

## Male reproductive health and the environment

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### *Are xenobiotics in the environment affecting fertility in Australian men?*

Australia is one of a long list of nations experiencing a recent and dramatic decline in fertility rate.<sup>1</sup> The reasons behind this trend are complex, recent, and generally appear to be independent of the socioeconomic status of the country. Deferred childbearing and improved contraceptive use are undoubtedly major factors. However, it is also intriguing that population growth is below replacement rate in several countries such as Sri Lanka, Denmark and Spain, where there have been no obvious increases in abortion rates or contraceptive use. This loss of fertility has affected countries such as Denmark to the point that about 7% of all newborn babies are now being generated by assisted conception.<sup>2</sup> In Australia and New Zealand, the number of babies born as a result of assisted conception procedures has increased threefold over the past 10 years and, despite recent increases, our birth rate is still well below that needed to maintain the population at its present level.

Although it has long been acknowledged that both male and female partners contribute to human infertility, the past 20 years have witnessed a growing awareness of the importance of the male factor in the aetiology of this condition. Indeed, the late Mike Hull and colleagues asserted that defective sperm function is the largest single, defined cause of human infertility.<sup>3</sup> Current estimates suggest that one in 20 Australian men suffer some degree of infertility.<sup>4</sup> Human semen quality is notoriously poor compared with other mammalian species, and in some major capital cities, such as Paris and Copenhagen, there is evidence that it is getting poorer over time.<sup>2</sup> Whatever factors are responsible for this deterioration in semen quality, they do not appear to be universal, because in other areas, such as Finland<sup>5</sup> or the United States,<sup>6,7</sup> similar changes have not been found. Nevertheless, at present, 30% of young Danish men seem to have sperm counts that are in the subnormal range according to World Health Organization guidelines and, in 10% of this population, the semen parameters are indicative of substantially reduced fertility prospects.<sup>2</sup>

The particularly low sperm counts recorded in Denmark are linked with other male reproductive pathologies, including one of the highest rates of testicular cancer in the world and an increasing occurrence of other male genital tract abnormalities such as cryptorchidism and hypospadias.<sup>2,8,9</sup> The increasing incidence, severity and interdependent nature of these pathologies has led to the suggestion that some cases of male infertility should be grouped together with other reproductive problems under one heading — the testicular dysgenesis syndrome (TDS).<sup>2,10</sup> Further, it has been proposed that environmental factors are involved in the aetiology of TDS and that these factors have their effect during early fetal life, when the male genital tract is attempting to differentiate away from the default female condition.<sup>2</sup> Whether the outcome of TDS is impaired spermatogenesis or testicular cancer may depend on the timing and nature of the xenobiotic attack and the genetic

background on which these factors are acting. In this context, a key factor will be the patient's polymorphism profile for proteins involved in detoxification, such as the cytochrome P450s and glutathione-S-transferases.

An important and intriguing feature of the pathologies comprising TDS is the way in which their incidence varies in different regions of the world. In northern Europe, for example, Denmark has high rates of testicular cancer and low sperm counts, but Finland has the opposite — high sperm counts and low rates of testicular cancer.<sup>2</sup> Such geographical variability, coupled with the rapidity with which male reproductive pathologies are increasing in affected countries, suggests an important contribution from environmental factors, including modern Western lifestyle.<sup>11</sup> This conclusion is supported by analysis of the incidence of testicular cancer in the offspring of Nordic parents who have migrated to Sweden, which adjusts to the rate typical of the host country.<sup>12</sup>

If environmental factors are truly responsible for impaired semen quality or testicular cancer, what kind of agents could be involved? Industrial growth since the end of World War II has introduced many complex chemicals into the environment that are novel to biological detoxification systems. Some of these molecules are reproductive toxicants, capable of impairing fertility and inducing developmental abnormalities in the embryo, including errors in normal sexual differentiation. To some extent, the inadvertent introduction of such toxicants reflects the complexity of the safety evaluation process, given the large numbers of xenobiotics used in modern industrialised societies. It may also reflect the inadequacy of the animal models used for screening purposes and a certain lack of commitment on the part of the regulatory agencies to undertake detailed analyses of reproductive toxicity. In societies dependent upon the chemicals industry, there is clearly a trade-off between economic and social advantage on the one hand and the aspiration to eliminate all risk on the other.

A well celebrated example of such an effect is the ability of environmental endocrine disruptors (including certain insecticides and detergent-derived products) to impair male sexual development in aquatic species, including oysters, alligators and fish.<sup>13</sup> Another example, closer to home, is the ability of vinclozolin, a fungicide used in the wine industry, to disrupt the fertility of male rats.<sup>14</sup> Alarmingly, just one exposure of a pregnant female rat to this fungicide was found to disrupt spermatogenesis in more than 90% of the male offspring for at least four generations via an effect that was exclusively transmitted through the male germ line.

The power of reproductive toxicants that target the germ line lies in their capacity to generate damage that can be passed down the generations via genetic or epigenetic means. Both vinclozolin and the pesticide methoxychor induce epigenetic changes in male germ cells, giving the resultant spermatogenic defect a high level of penetrance into subsequent generations.

