Medical Grand Rounds

Parkland Memorial Hospital

September 8, 1977

GYNECOMASTIA

I. General Review

II. Embryology of the Breast

III. Endocrinology of Breast Development

IV. Regulation of Testosterone and Estrogen Production in Men

V. Histopathology

VI. Classification

VII. Diagnostic Workup

VIII. Treatment

VI. Classification of Gynecomastia

A. Physiological

1. Newborn

2. Adolescence

3. Aging

B. Pathological

1. Testicular Deficiency (Diminished testosterone synthesis or action with or without elevated testicular synthesis of estradiol)

a. Primary
   1.) Congenital Anorchia
   2.) Klinefelter Syndrome
   3.) Androgen Resistance (Testicular feminization and Reifenstein syndrome)
   4.) Defects in Testosterone Synthesis

b. Secondary
   1.) Viral Orchitis
   2.) Trauma
   3.) Castration
   4.) Neurological Disease
   5.) Granulomatous Disease
   6.) Renal Failure

2. Increased Estrogen Production

a. Testicular (Testicular tumors and bronchogenic carcinoma)

b. Adrenal Estrogen Production
   1.) Feminizing Tumors
   2.) Androgenital Syndrome

c. Peripheral Estrogen Production
   1.) Idiopathic
   2.) Liver Disease
       Starvation and Refeeding
   3.) Thyrotoxicosis

3. Drugs

a. Inhibitors of Testosterone Synthesis and Action (Cyproterone, flutamide, spironolactone)

b. Estrogens (Stilbestrol, birth control pills, digitalis, marijuana, heroin)

c. Gonadotropins

c. Unknown Mechanisms (Cyproheptadine, busulphan, ethionamide, isoniazid, tricyclic antidepressants, androgens)

Enlargement of the male breast is not a disease but rather a symptomatic manifestation of any of several underlying disturbances in steroid hormone physiology. For the past 15 years my colleagues in the Department of Obstetrics and Gynecology have been investigating the pathogenesis of gynecomastia. During this time considerable insight has been obtained into normal androgen and estrogen dynamics and into the mechanisms by which these hormones exert their actions in cells. Six years ago at these rounds (9-23-71) I gave a progress report on these studies in which we proposed a new physiological classification of the various etiologies. Since that time we have gained additional insight into the causes of the disorder in some disease states, and a great deal of work has been published on various aspects of the problem from other laboratories. I propose this morning to summarize our current stage of understanding about the pathogenesis of gynecomastia.

I. GENERAL REVIEWS

1. Treves, N. Gynecomastia, The origins of mammary swelling in the male: an analysis of 406 patients with breast hypertrophy, 525 with testicular tumors, and 13 with adrenal neoplasms. Cancer 11:1083-1102, 1958.

2. Hall, P.F. Gynecomastia. Monograph of the Federal Council of the British Medical Association in Australia, Number 2. Australasia Medical Pub. Co., New South Wales, 1959.

3. Cardiano, C., G. Ninfo, G. Gayni, and A. Ottolenghi, Gynecomastia. Statistical and clinical findings on 203 observations. Int. Surgery 55:131, 1971.

These references summarize the cumulative clinical experience in some 2000 cases of gynecomastia and are of value only as catalogues of the various associated disease states. The bulk of clinical experience was gained prior to the development of quantitative endocrine techniques, and it is not known in the vast majority of cases whether other drugs were being taken, whether liver function tests were normal, or whether some underlying endocrinopathy was also present. Therefore, it is not possible to deduce reliable information as to the frequency of underlying endocrinological abnormalities in the various associated diseases.

II. EMBRYOLOGY OF THE BREAST

4. Raynaud, A. Morphogenesis of the mammary gland. In Milk: The Mammary Gland and Its Secretions, S.K. Kon and H.T. Cowie, Eds. New York, Academic Press, 1961, Vol. 1, pp. 3-46.

5. Kratochevil, K. In vitro analysis of the hormonal basis for the sexual dimorphism in the embryonic development of the mouse mammary gland. J. Embryol. Exp. Morph. 25:141-153, 1971.

6. Kratochevil, K. and P. Schwartz. Tissue interaction in androgen response of embryonic mammary rudiment of the mouse: identification of the target tissue for testosterone. Proc. Nat. Acad. Aci. USA 73:4041-4044, 1976.

7. Pfaltz, C.R. Das embryonale und postnatale Verhalten den Mannlichen Brustdruse beim Menschen. II. Das mammanorgan in Kindes-, Junglings-, Mannes-, und Greisenalten. Acta Anat. 8:293-328, 1949.

Although the embryogenesis of the human breast is fundamentally the same as in other species, in man the mammary line (well developed in the 7 mm embryo) shortens and condenses to give rise to only one functional mammary bud on each side. Between 20 and 30 mm the epithelial bud assumes a globular shape, and the breast is well differentiated by the end of the second month of intrauterine life. Little change occurs between the second and fifth months, but during the fifth month (120 to 150 mm) both the nipple and the secondary epithelial buds develop. During the remainder of embryonic life ductular proliferation continues so that by the time of birth 15-25 glands are present, each of which connects to the exterior (4). There is no evidence that the differentiation process of the breast proper is under endocrine control, but sexual dimorphism in the embryogenesis of the excretory duct system has been demonstrated in several species. In the male rodent the excretory ducts tend to regress during the latter phases of embryogenesis (as a result of testicular androgen secretion), and as a consequence the breast proper is left as an isolated island in the subcutaneous tissue (4-6). However, such dimorphism has never been documented to take place in the human embryo, and there does not appear to be any clear cut histological or functional difference between the breasts in children of the two sexes prior to the onset of puberty (7).

