

**TRAINING FOR THE HEALTH SECTOR**  
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**MALE REPRODUCTIVE HEALTH  
AND  
THE ENVIRONMENT**  
*(Draft for review)*

**Training Module 4**  
**Children's Environmental Health**  
Public Health and the Environment  
World Health Organization  
[www.who.int/ceh](http://www.who.int/ceh)

November 2011

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<<NOTE TO USER: Please add details of the date, time, place and sponsorship of the meeting for which you are using this presentation in the space indicated.>>

<<NOTE TO USER: This is a large set of slides from which the presenter should select the most relevant ones to use in a specific presentation. These slides cover many facets of the problem. Present only those slides that apply most directly to the local situation in the region.>>

<<NOTE TO USER: This module presents several examples of risk factors that affect reproductive health. You can find more detailed information in other modules of the training package that deal with specific risk factors, such as lead, mercury, pesticides, persistent organic pollutants, endocrine disruptors, occupational exposures; or disease outcomes, such as developmental origins of disease, reproductive effects, neurodevelopmental effects, immune effects, respiratory effects, and others.>>

<<NOTE TO USER: For more information on reproductive health, please visit the website of the Department of Reproductive Health and Research at WHO:  
[www.who.int/reproductivehealth/en/](http://www.who.int/reproductivehealth/en/)>>

## LEARNING OBJECTIVES

**After this presentation individuals should be able to understand, recognize, and know:**

- ❖ Common male reproductive disorders and potential links to environmental exposures
- ❖ How various prenatal environmental exposures may affect later reproductive disorders

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<<READ SLIDE.>>

According to the formal definition by the World Health Organization (WHO), *health is more than absence of illness. It is a state of complete physical, mental and social well-being. Similarly, reproductive health also represents a state of complete physical, mental and social well-being, and not merely the absence of reproductive disease or infirmity.*

This presentation will introduce you to the basics of male reproductive health disorders and the potential role that the environment may play in the development of these disorders.

*Refs:*

•WHO. Department of Reproductive Health and Research, Partner Brief. Geneva, Switzerland, *World Health Organization*, 2009. WHO/RHR/09.02. Available at [whqlibdoc.who.int/hq/2009/WHO\\_RHR\\_09.02\\_eng.pdf](http://whqlibdoc.who.int/hq/2009/WHO_RHR_09.02_eng.pdf) – accessed 15 June 2011

•WHO. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference. New York, United States of America, *World Health Organization*, 1946.

## OUTLINE

1. Introduction to male reproductive health and the environment
2. Overview of male reproductive health outcomes
  - A. Identified in newborns:
    - Hypospadias
    - Cryptorchidism
    - Reduced anogenital distance
  - B. Identified in puberty or later:
    - Infertility
    - Semen quality
    - Sperm motility/function
    - Testicular cancer
    - Testicular Dysgenesis Syndrome
    - Prostate cancer

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<<NOTE TO USER: You may decide to delete certain parts of the presentation depending on time. Please correct the outline accordingly.>>

## 1. INTRODUCTION TO MALE REPRODUCTIVE HEALTH

- ❖ Disorders related to male reproductive health may develop during fetal development, childhood, adolescence, or adulthood
- ❖ Multiple causes for alterations in male reproductive functioning
- ❖ Increasing evidence of involvement of environmental exposures



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Reproductive health involves all of the reproductive processes, functions and systems at all stages of human life. This definition implies that people are able to have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so.

Several male reproductive disorders may affect the health status and overall quality of life for a man. Male reproductive disorders may develop during various life phases. Alterations in proper reproductive functioning may be the result of various occurrences and experiences throughout fetal development, childhood, adolescence, or adulthood.

While much is known about the male reproductive system, its development, and many causes of specific disorders, the research pertaining to the mechanisms of action for certain pathologies is still largely unknown. However, exposure to environmental contaminants has been proposed in recent years to potentially contribute to male reproductive disorders. Research has been focused on exposures that occur during critical periods of development, however this is still an emerging field of research that demands greater scientific investigation.

**<<NOTE TO USER: For more information regarding the basics of male reproductive health, including male reproductive anatomy, please see Module 1: Introduction to Reproductive Health and the Environment.>>**

### *Refs:*

- UNDP/UNFPA/WHO/World Bank. Social science methods for research on reproductive health topics. Geneva, Switzerland, *UNDP/UNFPA/WHO/World Bank Special Programme on Research, Development, and Training in Human Reproduction*, 2006. Available at [whqlibdoc.who.int/hq/1999/WHO\\_RHR\\_HRP\\_SOC\\_99.1.pdf](http://whqlibdoc.who.int/hq/1999/WHO_RHR_HRP_SOC_99.1.pdf) - accessed 22 June 2010.
- WHO. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference. New York, United States of America, *World Health Organization*, 1946.

*Image:* WHO

## MALE REPRODUCTIVE HEALTH AND THE ENVIRONMENT

- ❖ Focuses on exposure to contaminants found in the environment, specifically during critical periods of development
- ❖ All the physical, chemical, biological and social factors that may affect the origin, growth, development and survival of a person in a given setting

*Some examples include:*

- **Specific synthetic chemicals**
- **Some metals**
- **Air contaminants**

**Still an  
emerging  
issue!**

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Reproductive health and the environment focuses on exposures to environmental contaminants during critical periods of human development. These periods are directly related to reproductive health throughout the life course, including the period before conception, at conception, fertility, pregnancy, child and adolescent development, and adult health.

Environmental toxicants may potentially induce effects in human reproductive processes, specifically, for male reproductive health. However, the extent of this hypothesis must be supported through greater levels of research. Currently, men's health care providers are growing increasingly aware of the potential for environmental factors to influence male reproductive health status.

*Refs:*

•WHO. Global assessment of the state of the science of endocrine disruptors. Geneva, Switzerland, WHO/PCS/EDC, 2002. Available at [www.who.int/ipcs/publications/new\\_issues/endocrine\\_disruptors/en/](http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/) - accessed 23 June 2010.

•Woodruff T. Proceedings of the Summit on Environmental Challenges to Reproductive Health and Fertility: executive summary. *Fertility and Sterility*, 2003, 89 (2),1-20.

<< **NOTE TO USER: For further information on occupational exposures of men, please refer to the module on "Occupational Exposures".>>**

## INTERNATIONAL ENVIRONMENTAL HEALTH RISKS

These include:

- ❖ Chemical hazards
- ❖ Indoor and outdoor air pollution
- ❖ Injuries and accidents
- ❖ Lack of appropriate hygiene and sanitation
- ❖ Unsanitary water supply
- ❖ Disease vectors



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These are the major risk factors identified to affect human health. Several environmental factors pose a direct hazard to human health, especially as it relates to reproductive development. For instance, certain chemicals are potential endocrine disruptors.

**<<NOTE TO USER: You may emphasize or provide examples of specific environmental health risks that pertain to your specific nation or region.>>**

*Refs:*

- WHO. Children's Health and the Environment. Ed: Pronczuk J. Geneva, Switzerland, *World Health Organization*, 2005.
- WHO. Global assessment of the state of the science of endocrine disruptors. Geneva, Switzerland, *WHO/PCS/EDC*, 2002. Available at [www.who.int/ipcs/publications/new\\_issues/endocrine\\_disruptors/en/](http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/) - accessed 23 June 2010.
- WHO. Preventing Disease Through Healthy Environments. Geneva, Switzerland, *World Health Organization*, 2006.

