

New Chapter in Old Story: Endocrine Disruptors and Male Reproductive System

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ABSTRACT

It is widely acknowledged that our environment is becoming increasingly contaminated with man-made chemicals. Mammals, as well as lower organisms, are vulnerable to exposure to these agents through a variety of different sources and routes and there are concerns that they may be having a detrimental effect on ecological and population health. Endocrine disruptors (EDs) have been described as exogenous agents that interfere with the production, release, transport, metabolism, binding, action or elimination of the natural ligands responsible for maintaining homeostasis and regulating body development. Many different EDs are present in the various compartments of the environment (air, water and land) and in foods (of plant and animal origin). They may originate from food packaging, combustion products, plant health treatments, detergents and the chemical industry in general. The potential effects of these compounds on adults, the sensitivity of embryos and fetuses to many of the xenobiotic compounds likely to cross the placenta has raised considerable concern and led to major research efforts. The deterioration in male reproductive health is at the heart of preoccupations and progress in analyses of the relationship between EDs and human health. This review aims to describe the current state of knowledge about endocrine disruption and its effect on the male reproductive system.

Introduction

During the past 50 years, tens of thousands of chemicals have been synthesized and released into the general environment. Some of these chemicals inadvertently interfere with hormone function in animals, and in some cases, humans[76]. There is increasing concern about chemical pollutants that have the ability to act as hormonal mimics. Because of the structural similarity with an endogenous hormone, and its ability to interact with hormone transport proteins, or its ability to disrupt hormone metabolism, these chemicals have the potential to mimic, or in some cases block, the effects of the endogenous hormone. In either case, these chemicals serve to disrupt the normal action of endogenous hormones and

thus become known as “endocrine disruptors” (EDs)[69]. An ‘endocrine disruptor’ is anything (not just an environmental chemical) which can cause an imbalance within the endocrine system. The endocrine system is not only concerned with the reproductive tract, but with all the hormone-producing organs/glands which maintain bodily homeostasis (e.g. thyroid, parathyroids, anterior and posterior pituitary, pancreas, adrenals, pineal, and the gonads [30]).

In Europe, endocrine disruptors (EDs) have been defined as substances foreign to the body that have deleterious effects on the individuals or their descendants, due to changes in endocrine function. In the United States, EDs have been described as exogenous agents that interfere with the production, release, transport, metabolism, binding, action or elimination of the natural ligands responsible for maintaining homeostasis and regulating body development. These two definitions are complementary, but both indicate that the effects induced by EDs probably involve mechanisms relating in some way to hormonal homeostasis and action. Many different EDs are present in the various compartments of the environment (air, water and land) and in foods (of plant and animal origin). They may originate from food packaging, combustion products, plant health treatments, detergents and the chemical industry in general[18].

The endocrine system can be regarded as a number of interconnecting and interacting axes. The major regulator of the mature reproductive system is the hypothalamo–pituitary–gonadal (HPG) axis that functions as a classical negative feedback system. This consists of the gonadotrophin-releasing hormone (GnRH) neurons in the hypothalamus (brain) that release GnRH into the portal blood supply. GnRH stimulates the release of gonadotrophins (luteinising hormone (LH) and follicle-stimulating hormone (FSH)) from the gonadotroph cells in the pituitary gland. LH and FSH travel through the systemic circulation and act on the endocrine active cells of gonad (testis or ovary). Within the testis, the Leydig cells secrete testosterone and oestradiol and the Sertoli cells secrete inhibin B. These gonadal signals a feedback to the pituitary and hypothalamus to regulate the release of GnRH and the gonadotrophins. There is the potential for endocrine disrupting chemicals (EDCs) to act at any level of the HPG axis but there is general support for the view that the development and programming of the axis during fetal life could be the most sensitive window to permanently alter the homeostatic mechanisms of the endocrine system[30].

Endocrine disruption is not a new phenomenon. In the 1930s studies involving laboratory animals demonstrated estrogenic properties of a number of industrial chemicals including bisphenol A, now widely used in plastics, resins and dental sealants[25, 76]. The feminizing effect of the pesticide DDT (dichlorodiphenyltrichloroethane) in roosters was reported in the 1950s[13, 76].

The life stages most vulnerable to endocrine disruption are the prenatal and early postnatal periods, because these are the times when organ and neural systems are changing most rapidly. Pubertal and peri-menopausal periods may also be sensitive windows of exposure because of changing hormonal effects during these periods [6, 33].

The epidemiologic data have also shown an increase in male reproductive function disorder over the past 50 years, with the suggestion of a relation with the increase in the amounts of endocrine disruptors in the environment[24]. Alterations in male reproduction were first observed in wild animals, in studies reporting the effects of accidental exposure of estrogenic chemicals on wildlife in the natural environment.

These changes in male reproductive function vary from very subtle changes to permanent alterations, such as feminization or changes in reproductive behavior[85]. Alteration caused by endocrine disruptors can be temporary or permanent[48, 66, 86]. Endocrine disruptors can cause the following, among others: reproductive anomalies (morphological and functional gonadal dysfunction, e.g., infertility and decreased libido) and congenital malformations (altered embryonic and fetal intrauterine development)[59, 86].

The principal effects of exposure to endocrine disruptors on male fertility are Deterioration of sperm quality[64], high incidence of cryptorchidism and hypospadias[55], increased incidence of testicular cancer[26], and altered sex ratio[56, 88].

Deterioration of sperm quality

It is undeniable that good quality semen is essential for reproductive success. This quality appears to have been directly affected in recent years. Since 1970s, various authors have reaffirmed that possible significant drop in sperm quality and consequently an increase in male infertility rates[58]. The actual causes of increased infertility remain controversial, but research suggests that many substances to which men are exposed can affect their fertility [66].