IIII. ENDOCRINOLOGY OF BREAST DEVELOPMENT

8. Cowie, H.T. and S.J. Folley. The mammary gland and lactation. In Sex and Internal Secretions. Second Edition, Baltimore, The Williams and Wilkins Co., 1961, p. 590.

9. Turkington, R.W. Hormone-dependent differentiation of the mammary gland. Research in Reproduction 2:2, 1970.

10. Meites, J. Control of mammary growth and lactation. In Neuroendocrinology, Vol. 1., L. Martini and W.F. Ganong, Eds. New York, Academic Press, 1961, p.669.

11. Lyon, W.R., C.H. Li, and R.F. Johnson. The hormonal control of mammary growth and lactation. In Recent Progress in Hormone Research, 14:219, 1958.

At puberty there ensues a profound sexual dimorphism in breast development, and in virtually all species estradiol is responsible for the growth, division and elongation of the tubular duct system of the female breast. In men, the percutaneous injection of estrogen into the breast directly or the administration of estrogens parenterally are quite effective in this regard. To produce true alveolar development at the ends of the ducts however, the synergistic action of progesterone is required; usually an estrogen:progesterone ratio of 1:20-1:100 is optimal. In the normal adult man no breast tissue can be palpated. Remnants of a duct system can be seen histologically, but the lining cells are atrophic.

The formation of milk in the differentiated breast is one of the most

complex endocrinological events known, requiring (in addition to estradiol and progesterone) insulin, growth hormone, hydrocortisone, prolactin or placental lactogen, and an epithelial growth factor. The complexity of this system probably explains why milk secretion by the male breast is unusual even when the breasts reach enormous size; it usually occurs only when estrogen and prolactin are both elevated in men.

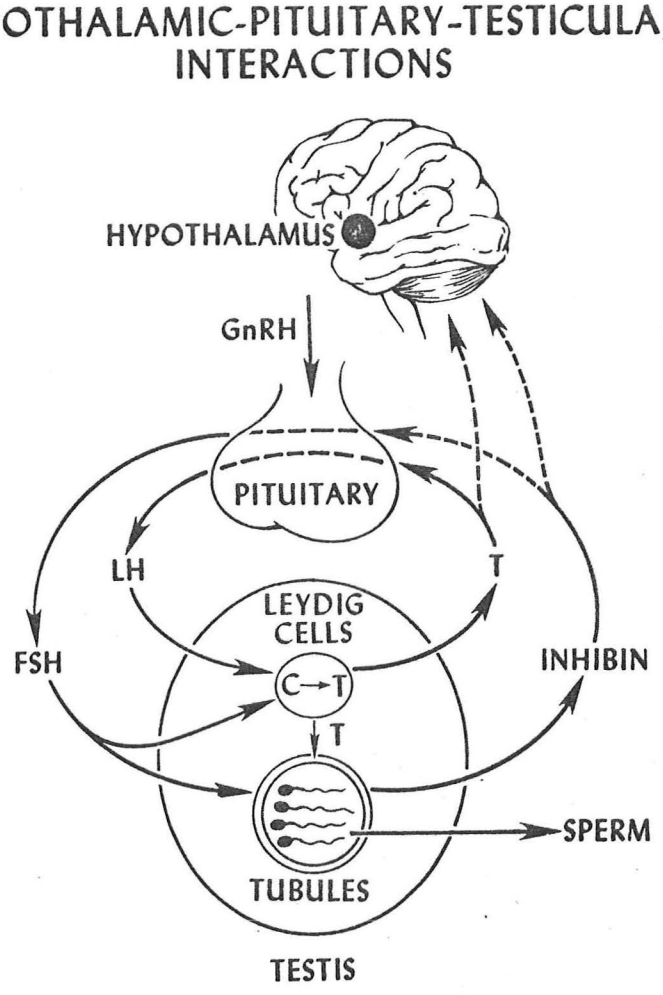
IV. REGULATION OF TESTOSTERONE AND ESTROGEN PRODUCTION IN MEN

12. Caminos-Torres, R., L. Ma and P.J. Synder. Testosterone-induced inhibition of the LH and FSH responses to gonadotropin-releasing hormone occurs slowly. J. Clin. Endocrinol Metab. 44:1142, 1977.

13. Santen, R.J. Is aromatization of testosterone to estradiol required for inhibition of luteininzing hormone secretion in men? J. Clin. Invest. 56:1555, 1975.

14. Stewart-Bently, M., W. Odell and R. Horton. The feedback control of luteininzing hormone in normal adult men. J. Clin. Endocrinol. Metab. 38:545, 1974.

