

Aromatase and gynecomastia

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Abstract

An imbalance between estrogen action relative to androgen action at the breast tissue level results in gynecomastia. Enhancement of aromatization of androgens to estrogens is important in the pathogenesis of gynecomastia associated with obesity, aging, puberty, liver disease, thyrotoxicosis, 17-oxosteroid reductase deficiency, Klinefelter's syndrome, and neoplasms of the testes, adrenals and liver. A primary aromatase excess syndrome with exuberant gynecomastia had been found both sporadically and in a familial setting. Although aromatase inhibition would appear to be an important class of drugs to treat gynecomastia, relatively little published data with these drugs exist and most concern the use of Δ^1 -testolactone, which reduces the size of the breast glandular tissue, but does not completely ameliorate the problem. Studies with the newer generation of more potent aromatase inhibitors need to be carried out.

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Introduction

Gynecomastia, which represents a benign proliferation of the breast glandular tissue, can be detected in up to 70% of boys during puberty and between one-third and two-thirds of adults (Braunstein 1993). This common clinical condition results from an imbalance in estrogen action relative to androgen action at the breast tissue level.

The estrogen/androgen imbalance may result from an increase in free estrogens through direct secretion from the testes or adrenal glands, extraglandular aromatization of estrogen precursors, displacement of more estrogen than androgen from the blood transport protein, sex hormone-binding globulin (SHBG), by certain drugs such as spironolactone or ketoconazole, decreased or altered metabolism of estrogens, or through the administration or exposure to exogenous estrogen or estrogen-like drugs. The imbalance may also occur from a decrease in free androgens through decreased secretion from the testes, altered metabolism of androgens or increased binding of androgens relative to estrogens by SHBG. Androgen receptor defects, either due to mutations in the receptor that reduce its function or to competitive displacement of androgens from the receptors by drugs such as spironolactone, flutamide, or cimetidine also reduce androgen action and, hence, the androgen antagonism of estrogen effect on the breast. Finally, in some individuals, gynecomastia may result from an enhanced sensitivity of breast tissue to normal concentrations of free estrogens and androgens (Braunstein 1993).

Table 1 lists the various causes of gynecomastia under their primary pathophysiological mechanism (Mathur & Braunstein 1997). However, it should be noted that, in many patients, multiple pathophysiological mechanisms account for the estrogen-to-androgen imbalance. The gynecomastia found with aging serves as an example of the many factors that may account for the breast stimulation. Aging is associated with an increase in body fat which results in enhanced aromatization of androstenedione to estrone and testosterone to estradiol (Siiteri & MacDonald 1973). Testosterone production also decreases with aging and this, together with the elevation in serum concentrations of SHBG seen with aging, leads to a reduction in the free testosterone levels. Finally, older individuals use a multitude of medications, many of which may be associated with gynecomastia (Table 2) (Mathur & Braunstein 1997).

Role of aromatase in gynecomastia

Aromatase or estrogen synthetase plays a pivotal role in the production of estrogens in men. The adult testes normally directly secrete almost 15% and <5% of the circulating levels of estradiol and estrone respectively. The rest of the estradiol and estrone in the circulation is produced in extraglandular sites through aromatization of testosterone (to estradiol) and the adrenal estrogen precursor, androstenedione (to estrone). Estrone and estradiol are interconverted, as are androstenedione and

