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 Δ1-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.

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 gynecomastia\(^1\)

<table>
<thead>
<tr>
<th>Physiological</th>
<th>Pathological</th>
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<tbody>
<tr>
<td>Neonatal</td>
<td>Increased serum estrogen</td>
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<tr>
<td>Pubertal</td>
<td>Increased aromatization (peripherally or glandular)</td>
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<td>Aging</td>
<td>Sertoli cell tumors</td>
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<td>Sex cord tumors</td>
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<td>Testicular germ cell tumors</td>
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<td>Leydig cell tumors</td>
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<td>Adrenocortical tumors</td>
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<td>Hermaphroditism</td>
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<td>Obesity</td>
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<td>Hyperthyroidism</td>
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<td>Liver disease</td>
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<td>Testicular feminization</td>
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<td>Refeeding after starvation</td>
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<td>Primary aromatase excess</td>
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<td>Displacement of estrogen from SHBG</td>
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<td>Spironolactone</td>
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<td>Ketoconazole</td>
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<td>Decreased estrogen metabolism</td>
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<td>Cirrhosis (?)</td>
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<td>Exogenous sources</td>
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<td>Topical estrogen creams and lotions</td>
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<td>Ingestion of estrogen</td>
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<td>Embalming fluid</td>
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<td>Eutopic hCG production</td>
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<td>Choriocarcinoma</td>
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<td></td>
<td>Ectopic hCG production</td>
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<td>Lung carcinoma</td>
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<td>Liver carcinoma</td>
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<td>Kidney carcinoma</td>
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<td>Gastric carcinoma</td>
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<td>Decreased testosterone synthesis</td>
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<td>Primary gonadal failure, congenital</td>
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<td>Anorchia</td>
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<td>Klinefelter's syndrome</td>
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<td>Hermaphroditism</td>
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<td>Hereditary defects in testosterone synthesis</td>
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<td>Primary gonadal failure, acquired</td>
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<td>Viral orchitis</td>
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<td>Castration</td>
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<td>Granulomatous disease (including leprosy)</td>
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<td>Testicular failure due to hypothalamic and/or pituitary disease</td>
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<td>Androgen resistance due to androgen receptor defects</td>
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<td>Other</td>
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<td>Chronic renal failure</td>
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<td>Chronic illness</td>
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<td></td>
<td>HIV</td>
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<td>Enhanced breast tissue sensitivity</td>
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\(^1\)The various disorders are listed under their primary pathophysiological mechanism. Modified 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 (P450arom), 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 P450arom 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 P450arom present in certain disease states, a functional classification of aromatase-associated gynecomastia can be developed (Table 3).

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).

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     |  |  |
| Alkylation agents                 |  |  |
| Methotrexate                      |  |  |
| Vinca alkaloids                   |  |  |
| Combination chemotherapy          |  |  |
| Cardiovascular drugs              |  |  |
| Amiodarone                        |  |  |
| Captopril                         |  |  |
| Digoxin                           |  |  |
| Diltiazem                         |  |  |
| Enalapril                         |  |  |
| Methyldopa                        |  |  |
| Nifedipine                        |  |  |
| Reserpine                         |  |  |
| Spironolactone                    |  |  |
| Verapamil                          |  |  |
| Psychoactive drugs                |  |  |
| Diazepam                          |  |  |
| Haloperidol                       |  |  |
| Phenothiazines                    |  |  |
| Tricyclic antidepressants         |  |  |
| Drugs of abuse                    |  |  |
| Alcohol                           |  |  |
| Amphetamines                      |  |  |
| Heroin                            |  |  |
| Marijuana (phytoestrogens)        |  |  |
| Methadone                         |  |  |
| Other                             |  |  |
| Auranofin                         |  |  |
| Diethylpropion                    |  |  |
| Domperidone                       |  |  |
| Eretinate                         |  |  |
| 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).
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 P450arom 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, Georgiatis 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
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

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**Table 3** Aromatase-associated causes of gynecomastia

<table>
<thead>
<tr>
<th>I. Increased precursors</th>
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<tbody>
<tr>
<td>Puberty</td>
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<tr>
<td>Adrenal tumors</td>
</tr>
<tr>
<td>17-oxosteroid reductase deficiency</td>
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<tr>
<td>Liver disease</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Increased aromatase activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased activity in normal tissue</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Aging</td>
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<tr>
<td>Aromatase dysregulation</td>
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<tr>
<td>Familial aromatase excess syndrome</td>
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<tr>
<td>Neoplasms</td>
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<tr>
<td>Eutopic production</td>
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<tr>
<td>Sertoli cell tumors</td>
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<tr>
<td>Isolated</td>
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<tr>
<td>Peutz-Jegher's Syndrome</td>
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<td>Carney complex</td>
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<tr>
<td>Trophoblastic tumors</td>
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<tr>
<td>Ectopic production</td>
</tr>
<tr>
<td>Feminizing adrenocortical neoplasms</td>
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<tr>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>?Melanoma</td>
</tr>
<tr>
<td>Mechanism unknown</td>
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<tr>
<td>Klinefelter's syndrome</td>
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<tr>
<td>Idiopathic gynecomastia</td>
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<tr>
<td>Thyrotoxicosis</td>
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<tr>
<td>Spironolactone</td>
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</tbody>
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![Figure 2](https://via-free-access.bioscientifica.com/)  
**Figure 2** Correlation of gynecomastia with body mass index. 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 I.2 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).
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 P450arom 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 P450arom 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 (Southern 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 Δ1-1-testolactone for 6 months with ‘moderate regression of the gynaecomastia’. However, after 6 months he escaped from the effects of the drug both clinically and biochemically. During the first three months on Δ1-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 Δ1-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 Δ1-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.

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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