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Is there a role for estrogens in the maintenance of men's health?

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ABSTRACT

This paper gives an overview of our own studies and the literature on the biosynthesis and metabolism of estrogens in elderly men, the estrogen action in the male, and the clinical usefulness of estrogen therapy, including the phytoestrogens. Finally, the paper includes a short review of our knowledge of xenoestrogens and men's sexual health.

A strong estrogen-deficient status is seen in male patients with mutations of the estrogen receptors or in cases of deviations of the aromatase gene. On the other hand, there are no clear age-dependent changes in estrogen secretion. But, in men with disorders of glucose metabolism and also of increased body mass index, the serum estrogen concentrations are significantly elevated. There are also strong positive correlations between serum estrogen levels and bone density, including prevalence of fractures and mood in men. New fields of interest are natural fatty esters of endogenous estrogens, e.g. lipoprotein-associated estrogens, and the role and clinical significance of tissue-specific, local estrogen biosynthesis (e.g. different promoters of the aromatase gene).

Exogenous estrogen treatment is focused today on patients with normal testosterone and low levels of circulating estrogens documented on several occasions and with clinical symptoms of hormone deficiency; male-to-female transsexuals; and selected patients with prostate cancer.

Some clinical studies show the benefits of estrogen treatment on some cardiovascular parameters and for treating selected signs of mental stress. An indirect estrogen replacement can occur if dehydroepiandrosterone is given orally to men. The clinical usefulness of dissociated estrogens, including non-feminizing estrogens and selective estrogen receptor modulators, is still an open question.

The beneficial action of phytoestrogens in lowering the clinical symptoms of benign prostatic hyperplasia is well documented. Finally, the question about the definitive influence of so-called endocrine disruptors (xenoestrogens) on sexual functions in men is also discussed.

INTRODUCTION

No area of hormone replacement in the elderly male has been discussed so controversially and is so little known as the sense or nonsense of estrogen replacement. However, other problems of estrogenic actions in men are also being argued in the scientific community as well as in the public media, such as non-feminizing estrogens, phytoestrogens, and other xenoestrogens – the so-called 'endocrine disruptors'. This paper gives a short updated overview of these topics. For more detailed information, see reviews in references 1–3.

BIOSYNTHESIS AND SECRETION OF ESTROGENS IN THE AGING MALE

Of the circulating estrogen in men, 75–90% arises from peripheral aromatization, mainly in adipose

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tissue, of both testosterone to 17β-estradiol (E2) and androstenedione (coming mainly from dehydroepiandrosterone (DHEA)) to estrone (E1). The testes synthesize the remaining 10–25%[4]. Elderly men have higher estradiol and estrone levels than postmenopausal women[5–7].

As an example, we give selected results of an epidemiological study performed on over 1000 men in different age groups. The subjects from the so-called LURIC study (Ludwigshafen Risk and Cardiovascular Health Study), a cooperation project of Ludwigshafen Heart Center with the Freiburg and Ulm University Hospitals, presented with suspected coronary heart disease, and serum samples were taken for different determinations[8]. We found that there was no age-dependent change in the serum levels of both 17β-estradiol and estrone. Based on the age-related increase in the sex hormone binding globulin (SHBG) levels, only the unbound free fractions were declining (Figure 1). On the other hand, Leifke and colleagues[9] found only a small age-dependent decrease in total 17β-estradiol in 572 healthy non-obese men, whereas there was a stronger inverse correlation between age and serum levels of bioavailable estrogen. In this context, it should be emphasized that, in contrast to women, in men the SHBG levels are independent of estrogens[10].

We also found in the LURIC study that nearly 3% of the volunteers showed normal serum testosterone levels above 14 nmol/l and extremely low estradiol concentrations below 10 pmol/l (for these limits, we developed a special, very sensitive immunoassay). But this picture of a partial aromatase deficiency was only transient. This means that, on repeat measurements, for example after 3 years, most of these patients showed normal estrogen levels[11].

ESTROGEN ACTION IN THE MALE

Generally, on the molecular biological level, there are no differences between the estrogenic action on female tissues and the estrogenic action on male tissues. The genomic estrogenic effect is mediated by the two estrogen receptor subtypes, α and β, whereas the non-genomic action is mediated by different kinases[12].