Conclusions from a meta-analysis have shown a decrease in sperm quality of 40% worldwide since the 1940s [15]. Olsen and his colleagues [61] questioned these results, but re-analysis by [80] confirmed the originally described time trend and pointed out that, at least, regional differences exist in sperm quality and/or concentrations. This has been substantiated by mono- and multilaboratory studies in e.g. Belgium [84], Finland [62], France[7] and Denmark [5]. The regional differences are suggestive of the involvement of environmental factors, which is corroborated by a number of exposure studies[26].

Bibbo and his colleagues [9] recorded a decrease of ejaculate volume, of sperm concentration and of the percentage of normal motile spermatozoa in sons of women, who were treated with diethylstilbestrol during pregnancy.

A recent study found an inverse correlation between the concentration of polychlorinated biphenyls (PCBs) metabolites in blood and seminal plasma and sperm motility as well as concentration [20]. Guo and his colleagues[37] concluded that heavy exposure to PCBs resulted in negative effects on sperm morphology and motility, but not on sperm concentration.

It became obvious from these studies that, in a number of cases, negative effects could be linked to exposure to environmental contaminants (beside genetic predisposition), when the latter occurred during a well-defined sensitive life stage, the so-called "critical window of exposure"[4, 5].

Increased incidence of testicular cancer

There was a significant increase in the incidence of testicular cancer in the 20th century, which could be correlated with the increase in male infertility[66].

Several studies have correlated the increase in testicular cancer with exposure to certain substances. As important as the chemical agent is the duration of exposure to inductive agent[47, 66]. There is evidence that poor semen quality, testicular cancer, undescended testes and hypospadias are symptoms of one underlying entity, testicular dysgenesis syndrome (TDS), which may be increasingly common due to adverse environmental influences. Experimental and epidemiological studies suggest that TDS is the result of disruption of embryonal programming and gonadal development during fetal life[74].

In Western countries, testicular cancer is the most common malignant tumour in young males. Testicular cancer arises from carcinoma in situ (CIS) cells, which should have their origin in fetal life. How these cells persist during development and what causes them to proliferate after puberty is not well understood, although it is thought that the factors that promote normal germ cell division may also be important in promoting CIS proliferation. Abnormal intrauterine hormone levels i.e. decreased androgen and/or increased estrogen levels are believed to be important in the occurrence of testicular cancer [30].

The main risk factor for testicular cancer is cryptorchidism, followed by hypospadias[14, 71]. Decreased androgen and/or increased estrogen levels have also been implicated in the occurrence of cryptorchidism, hypospadias and low sperm counts[73].

Ninety five per cent of the malignant tumours, arising in the testis, are classified as seminomatous or non-seminomatous, reflecting their origin in primordial germ cells [10].

During recent decades, there has been a significant increase in the prevalence of testicular cancer, albeit with clear racial and geographical differences[23]. The obvious regional differences in incidence and the association with birth cohorts suggest a possible involvement of environmental factors in the development of testicular cancer[53]. Ohlson and Hardell [60] reported with some reservation regarding the study design, a significantly increased risk of seminoma among plastic workers exposed to polyvinyl chloride (PVC).

The mycotoxin ochratoxin A, naturally occurs as a contaminant of cereals, pig meat, and other foods and is a known genotoxic carcinogen in animals. Schwartz,2002 [70] hy-

prothesizes that ochratoxin A could be a cause for the development of testicular cancer. Incidence rates for testicular cancer in 20 countries were significantly correlated with the per-capita consumption of coffee and pig meat, the principal dietary sources of ochratoxin A.

High incidence of cryptorchidism and hypospadias

Cryptorchidism is a disorder whereby the testis fails to descend into its normal position in the scrotum. It is the most common congenital condition in babies [3]. Prevalence values of cryptorchidism are difficult to compare due to differences in screening techniques[81].

Two English studies (one in the late 1950s and one in the 1980s), using the same diagnostic parameters, reported a prevalence of cryptorchidism of 1% and 5% respectively[45]. In exposure studies, the risk for cryptorchidism was higher in sons of women, working with pesticides[87], while significantly higher concentrations of hexachlorobenzene and heptachloroepoxide were found in adipose tissues of boys with testicular maldescent, compared to those of a control group [39].

Hypospadias is a displacement of the urethral meatus onto the underside of the shaft of the penis. As is the statistics of cryptorchidism, there are differences in the methods of analysis and in the definitions of this disorder [81]. Although these differences hamper cross-study comparisons, there are clear indications of a rise in incidence in a number of European countries, the United States and Japan[44] [22, 63]. Furthermore, exposure of fathers to dioxins in the Seveso accident in 1976 resulted in an increased incidence of hypospadias among their sons [8].

In addition, Klip and his Colleagues,[49] reported an increased transgenerational risk of hypospadias in sons of women that were exposed in utero to diethylstilbestrol (DES). Since registry data for cryptorchidism and hypospadias cases are highly unreliable, due to different diagnostic approaches, there is a need for prospective studies to make trustworthy conclusions [71].

Alteration in sex ratio

Under “normal” conditions, the ratio of newborn boys to girls is higher than one. Several studies reported a small but significant decrease in this sex ratio in Canada and the United States [21], the Netherlands, Denmark and several other European countries [52].

The finding of the very recent report on the Aamjiwnaang First Nation community in Canada are striking[51], the proportion of male live births in this community has been decreasing continually from 1990 to 2003, the sex ratio (number of male births/total number of births) reaching only 0.3.

The most important explanatory variables are probably related to the highly changed socio-economic situation in the Western countries since World War II. In addition, there are secular trends in sex ratios [42] which maybe related to hormonal factors.

Certain studies describe a negative influence of environmental pollution on the percentage of newborn boys. In Turkey, mothers exposed to high concentrations of hexachlorobenzene, beared a lower proportion of boys during their fer-

tile period [34, 43]. Gomez and his colleagues (34) noticed a remarkable decrease in the number of sons of fathers who were exposed to PCBs before (but not after) the age of 19 during the Yu-Cheng disaster.

