The Role of Natural and Manmade Estrogens in Prostate Development

Frederick S. vom Saal and Barry G. Trum

CONTENTS

11.1 Introduction ........................................................................ 308
11.2 Historical Overview of the Prostate ....................................... 309
11.3 Prostate Development .......................................................... 310
  11.3.1 Testosterone and 5α-Dihydrotestosterone ......................... 310
  11.3.2 Anatomic Regions of the Prostate .................................... 312
11.4 Homology: The Basis of Comparative Biology and Pathology .... 314
11.5 Estrogen and Prostate Development, Adult Function and Pathology ......................................................... 316
  11.5.1 The Dog and Noble Rat as Models for Human Prostate Disease ................................................................. 316
  11.5.2 The Intrauterine Position Phenomenon: Correlation Between Estradiol and Prostate Development in Male Mice .................................................................................. 316
  11.5.3 Stimulating Effects on Prostate Development of an Experimental Increase in Estradiol in Female Mice ........... 317
  11.5.4 Inhibition of Prostate Development with High, Pharmacological Doses of Estrogens ................................. 319
  11.5.5 Opposite Effects of High and Low Doses of Estrogen during Prostate Development .................................... 319
  11.5.6 Environmental Endocrine-Disrupting Chemicals that Mimic Estrogen Alter Prostate Development ............... 320
11.6 Summary .............................................................................. 322

References ................................................................................. 322
11.1 Introduction

There has been speculation for some time that estrogen plays a role in the normal development as well as subsequent disease of the prostate. One basis for this speculation is that embryologists recognized that the region of the developing prostatic glands just caudal to the bladder from which the prostatic ducts emerge during fetal life, is the homologous embryonic anlage of a portion of the vagina in females. It thus seemed reasonable to speculate that since the vagina is an estrogen-responsive organ, portions of the prostate might also be responsive to estrogen, and that estrogen might play a role in regulating prostate development and subsequent function, as well as diseases associated with aging.

In contrast to the above prediction that estrogen might play a role in normal prostate development, there are numerous reports that prenatal or neonatal exposure to high, pharmacological doses of diethylstilbestrol (DES) and other natural and synthetic estrogens dramatically interferes with prostate development in mice and rats. Prostate development in mice begins during late fetal life and continues through adolescence. These findings have led to confusion concerning the role of endogenous estrogen in normal prostate development. Many questions have been raised regarding the potential for environmental chemicals with estrogenic activity to alter prostate development at concentrations encountered in the environment (referred to as environmentally relevant doses of chemicals). What has not been recognized with regard to prostate development is that a very high dose of DES can produce an apparent effect (inhibition) on prostate development in comparison to a much lower dose. This is especially important when the dose is within a physiological range of estrogenic activity and can produce a stimulatory effect on development of the prostate. The view that dose is important is not a new concept in endocrinology, toxicology, or pharmacology. However, prior to recent findings based on manipulating estrogen levels within a physiological range in fetal mice, low, physiologically relevant doses of estrogen had not been examined. One reason for this was the difficulty associated with measuring estradiol in very small volumes of serum in rodents in which levels of lipid are very high, thus causing interference with the assays.

This chapter reviews recent studies showing that very small differences in circulating estradiol during fetal life in male mice can lead to differences in prostate differentiation that persist into adulthood. In some of these studies we have used the technique of computer-assisted three-dimensional reconstruction of the developing prostate to visualize and quantify prostate morphogenesis. Because the prostate is the most prone to disease during aging of any organ in humans, the potential for endogenous estrogens, and thus also low, environmentally relevant concentrations of environmental estrogens, to impact prostate pathogenesis is of immense importance as a
11.2 Historical Overview of the Prostate