Table 1 Causes of gynecomastia¹

Physiological	
	Neonatal
	Pubertal
	Aging
Pathological	
	Idiopathic
	Drug induced
	Increased serum estrogen
	Increased aromatization (peripherally or glandular)
	Sertoli cell tumors
	Sex cord tumors
	Testicular germ cell tumors
	Leydig cell tumors
	Adrenocortical tumors
	Hermaphroditism
	Obesity
	Hyperthyroidism
	Liver disease
	Testicular feminization
	Refeeding after starvation
	Primary aromatase excess
	Displacement of estrogen from SHBG
	Spironolactone
	Ketoconazole
	Decreased estrogen metabolism
	Cirrhosis (?)
	Exogenous sources
	Topical estrogen creams and lotions
	Ingestion of estrogen
	Embalming fluid
	Eutopic hCG production
	Choriocarcinoma
	Ectopic hCG production
	Lung carcinoma
	Liver carcinoma
	Kidney carcinoma
	Gastric carcinoma
	Decreased testosterone synthesis
	Primary gonadal failure, congenital
	Anorchia
	Klinefelter's syndrome
	Hermaphroditism
	Hereditary defects in testosterone synthesis
	Primary gonadal failure, acquired
	Viral orchitis
	Castration
	Granulomatous disease (including leprosy)
	Testicular failure due to hypothalamic and/or pituitary disease
	Androgen resistance due to androgen receptor defects
	Other
	Chronic renal failure
	Chronic illness
	HIV
	Enhanced breast tissue sensitivity

¹The various disorders are listed under their primary pathophysiological mechanism. Modified from Mathur & Braunstein (1997).

Table 2 Drugs associated with gynecomastia

Hormones	
Androgens	
Anabolic steroids	
Chorionic gonadotropin	
Estrogens	
Growth hormone	
Antiandrogens/inhibitors of androgen synthesis	
Cyproterone acetate	
Flutamide	
Finasteride	
Antibiotics	
Ethionamide	
Isoniazid	
Ketoconazole	
Metronidazole	
Antiulcer drugs	
Cimetidine	
Ranitidine	
Omeprazole	
Cancer chemotherapeutic drugs	
Alkylating agents	
Methotrexate	
Vinca alkaloids	
Combination chemotherapy	
Cardiovascular drugs	
Amiodarone	
Captopril	
Digitoxin	
Diltiazem	
Enalapril	
Methyldopa	
Nifedipine	
Reserpine	
Spirolactone	
Verapamil	
Psychoactive drugs	
Diazepam	
Haloperidol	
Phenothiazines	
Tricyclic antidepressants	
Drugs of abuse	
Alcohol	
Amphetamines	
Heroin	
Marijuana (phytoestrogens)	
Methadone	
Other	
Auranofin	
Diethylpropion	
Domperidone	
Etretinate	
Metoclopramide	
Phenytoin	
Penicillamine	
Sulindac	
Theophylline	

The association between many of the drugs listed and gynecomastia is based on case reports and therefore may not represent a true cause-and-effect relationship. From Mathur & Braunstein (1997).

testosterone through the action of 17-oxosteroid reductase, which is distributed widely in various tissues (Wilson *et al.* 1980, Braunstein 1993) (Fig. 1).

Aromatase activity is an enzymatic complex composed of the product of the CYP19 gene, aromatase cytochrome P450 (P450_{arom}), which binds C₁₉ steroid substrates and converts their A rings to a phenolic ring, and its associated flavoprotein, NADPH-cytochrome P450 reductase, present in the endoplasmic reticulum and which transfers reducing equivalents from NADPH to P450 (Simpson *et al.* 1994). The CYP19 is located on chromosome 15q21 and contains 10 exons (Chen *et al.* 1988, Toda *et al.* 1990). Regulation of P450_{arom} mRNA is tissue specific and involves alternate splicing of exon I and exon II whose expression is directed by five or more promoters (Bulun *et al.* 1993, Simpson *et al.* 1994).

Aromatase activity has been demonstrated in the placenta, ovary, testes, brain, skin fibroblasts, adipocytes, normal breast stromal cells, and fetal tissues (Simpson *et al.* 1994, Sasano *et al.* 1996, Santner *et al.* 1997). Promoter I.1 directs aromatase expression in the placenta, promoters I.3, I.4 and II in adipose tissue fibroblasts in a hormone- or cytokine-dependent fashion, promoter II in the ovary and testes, and promoter I.4 in fetal liver, intestine, brain and skin fibroblasts (Simpson *et al.* 1994).