Dioxin exposure during the Seveso accident resulted in a dose-dependent decrease in the sex ratio of the offspring of males that were younger than 19 years of age at the moment of exposure[57]

Endocrine disruption during male sexual differentiation and masculinisation

An increasing number of chemical compounds in the environment have been identified as endocrine disruptors using *in vitro* and *in vivo* bioassays. These include pesticides, industrial chemicals, pharmaceuticals and natural hormones acting as ligands for the estrogen-, androgen- or arylhydrocarbon receptor or exerting a combined action (e.g. estrogenic and anti-androgenic activity) [26].

One of the key areas of concern relating to ‘endocrine disruption’ and male reproduction is interference with male sex determination and sexual differentiation. Though these two processes form a continuum, with differentiation immediately following sex determination, they are traditionally distinguished as being separate events.

The term ‘sex determination’ is usually taken to describe the formation of a testis or ovary from the sexually indifferent genital ridge[12, 38] and this process is hormone-independent – the gonad has not yet formed and has not acquired the capability of making hormones. Once the gonad has formed and the relevant cell types have differentiated, hormones take over the next steps of ‘sexual differentiation’ (40) and this will be referred to as masculinisation. As the masculinisation process is completely hormone-dependent, it is theoretically at risk of endocrine disruption.

Male sexual differentiation and masculinisation

In mammals, the set-up program is for a fetus to develop into a female. This is not a completely default pathway, but it is designed to operate in such a way that the external genitalia and internal reproductive tract will develop along the female pathway without any specific intervention process being required[72] (Figure 1).

Thus, the Müllerian ducts will persist internally and develop into the fallopian tubes, uterus and upper part of the vagina, whereas the Wolffian ducts, which will otherwise develop into the epididymis, vas deferens and seminal vesicles (in the male), will spontaneously degenerate (Figure 1).

Similarly, development of the brain and other organs will proceed along the set-up female pathway without the need for any specific interventions of which we are aware.

To become a male requires intervention to modify the female set-up program [40]. This intervention is initiated by activation of the Sry gene on the Y chromosome. SRY is the principal initiator of the cascade of gene interactions that determines the development of a testis from the indifferent gonad [40]. Via processes that are completely understood – but which involve activation of factors such as WT1, SF1 and in particular Sox9 – the indifferent gonad takes its first step tow-

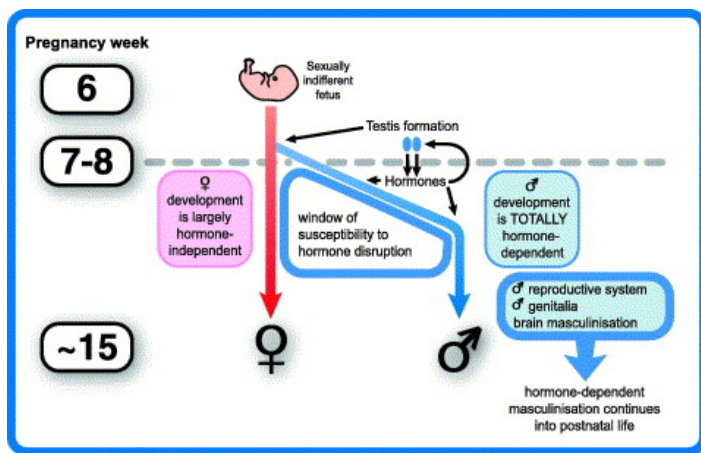


Figure 1. Sex determination and sexual differentiation in humans.

The preset program is for the sexually indifferent fetus to develop along the female pathway of development, and diversion from this pathway is achieved by formation of the testes. Hormone production by the testes is then responsible for the masculinisation process that makes up most of sexual differentiation. As a consequence, male development, but not female development, is totally hormone-dependent and is thus inherently more susceptible to endocrine disruption; from [72]

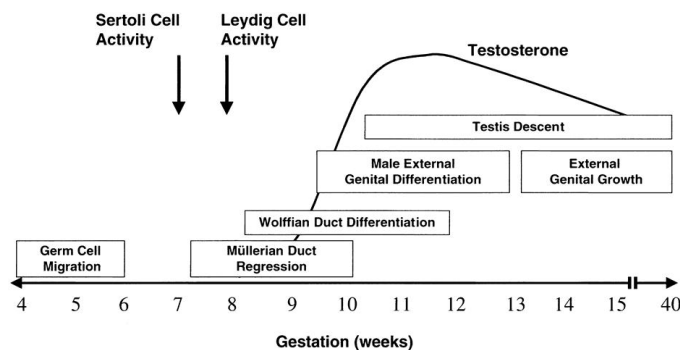


Figure 2. Embryologic events in male sex differentiation depicted in temporal fashion; from (40).

ards becoming a testis via differentiation of the Sertoli cells [12, 40, 72]. This is followed by a number of events that result in the formation of seminiferous cords containing premeiotic germ cells and, outside of and between the seminiferous cords, hormonally active Leydig cells. In this way a testis is formed (Figure 2).

Completion of testis formation does not, however, lead automatically to diversion of development along the male pathway of development (Figure 1). For this to happen, hormonal intervention is required on three separate but interrelated fronts, involving the production and secretion by the testis of anti-Müllerian hormone (AMH), testosterone and insulin-like factor 3 (Insl3) [72]. It should therefore be apparent that 'becoming a phenotypic male' is not just about forming a testis, it is very largely a hormone-dependent process,

with each of the hormones playing a role to divert development from the female pathway[72].

This recognition raises three key points, first, development into a male is inherently more susceptible to endocrine disruption than is female development, simply because of this hormone dependence; anything that interferes with the production and/or action of any of the three 'male' hormones will potentially disrupt the masculinisation process (Figure 1).