Pathology of the prostate was attributed in 1685 by Samuel Collins to “indulgence in senility” (the pursuit of sexual pleasure). Collins recognized that prostate enlargement was important to relieve the effects of prostatic enlargement on urethral obstruction. In 1769, James Paget observed that the prostate (and other accessory reproductive organs) underwent involution following castration. Zuckerman comments on the remarkable fact that even though the implication of this observation would suggest that castration might serve as a treatment to relieve the effects of prostatic enlargement on urethral obstruction, which results in death due to uremic poisoning if untreated, the implication of this observation was not grasped until almost a hundred years later. Castration as a treatment for enlargement of the prostate was finally proposed in 1889, after which it became the method of treating the disease. However, this approach was soon abandoned, because at that time, mortality associated with surgery was unacceptably high. In addition, although it might seem surprising today, at the end of the nineteenth century it was still considerable controversy concerning the role of the testes in accessory reproductive organ function. This controversy is interesting in that it had been reported in the middle of the nineteenth century that testicular grafts reversed the effects of castration in cockroaches, which led to attempts to reverse impotence in aging men by means of grafting animal testicular tissue. At this time it was believed that any effects of the testes on organs such as the prostate were probably mediated by nerves, not secreted substances. However, in 1897, methods for extracting gonadal steroids were described, and testosterone was finally identified as the most potent of the testicular hormones in 1935. Prostate growth in castrated rats was being routinely used as a bioassay for potency of testicular hormones by this time."
Our current understanding of prostate development and anatomy appears to have progressed steadily during the past 60 years but has been partially hindered by reliance on old anatomical descriptions. Recent advancements in computer technology now allow organ structure to be visualized by three-dimensional reconstruction from digitized serial sections, which provides a powerful tool for examining prostate anatomy. This technique has been useful particularly in understanding the complex pattern of ductal morphogenesis, a feature that is extremely difficult to grasp when viewing two-dimensional histological sections in a microscope. Three-dimensional reconstructions are accomplished using computer-assisted analysis of histological serial sections. This requires tracing, digitizing, and axial alignment of identified objects (anatomical structures) within each section. The main advantage of the computer-generated three-dimensional image data is that it allows easy comparison of data that can be used to study the effects on the developing prostate of experimental manipulations.

Descriptive anatomy prior to computer assisted three-dimensional reconstruction was aided by the use of wax modeling. Lowey made a wax reconstruction of serial histological sections from a fetal and newborn human male prostate, and generated considerable subsequent controversy due to his interpretation of the anatomy. Lowey’s description of prostatic lobes has since replaced the now widely accepted concept that the human prostate is better described as consisting of zones.

11.3 Prostate Development

11.3.1 Testosterone and 5α-Dihydrotestosterone

At about the eighth week of gestation in humans and at gestation day 12 in mice, Leydig cells in the testes begin production of androgen, with testosterone being the major androgen secreted throughout sexual differentiation. Testosterone mediates differentiation of the Wolffian (mesonephric) duct system (Figure 11.11). Secretion of Mullerian-inhibiting hormone (MIH) by the Sertoli cells, which line the seminiferous tubules, suppresses the development of the Mullerian (paramesonephric) ducts; estrogen antagonizes the action of MIH, while progesterone facilitates the action of MIH.

For normal masculinization of the urogenital sinus and perineal tissue (external genitalia) in males to occur, mesenchymal tissue associated with the urogenital sinus must express the enzyme 5α-reductase, which converts testosterone to 5α-dihydrotestosterone. This relates to the dose of androgen required to induce masculinization. 5α-Dihydrotestosterone has a higher affinity for androgen receptors relative to testosterone, thus enabling it to...
induce the same response as testosterone at a lower concentration, and the concentration of testosterone in the systemic circulation is not sufficient to result in normal prostate development. This is revealed by studies in which testosterone levels in the fetal blood are in a normal range and androgen receptor numbers in fetal tissues are normal, but 5α-reductase activity is inhibited by administration of drugs. If there is a deficiency in the capacity to normally produce 5α-dihydrotestosterone due to a genetic defect, normal development of the prostate and external genitalia does not occur.\(^{1,12}\)

5α-Dihydrotestosterone binds to androgen receptors expressed in urogenital sinus mesenchyme, which induces outgrowths (glandular buds) of the adjacent urothelium of the urogenital sinus. The epithelial buds show little capacity to bind androgens; they form the anlage of the prostate at about 16 weeks of gestation in humans and gestation day 17 in mice.\(^{1,12}\) These outgrowths begin as solid epithelial buds, which later branch extensively during late fetal life in humans, forming a compound tubuloalveolar gland.
structure. In mice, birth occurs within 2 d of the beginning of prostate differentiation, and extensive ductal branching occurs throughout infancy and adolescence, with the adult structure not achieved until approximately postnatal day 50.3 In humans, the pubertal reawakening of androgen secretion by the testes results in the prostatic glandular ducts forming patent lumens within the terminal actini, and the epithelial lining becomes highly differentiated and begins secretory activity.