Genetic changes in the germ line may be less efficient in generating transgenerational pathological phenotypes, but they are nonetheless important. Paternal smoking provides one example of such a genetic change. Men who smoke heavily generate spermatozoa that suffer from high levels of DNA damage, largely as a result of oxidative stress. One of the consequences of this DNA damage is that the children of such men exhibit an increased incidence of childhood cancer.<sup>15</sup> While we have traditionally focused on the ability of cigarette smoke to induce lung cancer, a far more sinister effect of this activity is its ability to induce DNA damage in the germ line and thereby influence the health and wellbeing of future generations. We are probably all carrying around in our genes the genetic legacy of our great-grandfather's pipe-smoking habit.

In light of such data, the search for reproductive toxicants is now being joined in earnest. Groups of toxicants that might be involved in the aetiology of male infertility and possibly TDS include phenols (including oestrogen-like compounds) and phthalate esters, both of which are heavily represented in the environments (including food) of industrialised countries. Such compounds may exert their genetic or epigenetic effects on the germ line via several potential routes of exposure. Firstly, women may be exposed to xenobiotics during pregnancy, thereby disrupting the normal differentiation of the germ line in the fetus; vinclozolin is a good example of such a reagent. Secondly, women exposed to toxicants may transmit xenobiotics to their offspring via breast milk. A third possibility involves paternally mediated toxicity through effects on DNA integrity in the male germ line. Once male germ cells have completed meiosis, they lose their capacity for DNA repair, discard their cytoplasm (containing the defensive enzymes that protect most cell types from oxidative stress) and eventually become separated from the Sertoli cells that have nursed and protected them throughout their differentiation into spermatozoa. In this isolated state, spermatozoa must spend a week or so journeying through the male reproductive tract and, uniquely in our species, a further period (up to 3 or 4 days) in the female tract waiting for an egg. During this period of isolation, sperm DNA is vulnerable to damage by both xenobiotics and electromagnetic radiation. Such DNA damage is associated with male infertility, and its aberrant repair in the fertilised egg may result in mutations in the embryo with the potential to either induce abortion or impair the health and fertility of the offspring.<sup>11,16</sup> Toxicological studies in animal models reporting infertility, abortion and birth defects as a result of male exposure to xenobiotics demonstrate that such associations are possible.<sup>16</sup> Epidemiological studies suggest that they are clinically significant.<sup>2,8</sup>

In conclusion, male infertility is a common condition that affects one in 20 Australian men. Although there are no data to suggest that semen quality in Australia is deteriorating with time, testicular cancer rates are rising in every state, and this may suggest an environmental effect on germ cell development. That exposure to environmental chemicals can impair semen quality is clearly plausible and, in some heavily polluted environments of Europe, such effects are clearly evident.<sup>2,17</sup>

However, it should be emphasised that most of the human data are correlative and involve mechanisms that await resolution. In light of the extensive efforts that are being made in Europe and the US to monitor the effects of toxicants on reproductive processes, there is clearly pressure on the equivalent Australian authorities to establish whether environmental factors are to blame for the significant rates of testicular cancer and infertility seen in Australian males.<sup>11</sup>

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@inproceedings{Sharpe2009MaleRH, title={Male Reproductive Health Disorders and the Potential Role of Exposure to Environmental Chemicals}, author={R. Sharpe}, year={2009} }. R. Sharpe. Published 2009. CHEM Trust, founded in 2007, raises awareness of the role that exposure to chemicals may play in ill health. The charity works to improve chemicals legislation and to protect future generations of humans and wildlife. From a human health perspective, CHEM Trust's mission is to ensure that future generations are healthy and can reach their full potential in terms of behaviour, intelligence and male reproductive health and environmental xenoestrogens. Environ Health Perspect 1996; 104 (Suppl. 4): 741-803. 70. WilliamsK, McKinnellC, SaundersPT. et al. Neonatal exposure to potent and environmental oestrogens and abnormalities of the male reproductive system in the rat: evidence for importance of the androgen-oestrogen balance and assessment of the relevance to man. Hum Reprod Update 2001; 7: 236-47. 71. McLachlanJA, NewboldRR, Bullock, B. Reproductive tract lesions in male mice exposed prenatally to diethylstilbestrol. The environment and male fertility: recent research on emerging chemicals and semen quality. Semin Reprod Med 2006; 24: 156-67. 21. RichthoffJ, RylanderL, JonssonBA. et al. Increasing concern exists regarding male reproductive health worldwide. This is due to the appearance of medical reports outlining apparent adverse trends, such as a worldwide decline in total fertility rate, and an increase in testicular disorders such as testicular cancer, cryptorchidism in parallel with a probable decline in semen quality. now growing evidence to suggest that this developmental programming and the foetal environment, which includes placental function, maternal metabolism, exposures and lifestyle factors (including maternal smoking), may influence additional systems including reproductive health and development in both males and females [5, 8].