Second, as each of the three hormones is produced by the foetal testis, anything that interferes with development and/or function of the testis via non-hormonal mechanisms may secondarily affect the masculinisation process by perturbing hormone production by the testis itself. Third, as the masculinisation process occurs within a defined period of development, susceptibility to endocrine disruption – for example from exogenous chemical exposures – is also confined to these periods(72).

Anti-Müllerian hormone (AMH)

The first hormonal event, temporally, is that the Sertoli cells secrete AMH into the bloodstream, which then acts on the Müllerian ducts to actively induce their regression (Figure 2, Figure 3).

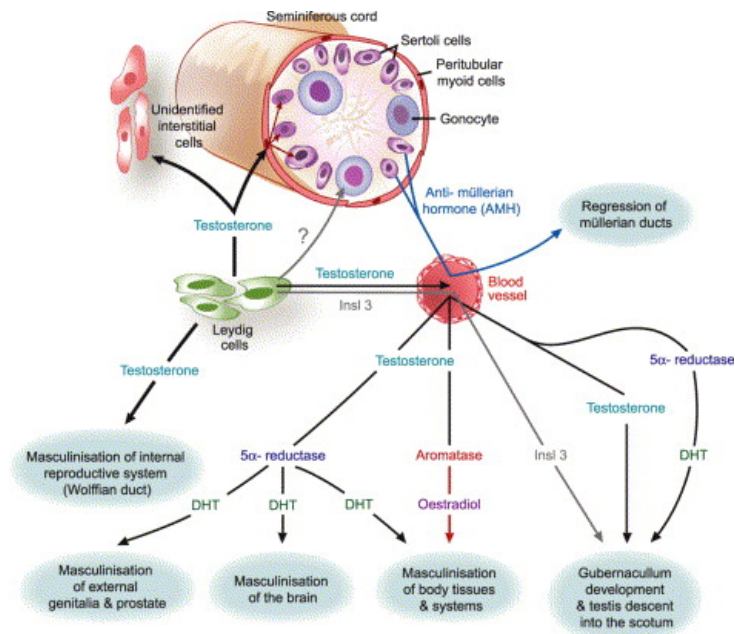


Figure 3. The hormonal processes involved in masculinisation

The diagram illustrates the sites of production and pathways to their target tissues of the three hormones – testosterone, Insl 3, and anti-Müllerian hormone (AMH) – responsible for the masculinisation process in the foetal male. Note that the majority of hormonal effects are achieved after transfer of the hormone into the bloodstream and delivery via this route to target sites. The exception is that testosterone is delivered to the Wolffian duct via a local transport mechanism and also has effects within the testis itself. Note also that the peripheral effects of testosterone are achieved primarily after an amplification step (conversion to 5 α -dihydrotestosterone, DHT) or after conversion to oestradiol; from [72]

The AMH acts via type II AMH receptors in the mesenchyme surrounding the epithelium of the Müllerian ducts [72, 91] and, via processes that are incompletely understood but which involve activation of matrix metalloproteinase 2 [67, 72], regression is induced via apoptosis of the epithelial cells.

So far, no environmental chemical has been identified that interferes with the production or action of AMH, and persistence of Müllerian ducts is a rather rare event [31] so AMH has not been a focus of endocrine disruption research.

Testosterone

The second and most important hormonal event of masculinisation, is the secretion of testosterone by the foetal Leydig cells. It is this hormone secretion that underpins most of the body-wide masculinisation process (Figure 3). Testosterone is delivered locally to the Wolffian duct from the testis to rescue it from its programmed degeneration, how this delivery occurs is unclear. It is presumably via the lumen of the Wolffian duct [82].

In contrast to this local delivery system, the effects of testosterone on the rest of the body – including its effects on the external genitalia to induce formation of a penis and scrotum – occur after its secretion into the bloodstream.

As the levels of testosterone in the bloodstream are relatively low, a hormonal ‘amplification’ step is activated locally in androgen target tissues to ensure that they will be fully masculinised. This amplification is achieved via the enzyme 5 α -reductase (Figure 3), of which there are two forms: type I and type II [40, 78]. Therefore, in tissues such as the prostate and external genitalia, 5 α -reductase converts testosterone delivered from the bloodstream into 5 α -dihydrotestosterone (DHT), which has 10-fold higher potency than does testosterone for activating the androgen receptors (ARs), and genes that are in turn regulated by activated ARs. It is emphasised that testosterone can also bind to the AR and activate the same genes/processes as DHT, but a higher concentration of testosterone would be required to achieve the same level of stimulation as a given level of DHT. 5 α -Reductase distribution in the body during foetal life, therefore provides some indication of ‘sites of masculinisation’, and the brain and skin (5 α -reductase type I) as well as the reproductive tract are among the tissues that express these enzymes during foetal life [27, 83]. An alternative is to survey tissues that express the AR in foetal life, and this extends to the majority of tissues in the foetus, notably including the brain (Figure 3).

The importance of 5 α -reductase in masculinisation of distal androgen target sites in the male is the demonstration in humans that XY individuals with mutations partially/completely inactivating 5 α -reductase type 2 usually present at birth with ambiguous genitalia [40, 78].

Circulating testosterone is able to partially masculinise these individuals, but the levels are insufficient to complete the process in foetal life. The extent to which other body tissues, including the brain, may also be ‘under-masculinised’ is a topic of considerable interest, but one which has received relatively little research attention [16]. 5 α -Reductase is also potentially a target for disruption by environmental chemicals, but no such effects have yet been reported.