*Image: WHO*

## 2. OVERVIEW OF MALE REPRODUCTIVE HEALTH OUTCOMES

### 2.A. Identified in newborns:

1. Hypospadias
2. Cryptorchidism
3. Reduced anogenital distance



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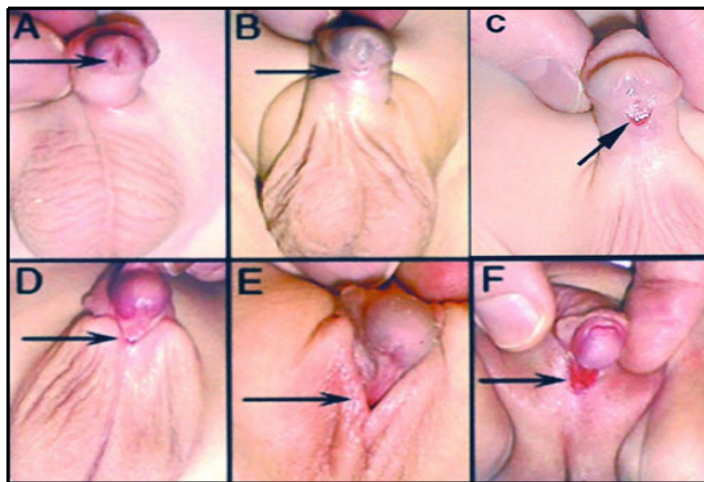
The next series of slides will outline several male reproductive health outcomes that can be identified in the newborn.

<<READ SLIDE.>>

*Image: WHO*

## 2.A.1. HYPOSPADIAS

Condition where the opening of the urethra is on the underside of the penis, instead of at the tip.



Baskin et al, 2001, Environmental Health Perspectives

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Hypospadias is one of the most common congenital anomalies occurring in approximately 1 of 200 to 1 of 300 live births. The condition is an arrest in normal development of the urethral, foreskin, and ventral aspect of the penis. This results in a urethral opening being anywhere along the shaft of the penis, within the scrotum, or even in the perineum. Moderate or severe cases of this condition may involve several operations to correct the abnormality.

Figure guide:

A Anterior opening - on inferior surface of glans penis. B Coronal opening - in balanopenile furrow. C Distal opening - on distal third of shaft. D Penoscrotal opening - at base of shaft in front of scrotum. E Scrotal opening - on scrotum or between the genital swellings. F Perineal opening - behind scrotum or genital swellings.

Ref:

•Baskin L. Hypospadias: anatomy, etiology, and technique. *Journal of Pediatric Surgery*, 2006, 41(3):463-472.

*Hypospadias is one of the most common congenital anomalies in the United States, occurring in approximately 1 in 250 newborns or roughly 1 in 125 live male births. It is the result of arrested development of the urethra, foreskin, and ventral surface of the penis where the urethral opening may be anywhere along the shaft, within the scrotum, or in the perineum. The only treatment is surgery. Thus, prevention is imperative. To accomplish this, it is necessary to determine the etiology of hypospadias, the majority of which have been classified as idiopathic. In this paper we briefly describe the normal development of the male external genitalia and review the prevalence, etiology, risk factors, and epidemiology of hypospadias. The majority of hypospadias are believed to have a multifactorial etiology, although a small percentage do result from single gene mutations. Recent findings suggest that some hypospadias could be the result of disrupted gene expression. Discoveries about the antiandrogenic mechanisms of action of some contemporary-use chemicals have provided new knowledge about the organization and development of the urogenital system and may provide additional insight into the etiology of hypospadias and direction for prevention*

*Image: Baskin LS, Himes K, Colborn T. Hypospadias and endocrine disruption: is there a connection? Environ Health Perspect. 2001, 109(11):1175-83. This image was reproduced with permission from Environmental Health Perspectives.*

## INCREASED INCIDENCE OF HYPOSPADIAS

- ❖ Incidence of hypospadias often derives from registry information
  - ❖ Under-diagnosis
  - ❖ Underreporting
  - ❖ Sometimes challenging to establish diagnosis and do surveillance in developing nations
  
- ❖ Nations with a reported increase in incidence of hypospadias:
  - ❖ England
  - ❖ Finland
  - ❖ France
  - ❖ Denmark
  - ❖ Australia
  - ❖ US
  - ❖ China



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<<READ SLIDE.>>

**Refs:**

•Baskin L. Hypospadias: anatomy, etiology, and technique. *Journal of Pediatric Surgery*, 2006, 41(3):463-472.

*Hypospadias is one of the most common congenital anomalies in the United States, occurring in approximately 1 in 250 newborns or roughly 1 in 125 live male births. It is the result of arrested development of the urethra, foreskin, and ventral surface of the penis where the urethral opening may be anywhere along the shaft, within the scrotum, or in the perineum. The only treatment is surgery. Thus, prevention is imperative. To accomplish this, it is necessary to determine the etiology of hypospadias, the majority of which have been classified as idiopathic. In this paper we briefly describe the normal development of the male external genitalia and review the prevalence, etiology, risk factors, and epidemiology of hypospadias. The majority of hypospadias are believed to have a multifactorial etiology, although a small percentage do result from single gene mutations. Recent findings suggest that some hypospadias could be the result of disrupted gene expression. Discoveries about the antiandrogenic mechanisms of action of some contemporary-use chemicals have provided new knowledge about the organization and development of the urogenital system and may provide additional insight into the etiology of hypospadias and direction for prevention.*

•Nassar N, Bower C, Barker A. Increasing prevalence of hypospadias in Western Australia, 1980-2000. *Arch Dis Child*, 2007, 92: 580-584.

•Nelson CP et al. The increasing incidence of congenital penile anomalies in the United States. *Journal of Urology*, 2005, 174: 1573-1576.

•Pierik FH et al. A high hypospadias rate in The Netherlands. *Hum Reproduction*, 2002, 17:1112-1115.

•Wu YQ et al. Secular trends of hypospadias in Chinese perinatals. *Sichuan Da Xue Xue Bao Yi Xue Ban*. 2005, 36:274-276

Image: WHO

## POTENTIAL ENVIRONMENTAL LINKS TO HYPOSPADIAS

- ❖ Urethral folds develop during fetal development
- ❖ Androgen production is critical to ensure normal location of urethra
- ❖ Certain environmental chemicals demonstrate androgen-antagonistic action *in utero* that may be responsible for occurrence of hypospadias
- ❖ *Direct link with environmental factors not well established*

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<<READ SLIDE.>>

Ref:

•Baskin L. Hypospadias: anatomy, etiology, and technique. *Journal of Pediatric Surgery*, 2006, 41(3):463-472.

*Hypospadias is one of the most common congenital anomalies in the United States, occurring in approximately 1 in 250 newborns or roughly 1 in 125 live male births. It is the result of arrested development of the urethra, foreskin, and ventral surface of the penis where the urethral opening may be anywhere along the shaft, within the scrotum, or in the perineum. The only treatment is surgery. Thus, prevention is imperative. To accomplish this, it is necessary to determine the etiology of hypospadias, the majority of which have been classified as idiopathic. In this paper we briefly describe the normal development of the male external genitalia and review the prevalence, etiology, risk factors, and epidemiology of hypospadias. The majority of hypospadias are believed to have a multifactorial etiology, although a small percentage do result from single gene mutations. Recent findings suggest that some hypospadias could be the result of disrupted gene expression. Discoveries about the antiandrogenic mechanisms of action of some contemporary-use chemicals have provided new knowledge about the organization and development of the urogenital system and may provide additional insight into the etiology of hypospadias and direction for prevention.*

## EVIDENCE OF ENVIRONMENTAL ASSOCIATION

Synthetic chemicals can act as androgen antagonists and induce hypospadias *in utero* (in animals)

Increased risk of hypospadias in the sons of women exposed to diethylstilbestrol (DES) *in utero*

Maternal occupational exposure to pesticides associated with a 36% increased risk of hypospadias

Environmental endocrine disruptors that cause hypospadias in laboratory animals.