As noted in Table 1, a number of conditions have been found to be associated with increased aromatization. Based upon steroid production rate and precursor-product studies in various conditions as well as the more recent molecular biological investigations which have defined the transcripts of P450_{arom} present in certain disease states, a functional classification of aromatase-associated gynecomastia can be developed (Table 3).

Relative or absolute increased circulating concentrations of androstenedione have been found in several conditions. Pubertal gynecomastia has been extensively studied and various pathophysiological causes have been implicated, including enhanced sensitivity of breast tissue, a transient elevation of estradiol levels at the onset of puberty, and relatively higher levels of estradiol in comparison to testosterone during the pubertal transition, since estradiol rises 3-fold from the prepubertal to adult state, while testosterone rises 30-fold, so adult or near-adult male estrogen levels may be reached before adult androgen concentrations are achieved. In addition, there is increased estrone production from androstenedione, which may be related to enhanced androstenedione production which, in turn, is related to body surface area, both of which increase during adrenarche (Hemsell *et al.* 1977, Wilson *et al.* 1980, Braunstein 1995).

Elevated production rates of androstenedione have been found in patients with feminizing adrenocortical neoplasms which would also lead to enhanced estrogen production from extraglandular aromatization (Zayed

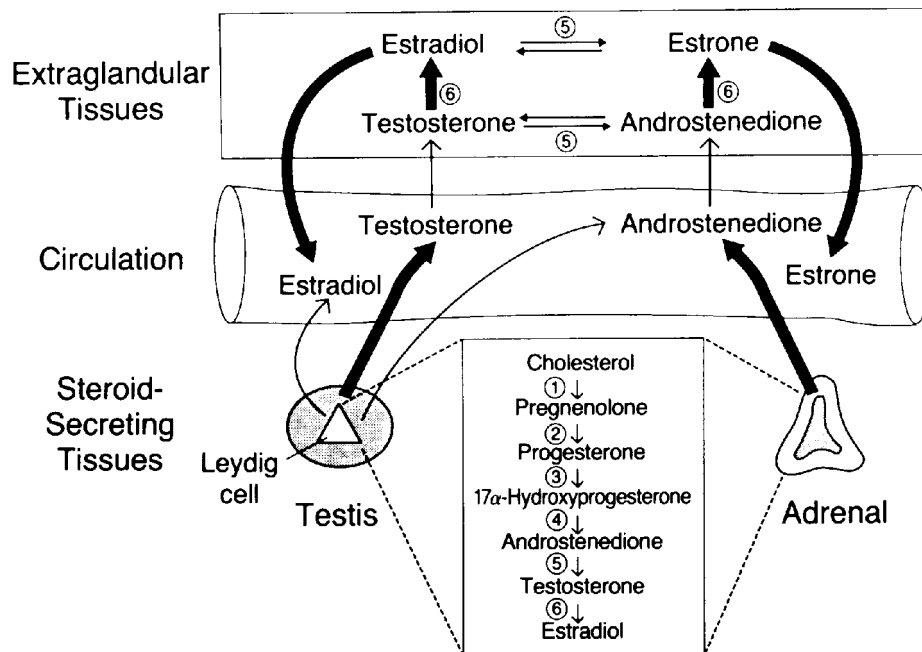


Figure 1 Glandular and peripheral origins and interrelations of testosterone, androstenedione, estrone and estradiol in males. Circled numbers denote the following enzymes: (1) cytochrome P450scc (cholesterol side-chain cleavage enzyme), (2) 3 β -hydroxysteroid dehydrogenase and Δ^5 , Δ^4 -isomerase, (3) cytochrome P450c17 (mediating 17 α -hydroxylase activity), (4) cytochrome P450c17 (mediating 17,20-lyase activity), (5) 17-oxosteroid reductase, and (6) aromatase. The thick arrows denote the major source of the hormone. From Braunstein (1993).

