Alterations in Male Reproductive Development:
The Role of Endocrine Disrupting Chemicals

Shanna H. Swan¹, Frederick S. vom Saal²

¹ Family and Community Medicine, MA306 Medical Sciences Building, University of Missouri-Columbia, Columbia MO 65212, USA
E-mail: swans@health.missouri.edu

² Division of Biological Sciences, 114 Le Fevre Hall, University of Missouri-Columbia, Columbia MO 65212, USA
E-mail: vomsaal@biosci.mbp.missouri.edu

In this chapter we will address the following question: to what extent does current evidence from reproductive biology and epidemiology support a causal role for endocrine disrupting chemicals (EDCs) in the pathogenesis of altered male reproductive function? We have divided this discussion into two parts; epidemiology, presented first, followed by the relevant reproductive biology. Our discussion will focus primarily on semen quality, testicular cancer, hypospadias, and cryptorchidism, which we will refer to collectively as “adverse male endpoints”. Other male reproductive parameters, including altered prostate development and prostate cancer, will also be discussed briefly. An historical overview of EDCs, beginning with the discovery of the first synthetic estrogen in 1933, is presented first.

The adverse male endpoints discussed here can result from perturbations of the hormonal environment during critical periods in fetal organogenesis. Such perturbations can result from multiple causes, including genetic defects and alterations in maternal physiology. These physiological changes are themselves related to a host of factors, which may include EDC exposure. For example, a number of aspects of pregnancy (e.g., birth order, birth weight, and multiplicity) or the pregnant woman (e.g., maternal age, ethnicity), referred to here as “pregnancy-related factors”, may be directly related to prenatal hormone levels and, consequently, to adverse male endpoints. Additionally, these pregnancy-related factors may themselves modify effects of EDC exposures. The multiplicity of factors capable of perturbing the prenatal hormonal milieu, and the potential for their interactions, presents a challenge to scientists working in this field.

Hormonal exposures incurred by the fetus during normal pregnancy (“endogenous hormones”) will be discussed as possible factors in the development of adverse male endpoints. We will also review studies on adverse male development in relation to pharmaceuticals with hormonal activity, particularly those to which the developing fetus may be exposed. These pharmaceuticals include oral contraceptives, hormones administered for pregnancy support including diethylstilbestrol (DES) and its congeners, and hormonal pregnancy tests.

For both endogenous and exogenous hormones, the most critical exposure period for adverse male endpoints appears to occur during organogenesis, during the embryonic and fetal stages of prenatal development. Changes induced by exposures at this time are typically irreversible. Moreover, as discussed below, exposure to extremely low doses during this time of heightened sensitivity may profoundly alter reproductive development. In contrast, reproductive changes induced during adulthood are usually reversible, and much larger doses are required to alter the reproductive system [1]. The impacts of such large doses on male reproduction can be seen in the occupational literature. Studies that report adverse male endpoints in association with occupational exposure to chemicals that are known or suspected to alter endocrine function will be summarized. There are also limited data from industrial accidents that have resulted in population exposure to EDCs and subsequent reproductive damage that will also be mentioned briefly.
We then turn to a discussion of the relevant reproductive biology. We begin this section with a discussion of the biological plausibility that EDCs play a causal role in the development of adverse male endpoints. We review laboratory studies showing a causal relationship between EDCs and adverse male endpoints in animals. We note, however, that these adverse endpoints can also occur as the result of a variety of factors in addition to developmental exposure to EDCs. This complicates the assessment of causality in studies investigating the relationship of EDCs to adverse male endpoints in human populations. In this regard, we note the critical absence of literature directly relating adverse male endpoints in humans with measurements of EDCs at environmental levels. We will discuss reasons for this information gap and suggest steps to fill it.

**Keywords.** Development, Diethylstilbestrol, Endocrine disruption, Low-dose effects, Reproduction, Semen quality, Testicular function, Xenoestrogen

1. Introduction .................................................. 133

2. Temporal Trends and Geographic Variability in Adverse Male Endpoints .................................................. 136
   2.1 Semen Quality ............................................. 136
   2.2 Incidence of Testicular and Prostate Cancer ................. 140
   2.3 Incidence of Hypospadias .................................. 141
   2.4 Incidence of Cryptorchidism ................................ 142

3. Adverse Male Endpoints in Relation to Exogenous Hormone Exposure .................................................. 142
   3.1 Testicular Cancer .......................................... 143
   3.2 Male Genital Tract Abnormalities and Semen Quality ........ 143

4. Adverse Male Endpoints in Relation to Endogenous Hormone Exposure .................................................. 145
   4.1 Testicular Cancer .......................................... 146
   4.2 Cryptorchidism .............................................. 147
   4.3 Hypospadias .................................................. 148

5. Exposures in the Workplace and from Industrial Accidents ....... 148

6. Plausibility of Adverse Effects of EDCs: Mechanisms of Gonadal and Accessory Reproductive Organ Differentiation .................. 150


8. Hormonally Mediated Variability in Mammalian Development: Relationship to Bioactive Serum Concentration of Natural Hormones and Endocrine Disruptors .................. 155