Type	Chemical
Agricultural and public health	
Insecticide	<i>p,p'</i> -DDE (breakdown product of DDT) <sup>a</sup>
Fungicides	Vinclozolin <sup>a</sup> Procymidone <sup>a</sup>
Herbicide	Linuron <sup>a</sup>
Industrial	
Plastic components	DBP <sup>a</sup> DEHP <sup>a</sup>
Persistent organochlorines	Dioxin (TCDD) <sup>b</sup> PCB 169 <sup>b</sup>

Data from Gray et al. (77) and Hurst et al. (72).

<sup>a</sup>Reduced anogenital distance, the most sensitive end point. <sup>b</sup>Only in females; in all other cases, females have not been examined to date.

Baskin et al, 2001, *Environmental Health Perspectives*

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Numerous studies have demonstrated a variety of chemical contaminants results in increased risk for hypospadias. Diethylstilbestrol (DES) is a synthetic nonsteroidal estrogen medication that was given to pregnant women to avoid miscarriage in the 1960s. It has been shown to increase risk for hypospadias in sons born to mothers who were exposed to this drug. Rodent studies with DES, dichlorodiphenyltrichloroethane (DDT), vinclozolin, polychlorinated biphenyls, bisphenol A, phthalates, flutamide (drug to treat cancer with anti-androgenic effect) or ethinyl estradiol (estrogenic drug in birth control pills) have been linked to hypospadias.

Similar results were shown in female farm workers. Approximately 60% of herbicides applied in the developing world have been shown to alter naturally-occurring hormonal pathways within the body.

### Refs:

•Klin H et al. Hypospadias in sons of women exposed to diethylstilbestrol *in utero*: a cohort study. *Lancet*. 2002, 359:1102–1107.

*Transgenerational effects of diethylstilbestrol (DES) have been reported in animals, but effects in human beings are unknown. Alerted by two case reports, we aimed to establish the risk of hypospadias in the sons of women who were exposed to DES in utero. We did a cohort study of all sons of a Dutch cohort of 16 284 women with a diagnosis of fertility problems. We used a mailed questionnaire assessing late effects of fertility treatment to identify boys with hypospadias. We compared the prevalence rate of hypospadias between boys with and without maternal DES exposure in utero. 16 284 mothers (response rate 67%) reported 8934 sons. The mothers of 205 boys reported DES exposure in utero. Four of these children were reported to have hypospadias. In the remaining 8729 children, only eight cases of hypospadias were reported (prevalence ratio 21.3 [95% CI 6.5–70.1]). All cases of hypospadias were medically confirmed. Maternal age or fertility treatment did not affect the risk of hypospadias. Children conceived after assisted reproductive techniques such as in-vitro fertilisation were not at increased risk of hypospadias compared with children conceived naturally (1.8, 0.6–5.7). Our findings suggest an increased risk of hypospadias in the sons of women exposed to DES in utero. Although the absolute risk of this anomaly is small, this transgenerational effect of DES warrants additional studies.*

•Palmer JR, et al. Urogenital abnormalities in men exposed to diethylstilbestrol *in utero*: a cohort study. *Environmental Health*. 2009; 8:37

•Program on Reproductive Health and the Environment. Shaping our legacy: reproductive health and the environment. *University of California, San Francisco*. 2008.

•Rocheleau et. al. Pesticides and hypospadias: A meta-analysis. *Journal of Pediatric Urology*, 2009, 5(1):17-24

*This meta-analysis showed that maternal occupational exposure to pesticides or agricultural work was associated with a 36% increased risk of hypospadias overall, and paternal occupational exposure to pesticides or agricultural work was associated with a 19% increased risk of hypospadias. Though modest, these elevated risks may be clinically relevant given the enormous psychological and economic impact of hypospadias on families. The elevated risk observed in this meta-analysis may be an underestimate. Challenges in exposure assessment created the potential for misclassification in the pooled studies; this could have biased the risk ratio estimates towards the null. Given the spectrum of severity of hypospadias, there was also the potential for incomplete case ascertainment in some previous studies; this also may have diluted the observed overall effect of pesticide exposure.*

•Titus-Ernstoff L, Troisi R, Hatch EE, et al. Birth defects in the sons and daughters of women who were exposed in utero to diethylstilbestrol (DES). *International Journal of Andrology* 2010, 33(2):377–384.

Image: Baskin LS, Himes K, Colborn T. Hypospadias and endocrine disruption: is there a connection? *Environ Health Perspect*. 2001, 109(11):1175-83. This image was reproduced with permission from *Environmental Health Perspectives*.

## CASE STUDY: HYOSPADIAS AND DIOXIN EXPOSURE

- ❖ Hypospadias was first correlated with the chemical compound TCDD (tetrachlorodibenzo-*p*-dioxin) after explosion in an Italian factory (1976)
- ❖ Boys exposed to TCDD *in utero* had an increased incidence of hypospadias
- ❖ TCDD may act on androgen receptors *in utero*

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2,3,7,8 tetrachlorodibenzo-*p*-dioxin (TCDD) was accidentally released in an Italian town in 1976 and occurrence of hypospadias among local boys, born after the accident, was associated with the incident.

Experimental data in animal models support the hypothesis that maternal exposure to endocrine disruptors (such as TCDD) cause hypospadias in the fetus.

Because sex hormones play a strong role in fetal genito-urinary development, *in utero* exposure to TCDD may contribute to hypospadias.

### Ref:

•Baskin LS, Colborn T, and Himes K. Hypospadias and endocrine disruption: is there a connection?. *Environ Health Perspect.* 2001, 109:1175–1183.

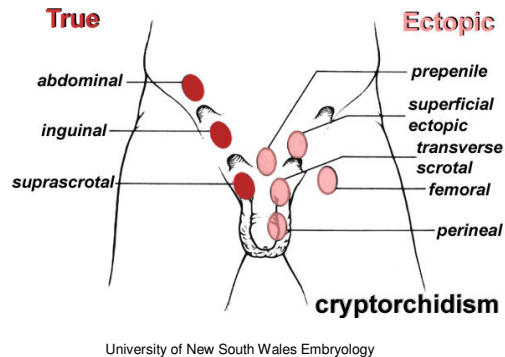
•Kim KS et al., Induction of hypospadias in a murine model by maternal exposure to synthetic estrogens. *Environ Res.* 2004, 94(3):267–275.

•Mastroiacovo P et al. Birth defects in the Seveso area after TCDD contamination. *JAMA*, 1998, 259(11):1668-1672.

*Hypospadias has been correlated with TCDD in boys born after an explosion in Seveso, Italy, in 1976. Exposure decreased across four zones extending distally from the factory site, based on soil contamination (92). Zone A was the area of highest exposure (TCDD = 192.8 µg/m<sup>2</sup>). Zones B and R had decreasing concentrations of TCDD that varied from 3 to 43.8 µg/m<sup>2</sup> in Zone B and 0.9 µg/m<sup>2</sup> to 9.7 µg/m<sup>2</sup> in Zone R. Zone Non-ABR (not affected by the explosion) was included in the study for comparison. Zone A had two mild birth defects (n = 26) and no hypospadias. Soon after the explosion, Zone A was affected by abortions (spontaneous and recommended) and stillbirths. There were 4 cases of hypospadias in 435 births in Zone B (~1:100 births or 1:54 male births), which decreased to 4 cases in 2,439 births in Zone R (~1:602 live births or 1:305 male births) and to 41 cases in 12,391 births in Zone Non-ABR (~1:300 live births or 1:150 male births). It is not clear if all hypospadias cases were reported. As with most epidemiologic studies looking for differences across a large number of birth defects, the data specific to hypospadias are inconclusive.*

## 2.A.2. CRYPTORCHIDISM

- ❖ Undescended or maldescended testicles at birth (or later in infancy)
- ❖ Most common male reproductive disorder
- ❖ Often self-resolving, though may indicate developmental malfunction *in-utero*



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Cryptorchidism literally means hidden or obscure testis and generally refers to an undescended or maldescended testis. It represents the most common genital problem encountered in pediatrics. It affects between 2 to 4% of boys worldwide at birth according to global registry data. Even though the disorder is often self-resolving, cryptorchidism at birth may indicate a malfunction in the normal developmental process *in utero*.