FIGURE 1



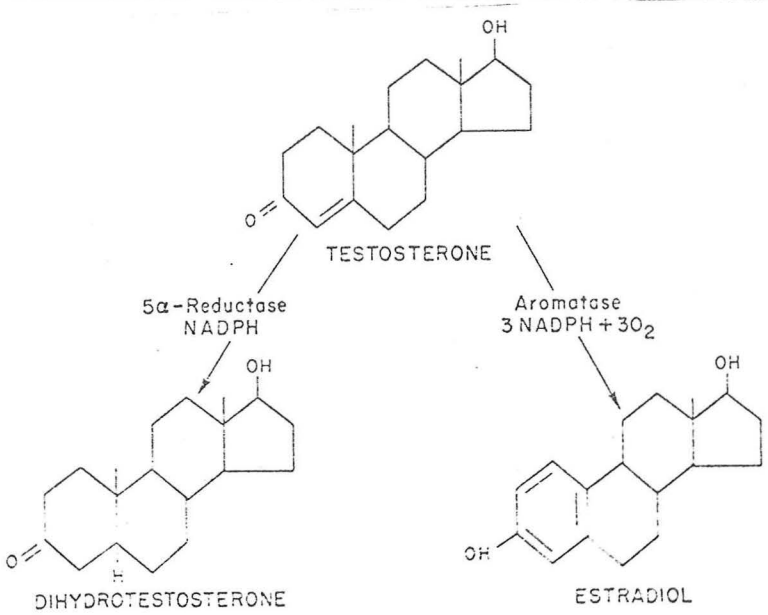
A basic knowledge of androgen physiology is essential to understanding estrogen physiology in normal men. Testosterone secretion by the testis is regulated largely by luteinizing hormone (LH) from the pituitary. Follicle stimulating hormone (FSH) may also augment testosterone secretion, possibly by regulating the number of LH receptors on the plasma membrane of the Leydig cell. Testosterone feeds back on the pituitary to alter the sensitivity of the gland to the hypothalamic releasing hormone GnRH. The molecular mechanism by which this negative feedback of testosterone on gonadotropin production is accomplished is believed (on the basis of studies of subjects with single gene defects) to be identical to that by which the hormone acts in other target cells: androgen combines with cytoplasmic receptor to form a hormone-receptor complex that diffuses into the nucleus and activates specific genes. Although enzymes that convert testosterone to estrogen and to dihydrotestosterone can be demonstrated in the pituitary, it is likely testosterone itself that regulates gonadotropin secretion. Whether testosterone also acts at the hypothalamus to regulate the rate of GnRH secretion is not clear. Under ordinary circumstances LH secretion is exquisitely sensitive to the feedback effects of testosterone with complete suppression demonstrable following the administration of exogenous androgen that approximates the normal daily secretion of the testis in the normal man (4-10 mg). However, chronic elevation of LH secretion (as in gonadal deficiency states such as the Klinefelter syndrome) renders the pituitary less sensitive to negative feedback control by exogenously administered androgens.

15. Siiteri, P.K. and P.C. MacDonald. Role of extraglandular estrogen in human endocrinology. In Handbook of Physiology, Section 7: Endocrinology, Vol. II, Female Reproductive System, Part 1, R.O. Greep and E.B. Astwood, Section eds. Washington, D.C, American Physiological Society, pp. 615-629.

16. Wilson, J.D. Metabolism of testicular androgens. In Handbook of Physiology, Section 7: Endocrinology, Vol. V, Male Reproductive System, R.O. Greep and E.B. Astwood, Section eds. Washington, D.C., American Physiological Society, 1975, p. 491.

FIGURE 2

CIRCULATING TESTOSTERONE SERVES AS A PROHORMONE



Testosterone serves as a circulating precursor or prohormone for the formation of two other types of active hormones which in turn mediate many of the physiological processes involved in androgen action. On the one hand, testosterone can undergo 5α-reduction to dihydrotestosterone that is thought to perform many of the differentiative, growth and functional actions involved in male sexual differentiation and virilization. On the other hand, circulating androgens are aromatized in the peripheral tissues of both sexes to estrogens. Thus, the physiological consequences of circulating testosterone represent the sum total of the combined effects of testosterone itself plus that of estrogen and dihydrotestosterone. For the purposes of this discussion we will assume that the active androgens (testosterone and dihydrotestosterone) act to virilize the male and that the important estrogen (estradiol) acts principally in opposition to androgens to feminize.

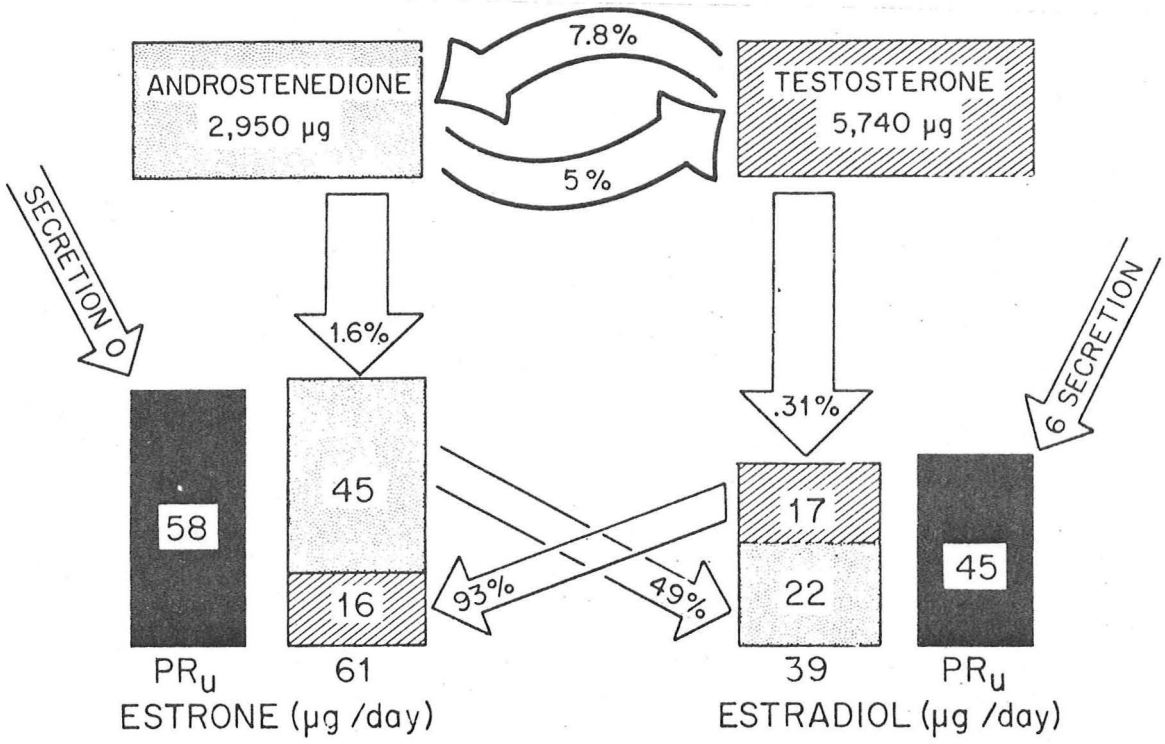
17. Kelch, R.P., M.R. Jenner, R. Weinstein, S.L. Kaplan, and M.M. Grumbach. Estradiol and testosterone secretion by human, simian and canine testes in males with hypogonadism and in male pseudohermaphrodites with the feminizing testis syndrome. J. Clin. Invest. 51:824, 1972.