An alternative to conversion of testosterone to DHT is to convert testosterone to oestradiol via activation of the aromatase enzyme (Figure 3). Any oestradiol generated locally in target tissues can then bind to oestrogen receptors (ER α or ER β) and induce biological effects. Though it may seem rather odd that a male uses a ‘female hormone’ like oestradiol to induce masculinisation, it should be remembered that this activity occurs locally within a given tissue, and so oestradiol levels in the bloodstream will probably remain very low thus non-detectable. It is well established that in rodents local conversion of testosterone to oestradiol within specific brain regions is responsible for ‘masculinising’ some areas of the brain, for example the regions that regulate sexual behaviour and the sex-specific differences in gonadotrophin secretion [41]. In the human it appears that testosterone/DHT are more important than oestrogens for masculinising the brain, which occurs during foetal life [16, 35, 79]. The most convincing pieces of evidence for this difference in the human are the apparently normal sexual orientation and behaviour of XY individuals who have either an inactivating mutation of the aromatase or ER genes, and who therefore cannot make/respond to oestradiol [36].

It may be that in the human, in whom very high levels of oestradiol occurs during pregnancy than occur in rodents during pregnancy [89], there would be the danger that any foetus could become masculinised as the result of placenta-derived oestradiol interacting with ERs in the brain, so the oestrogen pathway of masculinisation has been selected against.

In this regard, in both the human [19] and rat [46] foetus, ERs are expressed in the developing penis, indicating a role for oestradiol in penile development. It is fair to say, in summary, that we still have a poor understanding of the role of oestrogens in sex-specific programming of body development in foetal life, but the widespread distribution of ERs [11] is suggestive of considerable influence.

Insulin-like factor-3 (Insl3)

The third testicular hormone involved in masculinisation of the male is Insl3, produced—like testosterone—by the foetal Leydig cells (Figure 3) [72]. The importance of Insl3 was first identified serendipitously in transgenic mice in which the Insl3 gene had been ‘knocked out’ [2]. In male Insl3 $-/-$ mice there was complete failure of testicular descent due to lack of development of the gubernaculum. Conversely, transgenic over-expression of Insl3 results, in females, in ‘descent’ of the ovaries and inguinal hernias [1, 50].

In the normal male foetus, development of the gubernaculum is a key event in guiding the testis into the scrotum and fixing it there [2]; such descent of the testis is a prerequisite for normal spermatogenesis and fertility in adulthood. However, it is equally evident that testosterone and/or DHT also play a role in gubernacular development (Figure 3) [72]. This is indicated by the widespread expression of AR throughout the gubernaculum [77], the expression of 5 α -reductase [32], and *in vitro* evidence showing that androgens and Insl3 interact to regulate growth of the gubernaculum [28].

Estrogen may also affect gubernacular development, based on expression of ERs [77] and maldevelopment of the

gubernaculum in male mice exposed to abnormally high oestradiol levels during pregnancy[2]. As such oestrogen exposure can also suppress *Insl3* production by the foetal Leydig cells[29].

Irrespective of the relative importance of androgens, oestrogens and *Insl3* in development of the gubernaculum and subsequent testicular descent, the important point to recognize is that these are completely hormone-dependent processes, and that all of the hormones involved derive ultimately from the foetal testis (Figure 3). Therefore, when testicular descent is incomplete (i.e. there is cryptorchidism), it is likely to indicate that hormonal function of the foetal testis is abnormal[75]. Moreover, the complete hormone dependence of testicular descent renders this process inherently susceptible to endocrine disruption.

Identification of the points of vulnerability to endocrine disruption

As outlined earlier, the masculinisation process depends upon the conversion of circulating testosterone to either DHT or oestradiol within target tissues, via the actions of 5 α -reductase or aromatase, respectively.

Any environmental chemical that is able to alter activity of either of these enzymes is therefore also likely to affect the masculinisation process. So far there are no reports of compounds that can affect 5 α -reductase, but there is a well-established example from wildlife in which worldwide changes in infertility of certain marine snails has been impaired by exposure to a compound—tributyl tin [68] the main action of which is to inhibit aromatase activity[17]. In this instance, the main problem appears to be the build-up in the female snails of androgen precursors due to their lack of conversion to oestradiol, which then leads to the partial masculinisation of the females[72].

For androgens and oestrogens to act on their target tissues, there has to be expression of appropriate levels of androgen receptor (AR) and estrogen receptors (ERs), respectively. Any compound that alters the availability of these receptors can therefore potentially interfere with masculinisation[72]).

It is becoming increasingly apparent that expression of AR, and probably of steroid receptors in general, is regulated primarily via alteration of the rates of receptor degradation rather than from altering the rate of receptor gene transcription and mRNA translation. This has been most clearly demonstrated for the AR, in which altered proteosomal degradation has been shown to occur in response to abnormally high exposure to potent oestrogens [90].

This ability of over-exposure to oestrogens to dramatically reduce AR expression in reproductive target tissues in the male rat has been well described[54, 65], and raises the possibility that environmental oestrogenic chemicals could induce similar effects and thus interfere with masculinisation.

Summary

The epidemiologic data have shown an increase in male reproductive function disorder over the past 50 years, with the suggestion of a relation with the increase in the amounts of

endocrine disruptors in the environment. These changes in male reproductive functionary from very subtle changes to permanent alterations, such as feminization or changes in reproductive behavior. Alteration caused by endocrine disruptors can be temporary or permanent. Endocrine disruptors can cause the following, among others: reproductive anomalies (morphological and functional gonadal dysfunction, e.g., infertility and decreased libido) and congenital malformations (altered embryonic and fetal intrauterine development). An increasing number of chemical compounds in the environment have been identified as endocrine disruptors using *in vitro* and *in vivo* bioassays. These include pesticides, industrial chemicals, pharmaceuticals and natural hormones acting as ligands for the estrogen-, androgen- or arylhydrocarbon receptor or exerting a combined action (e.g. estrogenic and anti-androgenic activity).

One of the areas of concern relating to endocrine disruption and reproduction is interference with male sex determination which is hormone independent and sexual differentiation and masculinisation, it is completely hormone dependent and it is theoretically at risk of endocrine disruption. Three hormones, testosterone, *Insl3*, and anti mullerian hormone responsible for the masculinisation process, in the fetal male.