The image in the slide depicts the normal descent of the testicle into the scrotum compared to the maldescent of the testicle in cryptorchidism.

### Refs:

•Scorer CG. The descent of the testis. *Arch Dis Child*. 1964, 39: 605.

*Normal testicular development begins at conception. The testis-determining factor is identified as the SRY gene (sex-determining region on Y chromosome). The presence of this gene and an intact downstream pathway generally result in testicular formation. At 3-5 weeks' gestation, the gonadal ridge or indifferent gonad develops, and, at 6 weeks' gestation, primordial germ cell migration occurs. Soon after, Sertoli cells develop and secrete müllerian-inhibiting substance (MIS), the level of which remains high throughout gestation and causes regression of müllerian ducts. At 9 weeks' gestation, Leydig cells develop and secrete testosterone. Prenatal ultrasonography shows no testicular descent before 28 weeks' gestation, other than transabdominal movement to the internal inguinal ring. Transinguinal migration, thought to be under hormonal control, occurs at 28-40 weeks' gestation, usually resulting in a scrotal testis by the end of a full term of gestation.*

•Virtanen HE et al. Cryptorchidism: classification, prevalence and long-term consequences. *Acta Paediatr*. 2007, 96: 611-616.

*Image: Cryptorchidism. University of New South Wales Embryology. Available at [embryology.med.unsw.edu.au/Notes/genital2.htm#GonadalDescent](http://embryology.med.unsw.edu.au/Notes/genital2.htm#GonadalDescent) - accessed 3 August 2010. This image is public domain.*

## CRYPTORCHIDISM AND ENVIRONMENTAL EXPOSURES

- ❖ Testis development and descent is dependent on regulated androgen activity
- ❖ Some persistent environmental chemicals associated with testicular maldescent due to anti-androgen activity include:
  - polychlorinated pesticides
  - polybrominated flame retardants
  - diethylstilbestrol (DES)



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Corra

Scientific focus has also been directed to environmental hormone disrupting chemicals as the prevalence of testis cancer and cryptorchidism has increased and semen quality decreased in the last decades in several countries. It is hypothesized that environmental agents with anti-androgen and estrogen-like activity could result in cryptorchidism by interference with necessary hormones. Suspects include polychlorinated pesticides, polybrominated flame retardants, and the medication diethylstilbestrol (DES).

### Refs:

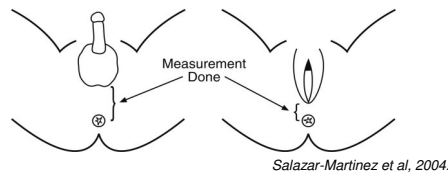
•Boisen KA et al. Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. *Lancet*. 2004, 17;363(9417):1264-9.

**BACKGROUND:** Several investigators have shown striking differences in semen quality and testicular cancer rate between Denmark and Finland. Since maldescent of the testis is a shared risk factor for these conditions we undertook a joint prospective study for the prevalence of congenital cryptorchidism. **METHODS:** 1068 Danish (1997-2001) and 1494 Finnish boys (1997-99) were consecutively recruited prenatally. We also established prevalence data for all newborns at Turku University Central Hospital, Finland (1997-99, n=5798). Testicular position was assessed by a standardised technique. All subtypes of congenital cryptorchidism were included, but retractile testes were considered normal. **FINDINGS:** Prevalence of cryptorchidism at birth was 9.0% (95% CI 7.3-10.8) in Denmark and 2.4% (1.7-3.3) in Finland. At 3 months of age, prevalence rates were 1.9% (1.2-3.0) and 1.0% (0.5-1.7), respectively. Significant geographic differences were still present after adjustment for confounding factors (birthweight, gestational age, being small for gestational age, maternal age, parity, mode of delivery); odds ratio (Denmark vs Finland) was 4.4 (2.9-6.7,  $p < 0.0001$ ) at birth and 2.2 (1.0-4.5,  $p = 0.039$ ) at three months. The rate in Denmark was significantly higher than that reported 40 years ago. **INTERPRETATION:** Our findings of increasing and much higher prevalence of congenital cryptorchidism in Denmark than in Finland contribute evidence to the pattern of high frequency of reproductive problems such as testicular cancer and impaired semen quality in Danish men. Although genetic factors could account for the geographic difference, the increase in reproductive health problems in Denmark is more likely explained by environmental factors, including endocrine disrupters and lifestyle.

•Emmen JM et al. Involvement of insulin-like factor 3 (Insl3) in diethylstilbestrol-induced cryptorchidism. *Endocrinology*. 2000, 141:846-849.

Image: L Corra. Child working with pesticides, Argentina. Used with permission.

## REDUCED ANOGENITAL DISTANCE



- ❖ Distance from anus to the base of the penis
- ❖ Changes in anogenital distance reflect *in-utero* hormonal effects
- ❖ Reduced anogenital distance is correlated with reproductive development disorders, especially testicular development
- ❖ Association with *in utero* exposure to phthalates and dichlorodiphenyltrichloroethane (DDT) seen in animal and human studies

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Measurement of anogenital distance serves as a way of assessing fetal androgen action in many animal studies due to the sensitivity of anogenital distance development *in utero* to androgenic activity. Anogenital distance is longer in males than females, also suggesting this phenotype in under hormonal influence of androgens. In human male, measurement of anogenital distance can serve as a potentially useful anthropometric measure and indicator of *in utero* androgen status.

Recent studies have reported that anogenital distance is reduced in male infants exposed to high *in utero* levels of phthalates.

Some studies also show that that human hypospadias and cryptorchidism may be associated with shortened anogenital distance.

