

GYNECOMASTIA

Pages with reference to book, From 100 To 101

Enlargement of male breast occurs as either a discrete, palpable subareolar plate of tissue or a more diffuse mass resembling the surrounding fat. Histologic appearance depends on the duration of the process; shortly after onset, there are prominent ductules embedded in loose connective tissue whereas after several years there are faint ductular structures in a dense, hyalinized and fibrous stroma (Nicolis et al., 1971). Palpable, asymptomatic gynecomastia is frequent in normal men. In 306 military reservists gynecomastia was detected in 36% with a modest increase in prevalence with advancing age (Nuttall, 1979). Histologic evidence of gynecomastia was described in 40% of 447 men examined at autopsy by Williams in 1963. There is strong evidence of a trophic and stimulatory effect of oestrogens on mammary epithelial tissues (Poinsett, 1977) and less support for an inhibitory action of androgens (Turkington, 1967). The condition may result from an alteration in the balance between these two influences. Defective androgen receptors, e.g., in testicular feminization and related syndromes, may also contribute through loss of inhibitory androgenic influences on breast development (MacDonald et al., 1979). Role of prolactin in the genesis of gynecomastia is not clear. Serum prolactin is normal in most patients with gynecomastia (Turkington, 1972) and vice versa. Prolactin may occasionally contribute through indirect effects on gonadal and possibly adrenal function leading to alterations in circulating oestrogens/androgens ratio (Frank et al., 1978).

Although gynecomastia occurs more commonly in primary testicular failure (Paulsen, 1974), it may be seen in secondary (pituitary-hypothalamic) hypogonadism (Hamilton et al., 1973). Serum oestrogens are usually normal or slightly elevated and testosterone levels are low or low-normal with increased oestrogen/androgen ratio. Disease occurs in majority of patients with Klinefelter's syndrome (Paulsen et al., 1968) and second X-Chromosome may predispose them in addition to the above mentioned mechanisms-involved in primary hypogonadism. Also it can be responsible for increase of male breast cancer. These patients require periodic examinations and should learn selfexamination too.

Feminizing adrenal tumours (mostly malignant) are rare, they may directly secrete oestrogens (Gabilove et al., 1965), or the oestrogen precursors (e.g. androstenedione). Half of the patients with these cancers have a palpable abdominal mass at the time of diagnosis; 2/3 have elevations of urinary 17-Ketosteroids (Gabilove et al., 1965). Leydig cell tumors of the testis (mostly benign) are also rare. Neoplastic Leydig cells produce excessive amounts of oestradiol (Gabilove et al., 1975) which suppress the pituitary secretion of luteinizing hormone leading to deficient androgen production from normal Leydig cells. A few tumours e.g. hepatoma (Kew et al., 1977) may produce oestrogen by biotransformation of its precursors. Urinary pregnancy tests are not very sensitive and serum HGG radioimmunoassay is recommended for the diagnosis. Gynaecomastia is relatively uncommon in pituitary tumors and when occurs is due to mechanisms involved in secondary hypogonadism.

War prisoners were observed to have developed gynaecomastia with tenderness on refeeding which regressed within a few months to 2 years (Jacobs, 1948). Similar phenomenon may occur during convalescence from any prolonged disease with notable loss and gain in weight. Term "refeeding gynaecomastia" is given to it and it is considered analogous to a "second puberty". Gynaecomastia commonly develops in patients with renal failure within several weeks or months after the initiation of haemodialysis which usually regresses with a year (Schmitt et al., 1968). Refeeding gynaecomastia, through patients well being and appetite improvement after initiation of dialysis, may have a role although a variety of hormonal changes have also been described in these patients e.g., low serum testosterone, elevated luteinizing hormone, normal or elevated serum oestrogens, an elevated oestrogen/androgen ratio and a modest elevation of serum prolactin (Morley and Melmed, 1979).