The future challenge is to collect evidence to confirm (or reject) suspected effects on the male reproductive system, and to faze out compounds with hormone disruptive characteristics.

REFERENCES

1. Adham IM, Steding G, Thamm T, et al. 2002. The over-expression of *Insl3* in female mice causes descent of the ovaries. *Molecular Endocrinology* 16:244-52
2. Adham M, Agoulnik AI. 2004. Insulin-like 3 signalling in testicular descent. *International Journal of Andrology* 27:257-65
3. Akre O, Lipworth L, Cnattinguis S, Sparen P, Ekblom A. 1999. Risk factor patterns for cryptorchidism and hypospadias. *Epidemiology* 10:364-9
4. Andersen AG, Jensen TK, Carlsen E, Jorgensen N, Andersson AM et al. 2000. High frequency of sub-optimal semen quality in an unselected population of young men. *Human Reproduction* 15:366-72
5. Anderson LMDBA, Fear NT, Roman E. 2000. Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. *Environmental Health Perspectives* 108:573-94
6. Andrea CG, Jerrold JH, Zoeller RT. 2006. Endocrine disruption for endocrinologists (and others) *Endocrinology* 147:S1-S3
7. Auger J, Jouannet P. 1997. Evidence for regional differences of semen quality among fertile french men. *Federation Francaise des Centres d'Etude et de Conversation des Oeufs et du sperme Humains. Human Reproduction* 12:740-5
8. Baskin LS, Himes K, Colborn T. 2001. Hypospadias and endocrine disruption: is there a connection? *Environ-*

- mental Health Perspectives 109:1175-83
9. Bibbo M, Hawnszel WM, Wied GL, Hubby M, Herbst AL. 1978. A twenty-five-year follow-up study of women exposed to diethylstilbestrol during pregnancy. 298 (1978), pp. 763-767. *New England Journal of Medicine* 298:763-7
 10. Bosl GJ, Motzer RJ. 1997. Testicular germ-cell cancer. *The New England Journal of Medicine* 337:242
 11. Brandenberger AW, Tee MK, ., Lee JY, et al. 1997. Tissue distribution of estrogen receptors alpha (ER-alpha) and beta (ER-beta) mRNA in the midgestational human fetus. *The Journal of Clinical Endocrinology and Metabolism* 82:3509-12
 12. Brennan J, Capel B. 2004. One tissue, two fates: molecular genetic events that underlie testis versus ovary development. *Nature Reviews Genetics* 7:509-21
 13. Burlington H, Lindeman VF. 1950. Effect of DDT on testes and secondary sex characters of white leghorn cockerels. *Proc Soc Exp Biol Med* 74:48-51
 14. Carbone P, Giordano F, Nori F, Mantovani A, Taruscio D et al. 2007. The possible role of endocrine disrupting chemicals in the aetiology of cryptorchidism and hypospadias: a population-based case control study in rural sicily. *International Journal of Andrology* 30:3-13
 15. Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. 1992. Evidence for decreasing quality of semen during past 50 years. *BMJ* 305:609-13
 16. Cohen-Bendahan CC, van de Beek C, Berenbaum SA. 2005. Prenatal sex hormone effects on child and adult sex-typed behavior: methods and findings. *Neuroscience and Biobehavioral Reviews* 29:353-84
 17. Cooke GM. 2002. Effect of organotins on human aromatase activity in vitro. *Toxicology Letters* 126:121-30
 18. Cravedi JP, Zalko D, Savouret JF, Meduet A, Jegou B. 2007. The concept of endocrine disruption and human health. *Med Sci (Paris)* 23:198-204
 19. Crescioli C, Maggi M, Vannelli GB, et al. 2003. Expression of functional estrogen receptors in human fetal male external genitalia. *The Journal of Clinical Endocrinology and Metabolism* 88:1815-24
 20. Dallinga JW, Moonen EJ, Dumoulin JC, Evers JL, Geraedts JP, Kleinjans JC. 2002. Decreased human semen quality and organochlorine compounds in blood. *Human Reproduction* 17:1973-9
 21. Davis DL, Gottlieb MB, Stampnitzky JR. 1998. Reduced ratio of male to female births in several industrial countries: a sentinel health indicator? *JAMA* 279:1018-23
 22. Dearnaley D, Huddart R, Horwich A. 2001. Regular review: Managing testicular cancer. *BMJ*. 322 (2001), pp. 1583-1588. *BMJ* 322:1583-8
 23. Dearnaley D, Huddart R, Horwich A. 2001. Regular review: Managing testicular cancer. *BMJ*. 322 (2001), pp. 1583-1588. *BMJ* 322:1583-8
 24. Delbes G, Levacher C, Habert R. 2006. Estrogen effects on fetal and neonatal testicular development. *Reproduction* 132:527-38
 25. Dodds EC, Lawson W. 1938. Molecular structure in relation to oestrogenic activity. Compounds without a phenanthrene nucleus. *Proc R Soc London* 125:222-32
 26. Eertmans F, Dhooge W, Stuyvaert F, Comhaire F. 2003. Endocrine disruptors: effects on male fertility and screening tools for their assessment. *Toxicology in Vitro*. 17:515-24
 27. Ellsworth K, Harris G. 1995. K. and G. Harris, Expression of the type 1 and 2 steroid 5 alpha-reductases in human fetal tissues. *Biochemical and Biophysical Research Communications* 215:774-80
 28. Emmen JM, McLuskey A, Adham IM, et al. 2000. Hormonal control of gubernaculum development during testis descent: gubernaculum outgrowth in vitro requires both insulin-like factor and androgen *Endocrinology* 141:4720-7
 29. Emmen JM, McLuskey A, Adham IM, et al. 2000. Involvement of insulin-like factor 3 (InsI3) in diethylstilbestrol-induced cryptorchidism. *Endocrinology* 141:846-9
 30. Fisher JS. 2004. Environmental anti-androgens and male reproductive health: focus on phthalates and testicular dysgenesis syndrome. *Reproduction* 127:305-15
 31. Gell JS. 2003. Müllerian anomalies *Seminars in Reproductive Medicine* 21:375-88
 32. George FW. 1989. Developmental pattern of 5 alpha-reductase activity in the rat gubernaculum. *Endocrinology* 124:727-32
 33. Golub MS, Hogrefe CE, Germann SL, Jerome CP. 2004. Endocrine disruption in adolescence: immunologic, hematologic, and bone effects in monkeys. *Toxicol Sci* 82:598-607
 34. Gomez DR, Marshall T, Tsai P, Shao YS, Guo YL. 2002. Number of boys born to men exposed to polychlorinated biphenyls. *Lancet* 360:143-4
 35. Gooren LJ, Kruijver FP. 2002. Androgens and male behaviour *Molecular and Cellular Endocrinology* 198:31-40
 36. Grumbach MM, Auchus RJ. 1999. Estrogen: consequences and implications of human mutations in synthesis and action *The Journal of Clinical Endocrinology and Metabolism* 84:4677-94
 37. Guo YL, Hsu PC, Hsu CC, Lambert GH. 2000. Semen quality after prenatal exposure to polychlorinated biphenyls and dibenzofurans. *Lancet* 356:1240-1
 38. Harley R, ClarksonmM.J., Argentaro A. 2003. The molecular action and regulation of the testis-determining factors, SRY (sex-determining region on the Y chromosome) and SOX9 [SRY-related high-mobility group (HMG) box 9], *Endocrine Reviews* 24:466-87
 39. Hosie S, Loff S, Witt K, Niessen K, Waag KL. 2000. Is there a correlation between organochlorine compounds and undescended testes?. *European Journal of Pediatric Surgery* 10:304-9
 40. Hughes IA. 2001. Minireview: sex differentiation, 142 (2001), pp. 3281-3287. *Endocrinology* 142:3281-7
 41. Hutchinson JB. 1997. Gender-specific steroid metabolism in neural differentiation. *Cellular and Molecular Neurobiology* 17:603-26
 42. James WH. 2000. Secular movements in sex ratios of