18. Weinstein, R.L., R.P. Kelch, M.R. Jenner, S.L. Kaplan and M. M. Grumbach. Secretion of unconjugated androgens and estrogens by the normal and abnormal human testis before and after human chorionic gonadotropin. J. Clin. Invest. 53:1-6, 1974.

See also Reference 15.

FIGURE 3

ESTROGEN AND ANDROGEN PRODUCTION IN FOUR NORMAL YOUNG MEN (15)



As measured by isotope dilution techniques urinary production rates for estrone and estradiol in four normal men averaged 58 and 45 μg/day. All the estrone and all but about 15% of the estradiol produced each day could be accounted for by the peripheral conversion from androstenedione and testosterone. Thus, in normal men only about 6 μg per day of estradiol is secreted directly into the circulation by the testes (15). Kelch et al. (17) and Weinstein et al. (18) reached identical conclusions as the result of studies of A-V differences in hormonal content across the testes under a variety of conditions. However, when pharmacological amounts of chorionic gonadotropins are given to normal men, direct secretion of estradiol by the stimulated testis increases in proportion to the enhancement of testosterone secretion itself (18). This finding presumably explains why estradiol secretion is usually elevated when plasma LH is elevated (Klinefelter's syndrome, testicular feminization, etc.). Thus, testicular secretion of estradiol is of minor significance in the normal but may be of profound significance in pathological states.

19. Payne, A.H., R.P. Kelch, S.S. Musich, and M.E. Halpern. Intesticular site of aromatization in the human. J. Clin. Endocrinol. Metab. 1081-1087, 1976.

It is likely that the Leydig cell is the principal site for estrogen synthesis within the human testis, although some enzymatic activity may be located in Sertoli cells also.

20. Rosen, P.P., C.J. Menendez-Botet, J.S. Nisselbaum, M.K. Schwartz, and J.A. Urban. Estrogen receptor protein in lesions of the male breast. A preliminary report. Cancer 37:1866-1868, 1976.

21. Rajendran, K.G., P.N. Shah, N.P. Bagli and S.N. Ghosh. Oestradiol receptors in non-neoplastic gynaecomastic tissue of phenotypic males. Horm. Res. 7:193-200, 1976.

Estradiol exerts its growth promoting properties in the male as in the female breast and other tissues via the high affinity cytoplasmic receptor protein that transfers the hormone to the nuclear receptors.