Several mechanisms may operate to produce relative oestrogen excess in gynaecomastia with hepatic

disorders especially cirrhosis. Alcohol (in alcoholic cirrhosis) may act on hypothalamic-pituitary system to lower testosterone levels. In cirrhotics, there is excessive production of oestrogens from circulating precursors and serum levels of sex-steroid binding globulins are also elevated with a reduction in circulating free testosterone whereas clearance of Oestrogens does not appear to be altered. Chopra and Tulchinsky (1974) revealed that 10-40% of men with hyperthyroidism have gynaecomastia usually reversible with euthyroid state and attributed it to increase in both serum testosterone and oestradiol levels due to increased circulating sex-steroid binding globulin but free testosterone, remains normal whereas free oestradiol is elevated.

Drug-induced gynaecomastia is seen in therapy with oestrogens by direct stimulation of breast (Poulsen, 1977) and with testosterone (Paulsen, 1974) possibly through conversion to oestrogens or through additional mechanisms (e.g. methyl-testosterone).

Spirolactone and cimetidine act by competitive displacement of dihydrotestosterone from its intracellular receptor (Ritka et al., 1977; Winters et al., 1979). Digitalis and I.N.H. presumably act by refeeding mechanisms in debilitated men with C.C.F. and Tuberculosis respectively. Several central nervous system drugs (Pheno-thiazines, Marijuana, Diazepam, Tricyclic anti-depressants, Amphetamines, Diethylpropion and Reserpine) may cause gynaecomastia, many of them by raising serum prolactin and inducing secondary hypogonadism. Cytotoxic drugs (Busulphan, Vincristine, Nitrosoureas, and their combinations) act by damaging the testes and producing primary hypogonadism (Glass and Berenberg, 1979). Drug-induced gynaecomastia is diagnosed by its association with recent use of any of these agents and is usually reversible (at least partially) on discontinuation of drug. Male breast cancer, 0.2% of all cancers in male: should be differentiated from benign gynaecomastia, sometimes employing biopsy as a definitive diagnostic procedure in suspicious cases. Patients of Klinefelter's syndrome with gynaecomastia are at special risk.

Investigation of these patients should include exclusion of breast cancer by clinical examination; duration of gynaecomastia, history of associated pain and tenderness (recent and symptomatic cases are more suspicious), drug history, altered physiology or systemic disease, recent weight loss and gain and examination of the testes for neoplasms. If cause is not obvious, screening tests e.g., serum HCG, dehydroepiandrosterone sulphate, oestradiol, prolactin, testosterone, gonadotropins and urinary 17-Ketosteroids should be performed to detect any tumour. Some of the cases remain idiopathic.

Gynaecomastia of puberty, refeeding or haemodialysis is usually transient and only reassurance is required. Correction of underlying cause (hyperthyroidism or tumour) or withdrawal of a drug may cause regression in others. Testosterone, with some reservation, has been used in some patients usually with hypogonadism. Encouraging preliminary results have been reported with antioestrogens (Clomiphene and tamoxifen) and danazol (Jefferys, 1979; Stepanas et al., 1977; Buckle, 1977). Effects of long term treatment with these agents are still to be evaluated.

Tariq Ahmad Mian

PMRC Research Centre, Jinnah Postgraduate Medical Centre, Karachi.

References

1. Buckle, R. (1977) Studies on the treatment of gynaecomastia with danazol (Danol). *J. Int. Med. Res.*, 5 Suppl: 3:114.
2. Chopra, I.J. and Tulchinsky, D. (1974) Status of Oestrogen-androgen balance in hyperthyroid men with Graves disease. *J. Clin. Endocrinol. Metab.*, 38:269.
3. Frank, S., Jacobs, H.S., Martin, N., Nabarro, J.D.N. (1978) Hyperprolactinaemia and impotence. *Clin. Endocrinol. (Oxf)*, 8:277.
4. Gabilove, J.L., Sharma, D.C., Weitz, H.H. and Dorman, R.I. (1965) Feminizing adrenocortical