et al. 1994). However, this is not the only mechanism by which adrenal tumors lead to gynecomastia. Young *et al.* (1996) described a 29-year-old male with progressive bilateral gynecomastia who had plasma estrone and estradiol levels that were 10 to 20 times higher than in normal men, but whose peripheral and tumor vein plasma androstenedione was within the normal range. The adrenal tumor venous estrone level was 8-fold higher than the peripheral venous plasma level and, thus, was due to the direct secretion of estrone by the tumor. In contrast to the normal adrenal in which P450_{arom} activity is not detected, a high level was found in the tumor tissue and only the gonadal type promoter II-specific transcripts were found (Young *et al.* 1996). Therefore, feminizing adrenocortical carcinoma may be associated with gynecomastia by either excessive precursor production and/or excessive aromatase activity.

Gynecomastia is a prominent feature of 17-oxosteroid reductase deficiency. Since this enzyme catalyzes the interconversion of androstenedione to testosterone and estrone to estradiol, patients have high concentrations of androstenedione, and hence, estrone, with low levels of testosterone and estradiol (Castro-Magana *et al.* 1993).

In patients with cirrhosis, the production rate and plasma concentrations of androstenedione are increased

without an alteration in the metabolic clearance rate of the hormone. The conversion rate of androstenedione to estrone and testosterone and the conversion rate of testosterone to estrone and androstenedione are also increased, leading to elevated estradiol levels, while the plasma testosterone concentrations are decreased (Gordon *et al.* 1975, Olivo *et al.* 1975). Increased androstenedione production has also been found in thyrotoxicosis (Southren 1974).

Increased aromatase activity in which normal amounts of precursors are produced but are converted into estrogens at an enhanced rate can be due to increased activity in normal tissues, dysregulation of P450_{arom} or they may be due to mechanisms that have yet to be defined (Table 3). Epidemiological studies have clearly shown that the prevalence of gynecomastia is related to body weight, in particular the fat compartment. Niewoehner and Nuttall (1984) found a close correlation between the percentage of patients with gynecomastia and the body mass index (BMI) (Fig. 2). In addition, they noted a significant correlation ($r=0.52$, $P<0.001$) between the breast tissue diameter and BMI in 214 subjects (Fig. 3). Similarly, Georgiadis and co-workers (1994) noted that in the 954 18- to 26-year-old men they studied, the subjects with gynecomastia had significantly greater weights than

Table 3 Aromatase-associated causes of gynecomastia

I. Increased precursors	
Puberty	
Adrenal tumors	
17-oxosteroid reductase deficiency	
Liver disease	
Thyrotoxicosis	
II. Increased aromatase activity	
Increased activity in normal tissue	
Obesity	
Aging	
Aromatase dysregulation	
Familial aromatase excess syndrome	
Neoplasms	
Eutopic production	
Sertoli cell tumors	
Isolated	
Peutz-Jegher's Syndrome	
Carney complex	
Trophoblastic tumors	
Ectopic production	
Feminizing adrenocortical neoplasms	
Hepatocellular carcinoma	
?Melanoma	
Mechanism unknown	
Klinefelter's syndrome	
Idiopathic gynecomastia	
Thyrotoxicosis	
Spironolactone	

those without. Studies carried out in postmenopausal women have shown a close correlation ($r=0.74$) between body weight and extent of conversion of androstenedione to estrone (Siiteri & MacDonald 1973) (Fig. 4), and similar results were reported by Schneider *et al.* (1979) in

obese men. These latter investigators also noted a progressive increase in urinary estrogen production rate with increasing obesity (Fig. 5). Since aromatase activity has been localized to adipose tissue, both histochemically (Sasano *et al.* 1996) and through adipose tissue cDNA analysis (Simpson *et al.* 1994), it is reasonable to conclude that enhanced conversion of androstenedione to estrone and testosterone to estradiol in obesity is due to the quantitative elevation of P450_{arom} activity present in the expanded fat mass.