11.3.2 Anatomic Regions of the Prostate

The ejaculatory ducts form from the embryonic Wolffian ducts. The ejaculatory ducts enter the prostatic urethra caudal and lateral to the site of the urothelium, which is the remnant of the Müllerian ducts as they merge and enter the posterior urogenital sinus (Figure 11.1). The urethra becomes enclosed in the central zone of the human prostate. Each ejaculatory duct (vas deferens) merges with the ipsilateral seminal vesicle duct, which differentiates during the thirteenth week of embryonic life in humans. The ejaculatory ducts lead into the prostatic urethra next to an enlarged portion of the urethral crest, the verumontanum (also referred to as the colliculus seminalis), in the posterior wall of the urethra (Figure 11.2).

In its passage through the prostate, the urethra is divided into a proximal segment (from bladder neck to verumontanum) and a distal segment (from verumontanum to external sphincter), forming a 35 to 45° angle at the verumontanum. The proximal urethra is surrounded by circular smooth muscle, which is referred to as the prostatic sphincter and functions to stop retrograde ejaculation into the bladder. In the proximal portion of the urethra in humans, prostatic glands that mingle with sphincteric stroma have been proposed as the potential site for pathogenesis of BPH.14 The prostatic ducts from this zone exit laterally from the urethra, but these ducts are quite short in comparison to the ducts leading to the peripheral zone. Hypertrophy of the short ducts during development of BPH impinges on the urethra, which can lead to obstruction. Carcinoma is found predominantly in glands originating from the distal segment which comprise the peripheral zone of the prostate in men. McNeal introduced the hypothesis of a reawakening of embryonic inductive interactions to describe the inappropriate new ductal budding that occurs in BPH. This was thought to result from nonprostatic stroma (the proximal urethral sphincter) inducing adjacent transition zone ducts to begin new ductal formation in areas of stromal proliferation. The significance of this stromal-epithelial interaction in prostate development has been the subject of many reviews.25

The prostate in mice contributes proteins involved in coagulation and various ions to seminal fluid. In male mice, removal of this organ reduces fertility.26 The morphology of the mouse prostate, which is divided into dorsolateral and ventral lobes, has been described in a series of papers by Sugimoto.19,20 Individual prostatic glandular ducts extend from the urethra...
FIGURE 11.2
Diagrams of frontal and sagittal sections of the male urogenital complex showing the anatomical position of the adult prostate and associated structures. The prostatic zones are central zone (CZ), peripheral zone (PZ) and transitional zone (TZ). The anterior fibromuscular stroma (AFS) is also shown. (From Thibault, R. C., Anatomical perspectives of prostate development, in Prostate: Basic and Clinical Aspects. Natl. R. H. Ed., CRC Press, New York, 1997, 36. With permission.)
and branch into three to six terminal ducts and are lined with pseudostratified columnar epithelium with interspersed basal cells. The ducts are surrounded by a layer of smooth muscle cells.

11.4 Homology: The Basis of Comparative Biology and Pathology

It has been proposed that the variety of interspecies differences observed in the structure of the adult prostate gland reflects a diversity that makes it difficult to find a suitable animal model for the study of human prostatic disease. Homology, which is based on structural and functional similarities in embryonic development rather than in adult appearance or even use of an organ, has been the basis for comparing the evolutionary relatedness of organs in different species for the past 150 years. A well-known example is the hand in humans and the fin in a whale, which share a common embryonic development and are homologous structures, but which appear in the adult quite different on superficial examination. Thus, attempting to elucidate the appropriateness of animal models for studying human prostate pathogenesis requires comparing humans and animals during prostate development, and not simply comparing the adult appearance of the organ.

