Environmental factors and male infertility

The effect of industrial and agricultural pollution on human spermatogenesis

Alfred Spira¹ and Luc Multigner

INSERM U292, Hopital de Bicêtre, 82 Rue du General Leclerc, 94276 Le Kremlin-Bicêtre Cedex, France

¹To whom correspondence should be addressed

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The male reproductive system is particularly vulnerable to the effects of the chemical and physical environment. This may be due to dramatic events or due to endemic conditions of the environment, e.g. earthquakes (Fukuda et al., 1996). In this respect, industrial and agricultural pollution are of important concern.

A gold example

Dibromochloropropane (DBCP), a liquid nematocidal agent, had been in use since the mid-1950s. In particular, it was used on bananas in tropical and subtropical areas of the World (Central America, Caribbean Islands, Israel...). Although its spermatotoxic effect in rats was discovered in the early 1960s, its deleterious effects on human spermatogenesis were only discovered in 1977 (Whorton et al., 1977). At that time, the workers in a DBCP plant in California noted that there was a paucity of children conceived by the men after each had started to work in DBCP production area. Subsequently to a film on work at the factory, five of these workers had their spermatozoa analysed: all were grossly abnormal (azoospermic or severely oligozoospermic, \( \leq 20 \times 10^6 / \text{ml} \)). A complete analysis of the 22 men working in this process showed a high correlation between duration of exposure to DBCP and sperm count; a first group (Whorton et al., 1973) of 22 men working in this process showed a high correlation with 124

Endocrine disrupters

Several reports in the literature have suggested a possible decline in human semen quality during the last 50–60 years. However, most of these reports were based on data from men attending infertility clinics or on very selected groups of fertile men, and therefore it was suspected that the decline in sperm counts may reflect changes in the policy of infertility treatment, or a bias in selection of patients rather than a time biological phenomenon.

A systematic analysis of 61 studies, including altogether 14,947 normal men, was undertaken by Carlsen et al. (1992). It showed a significant decrease in sperm concentration (from \( 113 \times 10^6 / \text{ml} \) to \( 66 \times 10^6 / \text{ml} \)) and semen volume (from 3.40 to 2.75 ml) over the period 1938–1990. These results have been discussed at length in the literature since their publication, and they have stimulated a lot of recent research. A recent reanalysis of all available data concerning this problem has been published by Swan et al. (1997). It shows clearly that confounding and selection bias are unlikely to account for the reported decline of sperm production. However, some intra-regional differences were as large as the mean decline in sperm density between 1938 and 1990 and recent reports from Europe and the US further support large inter-area differences in sperm density (Fédération Française de CECOS, 1997). Identifying the cause(s) of these regional and temporal differences, whether environmental or other, is clearly warranted.

A larger single study undertaken on this subject comes from the analysis of 1,351 healthy men volunteering for sperm donation in the sperm bank of Paris (Auger et al., 1995). From 1973 to 1992, these men experienced a decrease in sperm concentration from \( 89 \times 10^6 / \text{ml} \) to \( 60 \times 10^6 / \text{ml} \). Furthermore, the percentages of motile and morphologically normal spermatozoa also decreased significantly, whereas semen volume remained unchanged. After taking into account all potential covariates (especially year of birth, age and abstinence delay), there remains a yearly decrease of 2.6% in sperm concentration, 0.3% in motility percentage and 0.7% in the percentage of morphologically normal spermatozoa. Since the publication of this study, nine other studies on this matter have been published, showing conflicting results (Environment and Climate Research Programme, 1996). But, for a majority of them, a calendar decrease of sperm production has been reported. Even in Finland, a country in which semen concentration has remained unchanged between 1958 and 1992 (111 \( \times 10^6 / \text{ml} \) compared with \( 124 \times 10^6 / \text{ml} \)) and is higher than elsewhere in Europe (Suominen and Vierula, 1993), a recent study of necropsy series (1981–1991) concludes that the incidence of normal spermatogenesis has decreased among middle-aged Finnish men during this period, and that the incidence of disorders of spermatogenesis and pathological alterations of testicles increased (Pajarinen et al., 1997).

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For obvious reasons, none of these studies was undertaken on samples of men representative of the general population. It is mainly the consistency of the studies, undertaken in different settings, at different times and according to various selection procedures, which strengthen their findings. Over the same time period, the incidence of testicular cancer has increased 2–4% per annum in men aged <50 years (Adami et al., 1994). However, huge regional differences in sperm production do exist (Fédération Française de CECOS, 1997). These facts, along with the observed increase incidence of testicular cancer, cryptorchidism and of hypospadias have led Sharpe and Skakkebaek (1993) to propose the hypothesis that oestrogenic chemicals could be responsible for some disorders of human male development and involved in falling sperm counts (Sharpe, 1994). In animals, Sertoli cell multiplication is controlled to a large extent by FSH. The secretion of this hormone during fetal, neonatal and prepubertal life is exquisitely sensitive to inhibition by exogenously administered oestrogens. Oestrogen administration to animals in fetal and early neonatal life results in small testes and reduced sperm counts in adult life. The sons of women exposed to diethylstilbestrol (DES) during pregnancy show an increased incidence of low sperm counts, consistent with what would be predicted from animal data. It happens that many of the chemicals with which we have contaminated our environment in the past 50 years are weakly oestrogenic. These chemicals are remarkably resistant to biodegradation, are present in the food-chain and accumulate in our bodies. In wild life, high concentrations of these chemicals have been associated with reproductive abnormalities, including changes in semen quality. These products include many organochlorine compounds, such as dichloro-diphenyl-trichloroethane (DDT) or polychlorinated biphenyls.

Changes in human exposure to oestrogens are difficult to quantify. The assumption is that pregnant women, and mankind in general, are exposed to more, rather than less, oestrogens than was the case 50 years ago. Whether increased human exposure to oestrogens could account for the increased incidence of abnormalities in male reproductive development and function is unknown, but ‘weak oestrogens’ may be more potent in the fetus and neonate than in the adult. Thus, the mechanisms whereby oestrogen exposure could induce male reproductive abnormalities are offered as a hypothesis on which to focus discussion and research. However, the observed modifications in men could also be mediated at the level of the androgen receptor. A study by Kelce et al. (1995) reports that the major and persistent DDT metabolite, 1,1-dichloro-2–2bis (p-chlorophenyl) ethylene or (p.p' -DDE), has little ability to bind the oestrogen receptor, but inhibits androgen binding to the androgen receptor, androgen-induced transcriptional activity, and androgen action in developing, pubertal and adult male rats.

However, it is very difficult to provide an epidemiological demonstration of this endocrine disrupter hypothesis. On-going studies are in progress in Denmark and in France, concerning farmers exposed to various kinds of pesticides. These studies include a retrospective analysis of the time-to-pregnancy according to exposure level, as well as a semen analysis comparing sperm parameters before and after exposure to pesticides (P.Thonneau and J.P.Bonde, personal communication). Jensen et al. (1996) were able to study semen quality among members of organic food associations in Zealand, Denmark. Their results show that the sperm concentration was 43% [95% confidence interval (3.2–98.8%), P = 0.033] higher among men eating organically produced food. Seminal volume, total sperm count and sperm morphology were not statistically different in the two groups. As these authors did not find a clear dose–response association between eating habits and semen quality, they suggest that general lifestyle and/or geographical factors may have an effect on the sperm concentration.

Endocrine disrupters occur in everything, from plasticizers to pesticides. Even if more research is needed to understand their effects on male reproductive function, there is a growing public demand for recommending that manufacturers be obliged to name all the chemicals in their products and assure that these pose no developmental hazards (Nature, 1996).

References