V. HISTOPATHOLOGY OF GYNECOMASTIA

22. Karsner, H.T. Gynecomastia. Amer. J. Path. 22:225, 1946.

23. Lenson, N. Enlargement of the male breast in Naval personnel. Amer. J. Surg. 82:325, 1951.

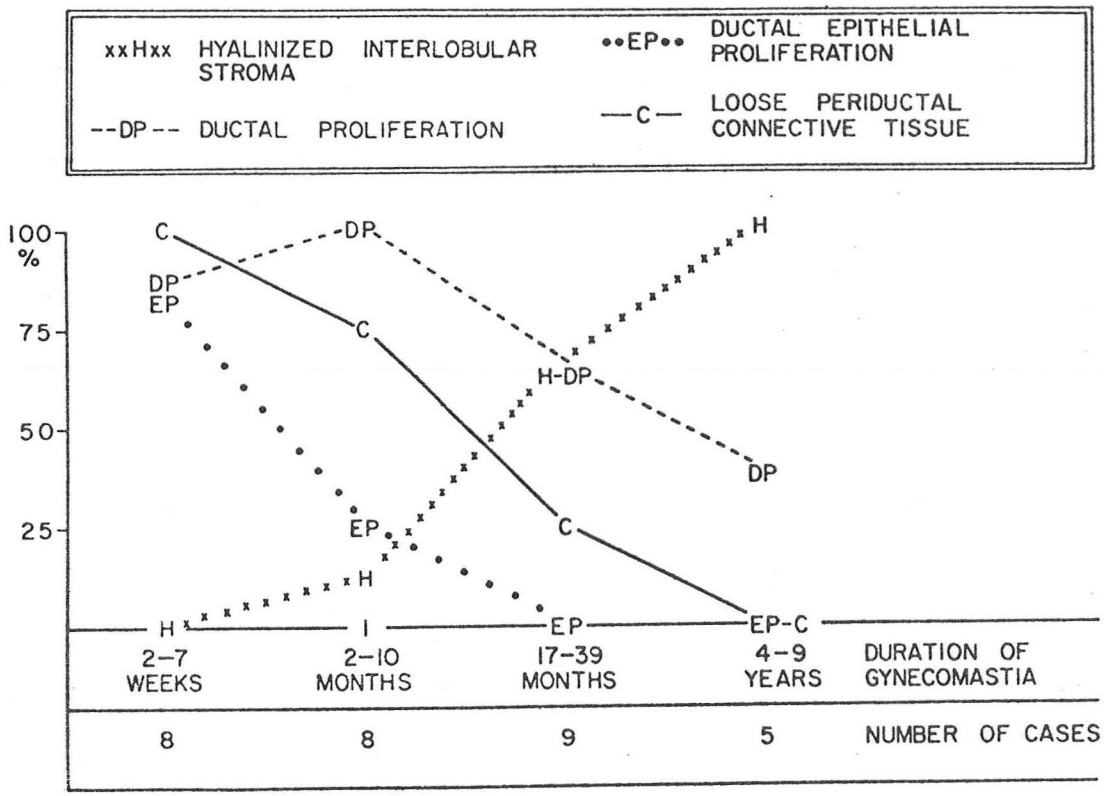
24. Levy, D.M. J.B. Erich, and A.B. Hayles. Gynecomastia. Postgrad. Med. 36:234, 1964.

25. Nicolis, G.L., R.S. Modlinger, and J.L. Gabrilove. A study of the histopathology of human gynecomastia. J. Clin. Endocr. 32:173, 1971.

26. Bannayan, G.A. and S.I. Hajdu. Gynecomastia: Clinicopathologic study of 351 cases. Amer. J. Clin. Path. 57:431, 1972.

FIGURE 4

HYPOTHETICAL SEQUENCE IN THE DEVELOPMENT OF GYNECOMASTIA (25)



Histologic changes in gynecomastia correlate better with the duration rather than with the etiology of the gynecomastia, suggesting a common pathogenesis of all gynecomastia. Early gynecomastia is characterized by proliferation both of the fibroblastic stroma and of the duct system which elongates, buds and duplicates. In gynecomastia of longer duration (even when the stimulation is continued as in stilbestrol administration) there is progressive fibrosis and hyalinization associated with regression of epithelial proliferation. Eventually, there is a decrease in the number of ducts. Mononuclear cell infiltration is a common feature.

Resolution occurs by reduction in size and epithelial content of the ducts with gradual disappearance of the ducts, leaving hyaline bands which eventually disappear. If the process is of sufficient duration fibrosis may become so extensive that complete resolution never occurs even when the underlying cause is removed.

Gross asymmetry in the development of gynecomastia is common; furthermore, unilateral gynecomastia frequently occurs as a temporary phenomenon in that one breast or the other may enlarge and become painful for years or months

before the other. In our experience, unilateral gynecomastia should be viewed only as a stage in the development of bilateral gynecomastia.

27. Scheike, O. and J. Visfeldt. Male breast cancer. 4. Gynecomastia in patients with breast cancer. Acta Path. Microbiol. Scand., Sect. A, 81:359-365, 1973.

28. Scheike, O. Male breast cancer. 5. Clinical manifestations in 257 cases in Denmark. Brit. J. Cancer 28:552-561, 1973.

Several features of male breast cancer seem to support the concept that gynecomastia may be a statistically significant premalignant state, particularly the lower mean age in cases of breast cancer with concurrent gynecomastia and the increased frequency of breast cancer in patients with the Klinefelter syndrome. If so, however, it is of not much clinical importance in view of the fact that carcinoma of the breast is so rare in patients with gynecomastia.

VI. CLASSIFICATION OF GYNECOMASTIA

29. Lewin, M.L. Gynecomastia. The hypertrophy of the male breast. J. Clin. Invest. 1:511, 1941.

30. Gabrilove, J.L. Some recent advances in virilizing and feminizing syndromes and hirsutism. Mt. Sinai J. Med. 41:636-654.

31. Gabrilove, J.L., G.L. Nicolis, H.A. Mitty and A.R. Sohval. Feminizing interstitial cell tumor of the testis: personal observations and a review of the literature. Cancer 35:1184-1202, 1975.

Lewin was apparently the first to suggest that all gynecomastia is due either to increased estrogen secretion or to a decreased androgen:estrogen ratio, a remarkable deduction considering the evidence available at the time. Gabrilove has recently pushed the concept of the androgen:estrogen ratio as the critical determinant in feminizing states in men. The problem is in the accurate measurement of such a ratio; plasma concentrations alone may be difficult to measure accurately and do not always reflect the concentration of free (unbound) hormone. The ideal state would be to measure the ratio of the plasma production rates of androgen to estradiol. As the result of the work done by Dr. MacDonald and his colleagues, it is possible to view all gynecomastia as a disturbance of the ratio of androgen to estrogen.

A. Physiological Gynecomastia

During three portions of male life, breast enlargement may be a physiological rather than a pathological event.