In this context, it is important that the main actions of androgens are dependent on their local aromatization to estrogens in a given tissue. This means that the serum steroid hormone levels are less relevant, as compared to the local intracellular equipment with steroid transforming enzymes, mainly the aromatase. Götz and Patchev[13] have found that the restoration of sexual behavior in castrated male rats by different androgens depends on the degree of aromatizability of the given molecule (highly aromatizable 7α-methyl-19-nortestosterone (MENT) > aromatizable

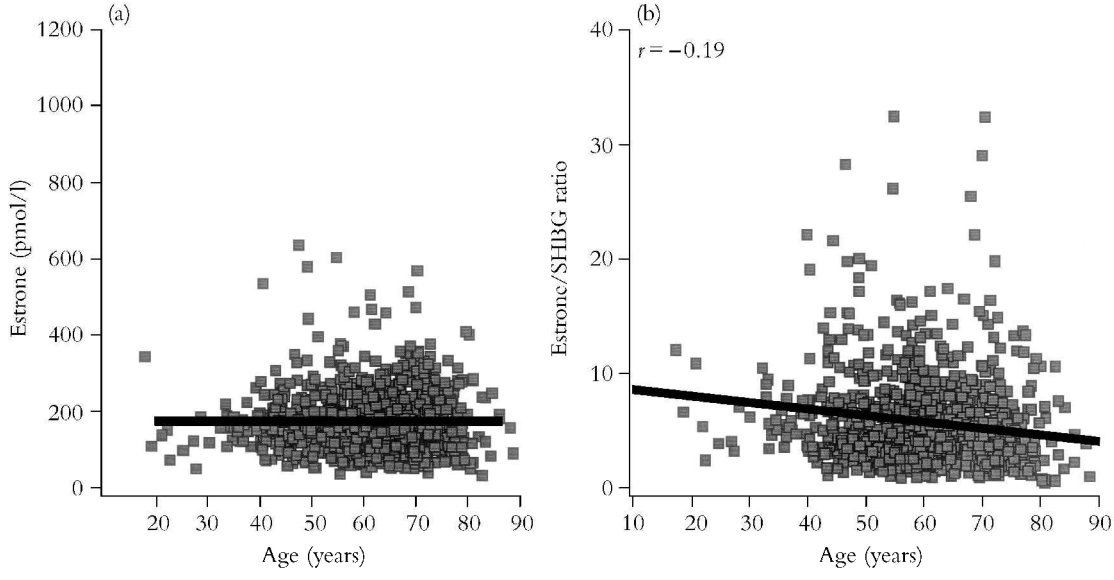

Figure 1 Serum estrone concentrations (a) and free estrone index (b) in 1014 men of different ages. Note a significant decrease of only free, unbound estrone. (LURIC–Jenapharm Study[2,8])

testosterone > non-aromatizable 5α-dihydrotestosterone (DHT) > non-aromatizable oxandrolone). In the same context, we have been able to demonstrate that the copulatory pattern in castrated male dogs can be restored by the administration of intramuscular testosterone enanthate, as well as by the oral administration of the depot estrogen ethinylestradiol isopropyl sulfonate, J 96[14]. The estrogen-dependent maintenance of sexual activity in male animals is mediated by estrogen receptor subtype α, whereas subtype β is not involved[15]. However, it should be stated that, in eugonadal young men suppressed by a gonadotropin releasing hormone (GnRH) antagonist in contrast to beneficial testosterone replacement alone, the additional administration of the aromatase inhibitor testolactone was without significant positive or negative effects on androgen-restored sexual behavior, indicating that circulating E2 levels have probably only a limited role in the regulation of sexual function in normal men[16].

In an epidemiological pilot study with 214 men aged 40–70 years in Turku/Finland, we found a positive correlation between the E2/free testosterone (FT) ratio and the severity of the reported decreased potency and between the E2/testosterone (T) ratio and the reported severity of decrease in morning erection frequency. This would suggest that use of aromatase inhibitors to reduce E2 and increase T might have a positive effect on potency. However, the results also demonstrate a negative correlation between E2/FT and irritability and nervousness, while there might be positive effects on potency. This is a good example of the Janus Face of estrogens in men[17].