### Refs:

- Hsieh M. Associations Among Hypospadias, Cryptorchidism, Anogenital Distance, and Endocrine Disruption. *Curr Urol Rep.* 2008, 9(2):137-42.
- Salazar-Martinez E et al. Anogenital distance in human male and female newborns: a descriptive, cross-sectional study. *Environmental Health: A Global Access Science Source*, 2004, 3:8.
- Swan SH et al. Decrease in Anogenital Distance among Male Infants with Prenatal Phthalate Exposure. *Environ Health Perspectives*, 2005, 113(8).  
*Prenatal phthalate exposure impairs testicular function and shortens anogenital distance (AGD) in male rodents. We present data from the first study to examine AGD and other genital measurements in relation to prenatal phthalate exposure in humans. A standardized measure of AGD was obtained in 134 boys 2–36 months of age. AGD was significantly correlated with penile volume ( $R = 0.27$ ,  $p = 0.001$ ) and the proportion of boys with incomplete testicular descent ( $R = 0.20$ ,  $p = 0.02$ ). We defined the anogenital index (AGI) as AGD divided by weight at examination [ $AGI = AGD/weight$  (mm/kg)] and calculated the age-adjusted AGI by regression analysis. We examined nine phthalate monoester metabolites, measured in prenatal urine samples, as predictors of age-adjusted AGI in regression and categorical analyses that included all participants with prenatal urine samples ( $n = 85$ ). Urinary concentrations of four phthalate metabolites [monoethyl phthalate (MEP), mono-n-butyl phthalate (MBP), monobenzyl phthalate (MBzP), and monoisobutyl phthalate (MiBP)] were inversely related to AGI. After adjusting for age at examination, p-values for regression coefficients ranged from 0.007 to 0.097. Comparing boys with prenatal MBP concentration in the highest quartile with those in the lowest quartile, the odds ratio for a shorter than expected AGI was 10.2 (95% confidence interval, 2.5 to 42.2). The corresponding odds ratios for MEP, MBzP, and MiBP were 4.7, 3.8, and 9.1, respectively (all p-values < 0.05). We defined a summary phthalate score to quantify joint exposure to these four phthalate metabolites. The age-adjusted AGI decreased significantly with increasing phthalate score (p-value for slope = 0.009). The associations between male genital development and phthalate exposure seen here are consistent with the phthalate-related syndrome of incomplete virilization that has been reported in prenatally exposed rodents. The median concentrations of phthalate metabolites that are associated with short AGI and incomplete testicular descent are below those found in one-quarter of the female population of the United States, based on a nationwide sample. These data support the hypothesis that prenatal phthalate exposure at environmental levels can adversely affect male reproductive development in humans.*
- Torres-Sanchez L et al. Dichlorodiphenyldichloroethylene exposure during the first trimester of pregnancy alters the anal position in male infants. *Ann N.Y. Acad. Sci.* 2008, 1140:155-162  
*A doubling increase of maternal DDE serum levels during the first trimester of pregnancy were associated with significant reduction of anogenital distance (measured through a anal position index)*

Image: Salazar-Martinez E et al. Anogenital distance in human male and female newborns: a descriptive, cross-sectional study. *Environmental Health: A Global Access Science Source*, 2004, 3:8.

## STUDIES ON PHTHALATE INTERACTION

- ❖ Reduced anogenital distance very sensitive endpoint for phthalate exposure
  - increased likelihood of testicular maldescent
  - small and indistinct scrotum
  - smaller penile size
  
- ❖ Direct association between *in utero* exposure to phthalates and reduced anogenital distance in animal studies

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Phthalates are plasticizers found in plastics have been ubiquitous environmental pollutants because of their widespread use and disposal. They can migrate from plastic into the environment. Some phthalates are estrogenic and have exhibited adverse reproductive health defects in fetal development.

Animal studies have documented a significant increase in the incidence of undescended testes and decrease in the anogenital distance in males following *in utero* exposure to phthalates.

### Refs:

•Ema M et al. Decreased anogenital distance and increased incidence of undescended testes in fetuses of rats given monobenzyl phthalate, a major metabolite of butyl benzyl phthalate. *Reproductive Toxicology*.2003, 7(4):407-412.

*The objective of this study was to determine the adverse effects of monobenzyl phthalate (MBeP), a major metabolite of butyl benzyl phthalate (BBP), on the development of the reproductive system, and to assess the role of MBeP in the antiandrogenic effects of BBP. Pregnant rats were given MBeP by gavage at 167, 250, or 375 mg/kg on days 15–17 of pregnancy. Fetuses were examined on day 21 of pregnancy. Maternal body weight gain and food consumption were significantly decreased at 167 mg/kg and higher. Fetal weight was significantly decreased at 375 mg/kg. A significant increase in the incidence of undescended testes and decrease in the anogenital distance (AGD) and ratio of AGD to the cube root of body weight was found in male fetuses at 250 mg/kg and higher. The AGD and ratio of AGD to the cube root of body weight of female fetuses in the MBeP-treated groups were comparable to those in the control group. The present data indicate that MBeP produces adverse effects on the development of the reproductive system in male offspring and suggest that MBeP may be responsible for the antiandrogenic effects of BBP.*

•Swan S et al. Decrease in Anogenital Distance among Male Infants with Prenatal Phthalate Exposure. *Environmental Health Perspectives*. 2005, 113 (8).

*Prenatal phthalate exposure impairs testicular function and shortens anogenital distance (AGD) in male rodents. We present data from the first study to examine AGD and other genital measurements in relation to prenatal phthalate exposure in humans. A standardized measure of AGD was obtained in 134 boys 2-36 months of age. AGD was significantly correlated with penile volume ( $R = 0.27$ ,  $p = 0.001$ ) and the proportion of boys with incomplete testicular descent ( $R = 0.20$ ,  $p = 0.02$ ). We defined the anogenital index (AGI) as AGD divided by weight at examination [ $AGI = AGD/weight$  (mm/kg)] and calculated the age-adjusted AGI by regression analysis. We examined nine phthalate monoester metabolites, measured in prenatal urine samples, as predictors of age-adjusted AGI in regression and categorical analyses that included all participants with prenatal urine samples ( $n = 85$ ). Urinary concentrations of four phthalate metabolites [monoethyl phthalate (MEP), mono-n-butyl phthalate (MBP), monobenzyl phthalate (MBzP), and monoisobutyl phthalate (MiBP)] were inversely related to AGI. After adjusting for age at examination,  $p$ -values for regression coefficients ranged from 0.007 to 0.097. Comparing boys with prenatal MBP concentration in the highest quartile with those in the lowest quartile, the odds ratio for a shorter than expected AGI was 10.2 (95% confidence interval, 2.5 to 42.2). The corresponding odds ratios for MEP, MBzP, and MiBP were 4.7, 3.8, and 9.1, respectively (all  $p$ -values  $< 0.05$ ). We defined a summary phthalate score to quantify joint exposure to these four phthalate metabolites. The age-adjusted AGI decreased significantly with increasing phthalate score ( $p$ -value for slope = 0.009). The associations between male genital development and phthalate exposure seen here are consistent with the phthalate-related syndrome of incomplete virilization that has been reported in prenatally exposed rodents. The median concentrations of phthalate metabolites that are associated with short AGI and incomplete testicular descent are below those found in one-quarter of the female population of the United States, based on a nationwide sample. These data support the hypothesis that prenatal phthalate exposure at environmental levels can adversely affect male reproductive development in humans.*

## 2. OVERVIEW OF MALE REPRODUCTIVE HEALTH OUTCOMES

### 2.B. Identified in puberty or later

1. Infertility
2. Semen quality
3. Sperm motility and function
4. Testicular cancer
5. Testicular dysgenesis syndrome
6. Prostate cancer



WHO

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The next series of slides will outline several male reproductive health outcomes that can be identified in the male during puberty or in later life.

<<READ SLIDE>>

*Image:* WHO

## 2.B.1. MALE INFERTILITY

- ❖ An important consequence of exposure to reproductive toxicants is infertility
- ❖ Males produce sperm cells throughout their lives
  - Long-term susceptibility windows for environmental exposures
- ❖ Factors affecting male infertility:
  - Sperm count
  - Sperm quality
  - Reproductive organ function
  - Sexual behavior
  - Systematic toxicity



WHO

<<READ SLIDE.>>

Infertility is defined as the inability to conceive after a year of sexual intercourse without the use of contraceptives. While infertility describes the contribution of both the male and the female reproductive health, male infertility relates specifically to dysfunction of the male reproductive processes responsible for healthy sperm and reproductive organ function. Approximately half of all cases of infertility can be attributed to a male reproductive dysfunction. Factors that may affect male fertility are sperm count, sperm quality, reproductive organ dysfunction, sexual behavior, and systemic toxicity. However, other disturbances of male reproductive function remain unknown.

