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CHANGES IN SPERM COUNT AND FUNCTION

A recent report from researchers in Edinburgh[1] found a deterioration in semen quality among sperm donors born after 1970 compared to those born before 1959. Measures of sperm concentration and motility were made from semen samples that were provided by 577 Scottish men, almost half of whom were of proven fertility. The men were born between 1951 and 1973; this time period was divided into four "birth cohorts" for comparison. Sperm concentration decreased by 2.1% per year ($p=0.003$), and the total number of motile sperm in the ejaculate decreased by 2.04% per year ($p=0.0001$). Overall motility increased by 0.18% per year ($p=0.0322$). The authors conclude that their data indicate that a later year of birth is associated with poorer semen quality in adult life, which is consistent with the hypothesis advanced by Sharpe and Skakkebaek (1993) that environmental factors acting before or just after birth may have effects on adult reproductive performance.

Researchers in Belgium[2] analyzed sperm donations from 416 healthy young men (aged 20 to 40 years) presenting as sperm donors, including men who were not of proven fertility. The study period was from 1977 to 1995, and the data were analyzed using regression methods as well as comparison of early (1977-1980) and late (1990-1995) periods. A weak negative correlation of sperm concentration with time was found ($r=-0.09$, $p=0.08$), but there was also an increase of ejaculate volume with time ($r=0.10$, $p<0.01$), so the total count of spermatozoa per ejaculate did not change ($p=0.93$). Significant decreases ($p<0.0001$) were found in several measures of sperm motility and morphology. The average proportion of spermatozoa with normal morphology decreased from 39.2% to 26.6% between the early and late periods ($p<0.0001$), and the mean percentage of spermatozoa with rapid progressive motility decreased from 52.7% in the early period to 31.7% in the late period ($p<0.0001$). When a quadratic regression model was used to analyze the data on rapid progressive motility, the curve appeared to level off after 1990.

The authors conclude that their data reflect degeneration of sperm production among men aged between 20 and 40 years. Further, the authors propose that lifestyle changes or unusual toxic exposures were unlikely to be the cause for the apparent degeneration, and that environmental factors such as estrogenic chemicals may be responsible. The evident stabilization of the decline in sperm motility since 1989-1990 may relate to the reported stabilization of environmental pollution with organochlorine compounds during the past 5 or 6 years.

These two reports lend support to the findings reported in early 1995 by French researchers[3]. In the earlier French study, sperm concentration, morphology and motility were studied in sperm donations from 1973 to 1992, and a decrease in sperm concentration of 2.1% per year was found, along with significant ($p<0.0001$) decreases in percentages of motile and normal spermatozoa over time.

In addition, a meta-analysis[4] of 61 studies also found a trend toward decreasing sperm count over 50 years, along with an increase in the number of men with low (<40 million/ml) sperm counts and a decrease in the number of men with high (>100 million/ml) sperm counts. The findings of the meta-analysis were challenged by Olsen et al.[5], who found that non-linear relationships, showing a sudden drop in sperm count during the 1960s followed by stabilization or a slight increase in recent years, to better represent the data. The authors also argue that the data are only "robust" for the last 20 years of the analysis, in which stabilization or slightly increased sperm counts are seen.

Sharpe and Skakkebaek (1993)[6] proposed environmental causes for decreasing sperm counts, attributing reproductive abnormalities to increased estrogen exposures in utero. The authors cite animal studies in which prenatal estrogen exposure results in smaller testes and reduced sperm counts in adult males, and propose that exposure to synthetic estrogens and estrogenic chemicals may have the same effect in human males.

However, two recent publications do not support earlier reports of declining sperm quality over time. French researchers[7] analyzed sperm concentration in semen donations received from 302 healthy fertile men between 1977 and 1992 in Toulouse, and found no significant difference in sperm concentration with time. In fact, before adjusting for age, the sperm concentration appeared to increase with increasing year of donation ($p<0.05$; $p=0.09$ after adjusting for age).

A study of sperm quality in men living in rural areas in Finland[8] also found no indication of changes in sperm count. Sperm samples collected in 1984-6 from 238 men of unknown fertility were analyzed, and the results compared to results of a 1951 study of fertile men from New York. The sperm density in the Finnish sperm samples was 133.9 million/ml, the highest sperm count reported since 1956. The authors also analyzed sperm samples from 5481 men during 1967-1994 from infertile couples, and found a significant decrease in semen volume ($p<0.0001$) but an increase in sperm density from 82.4 to 85.2 million/ml. Total sperm count decreased from 344.5 to 324.8 million between 1967 and 1994; the change was not statistically significant.

Sherins[9] questioned the statistical analyses in the studies that find decreasing sperm counts and challenged the studies' conclusions, since there is no evidence that overall male fertility has decreased with time. In an editorial accompanying the most recent studies, deKretser[10] argues the need for vigilance in undertaking studies to confirm or refute the environmental estrogen hypothesis, offering the example of a syndrome that was characterized by epididymal obstruction and no sperm production, that disappeared after mercury was removed from teething powders.

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ESTROGENIC EFFECTS OF ENVIRONMENTAL CHEMICALS

Estrogenic Behavior of Some Environmental Chemicals

In a study at Brunel University, Middlesex, UK,[11] a variety of environmentally persistent compounds were tested for interference with estrogen binding to the fish estrogen receptor, and for their ability to stimulate the growth of human breast cancer cells. Nine of the chemicals reduced estrogen binding to the fish estrogen receptor. Three of this subgroup (butyl benzyl phthalate, di-n-butylphthalate and butylated hydroxyanisole (BHA)) were also found to interact with human breast cancer cells. All were less potent than 17 *a*-estradiol, but the phthalate esters were found to act as agonists of the receptor, indicating that their effect would be additive in the presence of endogenous estrogens.