- adults and of births in populations during the past half-century. *Human Reproduction* 15:1178-83
43. Jarrell JF, Gocmen A, Akyol D, Brant R. 2002. Hexachlorobenzene exposure and the proportion of male births in Turkey 1935-1990. *Reproductive Toxicology* 16:65-70
 44. Jensen TK, Toppari J, Keiding N, Skakkebaek NE. 1995. Do environmental estrogens contribute to the decline in male reproductive health?. 41 (1995), pp. 1896-1901 *Clinical Chemistry* 41:1896-901
 45. Jensen TK, Toppari J, Keiding N, Skakkebaek NE. 1995. Do environmental estrogens contribute to the decline in male reproductive health?. 41 (1995), pp. 1896-1901 *Clinical Chemistry* 41:1896-901
 46. Jesmin S, Mowa CN, Matsuda N, et al. 2002. Evidence for a potential role of estrogen in the penis: detection of estrogen receptor-alpha and -beta messenger ribonucleic acid and protein. *Endocrinology* 143:4764-74
 47. Joffe M. 2001. Are problems with male reproductive health caused by endocrine disruption? *Environ Med* 58:281
 48. Kavlock RJ, Daston GP, Derosa C, Fenner-Crisp P, Gray LE et al. 1996. Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U.S.EPA-sponsored workshop. *Environmental Health Perspectives* 104:715-40
 49. Klip H, Verloop J, Van Gool JD, Koster ME, Burger CW, Van Leeuwen FE. 2002. Hypospadias in sons of women exposed to diethylstilbestrol in utero: a cohort study. *Lancet* 359:1102-7
 50. Koskimies P, Suvanto M, Nokkala E, et al. 2003. Female mice carrying a ubiquitin promoter-Ins13 transgene have descended ovaries and inguinal hernias but normal fertility. *Molecular and Cellular Endocrinology* 206:159-66
 51. Mackenzie CA, Lockridge A, Keith M. 2005. Declining sex ratio in a first nation community. *Environmental Health Perspectives* 113:1295-8
 52. Martuzzi M, Di Tanno ND, Bertollini R. 2001. Declining trends of male proportion at birth in Europe. 56 (2001), pp. 358-364 *Archives of Environmental Health* 56:358-64
 53. McKiernan JM, Goluboff ET, Liberson GL, Golden R, Fisch H. 1999. Rising risk of testicular cancer by birth cohort in the United States from 1973 to 1995. *Journal of Urology* 162:361-3
 54. McKinnell C, Atanassova N, Williams K, et al. 2001. Suppression of androgen action and the induction of gross abnormalities of the reproductive tract in male rats treated neonatally with diethylstilbestrol. *Journal of Andrology* 22:323-38
 55. Melnick RL. 1999. Introduction-Workshop on characterizing the effects of endocrine disruptors on human health at environmental exposure level. *Environmental Health Perspectives* 107:603-4
 56. Mocarelli P, Brambilla PM, Gerthoux DG, Patterson N. 1996. Changes in sex ratio with exposure to dioxin. *Lancet* 348:409
 57. Mocarelli P, Gerthoux PM, Ferrari E, Patterson DG, Kieszak SM et al. 2000. Paternal concentrations of dioxin and sex ratio of offspring. *Lancet* 355:1858-63
 58. Nelson C, Bunge R. 1974. Semen analysis : evidence for changing parameters of male infertility potential. *Fertility and Sterility* 25:503-7
 59. Nelson P. 2003. Epidemiology, biology, and endocrine disruptors. *Occup Environ Med* 60:541-2
 60. Ohlson CG, Hardell L. 2000. Testicular cancer and occupational exposures with a focus on xenoestrogens in polyvinyl chloride plastics. *Chemosphere* 40:1277-82
 61. Olsen GW, Bodner KM, Ramlow JM, Ross CE, Lipshultz LI. 1995. Have sperm counts been reduced 50 percent in 50 years? A statistical model revisited. *Fertility and Sterility* 63:887-93
 62. Pajarinen J, Laippala P, Penttila A, Karhunen PJ. 1997. Incidence of disorders of spermatogenesis in middle aged finnish men, 1981-91: two necropsy series. *BMJ* 314:13-8
 63. Paulozzi LJ, Erickson JD, Jackson RJ. 1997. Hypospadias trends in two US surveillance systems. 100 (1997), pp. 831-834 *Pediatrics* 100:831-4
 64. Pflieger BS, Schuppe HC, Schill WB. 2004. The male reproductive system and its susceptibility to endocrine disruptors chemicals. *Andrologia* 36:337-45
 65. Prins GS. 1992. Neonatal estrogen exposure induces lobe-specific alterations in adult rat prostate androgen receptor expression. *Endocrinology* 130:3703-14
 66. Retto de Queriroz EK, Waissmann W. 2006. Occupational exposure and effects on the male reproductive system. *Cad Saude Publica* 22:485-93
 67. Roberts LM, Visser JA, Ingraham HA. 2002. Involvement of a matrix metalloproteinase in MIS-induced cell death during urogenital development *Development* 129:1487-96
 68. Rotchell M, Ostrander GK. 2003. .Molecular markers of endocrine disruption in aquatic organisms. *Journal of Toxicology and Environmental Health Part B Critical Reviews* 6:453-96
 69. Sausan LS, Widholm JJ. 2001. Cognitive effects of endocrine-disrupting chemicals in animals. *Environmental Health Perspectives*. 109:1197-206
 70. Schwartz GG. 2002. Hypothesis: does ochratoxin A cause testicular cancer? *Cancer Causes Control* 13:91-100
 71. Sharp RM. 2003. The 'oestrogen hypothesis'- where do we stand now?. *International Journal of Andrology* 26:2-15
 72. Sharp RM. 2006. Pathways of endocrine disruption during male sexual differentiation and masculinisation. *Best Practice & Research Clinical Endocrinology & Metabolism* 20:91-110
 73. Sharp RM, Skakkebaek NE. 1993. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 341:1392-5
 74. Skakkebaek NE. 2003. Testicular dysgenesis syndrome *Hormone Res.* 60:49
 75. Skakkebaek NE, Rajpert-De Meyts E, Main KM. 2001. Testicular dysgenesis syndrome: an increasingly com-