Aging has also been associated with an increase in conversion of androstenedione to estrone ($r=0.62$, $P<0.001$) (Siiteri & MacDonald 1973, Hemsell *et al.* 1974, Niewoehner & Nuttall 1984) (Fig. 6). This may well be related to age related DNA increase in aromatase specific activity in adipose tissue (Cleland *et al.* 1985), as well as, alterations in fat mass since after age 65 there is a decrease in body weight, height, and lean cell mass, while body fat increases (Forbes & Reina 1970, Novak 1972).

Dysregulation of P450_{arom} is seen in patients with idiopathic excessive peripheral aromatase expression or with neoplasms. The first well-described patient with the excessive peripheral aromatase syndrome was reported by Hemsell and colleagues (1977). They studied an adopted boy aged 10 years and 7 months who developed severe feminization with gynecomastia at 8 years and 7 months, associated with accelerated growth rate and bone age advancement. His androstenedione production rate was normal for a child undergoing adrenarche, but he had 50 times the normal extraglandular conversion of androstenedione to estrone and the fractional conversion of testosterone to estradiol was also 50 times greater than in normal young adult men. The estrone produced was, in turn, sulfurylated at the sites of aromatization before entering the circulation. Hence, the primary product was

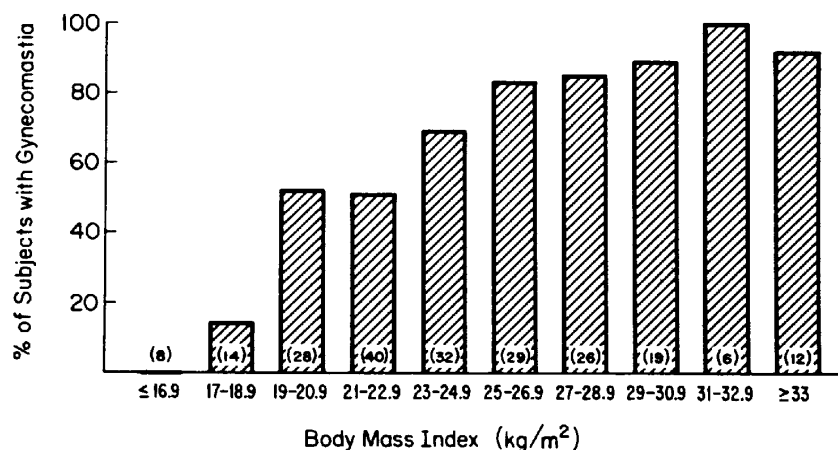


Figure 2 Correlation of gynecomastia with body mass index. From Niewoehner & Nuttall (1984).

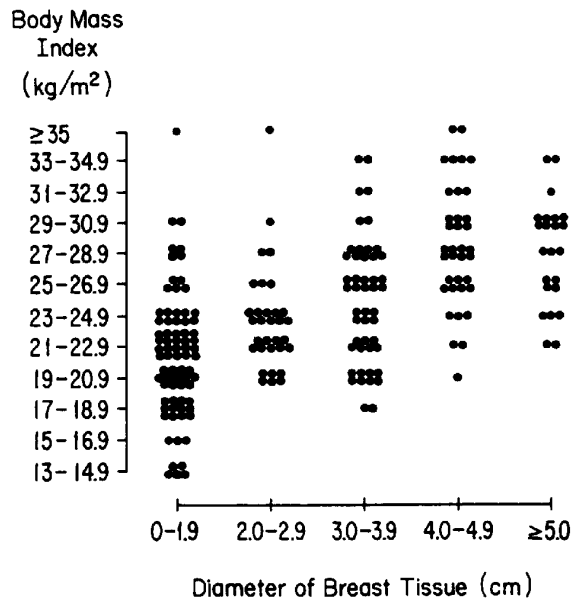


Figure 3 Correlation of breast tissue diameter with body mass index in 214 subjects. $r=0.52$, $P<0.001$. From Niewoehner & Nuttall (1984).

