring nuclear research operation along the Elbe River in northern Germany. By 2005, another nine cases of leukemia had been discovered in the area. Most of the cases were acute lymphatic leukemia in males under five years of age.

Krümmel nuclear power plant, Geestacht

Several expert commissions investigated, and found moderate levels of cesium in rainwater and air samples, along with plutonium and americium in household dust near the plant. There was also some evidence of chromosomal damage to lymphocytes among the local population. One panel deemed these observations consistent with fallout from a possible accident at the research facility that would have to have occurred around September 1986, but so far no such accident has been proved. Another panel suggested instead that chance or population mixing—the commingling of local people with newcomers from various places—might have caused the cluster.

In the current study, researchers compared the number of observed leukemia cases in the sparsely populated Geesthacht area to the number of predicted cases based on nearby county and national incidence rates from 1990 to 2005. The five cases found in 1990 and 1991 significantly exceeded the expected incidence for that period of 0.45 cases. After studying medical records from all treatment facilities in the vicinity and in Hamburg, the team concluded that the Geesthacht cluster is the "largest series of childhood leukemia cases reported to date" among European leukemia clusters near nuclear facilities, including those at Dounreay, Scotland; LeHague, France; and Sellafield, England.

The authors state that population mixing is unlikely to account for the leukemia incidence because the population remained stable over the years studied. Nor would an alleged one-time release of radiation in 1986 readily explain the cluster, given that the excess incidence persisted over at least 15 years. Thus, they conclude, the elevated incidence of childhood leukemia around Geesthacht remains "another piece in a growing puzzle" of childhood leukemia's association with nuclear installations—and its severity and persistence emphasize the need to keep investigating. **–Valerie J. Brown**

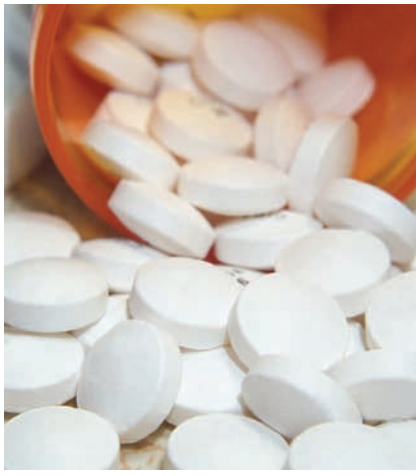
A Twist in the Ritalin Riddle

Drug-Related Genomic Damage Not Confirmed in Children

The frequently prescribed central nervous system stimulant methylphenidate (MPH), better known by brand names that include Ritalin, does not cause genomic damage in children, contrary to earlier reports, according to new work published this month [***EHP* 115:936–940; Walitza et al.**]. In use for more than 50 years and now prescribed more than 5 million times a year in the United States, MPH is the drug of choice for attention deficit/hyperactivity disorder (ADHD). ADHD is the most frequently diagnosed psychiatric disorder in children and adolescents, with an estimated 6–12% of minors worldwide thus diagnosed.

A 2005 report published in *Cancer Letters* had showed that gross genomic damage—reflected by chromosome aberrations including sister chromatid exchanges and formation of micronuclei (smaller-than-normal cell nuclei containing partial genomes)—was found in nucleated lymphocytes taken from peripheral circulation of children who had been taking the drug for only three months. Because large chromosomal breaks are associated with cancer, the study raised concerns about the potential for cancer risk in the millions of people who have taken the stimulant.

That 2005 study found an increased frequency of chromosomal abnormalities in all of the 12 children whose lymphocytes were examined, lending urgency to future studies. The current study looked at micronuclei as an indicator of genomic damage in the lymphocytes of 38 children newly prescribed the drug, following some but not all of them out to six months.



The children, 29 boys and 9 girls, took a variety of doses and formulations of the drug. Some subjects were lost to follow-up during the study; others switched to other medications or dropped out because they did not respond to the drug. Eight children stayed in the study through the whole six months.

Overall, there was no significant increase in the formation of micronuclei at any time point, though some individual children had elevated numbers of micronucleated lymphocytes at one time point or another. Further, the lymphocytes of 9 children who had been taking the drug for more than six months at the start of the study did not show increased levels of micronucleation compared to the pretreatment levels seen in drug-naïve children.

The marked difference in results between the 2005 study and the current one raises the possibility of unexplained genetic differences between the study populations. Whereas the first study population included six white, four black, and two Hispanic children, the latter study focused on a more uniform group of ethnically German children. The authors say further work, especially on the long-terms effects of MPH, is called for. **–Victoria McGovern**