A strong estrogen-deficient status in men is seen where there are mutations of the estrogen receptors or deviations of the aromatase gene. The main clinical findings in aromatase deficiency are normal pubertal development, and extremely tall height (> 3 SD), with continued linear growth into adulthood, osteoporosis, and macroorchidism. The main laboratory findings are undetectable E1 or E2 levels in serum despite normal testosterone levels and markedly elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels, severely retarded bone age with unfused epiphyses, densitometric and biochemical evidence of osteoporosis, elevated basal insulin level, and decreased high density lipoprotein/low density lipoprotein (HDL/LDL) cholesterol ratio[18–20]. These patients respond very favorably to estrogen replacement[21]. The clinical features of estrogen resistance caused by a mutation in the estrogen receptor gene are similar to the picture of aromatase deficiency[22].

The clearest clinical evidence of the benefits of estrogen in men comes from studies on the skeleton. Estrogen effects on bone formation and development are focused on terminally differentiating chondrocytes and the mineralization of the bone[23]. Both ERα and ERβ are expressed in men in osteoblasts as well as in chondrocytes *in vivo*[24]. More effective than testosterone, the bone mineral density and the prevalence of vertebral fractures (at least one fracture) are positively correlated with the serum estrogen concentrations in men[25–30].

On the other hand, fat mass, especially abdominal fat mass, is positively correlated with serum estrogen levels[31]. We have also found the well-known positive correlations between body mass index and estrogen serum levels in our two epidemiological studies in Turku, as well as in Ludwigshafen (Figure 2). On the same level is our observation in Finland, namely, that relatively low serum estrogen concentrations (in relation to testosterone) are seen in men with the highest score of exercise/physical activity.

The results of our Dresden/Jenapharm study are directed at the same issue: men with disturbances of glucose metabolism, e.g. diabetes mellitus, showed elevated serum levels of 17β-estradiol[32]. Regarding the metabolic effects of increased or decreased serum estrogen levels in men, it should be taken into account that these effects reflect rather the

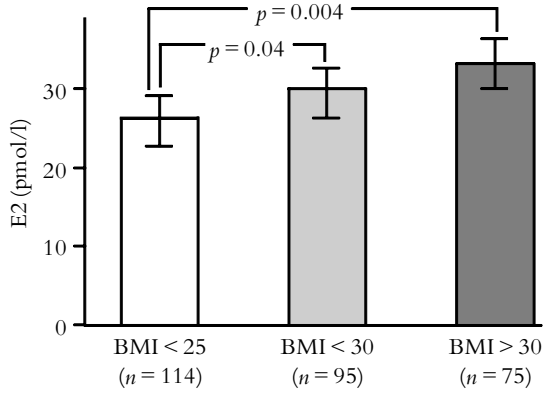

Figure 2 Relationship between E2 serum levels and body mass index (BMI) in 384 men, aged 43–88 years with assumed coronary heart disease (no statins, digitalis, glucocorticoids or diabetes). (LURIC–Jenapharm Study)

well-known correlations of high or low body mass index (with the dependence of the total aromatase activity on fat volume). An analogy that could be considered is overweight being the 'hen', while the elevated estrogen serum levels are the 'egg'. Therefore, the best aromatase inhibitor could be exercise. No associations between plasma levels of sex steroid hormones and insulin resistance, hepatic glucose output, or insulin secretion were found to be independent of obesity[33]. Heavier men possess a better skeleton and (as the example of Julius Caesar shows) are less nervous and irritable.

Another problem of elevated estrogen biosynthesis in men should not be overlooked. As early as in 1995, Gann and colleagues found that low serum testosterone levels and elevated serum estradiol levels were associated with a significantly higher adjusted odds ratio for benign prostatic hyperplasia (BPH) (adjusted for age, E1, diastolic blood pressure, exercise, and alcohol)[34].