estrone sulfate. The authors hypothesized that the syndrome was the result of a failure in the normal decline in expression of both P450_{arom} and sulfokinase enzyme activities after birth (Hemsell *et al.* 1977). Subsequently, several families with this syndrome have been described with apparent autosomal dominant and X-linked recessive or sex-linked autosomal dominant modes of inheritance described (Berkovitz *et al.* 1985, Leiberman & Zachmann

1992, Stratakis *et al.* 1998). Males exhibit heterosexual precocity with gynecomastia, accelerated height and bone age in childhood and adolescence and shortened final adult height, while females have isosexual precocity and macromastia. Studies by Stratakis and colleagues (1998) in one family have shown that the disorder cosegregates with a polymorphism of the P450_{arom} gene and appears to be associated with the utilization of a novel exon I of the P450_{arom} cDNA. Bulun and co-workers (1997) studied a 17-year-old male with this syndrome and showed that the P450_{arom} mRNA levels in buttock and thigh adipose tissue were 14 to 21 times higher than in a normal adolescent boy. The aromatase expression was regulated by promoters I.3 and II, similar to those found in normal adipose tissue. Recently, Bulun (1998) described a male with the syndrome apparently occurring sporadically who had an inversion mutation in chromosome 15q21.1 which gave rise to a direction reversal of the promoter of an unrelated gene which caused the aberrant transcription of the P450_{arom} gene.

Dysregulation of P450_{arom} is also found in patients with large cell calcifying Sertoli cell (sex-cord) tumors of the testicle, which can occur as an isolated abnormality or in association with the autosomal dominant Peutz-Jegher's syndrome (gastrointestinal polyposis and oval, irregularly pigmented lip macules) or with the autosomal dominant Carney complex (cardiac myxomas, spotty cutaneous pigmentation, primary pigmented nodular adrenocortical disease with hypercortisolism) (Coen *et al.* 1991, Young *et al.* 1995, Berensztein *et al.* 1995, Diamond *et al.* 1996). The gonadal promoter II directs the P450_{arom} gene expression in the tumors associated with the Peutz-Jegher's syndrome (Bulun *et al.* 1993, 1997).

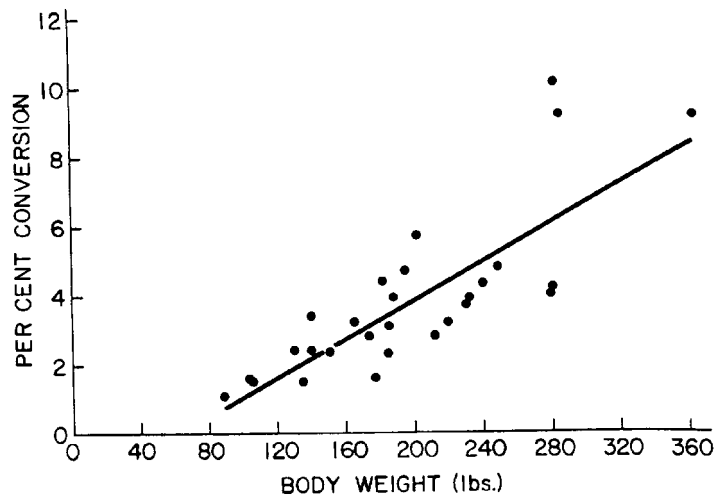


Figure 4 Correlation of extent of conversion of androstenedione to estrone with body weight in postmenopausal women ($r=0.74$). From Siiteri & MacDonald (1973).

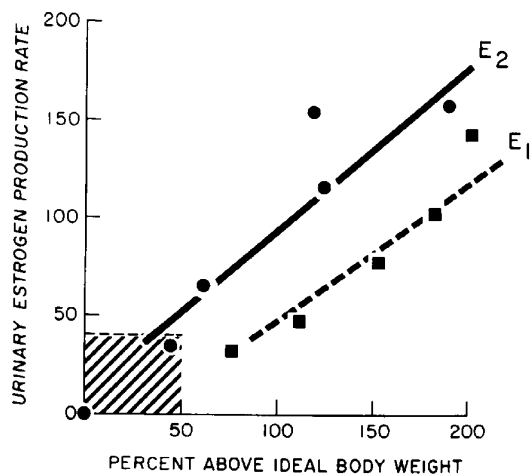


Figure 5 Urinary estradiol and estrone production rates, expressed as micrograms per day and plotted against the percentage above ideal body weight for 10 obese men. (●), estradiol (E₂) production; (■), estrone (E₁) production; (shaded area), normal range. From Schneider *et al.* (1979).