- tumours in the male; a review of 52 cases including a case report. *Medicine (Baltimore)*, 44:37.
5. Gabrilove, J.L., Nicolis, G.L., Mitty, H.A. and Sohval, A.R. (1975) Feminizing interstitial cell tumour of the testis personal observations and a review of the literature. *Cancer*, 35:1184.
 6. Glass, A.R. and Berenberg, J. (1979) Gynecomastia after chemotherapy for lymphoma. *Arch. Intern. Med.*, 139:1048.
 7. Hamilton, C.R. Jr., Henkin, R.I., Weir, G. and Kliman, B. (1973) Olfactory status and response to Clomiphene in male Gonadotropin deficiency. *Ann. Intern. Med.*, 78:47.
 8. Jacobs, E.C. (1948) Effect of starvation of sex hormones in the male. *J. Clin. Endocrinol. Metab.*, 8:227.
 9. Jefferys, D.B. (1979) Painful gynecomastia treated with tamoxifen. *Br. Med. J.*, 1:1119.
 10. Kew, M.C., Kirschner, M.A., Abrahams, G.F. and Katz, M. (1977) Mechanism of feminization in primary liver cancer. *N. Engl. J. Med.*, 296:1084.
 11. MacDonald, P.C., Madden, J.D., Brenner, P.F., Wilson, J.D. and Siiteri, P.K. (1979) Origin of Oestrogen in normal men and in women with testicular feminization. *J. Clin. Endocrinol. Metab.*, 49:905.
 12. Nicolis, G.L., Modlinger, R.S. and Gabrilove, J.L. (1971) A study of the histopathology of human gynecomastia. *J. Clin. Endocrinol. Metab.*, 32:173.
 13. Nuttall, F.Q. (1979) Gynecomastia as a physical finding in normal men. *J. Clin. Endocrinol. Metab.*, 48:338.
 14. Paulsen, C.A., Gordon, D.L., Carpenter, R.W., Gandy, H.M. and Drucker, W.D. (1968) Klinefelter's syndrome and its variants; a hormonal and chromosomal study. *Recent Prog. Horm. Res.*, 24:321.
 15. Paulsen, C.A. The testes, in *textbook of endocrinology*. Edited by Robert H. Williams. 5th ed. Philadelphia, Saunders, 1974, p. 358.
 16. Poulsen, H.S. (1977) Demonstration of hormonal sensitivity in gynecomastic tissue by thymidine incorporation in vitro. *Acta Pathol. Microbiol (Scand.)*, 85:19.
 17. Rifka, S.M., Pita, J.C., Vigersky, R.A., Wilson, Y.A. and Loriaux, D.L. (1978) Interaction of digitalis and spirino-lactone with human sex steroid receptors. *J. Clin. Endocrinol. Metab.*, 46:338.
 18. Schmitt, G.W., Shehadeh, I. and Sawtn, C.T. (1968) Transient gynecomastia in chronic renal failure during chronic intermittent haemodialysis. *Ann. Intern. Med.*, 69:73.
 19. Stepanas, A.V., Burnet, R.B., Harding, P.E. and Wise, P.H. (1977) Clomiphene in the treatment of pubertal-adolescent gynecomastia; a preliminary report. *J. Pediatr.*, 90:651.
 20. Turkington, R.W. and Topper, Y.J. (1967) Androgen inhibition of mammary gland differentiation in vitro. *Endocrinology*, 80:329.
 21. Turkington, R.W. (1972) Serum prolactin levels in patients with gynecomastia. *J. Clin. Endocrinol. Metab.*, 34:62.
 22. Williams, M.J. (1963) Gynecomastia its incidence, recognition and host characterization in 447 autopsy cases. *Am. J. Med.*, 34:103.
 23. Winters, S.J., Banks, J.L. and Loriaux, D.L. (1979) Cimetidine is an antiandrogen in the rat. *Gastroenterology*, 76:504.