Using a computer-assisted three-dimensional approach to visualize the microanatomy of prostate development, Timms has compared the ductal budding patterns during prostate morphogenesis in rat, mouse, and human (Figure 11.3). The three-dimensional reconstruction procedure revealed marked similarities between rodents and human prostate gland anatomy, leading Timms to propose that the site of opening of the prostatic glandular ducts into the urethra provides a basis for assessing homologous regions of the prostate in rodents and humans. Prostatic ducts that originate from similar regions of the urethral sinus in different species are proposed to be homologous in that they share a common structural and functional developmental pattern. This finding is significant in that Price observed that the relationship of prostate ductal openings into the urethra persists in the adult in the same relative position as in the fetus. That the overall appearance of the prostate and the organization of the terminal regions of the glands (as opposed to their origin at the urethra) differ is the adult makes it appear as if the prostate in the mouse and human are quite different. In contrast, the budding patterns of the glandular ducts from the urethral sinus in mice and humans during fetal development are remarkably similar, as described for the human hand and whale's fin. There is now no question that the formation of the fetal prostatic ducts in humans and rodents occurs from the ventral, lateral, and dorsal aspect of the urethral sinus. The question that remains to be answered relates to the grouping of these ducts into recognizable

![Image](image-url)
FIGURE 11.3

Computer-assisted serial section reconstructions from a fetal mouse (gestation day 18, left) and human prostate (30 min, CR length/11 weeks, right). The seminal vesicle (SV) and vas deferens (VD) on the right side of each reconstruction have been omitted to facilitate viewing of the prostatic budding patterns. In the mouse, dorsal prostatic bud outgrowths (D) are associated with the prostatic furrows of the urogenital sinus along the caudal-cranial axis. The threethree gland (DG) exhibits three pairs of outgrowths and is associated with the dorsolateral aspect of the urogenital sinus. The human fetal prostate shows dorsal outgrowths (D) that form a horseshoe-shaped pattern around the ejaculatory ducts and prostatic utricle (U). A parallel line of buds grows from the lateral wall of the urogenital sinus (L). The most caudal of these buds exhibit an anterior direction of growth (>). Several small perinatal outgrowths are evident in the proximal portion of the urogenital urethra (arrow). The seminal vesicle appears as a dorsal swelling on the vas deferens. Both views are from a superior right dorsal-lateral perspective. At these stages of fetal growth, the mouse and human prostate budding patterns demonstrate striking similarities. Prostate vertex (L).

Tubes or zones and whether these can be identified with histological, biochemical, or pathological distinctions.

Dogs and cats have homogeneous prostate tissue similar to the peripheral zone in humans, while the seminal vesicles and the central zone of the prostate are absent. The glandular ducts that lead from the urethra to the zones of the prostate that are prone to BPH in men, the transition and central zones, are thus absent in dogs.
11.5 Estrogen and Prostate Development, Adult Function and Pathology

There is considerable evidence for estrogen responsiveness of the prostate in rodents and other mammals. Our findings show that during prostate development in fetal rats (on gestation day 20), stroma strongly expresses mRNA for estrogen receptors, while estrogen receptor mRNA in urogenital sinus epithelium is at background levels (unpublished observation). A necessity for morphogenetic processes appears to be living stromal cells, through which trophic induction of epithelial proliferation is mediated.

11.5.1 The Dog and Noble Rat as Models for Human Prostate Disease

Exposure to supplemental estrogen (in combination with androgen) in adult-hood has been related to hyperplasia of the prostate in dogs and Noble rats. In Noble rats, neoplastic tumors can be induced to form in the dorsolateral prostatic lobes, while Sprague-Dawley rats typically do not develop tumors. Although fewer than 1% of Noble rats spontaneously develop adenocarcinoma of the prostate, treatment with a combination of low doses of testosterone and estradiol-17β (via silastic capsules) for 4 months leads to multifocal epithelial dysplasia, and longer treatment (about 10 months) results in the transition from dysplasia to neoplastic tumors in about 20% of treated males. Histological examination of prostatic tumors in Noble rats treated with androgen and estrogen showed that they primarily involved glandular epithelium, and metastases after transplantation into hosts revealed differentiated epithelial components. Neoplastic development occurs in specific regions of the peripheral zone of the human prostate gland. Dysplasia in the dorsolateral lobe of testosterone and estradiol treated Noble rats is almost identical to the premalignant lesions described in the human gland.

11.5.2 The Intrauterine Position Phenomenon: Correlation Between Estradiol and Prostate Development in Fetuses of Mice

Our interest in the relationship between estrogen and prostate development began with an observation that, at first, appeared to contrast with the accepted view that exposure to an increase in estrogen inhibited normal prostate development in rodents. We had observed that there were higher serum concentrations of estradiol in fetal relative to male mouse fetuses, and higher serum testosterone levels in male relative to female mouse fetuses. There is transport of both estradiol and testosterone between adjacent fetuses within a uterine horn, which serves as a source of variation

The Role of Natriuretic Peptide in these steroid phenotypes, the placental transport between male fetuses and female fetuses of estradiol (about 20% male fetuses) differ as a function of androgens, androgens, hormone levels, and growth retardation.