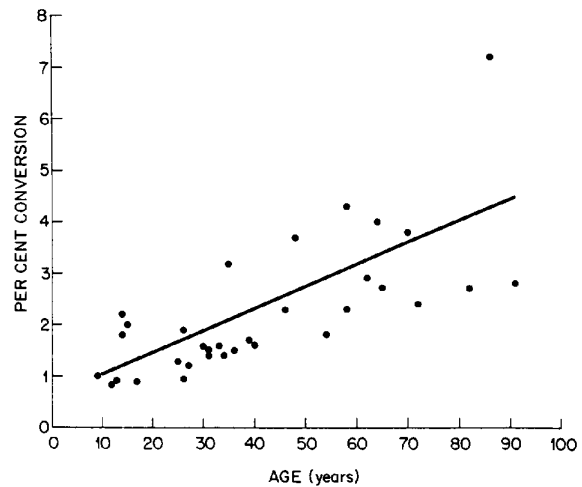


Figure 6 Correlation of the extent of conversion of androstenedione to estrone with age in males ($r=0.62$). From Siiteri & MacDonald (1973).

Testicular trophoblastic tumors are also capable of converting estrogen precursors to estrogen (MacDonald & Siiteri 1966), although the tissue-specific P450_{arom} promoter type has not been identified.

Ectopic production of aromatase refers to aromatase expression by neoplasms that use promoters that are not normally expressed by the tissue from which the tumor arose. As noted above, the gonadal promoter II has been found in association with an aromatase-expressing adrenocortical carcinoma (Young *et al.* 1996), and recently Agarwal *et al.* (1998) described a 17½-year-old male with severe gynecomastia and a large fibrolamellar hepatocellular carcinoma that exhibited high levels of P450_{arom} that was not present in the adjacent normal liver or adult liver samples. Promoters I.3 and II, rather than the normal fetal liver I.4 promoter, were used by the tumor to direct the P450_{arom} expression. Aromatase activity has also been found in some malignant melanomas (Santen *et al.* 1988). Whether the aromatase activity is responsible for the occasional patient found with gynecomastia in association with the tumor or due to the ectopic production of human chorionic gonadotropin is not known at this time (Braunstein 1991).

Finally, several conditions have been shown to be associated with increased conversion of androstenedione to estrone and/or testosterone to estradiol without the mechanism being defined. These include Klinefelter's syndrome (Wang *et al.* 1975), thyrotoxicosis (Southren *et al.* 1974, Olivo *et al.* 1975), and the use of spironolactone (Huffman & Azarnoff 1975). Bulard and

co-workers (1987) found increased aromatase activity in pubic skin fibroblasts from six patients with persistent pubertal gynecomastia and two with idiopathic gynecomastia, raising the possibility that local dysregulation of breast tissue aromatase may lead to a local estrogen to androgen imbalance.

Use of aromatase inhibitors for gynecomastia

Considering the important role that aromatase plays in the production of elevated quantities of estrogen in males with gynecomastia, it would be anticipated that aromatase inhibitors would have been a mainstay in the therapy of the disorder. However, there is relatively little information available and what published data exist concern only the early generation aromatase inhibitor, Δ¹-testolactone. Coen and colleagues (1991) treated a 5½-year-old boy with Peutz-Jehger's syndrome and prepubertal gynecomastia from an aromatase-producing sex-cord tumor with 450 mg Δ¹-testolactone given orally daily for 11 months. This led to a slight decrease in height velocity, but did not affect the advancing bone age. On the medication there was an increase in serum levels of testosterone and androstenedione, but no alteration in serum estradiol or estrone levels. Lieberman & Zachmann (1992) described a family in whom 5 of 10 members had gynecomastia, early growth, advanced bone age, and short final stature, presumably due to excessive aromatization of adrenal precursors. A 13-year-old male member of that family