Doubtless, steroid hormone secretions are correlated with men's health status. In particular, chronic diseases have a profound influence on hormone secretions or their serum levels. The Massachusetts Male Aging Study has demonstrated that, in men with chronic diseases, the age-related decrease of testosterone secretion is more pronounced than in healthy men[35,36]. These findings from the Massachusetts study have inspired me to suggest a hypothetical model by adding our findings on serum estrogen levels in diabetic men. In contrast to testosterone, in men with chronic illness such as disturbances of glucose metabolism, estrogen secretion is age-dependently increasing, whereas, in healthy men, there are no age-related important changes in estrogen biosynthesis (Figure 3).

Interestingly, whereas obesity and normal estrogen biosynthesis or serum estrogen concentrations in men are positively correlated, in contrast to this, obesity is probably in inverse ratio with the so-called lipoprotein-associated estrogens. The discovery of a family of hormonal endogenous steroids esterified with fatty acid has raised questions concerning their physiological role. Because of their water insolubility, these natural estrogen esters are only present in the circulation as components of lipoprotein particles. Current evidence supports the hypothesis that estrogen esterification is catalyzed by lecithin : cholesterol acyltransferase associated with HDL. In addition, recent results indicate that estradiol esters are transferred from HDL to LDL particles in a cholesteryl ester transfer protein (CETP)-associated process. Scientific and clinical interests now focus on the various possible physiological roles proposed for these hormone derivatives:

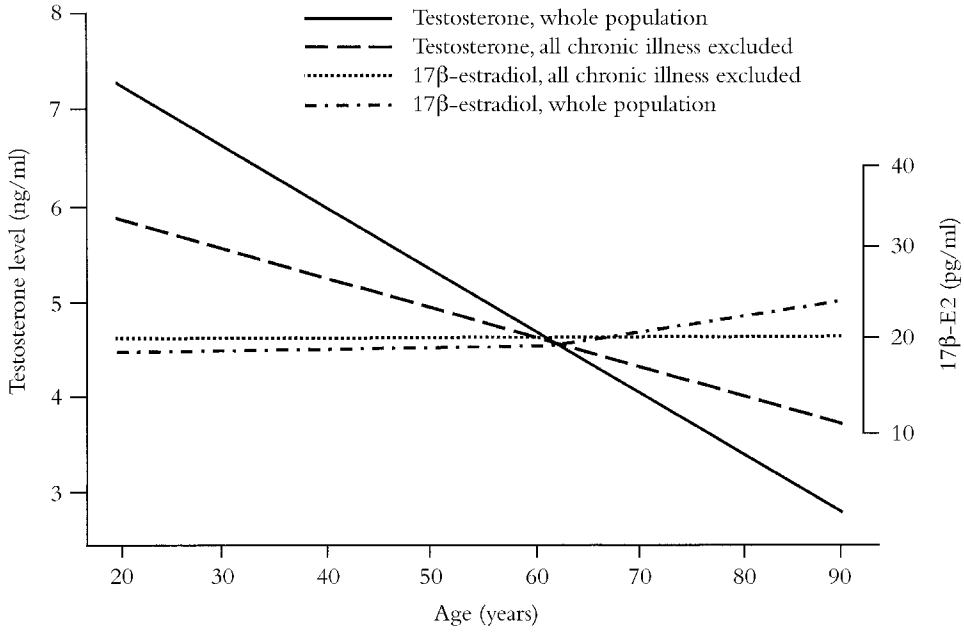

Figure 3 Correlation of age-related serum testosterone, estrogens and general health conditions (hypothetical model)[32,35,36]

(1) Functioning as fat-soluble antioxidants incorporated in lipoproteins, rendering protection against oxidation of these particles;

(2) Providing a mechanism for hormonal storage in lipoproteins and fat tissues; and

(3) Providing a novel hormone transport system using lipoproteins as carriers and lipoprotein receptors for entry into cells[37].

Oleoyl estrone is an estrone fatty acid ester found in all three lipoprotein fractions from rat plasma, although at different concentrations. It is the major estrone component in lipoproteins and is synthesized in the white adipose tissue[38]. Surprisingly, the plasma estrone–fatty acid ester levels in obese men are significantly lower at 51.5 ± 3.9 pmol/l than in lean men at 192 ± 13.9 pmol/l[39]. Thus, the behavior of the natural estrogen–fatty acid esters is completely different from that of free, non-esterified 17β-estradiol and estrone fractions that are significantly increased in obese men (see above). It is speculated that exogenously administered oleoyl estrone could show great potential as a possible anti-obesity drug[40].