*Refs:*

- Irvine D. Epidemiology and aetiology of male infertility. *Hum Reprod.* 1998, 13(1):33–44.
- Sheiner EK et al. Effects of occupational exposures on male fertility: literature review. *Ind Med.* 2003, 41:55–62.
- Sheynkin Y et al. Increase in scrotal temperature in laptop computer users. *Hum Reprod.* 2005, 20(2):452-5.
- WHO. Laboratory manual for the examination of human semen and sperm-cervical mucus interaction. Cambridge: Cambridge University Press. WHO, 1999

*Image: WHO*

## ENVIRONMENTAL FACTORS AFFECTING MALE FERTILITY

- ❖ Air pollutants
- ❖ Drinking water pollutants
- ❖ Persistent organochlorines
- ❖ Tri-halomethanes
- ❖ Pesticides
- ❖ Electromagnetic radiation
- ❖ Heat



WHO

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Several environmental factors exist that have been linked to affected male fertility. Major air pollutants, such as sulphur dioxide, nitrogen oxides, particulate matter, and ozone have shown to affect male fertility by decreasing sperm quality. Human studies have found a significant association between exposure to high levels of air pollution and the percentage of sperm with DNA fragmentation. Various drinking water pollutants that exhibit endocrine disrupting activity may also affect male fertility. Persistent organochlorines have been shown in human studies to reduce sperm count and adversely affect sperm motility and morphology. Tri-halomethanes, a byproduct of the water treatment process, have consistently shown to decrease sperm quality and motility and lead to histopathologic changes in the male reproductive system in animal studies. Pesticides have been widely shown to induce direct damage on the spermatozoa and disrupt endocrine function in multiple stages of hormones regulation necessary for normal male reproductive function. Human studies of electromagnetic radiation (EMR) and male fertility have shown an association between exposure to EMR and decreased sperm motility and function. In men repeatedly subject to high temperatures at testicular level (e.g. drivers) there may be thermo-dysregulation which may result in changes in sperm characteristics.

### Refs:

- Graves CG, Matanoski GM, Tardiff RG. Weight of evidence for an association between adverse reproductive and developmental effects and exposure to disinfection by-products: A critical review. *Regul Toxicol Pharmacol.* 2001, 34:103–24.
- Hauser R et al. Environmental organochlorines and semen quality: results of a pilot study. *Environ Health Perspect.* 2002, 110:229–33
- Irvine D. Epidemiology and aetiology of male infertility. *Hum Repro.* 1998, 13(1):33–44.
- Jensen TK, Bonde JP, Joffe M. The influence of occupational exposure on male reproductive function. *Occup Med.* 2006, 56:544–53.
- Rubes J et al. Episodic air pollution is associated with increased DNA fragmentation in human sperm without other changes in semen quality. *Hum Reprod.* 2005, 20(10):2776–83.
- Sheiner EK et al. Effects of occupational exposures on male fertility: literature review. *Ind Med.* 2003, 41:55–62.
- Sheynkin Y et al. Increase in scrotal temperature in laptop computer users. *Hum Reprod.* 2005, 20(2):452-5.
- Thonneau P et al. Occupational exposure and male fertility: a review. *Hum Reprod.* 1998, 13(8):2122-2125.

Image: WHO

## WINDOWS OF DEVELOPMENT: FATHERS AND THEIR OFFSPRING

- ❖ Paternal exposure to: Mercury, ethylene oxide, rubber chemicals, solvents, linked to spontaneous abortion
- ❖ Paternal occupation: Painters – anencephaly  
(Brender. *Am J Epidemiol*, 1990, 131(3):517)  
Mechanics, welders – Wilms tumour  
(Olshan. *Cancer Res*, 1990, 50(11):3212)  
Textiles – stillbirth, pre-term delivery  
(Savitz. *Am J Epidemiol*, 1989, 129(6):1201)

Possible mechanism: impairment of a paternal gene required for the normal growth and development of the fetus

20

Preconception paternal exposures are now increasingly recognized as important to the health and development of the fetus.

Such exposures may increase the chance of certain diseases or adverse pregnancy outcomes as seen in the offspring. This is supported by research in animals and may well have a genetic or epigenetic mechanism.

<<READ SLIDE.>>

<<NOTE TO USER: you may want to stress exposures/occupations that are regionally specific if there are data to support prenatal or preconception effects.>>

### Refs:

•Bearer CF. The special and unique vulnerability of children to environmental hazards. *Neurotoxicology*, 2000, 21:925-34.

•Brender JD. Paternal occupation and anencephaly. *Am J Epidemiol*, 1990, 131:517-21.

•Olshan AF et al. Wilms' tumor and paternal occupation. *Cancer Res*, 1990, 50:3212.

*A case-control study was conducted to examine the relationship between Wilms' tumour and paternal occupational exposures. The case group consisted of 200 children diagnosed as having Wilms' tumour who were registered at selected National Wilms' Tumour Study institutions during the period 1 June, 1984, to 31 May, 1986. Disease-free controls were matched to each case using a random digit dialling procedure. The parents of cases and controls completed a self-administered questionnaire. There was no consistent pattern of increased risk for paternal occupational exposure to hydrocarbons or lead found in this study. However, certain paternal occupations were found to have an elevated odds ratio (OR) of Wilms' tumour, including vehicle mechanics, auto body repairmen, and welders. Offspring of fathers who were auto mechanics had a 4- to 7-fold increased risk of Wilms' tumour for all three time periods. The largest increased odds ratio for auto mechanics was in the preconception period [OR = 7.58; 95% confidence interval (CI) = 0.90-63.9]. Welders had a 4- to 8-fold increased odds ratio, with the strongest association during pregnancy (OR = 8.22; CI = 0.95-71.3). Although chance cannot be excluded as a possible explanation, association of Wilms' tumour with these occupations has been reported in previous studies. Further study is needed to provide data on the specific occupational exposures involved.*

•Sallmén M. Fertility among workers exposed to solvents or lead. Finnish Institute of Occupational health, Helsinki. *People and work. Research reports* 37. 2000.

•Savitz DA et al. Effect of parents' occupational exposures on risk of stillbirth, preterm delivery, and small-for-gestational-age infants. *Am J Epidemiol*, 1989, 129:1201-18.

## 2.B.2. SEMEN QUALITY

- ❖ Semen quality used as measure of male fertility
- ❖ Semen parameters include: *motility; volume; pH; concentration; morphology; and white blood cell count*
- ❖ Various toxicants are suspected to affect semen quality:

### DURING DEVELOPMENT:

- Cigarette Smoke
- Polybrominated diphenyl ethers (PBDEs)
- Bisphenol A

### IN ADULTHOOD:

- Cigarette smoke
- Solvents
- Phthalates
- Organochlorine pesticides
- Bisphenol A
- Cadmium, lead
- Dibromochloropropane
- Polychlorinated biphenyls (PCBs)

<<READ SLIDE.>>

WHO protocols for evaluating the quality of male sperm include factors such as volume, pH, concentration, motility, morphology, and white blood cell count. It is important to note that a lack of data exists for this topic and additional research is necessary to truly understand the environmental factors that account for decreasing semen quality.

In 1977, male workers working at a dibromochloropropane (DBCP) pesticide plant in California were identified as subfertile or infertile and the couples tended to have with higher rates of pregnancy loss and more boys than girls. DBCP was found to be toxic to sperm. Since then, new toxicants have been found to affect semen quality.