Estrogenic Behavior in Phytoestrogens

Some environmental estrogens have a natural origin, for example, phytoestrogens such as *B*-sitosterol are present in wood products. In a laboratory study at the University of Guelph, Canada[12], *B*-sitosterol was found to significantly reduce concentrations of testosterone and testosterone metabolites in the plasma of male fish, and the effects increased with the higher dose. Female fish had significantly decreased plasma levels of testosterone and 17 *a*-estradiol after treatment with *B*-sitosterol. The authors refer to monitoring data that indicate levels of *B*-sitosterol of 1200 µg/l in bleached kraft mill effluent after primary treatment, and 280 µg/l after secondary treatment. The authors suggest that *B*-sitosterol could be a contributing factor to the reproductive dysfunction observed in fish exposed to pulp mill effluent.

Researchers in Finland[13] assessed the estrogenic effects of a variety of wood-derived compounds, including lignan, five stilbenes (isorhapontigenin, isorhapontin, pinosylvin, piceatannol, resveratrol), betulin, citrostadienol, *B*-sitosterol, *B*-sitostanol, an abietic acid mixture and debarking effluent. In an assessment of estrogenic activity in two breast cancer cell lines, seven of the compounds showed some activity (isorhapontin, isorhapontingenin, abietic acid, betulin, pinosylvin, *B*-sitosterol and *B*-siterostanol); *B*-siterosterol was active in just one of the two cell lines. Only *B*-siterosterol, abietic acid and debarking effluent caused expression of the vitellogenin gene in males (normally a female trait). The authors conclude that wood-derived compounds such as *B*-siterosterol may account for the weak estrogenicity of debarking effluent in the vitellogenin expression bioassay.

Protein Binding of Chemicals and Their Behavioral Effects

The degree to which a chemical is bound to blood plasma proteins can significantly alter its toxicological effects. Researchers from the University of Missouri and the Universita degli Studi Di Parma (Parma, Italy)[14] used a relative binding affinity-serum modified access assay to assess the degree to which environmental chemicals interact with the estrogen receptor. Male urine-marking was used as an indicator of behavioral effects of DES (diethylstilbestrol), o,p'-DDT or methoxychlor exposure. The test of relative binding affinity indicate that DES (a synthetic estrogen) and o,p'-DDT both had enhanced access to cells in serum as compared to the serum-free medium. Methoxychlor did not have increased access in serum, and equol, a phytoestrogen, had 10-fold reduced access to cells in serum. In the behavioral study, the rate of urine marking increased dramatically ($p<0.05$) with low doses of DES (relative to controls) and then decreased significantly at the highest dose administered prenatally. Methoxychlor and o,p'-DDT also altered social behavior in male mice in doses that were predicted based on the chemicals' relative binding assay results. The authors suggest that these data support the hypothesis that effects on behavior are mediated by binding to estrogen receptors in the developing brain.

Inhibition of Testicular Growth in Fish Exposed to Xenoestrogens

English researchers[15] exposed maturing fish to low-level concentrations of 4 alkylphenolic compounds that had been found to show estrogenic activity in previous studies. Young male rainbow trout were exposed to 4-nonylphenol (NP), 4-tert-octylphenol (OP), 4-nonylphenoxycarboxylic acid (NP1EC) and nonylphenoldiethoxylate (NP2EO) in water at concentrations of approximately 30 ng/l (believed to be representative of effluent concentrations). A synthetic estrogen, 17-*a*-ethynylestradiol, was administered as a positive control in a concentration of 2 ng/l. All alkylphenolic compounds caused significant ($p<0.001$) elevations in vitellogenin concentrations, with OP being the most potent compound. The increased vitellogenin concentrations were accompanied by significant decreases ($p<0.05$) in the rate of testicular growth. In a second series of experiments, the dose-response relationship of reproductive effects with alkylphenol (NP and OP) exposure was assessed, and dose-response relationships were seen for NP with both vitellogenin production and testicular growth inhibition, but only vitellogenin production showed a dose-response relationship with OP exposure. The authors determined that 10 ug/l is a threshold concentration for NP and vitellogenin production increase, while the threshold concentration of OP is about 3 ug/l. Data from earlier studies indicate that, while levels of NP rarely exceed 10 ug/l in rivers, the threshold concentration of NP may be exceeded in rivers receiving significant amounts of industrial effluents. The authors conclude that situations may already exist where estrogenic chemicals are causing potentially deleterious consequences in fish populations.

Xenoestrogen Exposure and Reduced Testicular Size and Sperm Production in Rats

Researchers in Scotland[16] studied the effect of prenatal or perinatal exposure to environmental estrogenic chemicals. Adult female rats were treated during mating, gestation and nursing periods with low doses of chemicals that have shown estrogenic activity in previous studies, 4-octylphenol (OP) and butyl benzyl phthalate (BBP). The females were treated either during the nursing period only, or prior to mating and throughout gestation and nursing. Reduced testis weight was found in each type of exposure, with significant reduction at OP or BBP concentrations of 1000 ug/l ($p<0.001$), and reductions of 10-21% in daily sperm production. The phthalate esters are used as plasticizers and are thus ubiquitous pollutants, as are alkylphenols, such as OP. The authors conclude that these findings provide evidence that gestational or neonatal exposure to environmental estrogenic chemicals can result in reduced testicular size and sperm production in adult rats, and urge further study of the possible risk to humans.

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