EXOGENOUSLY ADMINISTERED ESTROGENS IN MEN

The story of estrogen replacement in men began in the 1950s with a serious misinterpretation of a well-designed clinical study. Stamler and co-workers[41] reported that 1.25 or 2.25 mg of conjugated estrogens daily given immediately after a myocardial infarction significantly prolonged the survival rate. But unfortunately or typically, only the poor results with the extremely high dosage of 10 mg Premarin per day were communicated in the following decades, generally bringing estrogen substitution in men into discredit. Yet, the advantages of estrogen treatment with correct diagnosis, correct selection of the patient group, and correct dosage are evident. *In vitro*, 17β-estradiol relaxes coronary artery rings obtained from females as well as from males[42]. And, *in vivo*, estrogen treatment antagonizes the endothelium-dependent effects of acetylcholine on forearm blood flow and forearm vascular resistance[43]. In male patients with chronic heart failure, acute estrogen administration improves the indices of cardiac systolic performance and decreases pulmonary and systemic vascular resistance. These findings could imply a beneficial effect of estrogen in selected patients with chronic heart failure[44].

Finally, the response of a standardized mental stress (e.g. stress-induced increase in serum adrenaline and noradrenaline levels) is abolished by the administration of estradiol in healthy men[45,46]. Table 1 summarizes the proved and expected indications for estrogen treatment in men.

On the other hand, we have come to one of the main problems of hormone replacement in both women and men: serum steroid levels determined at certain time points frequently show unsatisfactory correlations of the picture or severity of clinical signs or symptoms of a hormone deficiency. In principle, the respective local estrogen concentration in the tissue is of clinical importance rather than the pharmacokinetics in the blood. Increasingly, we better understand that estrogens not only act as hormones, but also as paracrine and intracrine factors. Considering the situation in men, it is remarkable that serum testosterone concentrations are of the same order of magnitude as the K_m value of aromatase (20–30 nmol/l), i.e. a metabolism of testosterone to E2 can very efficiently take place locally in the tissue. The conversion does not much depend on the concentration of the precurser testosterone, but mainly on the aromatase concentration. It could therefore be speculated that, in spite of the age-dependent decrease of the testosterone secretion in men, sufficient E2 should actually be available locally to enable a transactivation of the two estrogen receptor subtypes α and β

Table 1 Estrogen treatment in the human adult male

- Patients with repeatedly documented normal testosterone and low levels of circulating estrogens and (mandatory) with corresponding clinical symptoms of hormone deficiency
- Male-to-female transsexuals
- Prevention and treatment of hot flushes and osteoporosis in patients treated with gonadotropin releasing hormone analogs
- Prevention and treatment of osteoporosis in men, if androgens and other treatments are contraindicated
- Treatment of prostate cancer (in the past, unsuitable stilbenes in extremely high dosages instead of modern estrogens and estrogen dosage forms)
- Patients with mild cognitive impairment?

($K_D \sim 1$ nmol/l)[47]. In this respect, the odds seem to be on the side of men rather than of postmenopausal women. Their serum testosterone concentrations, at 10–30 nmol/l, are higher by one order of magnitude, compared with 0.5 nmol/l, whereas androstenedione is measurable in the serum at the same concentration in both genders at about 2.5 nmol/l. Seen from this viewpoint, it is therefore relatively difficult to presume a local, specific estrogen deficiency with broad relevance to health policy. Are these factors also the reason for the lower incidence of osteoporosis and Alzheimer disease in men as compared with women?

It should, however, be borne in mind that, in aromatase induction, sex-specific differences and, to a much greater extent, tissue-specific peculiarities should be considered[48]. Great interest is raised in this context by tissue-specific promotors of the CYP 19 gene which, occurring in different tissues and dependent on the respective ligand, can differently influence or control aromatase expression and thus local estrogen production in different tissues[49].