1. Gynecomastia in the Newborn

32. Bronstein, I.P. and E. Cassorla. Breast enlargement in pediatric practice. Med. Clin. N. Amer. 30:121-133, 1946.

The visible enlargement of the neonatal breast that occurs in many normal newborn probably results from the action of maternal and/or placental estrogens. The swelling ordinarily disappears in a few weeks, although it may persist longer in exceptional cases.

2. Adolescent Gynecomastia

33. Nydick, M., J. Bustos, J.H. Dale, Jr., and R.W. Rawson. Gynecomastia in adolescent boys. J. Amer. Med. Assoc. 178:449-454, 1961.

Of 1855 adolescent boys of different ages examined at a Boy Scout camp, 39% had gynecomastia. Furthermore, 65% of boys between 14 and 14.5 years were affected. Since it is transient in some and may occur earlier, the projection has been made that virtually all boys have gynecomastia at some time during puberty. Although the median age of onset is 14, it may start much later on occasion. In many boys it is grossly asymmetrical and frequently tender. By age 20 only a small number of men have palpable vestiges of the gynecomastia in one or both breasts.

34. Bidlingmaier, F. and D. Knorr. Plasma testosterone and estrogens in pubertal gynecomastia. Z. Kinderheilk, 115:89-94, 1973.

35. Lee, P.A. The relationship of concentrations of serum hormones to pubertal gynecomastia. J. Pediatr. 86:212-215, 1975.

36. LaFranchi, S.H., A.F. Parlow, B.M. Lippe, J. Coyotupa and S.A. Kaplan. Pubertal gynecomastia and transient elevation of serum estradiol level. Amer. J. Dis. Child. 129:927-931, 1975.

37. Editorial. Pubertal gynaecomastia, Brit. Med. J. 1238-1239, 1976.

On the basis of work done in three laboratories, adolescent gynecomastia can be explained as due to the fact that plasma estradiol reaches the adult level in men before the adult level of plasma testosterone is attained. As a result the plasma ratios of T:E_2 do not achieve the adult level until late in puberty. This is presumably either due to the fact that the aromatase system in the Leydig cell completes maturation before the testosterone synthesizing machinery achieves the adult level or to the fact that the peripheral aromatase enzymes do not achieve adult levels of activity (and can utilize adrenal androgen) until after testosterone synthesis reaches its maximum so that the ratio of estrogen formed in the periphery to testosterone secreted by the testis is temporarily high.

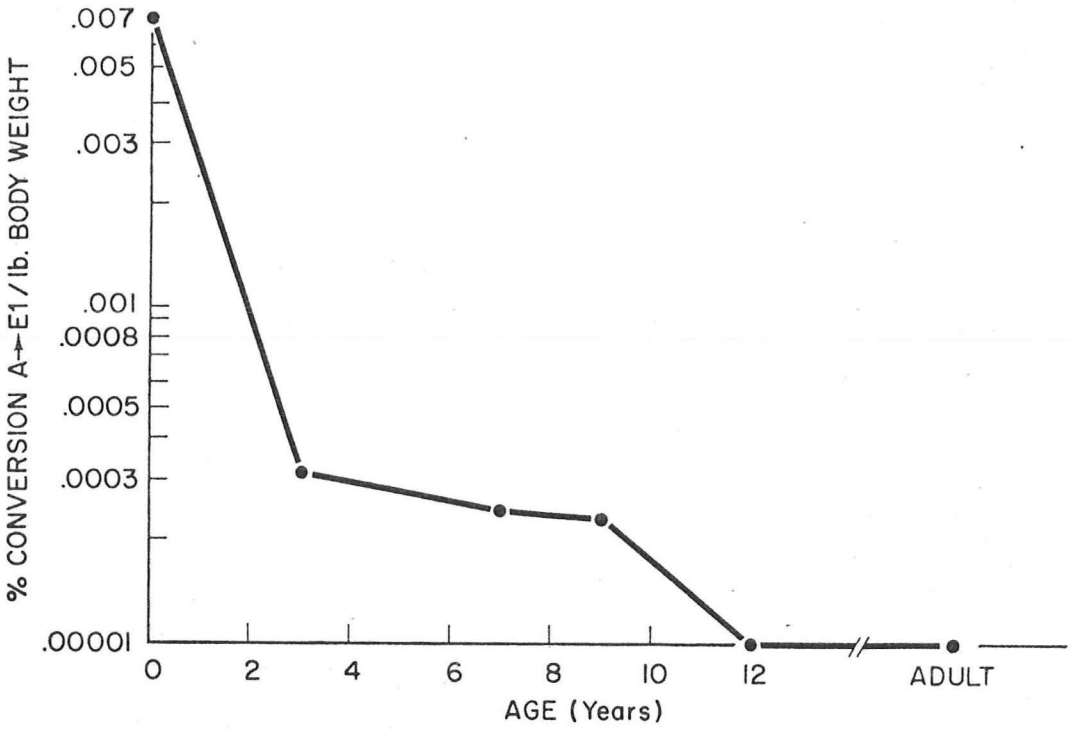
TABLE I

MEAN TESTOSTERONE-ESTROGEN RATIOS DURING MALE PUBERTY (34)

Pubertal stage	Testosterone : Estrone	Testosterone : Estradiol
I	8:1	12:1
II	20:1	30:1
III	30:1	40:1
IV	60:1	90:1
V	85:1	130:1

FIGURE 5

CORRELATION BETWEEN CONVERSION ANDROSTENEDIONE TO ESTRONE PER POUND BODY WEIGHT AND AGE IN PREPUBERTAL CHILDREN



3. Gynecomastia of Aging

38. Williams, M.J. Gynecomastia. Its incidence, recognition, and host characterization in 447 autopsy cases. Amer. J. Med. 34:103, 1963.