*Note: OC Pesticides = Organochlorine pesticides; PBDEs: Polybrominated diphenyl ethers*

**<<NOTE TO USER: For more information about WHO protocols for measuring sperm quality, please see: WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction. Cambridge University Press, 5<sup>th</sup> edition, 2010>>**

*Refs:*

- WHO. World Health Organization reference values for human semen. *World Health Organization, Department of Reproductive Health and Research*, 2009.
- WHO. WHO laboratory manual for the examination and processing of human semen. Fifth edition. *World Health Organization, Department of Reproductive Health and Research*, 2010.
- Woodruff T. Proceedings of the Summit on Environmental Challenges to Reproductive Health and Fertility: executive summary. *Fertility and Sterility*. 2008, 89(2), 281-300.

## 2.B.3. SPERM MOTILITY & FUNCTION

- ❖ Prime measure of male reproductive health
- ❖ Essential for healthy reproduction
- ❖ Potential contaminants that may impair sperm motility and function:
  - Polychlorinated biphenyls (PCBs)
  - Diethylstilbestrol (DES) exposure *in utero*

22

Sperm motion is important for sperm functional capacity, and the assessment of sperm motion is considered to be useful for detection or evaluation of male reproductive toxicity.

When exposed to EDCs, sperm mature too quickly and fail to reach and fertilize the egg. Researchers found that mouse sperm bathed in endocrine disrupting chemicals matured early and released the enzymes they need to penetrate the egg's jelly coat before making contact with the egg. Human sperm is known to be even more sensitive than mouse sperm to female hormones such as estrogen. It is possible that sperm face exposure to multiple endocrine disrupting chemicals, with possible synergistic effects.

A recent animal study found an inverse correlation between polychlorinated biphenyls (PCBs) metabolites and sperm motility as well as concentration. Heavy exposures to PCBs resulted in negative effects on sperm morphology and motility.

Also, human studies show that the intake of diethylstilbestrol (DES) during pregnancy has resulted in impaired sperm quality in the male offspring.

### Refs:

- Dallinga JW et al. Decreased human semen quality and organochlorine compounds in blood. *Human Reproduction*, 2002, 17:1973–1979.
- Kaneto, M. Epididymal sperm motion as a parameter of male reproductive toxicity: sperm motion, fertility, and histopathology in ethinylestradiol-treated rats. *Reproductive Toxicology*. 1999, 13(4). 279-289.

*The present study was designed to characterize the effect of ethinylestradiol (EE) on epididymal sperm motion using a computer-assisted sperm analysis system (CASA), and to elucidate the correlation between sperm motion endpoints and other measures including fertility, histopathologic, and endocrinologic endpoints. EE was orally given to adult male rats at a daily dosage of 10 mg/kg for 3 and 5 d, and at daily dosages of 1 and 10 mg/kg for 1, 2, 3, and 4 weeks. Changes in sperm motion were first detected after one week of treatment. Of nine sperm motion parameters, the percentage of motile sperm, velocity, and amplitude of the lateral head displacement (ALH) were decreased in the 10 mg/kg dosing group. Accompanying the decreases in those parameters, the male fertility indices in the 10 mg/kg dosing group were reduced after one week of treatment, and no males in this group could impregnate intact females after 2 weeks or more of treatment. The number of sperm heads in the cauda epididymis in the 10 mg/kg dosing group was reduced to about one-half that in the control group after one week of treatment, whereas the total number of homogenization-resistant advanced spermatids in the testis was not altered and only a slight change was detected in the number and morphology of germ cells in the testis. These results suggest that reduction in the number of epididymal sperm and in sperm motion are not secondary to testicular alteration. However, after 3 weeks of treatment, the number of sperm heads in the testis was drastically reduced with severe atrophy of the seminiferous tubules both in the 1 and 10 mg/kg dosing groups. The profiling of epididymal luminal fluid proteins indicated that two major bands that migrated with molecular weights of about 22 and 23 kDa were weakened and their density was reduced to approximately 70% of the control after 5-d and one week treatments in the 10 mg/kg dosing group. Circulating testosterone declined drastically after 3 d of treatment and remained at undetectable levels with a concomitant decline of circulating LH and FSH, suggesting that EE inhibits testosterone secretion immediately via a negative feedback system, and there follow changes in the accessory reproductive organs including the epididymis.*

*These results indicate that EE affects epididymal spermatozoa before testicular germ cells via a testosterone deficiency, when it is administered at extremely high dosages. The reduction in the sperm motion manifested as decreases in the percentage of motile sperm, ALH, and velocity, is considered to be responsible for the onset of infertility. Sperm motion analysis could be particularly useful for detecting the toxic effects of chemicals that act through the endocrinologic system on the epididymis.*

- McLachlan JA et al. From malformations to molecular mechanisms in the male: three decades of research on endocrine disrupters. *Acta Pathologica, Microbiologica et Immunologica Scandinavica*, 2001, 109:263–272.
- Titus-Ernstoff L et al. Birth defects in the sons and daughters of women who were exposed in utero to diethylstilbestrol (DES). *International Journal of Andrology*. 2010, 33(2):377–384.

## 2.B.4. TESTICULAR CANCER

- ❖ Testicular cancer development may originate in cells formed during fetal development
  - Fetal cells found in testes of men with testicular cancer
- ❖ Sertoli cell formation *in utero* partly determined by follicle stimulating hormone (FSH)

### TESTICULAR DYSGENESIS SYNDROME (TDS):

*Hypothesis: exposure to environmental estrogens/antiandrogens leads to:*

- ❖ decrease in Sertoli cell function
- ❖ altered levels of FSH and/or androgens
- ❖ decrease in sperm quantity and quality
- ❖ male reproductive birth defects
- ❖ testicular cancer

23

Reproductive disorders of newborn (cryptorchidism, hypospadias) and young adult males (low sperm counts) are common and may potentially be increasing in incidence. However, a lack of global data and substantial under reporting have not confirmed a true increase in incidence of male reproductive disorders. However, it has been hypothesized that these disorders may comprise a testicular dysgenesis syndrome (TDS) with a common origin in fetal life. This has been supported by findings in an animal model of TDS involving fetal exposure to n(dibutyl) phthalate, as well as by new clinical studies. Recent advances in understanding from such studies have led to a general acceptance of the TDS hypothesis in the reproductive health field, highlighting the central role that deficient androgen production/action during fetal testis development, may play in the development of future male reproductive disorders.

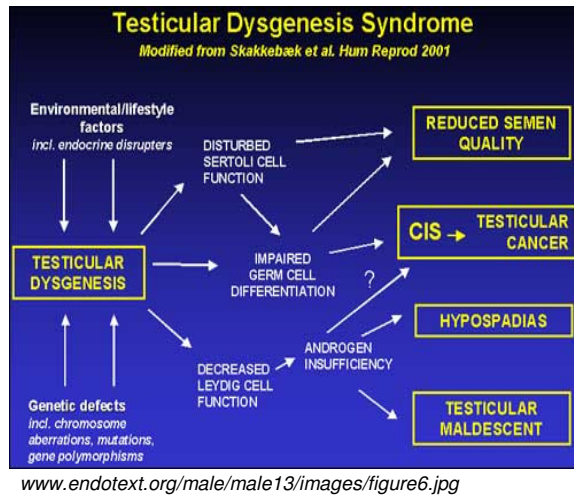
#### *Refs:*

•Sharpe RM, Skakkebaek NE. Testicular dysgenesis syndrome: mechanistic insights and potential new downstream effects. *Fertil Steril.* 2008, 89(2):e33-8.

*Reproductive disorders of newborn (cryptorchidism, hypospadias) and young adult males (low sperm counts, testicular germ cell cancer) are common and/or increasing in incidence. It has been hypothesized that these disorders may comprise a testicular dysgenesis syndrome (TDS) with a common origin in fetal life. This has been supported by findings in an animal model of TDS involving fetal exposure to n(dibutyl) phthalate, as well as by new clinical studies. Recent advances in understanding from such studies have led to refinement of the TDS hypothesis, highlighting the central role that deficient androgen production/action during fetal testis development, may play in the origin of downstream disorders.*

•Skakkebaek NE. Possible carcinoma-in-situ of the testis. *Lancet.* 1972, 2(7776):516-7.