Considering these molecular biological peculiarities of aromatase expression, what we are presented with as a reasonable diagnostic task to prove an estrogen deficiency (and thus, the clear assignment of a clinical picture) is the determination of local estrogen concentrations or of the mRNA of the aromatase gene in the tissue of interest. For future research work, it would be worthwhile to find patient-friendly methods to do this.

Indirect estrogen replacement can be achieved by giving DHEA orally to men. Despite the recent discovery of a specific DHEA receptor in the endothelium[50], the most important clinical effects of DHEA depend on the bioconversion of this adrenal steroid to androgens or to estrogens. Together with Bruno Allolio's group in Würzburg, we have found that, in contrast to women, in men with DHEAS concentrations below 4.1 μmol/l or with an age-related decline of DHEA secretion, the serum estrone and partially the 17β-estradiol levels were elevated, whereas there was no change in testosterone concentrations. The reason for this phenomenon is our observation that, instead of androstenedione levels after DHEA intake being increased, the conversion/reduction of androstenedione to testosterone is hampered, obviously by the inhibition of 17β-steroid dehydrogenase[51,52].

NON-FEMINIZING ESTROGENS

Based on the possibility that exogenous estrogens in men can induce gynecomastia and also fat accumulation, notably in the abdominal region, we started a project for the development of so-called non-feminizing estrogens possessing all the benefits, if possible, and avoiding the typical side-effects of 'classical' estrogens. This class of estrogens should also not induce prostatic stromal proliferation leading to BPH or increased prolactin secretion. As a lead compound, we selected 17α-estradiol, the weak estrogenic epimer of the common female hormone 17β-estradiol. 17α-Estradiol shows low binding to the estrogen receptor (~ 23%) and 10–100 times lower 'classical' genomic action (e.g. on the uterus *in vivo* and on human breast cancer cells *in vitro*[53]). In principle, endogenous 17α-estradiol can be formed by aromatization from epi-testosterone[54,55]. However, we only succeeded in sporadically detecting 17α-estradiol in the serum of untreated and treated men using gas chromatography/liquid chromatography mass. The reason is an enormous first-pass effect in the liver[56].

This gave us the reason to develop better designed, more stable derivatives of 17α-estradiol. These compounds showed an excellent pharmacodynamic profile *in vitro* as well as *in vivo*[3,57]. Unfortunately, in our own clinical studies, the desired dissociation between strong estrogenic action on the central nervous system and cardiovascular system and failing or very low estrogenic activities on the genital apparatus was not seen. Nor did the administration of the selective estrogen receptor modulator (SERM) raloxifene show the expected results in men[58]. Therefore, the clinical usefulness of dissociated estrogens in andrology is still an open question.

PHYTOESTROGENS

Great expectations and speculations surround the use of phytoestrogens in men (for example, soy isolates, coumestrol, genistein, daidzein, biochanin A). The genomic estrogenic action of these plant compounds via classical nuclear estrogen receptors is very low[59], and other possibilities for the mode of action of the 'phytos' have to be raised for scientific discussion. Should phytoestrogens actually have a therapeutic or preventive effect after oral

administration in men, this effect can be explained only by a non-genomic, membrane-dependent mode of action. The clinical findings are controversial[60]. Nevertheless, as shown by the European PERMAL study with 98 centers in 11 European countries (double-blind, randomized trial), the beneficial action of phytoestrogens in lowering the clinical symptoms of BPH in comparison to the market leader tamsulosin is very clear[61].

Furthermore, indole-3-carbinol, a phytochemical in cruciferous vegetables (known to occur preferentially in cabbage, broccoli, cauliflower) induces the beneficial 2-hydroxylation of 17β-estradiol with minimal effect on undesirable 16α-hydroxylation[62,63]. This example shows that, despite direct hormonal effects, plant compounds can act indirectly via specific steering of the endogenous steroid metabolism.