The fact that gynecomastia occurs in otherwise healthy, elderly men has been known for many years; since it can also be an indication of some serious underlying disease, involutional gynecomastia can be diagnosed only by exclusion. What is remarkable is the frequency of this disorder; in an autopsy study, Williams reported that 40% of elderly men have true gynecomastia and that this is due to a true increase in frequency. However, no real attempt has been made to correlate the occurrence of involutional gynecomastia with drug therapy (such as digitalis) or liver function, and it is possible that the entity, if it exists at all, is rare.

39. Vermuelen, A., R. Reubens, and L. Verdonck. Testosterone secretion and metabolism in male senescence. J. Clin. Endocr. 34:730-735, 1972.

40. Stearns, E.L., J.A. MacDonnell, B.J. Kaufman, R. Padua, T.S. Lucman, J.S.D. Winter, and C. Faiman. Declining testicular function with age: hormonal and clinical correlates. Amer. J. Med. 57:761-766, 1974.

41. Pirke, K.M. and P. Doerr. Age related changes in free plasma testosterone, dihydrotestosterone, and eostradiol. Acta Endocrinol. 80:171-178, 1970.

42. Snyder, P.J. Effect of age on the serum LH and FSH responses to gonadotropin-releasing hormone. In Benign Prostatic Hyperplasia, J.T. Grayhack, J.D. Wilson and M.J. Scherbenske, Eds. DHEW Publication No. (NIH)76-1113, 1976.

43. Vermuelen, A. Testicular hormonal secretion and aging in males. In Benign Prostatic Hyperplasia, J.T. Grayhack, J.D. Wilson and M.J. Scherbenske, Eds. DHEW Publication No. (NIH) 76-1113, 1976.

(See also Reference 15)

However, in virtually all aging men, endocrine changes occur that might result in breast enlargement. Beginning at age 70 the plasma T starts to fall, there is a simultaneous elevation in plasma testosterone-estrogen binding globulin so that the level of testosterone falls even more (39-41). There is an associated rise in plasma luteinizing hormone (42) and an increase in the rate of peripheral aromatization (15) so that the effective ratio of androgen to estrogen is changed significantly (43).

FIGURE 6

CORRELATION OF EXTENT OF CONVERSION OF ANDROSTENEDIONE TO ESTRONE WITH AGE IN MEN (15)

Correlation coefficient = 0.62

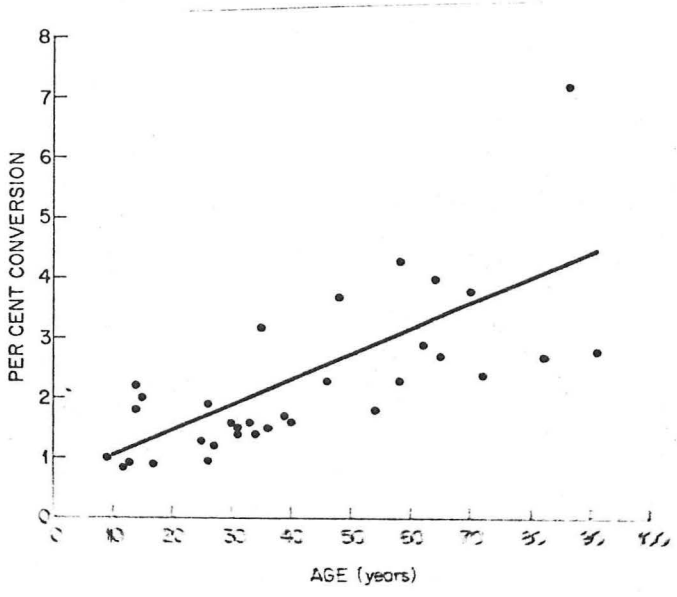


TABLE II

PLASMA TESTOSTERONE AND ESTRADIOL AS A FUNCTION OF AGE IN 60 NORMAL MEN (43)

	<50 years	>65 years
TEBG Capacity, nM	35	89
Luteinizing Hormone, MIU/ml	13.0	22.5
Mean Plasma Testosterone, ng/dl	487	264
Mean Free Testosterone, ng/dl	10.6	3.6
Mean Plasma Estradiol, ng/dl	1.4	2.1
Mean Free Estradiol, ng/dl	0.026	0.028
Ratio Plasma T/E_2	348	126
Ratio Free T/E_2	410	128

B. Pathological Gynecomastia

1. Testicular Deficiency

When gynecomastia occurs as the consequence of a failure of testosterone synthesis (or action) it is generally associated with elevations of plasma gonadotropins and may or may not be associated with a secondary rise in testicular estrogen secretion.

a.) Primary

1.) Congenital Anorchia

44. Heller, C.G., W.O. Nelson, and A.C. Roth. Functional prepubertal castration in males. J. Clin. Endocr. 3:573, 1943.

45. Howard, R.P., R.C. Sniffer, F.A. Simmons, and F. Albright. Testicular deficiency: a clinical and pathological study. J. Clin. Endocr. 10:121, 1950.

46. Kirschner, M.A., J.B. Jacobs, and E.E. Fraley. Bilateral anorchia with persistent testosterone production. N. Engl. J. Med. 289:240-244, 1970.

47. Hall, J.G., A. Morgan, R.M. Blizzard. Familial congenital anorchia. In Genetic Forms of Hypogonadism. Birth Defects: Original Article Series, D. Bergsma, Ed. New York, Stratton Corp. 11:No. 4:115, 1975.