11.5.3 Sdr Inc.

We examined logical range experimental data with a Sdr which resulted in a 0.3 pg/ml of 0.1 biologically. In fact, the concentration of 32 pg/ml.
in these steroids during fetal life. We refer to this as the intrauterine position phenomenon, which is mediated by steroid transport between fetuses across the placental membranes via the amniotic fluid. As a consequence of steroid transport between fetuses, male mice that develop in utero between two female fetuses (2F males) are exposed to higher blood concentrations of estradiol (about 30% difference) and lower blood concentrations of testosterone (about 30% difference) than are male fetuses that develop between two male fetuses, referred to as 2M males. There is a wide range of traits that differ as a function of random intrauterine placement in comparisons of both males and females. With regard to the prostate and other reproductive organs, however, the logical prediction was that 2M males would have enlarged reproductive organs relative to 2F males. As predicted, adult 2M males were found to have larger seminal vesicles relative to 2F males, which was associated with higher levels of 5α-reductase activity in the seminal vesicles of 2M relative to 2F males (unpublished observation). In contrast, the prostate in 2F males was found to be significantly larger (by about 30%) than that in 2M males. The enlarged prostate in 2M males was associated with a three-fold greater number of prostatic androgen receptors in 2F relative to 2M males.

In dogs, estradiol synergizes with dihydrotestosterone to increase androgen binding in prostatic cells and thus increases prostate growth. Studies have also shown that estradiol influences hypothalamic androgen receptors in adult male rats. In addition, estradiol regulates the expression of receptors for a number of hormones, such as estrogen receptors and both uterine and brain progesterone receptors. Taken together, these findings show that the physiological effects of exposure to estrogen can include changes in the functioning of a variety of tissues due to changes in the receptors for other hormones that regulate these tissues. Importantly, when exposure to estrogen occurs during critical periods in development, effects on tissue function are permanent.

11.5.3 Stimulating Effects on Prostate Development of an Experimental Increase in Estradiol in Male Mouse Fetuses

We examined the hypothesis that an increase in estradiol within a physiological range during fetal life would permanently increase prostate size. We experimentally increased serum estradiol levels in male mouse fetuses during the time of fetal prostate development by implanting pregnant females with a Silastic capsule containing estradiol. The dose of estradiol that we chose to administer via Silastic capsule resulted in a 90% increase in free serum estradiol in male mouse fetuses from 0.2 pg/ml (in controls) to 0.3 pg/ml; the free (unbound) fraction of estradiol (and other steroids) is the biologically active fraction of total circulating steroid. This 0.1 pg/ml increase in free serum estradiol was associated with an increase in total serum estradiol of 52 pg/ml (from 94 pg/ml in controls to 146 pg/ml), the percent free
estradiol in fetal mouse serum is 0.2%). This increase in estradiol was chosen since it produced a mean value for serum estradiol in all treated male fetuses that was at the high end of the normal range of estradiol values measured in the serum of 2F males, and thus represented an increase in estradiol that was within the normal physiological range.

The 0.1 ml/ml increase in free serum estradiol increased the number of developing prostate glands (by 40%) based on three-dimensional reconstruction of the prostate collected from male fetuses on gestation day 18, 1 day after initiation of fetal prostate development (Figure 11.4). The developing prostatic glandular ducts in the dorsal region of the urethral sinus were also enlarged in estrogen-treated males relative to control males. This effect on the prostate was permanent. In adulthood, males exposed to the 50% increase in estradiol during fetal life had enlarged, hyperplastic prostates (by 40%) that showed a six-fold increase in prostatic androgen receptors relative to prenatally untreated males. The same permanent stimulation of prostate growth in male mice occurred with maternal ingestion of 0.02, 0.2, or 2 ng of the mammalian estrogen, DES per gram body weight per day from gestation day 11 through 17. Males exposed during fetal life to these low doses of DES had significantly enlarged prostates in adulthood relative to control males.4