OTHER XENOESTROGENS: 'ENDOCRINE DISRUPTORS'

Today, apart from phytoestrogens, other xenoestrogens or the so-called endocrine disruptors are under discussion. We have found that both natural and synthetic steroids are very easily metabolized by microorganisms, Gram-positive as well as Gram-negative bacteria and also fungi[64]. Therefore, we can postulate that environmental steroids are not toxicologically or clinically relevant. Chemicals, namely pesticides or herbicides with a phenolic ring are another matter (Figure 4). These compounds show estrogenic activities and can persist in the environment for a long time, but, based on recent publications, adverse endocrine disruptive effects or other risks to men's health appear to be rather unlikely[65–69].

Nevertheless, concerns about harmful activities of xenoestrogens have supported reports on the decline of sperm density and sperm quality from decade to decade in the last century[70]. But, today, we must state that re-analysis of the data, showing that mean sperm counts decreased by over 40% between 1940 and 1990, indicates that methodologic inconsistencies and inadequate statistical methods were used and that the presented data did not support a significant decline in sperm count[71].

There is also the concern whether xenoestrogens have an influence on potency, including erectile dysfunction. Quinn and co-workers, in a chemical plant producing phenolic chemical intermediates, found that 37% of the plant workers showed reduced testosterone levels, 36%

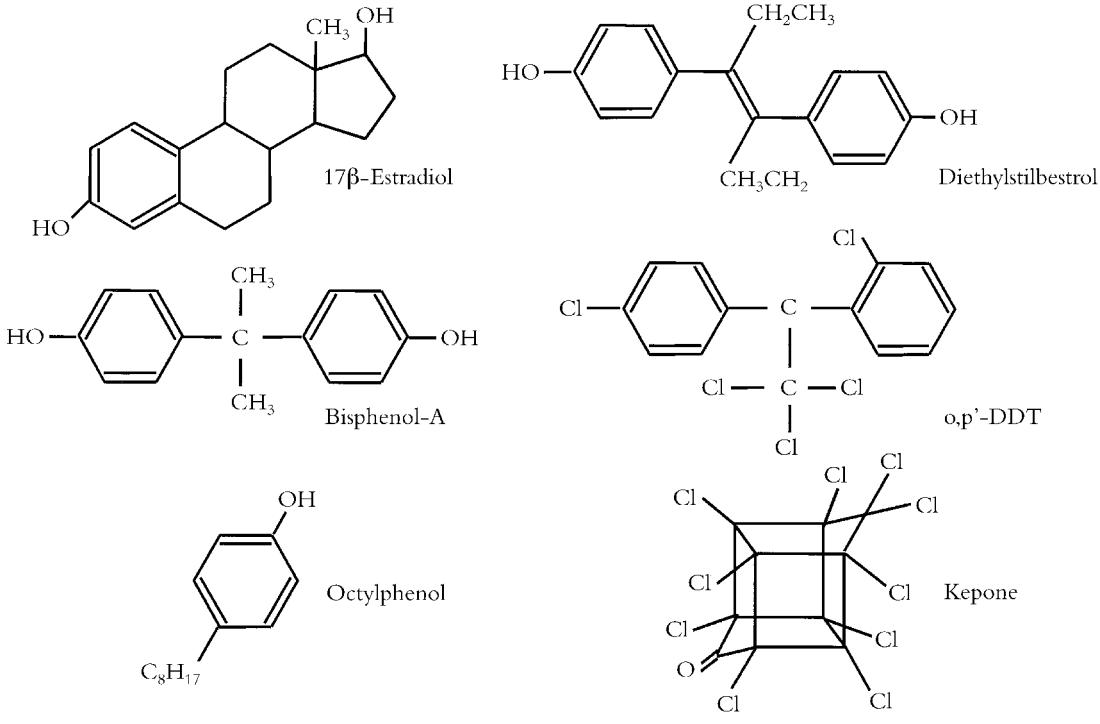

Figure 4 Similar to 17β-estradiol and diethylstilbestrol, many xenoestrogens also bind to the estrogen receptor

decreased libido, and 14% erectile dysfunction[72]. In another study, Oliva and colleagues found that pesticide exposure led to a flat erectile pattern[73]. The number of included volunteers is too small in both studies, and therefore larger epidemiological studies are necessary to answer the question whether xenoestrogens can influence male sexual behavior, and in what dosage.

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