## TESTICULAR DYSGENESIS SYNDROME (TDS)



Testicular dysgenesis syndrome may be the result of the poor gonadal development caused by exposure to adverse environmental contaminants and lifestyle factors

24

An increase in male reproductive disorders and cancers has led to increased scientific research. The association of poor testicular function, atrophy, maldescent and abnormal testicular differentiation with testicular germ cell cancer has led to a hypothesis that poor gonadal development and testicular neoplasia are etiologically linked. A new concept of testicular dysgenesis syndrome (TDS), in which testicular cancer is the rarest, but also one of the most severe outcomes, has been proposed. Some of the risk factors for this syndrome include intrauterine growth restriction, prematurity, maternal stress and genetic disorders. New studies are linking endocrine disrupting chemicals and testicular dysgenesis in humans. For example, the parent's exposure to pesticides at work has been associated with higher rates of undescended testes and mothers of sons with testicular cancer have been found to have high levels of polychlorinated biphenyls (PCBs).

*CIS: carcinoma in situ*

*Refs:*

- Skakkebaek NE. Possible carcinoma-in-situ of the testis. *Lancet*. 1972, 2(7776):516-7.
- Program on Reproductive Health and Environment. Shaping our legacy: reproductive health and the environment. *University of California, San Francisco*, 2008.

*Image: [www.endotext.org/male/male13/images/figure6.jpg](http://www.endotext.org/male/male13/images/figure6.jpg) - accessed March 20, 2010. Copyright permission by the authors granted.*

## 2.B.5. PROSTATE CANCER

- ❖ Prostate gland develops in fetal stage
  - Sensitive to estrogen imprinting
- ❖ Bisphenol A (synthetic estrogen) associated with prostate changes that may confer cancer risk
- ❖ Some environmental exposures linked to prostate cancer risk

25

Estrogens have been associated with increased prostate cancer risk in men.

In rodent models, brief perinatal exposure to pharmacologic doses of natural or synthetic estrogens permanently alters prostate growth and differentiation.

Bisphenol A (BPA) is widely used as a in the manufacture of polycarbonate plastics and epoxy resins. Although Bisphenol A binds to classic estrogen receptors and it can also activate non-classic membrane estrogen receptors.

*Refs:*

•Alavanja MCR et al. Use of Agricultural Pesticides and Prostate Cancer Risk in the Agricultural Health Study Cohort. *Am. J. Epidemiol.* 2003, 157 (9):800-814.

*The authors examined the relation between 45 common agricultural pesticides and prostate cancer incidence in a prospective cohort study of 55,332 male pesticide applicators from Iowa and North Carolina with no prior history of prostate cancer. Data were collected by means of self-administered questionnaires completed at enrollment (1993–1997). Cancer incidence was determined through population-based cancer registries from enrollment through December 31, 1999. A prostate cancer standardized incidence ratio was computed for the cohort. Odds ratios were computed for individual pesticides and for pesticide use patterns identified by means of factor analysis. A prostate cancer standardized incidence ratio of 1.14 (95% confidence interval: 1.05, 1.24) was observed for the Agricultural Health Study cohort. Use of chlorinated pesticides among applicators over 50 years of age and methyl bromide use were significantly associated with prostate cancer risk. Several other pesticides showed a significantly increased risk of prostate cancer among study subjects with a family history of prostate cancer but not among those with no family history. Important family history-pesticide interactions were observed.*

•Henderson BE et al. The early in utero oestrogen and testosterone environment of blacks and whites: potential effects on male offspring. *Br J Cancer.* 1988, 57:216–8.

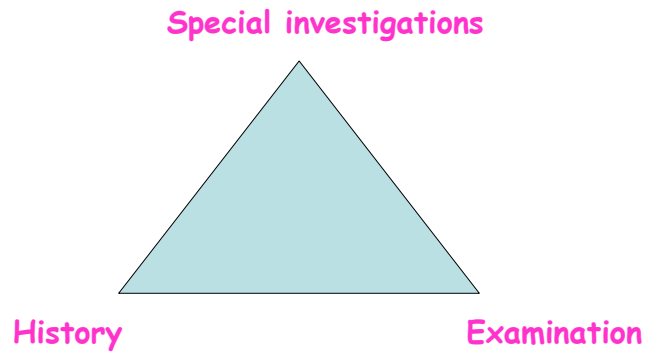
*Developmental Exposure to Estradiol and Bisphenol A Increases Susceptibility to Prostate Carcinogenesis and Epigenetically Regulates Phosphodiesterase Type 4 Variant 4.*

*Early developmental perturbations have been linked to adult-onset prostate pathology, including excessive exposure to estrogenic compounds; however, the molecular basis for this imprinting event is not known. An important and controversial health concern is whether low-dose exposures to hormonally active environmental estrogens, such as bisphenol A, can promote human diseases, including prostate cancer. Here, we show that transient developmental exposure of rats to low, environmentally relevant doses of bisphenol A or estradiol increases prostate gland susceptibility to adult-onset precancerous lesions and hormonal carcinogenesis. We found permanent alterations in the DNA methylation patterns of multiple cell signaling genes, suggesting an epigenetic basis for estrogen imprinting. For phosphodiesterase type 4 variant 4 (PDE4D4), an enzyme responsible for cyclic AMP breakdown, a specific methylation cluster was identified in the 5'-flanking CpG island that was gradually hypermethylated with aging in normal prostates, resulting in loss of gene expression. Early and prolonged hypomethylation at this site following neonatal estradiol or bisphenol A exposure resulted in continued, elevated PDE4D4 expression. Cell line studies confirmed that site-specific methylation is involved in transcriptional silencing of the PDE4D4 gene and showed hypomethylation of this gene in prostate cancer cells. Importantly, the PDE4D4 alterations in the estrogen-exposed prostates were distinguishable before histopathologic changes of the gland, making PDE4D4 a candidate molecular marker for prostate cancer risk assessment as a result of endocrine disruptors. In total, these findings indicate that low-dose exposures to ubiquitous environmental estrogens affect the prostate epigenome during development and, in so doing, promote prostate disease with aging.*

•Schottenfeld D, Fraumeni J. Cancer epidemiology and prevention. Second edition. *Oxford University Press.* 1996, 1180.

*An excess of prostate cancer was observed in early epidemiological studies among workers exposed to cadmium. There is also some evidence of an increased incidence of prostate cancer among agricultural workers and employees of rubber companies.*

## **EVALUATION: INFERTILE MALE**



Males must be evaluated and one must have at least 2 semen analyses for an opinion on semen quality and be followed up by someone trained in andrology who can also take a relevant history, fully examine the genitals and interpret a semen analysis. A spermiogram should not be analyzed in isolation without the health/environmental history and examination.

*Slide kindly provided by Dr Riana Borman, University of Pretoria, South Africa.*

## FUTURE NEEDS

- ❖ More research is needed in this area
- ❖ Coordinated research plan
- ❖ Better surveillance with relevant health and environment databases
- ❖ Identification and action on risk factors
- ❖ Adequate risk assessment, management & communication
- ❖ National, regional, global strategies

The time to act is now: Creating healthier environments for healthier people



WHO

<<READ SLIDE>>

## POINTS FOR DISCUSSION

**<<NOTE TO USER: Add points for discussion according to the needs of your audience.>>**

**ACKNOWLEDGEMENTS**

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