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An interesting additional observation is that the 50% increase in serum estradiol also resulted in a significant decrease in the size of the urethra and a significant enlargement of the uriculus in male tisues. It is well known that elevated levels of estrogen inhibit regression of the Müllerian ducts. For example, treatment of pregnant females with DES inhibits the action of Müllerian inhibiting hormone on Müllerian duct regression in mice and humans. The uriculus is the Müllerian duct remnant that persists within the central zone of the human prostate, and the size of this area of the prostate in men may thus correlate with fetal estradiol exposure; this portion of the Müllerian duct differentiates into the dorsocentral portion of the vagina in females. A critical aspect of these findings with regard to the role of estrogen in prostate differentiation, as well as effects on other reproductive organs, is that in no other in vivo experimental studies in rodents has the administered dose of estrogen been determined to be within a physiological range.

11.5.4 Inhibition of Prostate Development with High, Pharmacological Doses of Estrogens

An extensive literature relating to the effects of exposure to synthetic estrogens during differentiation of the prostate and other accessory reproductive organs in rodents consistently shows inhibitory effects of estrogen on prostate function. The research concerning the effects of estrogen during early life on accessory reproductive organs in male rodents has involved the use of high doses of synthetic estrogens, such as DES, and exposure to a high dose of DES (or other synthetic estrogens) causes abnormal development and lesions throughout the reproductive system in males. Administration of high, nonphysiological levels of androgen during sexual differentiation has similar effects. For example, squamous metaplasia of prostatic and coagulating gland (dorsocentral prostate) ductal epithelium in male mice and rats has been reported after exposure to exogenous estrogen during early life. Similar effects of estrogen on rat prostatic cells in culture have been reported. Damage to reproductive organs in females is also seen with developmental exposure to high doses of synthetic estrogens.

11.5.5 Opposite Effects of High and Low Doses of Estrogen during Prostate Development

We found that a small increase in estradiol, within a physiological range, led to an increase in prostate size, associated with an increase in prostatic androgen receptors, while numerous prior studies showed that the opposite effect of much higher doses of mammalian estrogen. We thus administered increasing doses of both estradiol (via Silastic capsule) and DES (via feeding) to pregnant female mice and examined the prostate in male offspring in adulthood. Following fetal exposure to both estradiol and DES, we
found an inverted-U dose-response relationship for adult prostate weight. Specifically, as serum estradiol concentrations were increased in male mouse fetuses via maternal Silastic implants from 50%-80% relative to controls, first an increase and then a decrease in adult prostate weight was observed in male offspring. Similarly, while maternal doses of 0.02, 0.2, and 2 ng/g body weight per day increased prostate weight in male offspring, a DES dose of 20 ng/g led to prostate weight that did not differ significantly from control males, while 200 ng DES per gram significantly decreased adult prostate weight. Taken together, the above findings provide evidence that with regard to prostate development, effects seen in response to high, pharmacological/toxicological doses of natural or man-made estrogens are opposite to effects seen with low doses within the normal physiological range of estrogen activity.

11.5.6 Environmental Endocrine-Disrupting Chemicals that Mimic Estrogen Alter Prostate Development

Studies now identify that many chemicals have the capacity to disrupt the functioning of the estrogenic system, either by binding to endogenous hormone receptors, interfering with enzyme activity, or via other mechanisms, such as interfering with plasma transport of hormones. There are thus chemicals being used in common household products that, prior to being used to manufacture these products, were not tested for the possibility that they might be able to bind to receptors for natural steroids, such as estrogen and androgen. Because development of all organs is coordinated by estrogen signals, the disruption of estrogen signals during critical periods in organ development can lead to permanent effects on organ function. Functional effects might not be noticed based only on examination for gross malformations, which, along with cancer, has been the focus of toxicological testing.

We recently examined the effects of topical exposure to bisphenol A, an estrogen-mimicking chemical. Bisphenol A is used to make polycarbonate plastic (for example, baby-bottle bottles are made from polycarbonate). Bisphenol A is also a component of the inner lining of food and beverage cans, in dental sealants, and many other plastic products. Approximately 2,000,000,000 pounds of bisphenol A are used per year, and another 100,000,000 pounds of brominated bisphenol A are used as flame retardants in a wide variety of products.