with severe gynecomastia was treated with 450 mg/day Δ^1 -testolactone for 6 months with 'moderate regression of the gynecomastia'. However, after 6 months he escaped from the effects of the drug both clinically and biochemically. During the first three months on Δ^1 -testolactone, the serum levels of testosterone increased twofold, the androstenedione levels by tenfold, and estradiol was decreased by 50% without a change in estrone levels, but the levels returned to baseline by 6 months. Stratakis *et al.* (1998) treated a brother and sister, aged 10 and 7½ years respectively, who suffered from the excessive peripheral aromatase syndrome, with a combination of gonadotropin releasing hormone analog and Δ^1 -testolactone (40 mg/kg/day orally). The combination decreased pubertal progression, skeletal age, estrone and estradiol levels, but the authors did not comment on the effects on breast development, other than to state that the boy was treated with bilateral reductive mammoplasties.

Zachmann and colleagues (1986) treated 22 boys with pubertal gynecomastia with 450 mg Δ^1 -testolactone by mouth daily for two to six months without side effects. Before therapy, the mean breast diameter was 4.4 cm (median=3.8, $n=22$). After 2 months of therapy, the mean diameter had decreased to 3.3 cm (median=3.0, $n=22$), after 4 months to a mean of 3.2 cm (median=2.8, $n=14$), and after 6 months to a mean of 1.7 cm (median=1.5, $n=4$). They noted that several weeks before the reduction in the breast size there was a softening of the glandular tissue. During therapy, pubic hair and testicular volume increased normally. While on therapy, there were significant increases in serum testosterone (to a maximum of 1.5 times baseline), androstenedione (13.5 times baseline), dehydroepiandrosterone (1.2 times baseline), estrone (1.6 times baseline) and follicle-stimulating hormone (1.3 times baseline), but no significant change in estradiol, luteinizing hormone, or prolactin concentrations. These authors did not note how many of their patients had complete disappearance of the gynecomastia or how many were satisfied with the results.

In an unpublished, prospective study of 4 patients with idiopathic gynecomastia of long standing duration, we gave escalating doses of Δ^1 -testolactone at doses of 150 mg for 2 months, then 300 mg for 2 months, and finally 750 mg for 2 months. On this regimen, the mean breast size decreased 28% at 2 months, 32% at 4 months, and 47% at 6 months ($P<0.05$), results that are similar to those found by Zachmann *et al.* (1986). However, of the 8 breasts in the 4 men, only one had complete disappearance of the gynecomastia, indicating that although breast size reduction may be possible with this drug, complete disappearance may not occur.

To date there have been no published studies on the use of newer generation aromatase inhibitors such as

letrozole, anastrozole, fadrozole, fromestane or exemestane in the treatment of gynecomastia, although at a recent conference, Bulun (1998) presented information on three patients with gynecomastia associated with aromatase excess who were successfully treated with anastrozole. However, when using these drugs or any other type of medical therapy in any patient with gynecomastia, it is important to remember that drugs would probably be most effective during the early, florid (painful) phase of gynecomastia that is present during the first 6 months after the onset of the disorder, during which there is ductal proliferation and epithelial and stromal hyperplasia. After the gynecomastia has been present for over a year, the proliferative phase is replaced by a fibrotic stage in which there is increased stromal hyalinization and dilatation of the ducts - a stage during which medications are unlikely to be beneficial (Nicolis *et al.* 1971, Bannayan & Hajdu 1972). Also, when studying medications, one must keep in mind the high rate of spontaneous regression of the disease (Braunstein 1993). Therefore, ideally all drug trials should be placebo controlled.

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