- mon developmental disorder with environmental aspects
Human Reproduction 16:972-8
76. Solomon GM, Schettler T. 2000. Environment and Health: 6. Endocrine disruption and potential human health implications. *CMAJ* 163:1471-6
 77. Staub C, Rauch M, Ferriere F, et al. 2005. C. , M. Rauch and F. Ferriere et al., Expression of estrogen receptor ESR1 and its 46 kDa variant in the gubernaculum testis, *Biology of Reproduction* 73:712
 78. Sultan C, Paris F, Terouanne B, et al. 2001. Disorders linked to insufficient androgen action in male children. *Human Reproduction* 7:314-22
 79. Swaab DF. 2004. Sexual differentiation of the human brain: relevance for gender identity, trans-sexualism and sexual orientation *Gynecological Endocrinology* 19:301-12
 80. Swan SH, Elkin EP, Fenster L. 1997. Have sperm densities declined? A reanalysis of global trend data. *Environmental Health Perspectives* 105:1228-32
 81. Toppari J, Kaleva M, Virtanen HE. 2001. Trends in the incidence of cryptorchidism and hypospadias, and methodological limitations of registry-based data. *Human Reproduction Update* 7:282-6
 82. Tsuji M, Shima H, Cunha GR. 1991. In vitro androgen-induced growth and morphogenesis of the Wolffian duct within the urogenital ridge 128 (1991), pp. 1805-1811 *Endocrinology* 128:1805-11
 83. Tsuruo Y. 2005. Topography and function of androgen-metabolizing enzymes in the central nervous system. *Anatomical Science International* 80:1-11
 84. Van Waeleghem K, De Clercq N, Vermeulen L, Schoonjans F, Comhaire F. 1996. Deterioration of sperm quality in young healthy Belgian men. *Human Reproduction* 11:325-9
 85. Vos JG, Dybing E, Greim HA, Ladefoged O, Lambre C et al. 2000. Health effects of endocrine disrupting chemicals on wildlife, with special reference to the European situation. *Critical Reviews in Toxicology* 30:71-133
 86. Waissmann W. 2002. Health surveillance and endocrine disruptors. *Cad Saude Publica* 18:511-7
 87. Weidner IS, Moller H, Jensen TK, Skakkebaek NE. 1998. Cryptorchidism and hypospadias in sons of gardeners and farmers. 106 (1998), pp. 793-796 *Environmental Health Perspectives* 106:793-6
 88. Whitten PL. 1992. Effects of a phytoestrogen diet on estrogen-dependent reproductive processes in immature female rats. *Advances of Modern Environmental Toxicology* 21:311
 89. Witorsch RJ. 2002. Low-dose in utero effects of xenoestrogens in mice and their relevance to humans: an analytical review of the literature. *Food and Chemical Toxicology* 40:905-12
 90. Woodham C, Birch L, Prins GS. 2003. Neonatal estrogen down-regulates prostatic androgen receptor through a proteasome-mediated protein degradation pathway. *Endocrinology* 144:4841-50
 91. Xavier F, Allard S. 2003. Anti-Müllerian hormone, beta-catenin and Müllerian duct regression. *Molecular and Cellular Endocrinology* 211:115-21

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