We used a screening assay involving human breast cancer cells (MCF-7) to assess the estrogenic potency of bisphenol A. Our findings suggested that developing mouse fetuses would respond to doses of bisphenol A within the range of human exposure to this chemical through the use of polycarbonate to store food, eating canned products, and having dental sealant applied to protect teeth. Based on predictions from our in vitro assay, we fed pregnant mice 2 or 20 billlions of a gram of bisphenol A per gram body weight per day to and during numerous effec-
weight per day (2 or 20 mg/g/day) for 7 d from gestation day 11-17, prior to and during the initial period of prostate development. We observed numerous effects in male offspring, including abnormal body growth, permanent enlargement of the prostate and seminal glands, a decrease in testicular sperm production, and a decrease in seminal vesicle and epididymal size. In female offspring, we observed abnormal body growth and an early onset of puberty. Other estrogenic effects of bisphenol A on the breast and phallic gland have been reported recently in studies with rats.

The Wolffian ducts and urogenital sinus express estrogen receptors during prenatal development in the mouse. Therefore these organs potentially can be directly affected by compounds that bind to estrogen receptors, such as bisphenol A. The decrease in the size of the epipatymis and seminal vesicles suggests that bisphenol A interfered with the normal development of the Wolffian ducts as well as the testes. In contrast, bisphenol A significantly increased the size of the prostatic glands and prostate relative to untreated males.

The finding that an elevation in an estrogenic chemical during fetal life decreased seminal vesicle size in adulthood is consistent with our prior findings. Specifically, male mice that developed in utero between two female fetuses (2F males), and were then exposed to elevated estradiol via diffusion from the adjacent females, had smaller seminal vesicles in adulthood than their siblings who developed in utero between two male fetuses (2M males).

Subsequent studies have suggested that this effect was mediated by a permanent "imprinted" decrease in seminal vesicle 3α-reductase activity in 2F males relative to 2M males (unpublished observation). However, the larger seminal vesicles found in 2M male mice were initially thought to be due solely to the supplementation of testosterone that 2M males received due to being positioned in utero between male fetuses. The finding that a low dose of an estrogenic chemical during fetal life can permanently decrease seminal vesicle and epididymal size suggests that the elevated estradiol in 2F males may have contributed to the development of small seminal vesicles in these males. It has been reported that estrogen exerts an inhibitory effect on 3α-reductase activity in accessory reproductive organs.

In contrast to findings regarding organs that differentiate from Wolffian ducts, adult 2F male mice, as well as male mice exposed experimentally as fetuses to a 50% increase in serum estradiol, exhibited enlargement of the prostate that was associated with a permanent increase in prostatic androgen receptors. As mentioned above, the prostate develops from the urogenital sinus, while seminal vesicles develop from a different embryonic tissue, the Wolffian ducts. Under different hormonal control. Taken together these findings provide evidence that during fetal life, the specific genes influenced by estrogen are different in the Wolffian ducts and urogenital sinus. Thus, what appeared initially as contradictory findings, with some organs increasing in size and others decreasing in size associated with a small increase in serum
estradiol during fetal life, now has proven to be a consistent outcome following administration of estrogenic chemicals during fetal life. The recent discovery of two types of estrogen receptor (ER-α and ER-β) and their differential localization in prostate epithelium and stroma has led to speculation about different biological effects. This is particularly relevant when comparing effects of natural and environmental estrogens. For example, bisphenol A shows a higher binding affinity for ER-β relative to ER-α, which should result in organs, such as the prostate, which express ER-β having a greater responsiveness to bisphenol A than organs that only express ER-α.

11.6 Summary

There is no information concerning whether prostate enlargement in men might be related to exposure during fetal life to estrogenic chemicals. However, there has been a doubling of the incidence of abnormal penis development in male babies over the past 20 years in the U.S., suggesting that an environmental factor is involved. There is historical evidence that sperm count in men has declined by 50% over the past 50 years, while the incidence of testicular and prostate cancer has increased; there are regional differences in sperm count as well as prostate and testicular cancer rates, which suggests that environmental factors are mediating these effects. Prospective studies in humans designed to examine the relationship of exposure to estrogenic chemicals during fetal life (via the mother) and health effects, such as incidence of or age of onset of prostate disease, are warranted based on findings from animal studies.

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The Role of Nature.
The Role of Natural and Mannose Estrogens in Prostate Development


Endocrine Disruptors: Effects on Male and Female Reproductive Systems