48. Edman, C.D., A.J. Winters, J.C. Porter, J.D. Wilson, and P.C. MacDonald. Embryonic testicular regression. A clinical spectrum of XY agonadal individuals. Obstet. Gynecol. 49:209-217, 1977.

Congential anorchia is a disorder (often occuring in families) in which testes are missing in phenotypically normal, 46,XY males. Affected individuals are thought to have bilateral cryptorchidism at birth, and on abdominal exploration no testes whatever can be located. Since male sexual differentiation is normal it is believed that testes are present and functioned normally until late in embryonic life and then regressed for unknown reasons. Kirschner and his colleagues have shown that even when testes cannot be located anatomically remnants of Leydig cells are present in some patients somewhere along the old

urogenital ridge and may secrete small amounts of testosterone into the circulation (46). We have had the opportunity of studying two patients with congenital anorchia, one without and one with gynecomastia.

Case 1. Congenital Anorchia without Gynecomastia

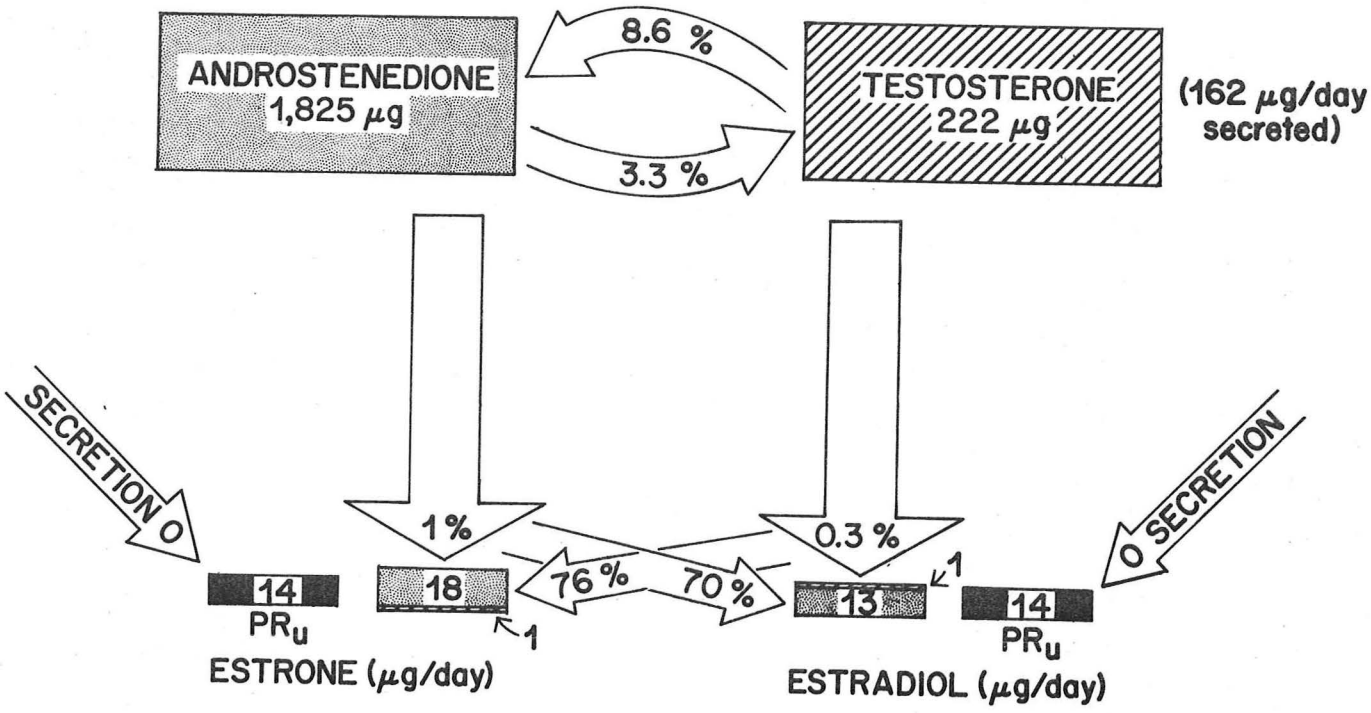
CHS (51-29-90)

Undescended testes were noted at birth (5-29-52). At age 4 an exploratory laparotomy was performed at CMC; bilateral vas deferens and epididymides were present, and the spermatic artery and pampiniform plexus of veins were present but terminated blindly. No testes or testis remnants were located. At age 10, bilateral prostheses were placed in the scrotum, and he was placed on methyl testosterone by mouth (prescribed dose uncertain), which he took intermittently. The development of secondary sex characteristics was incomplete. He was referred here in August of 1976; no gynecomastia was present. IVP was normal, and no testicular tissue was located with Technium 99 scintiscan. The renal veins were catheterized, and the gonadal veins were visualized. Plasma testosterone was undetectable in either the peripheral plasma or in plasma from either renal vein. He was transferred to the CRC for studies of androgen and estrogen dynamics (see below). He was subsequently placed on testosterone enanthate and did well. In June of 1977 he was killed in an accident. At postmortem no testicular tissue was found.

Endocrine Data (Mean of 6 determinations each)

Plasma T,	ng/ml	0.28
Plasma E_2,	pg/ml	<15
Plasma LH,	MIU/ml	79
Plasma FSH,	MIU/ml	83

FIGURE 7

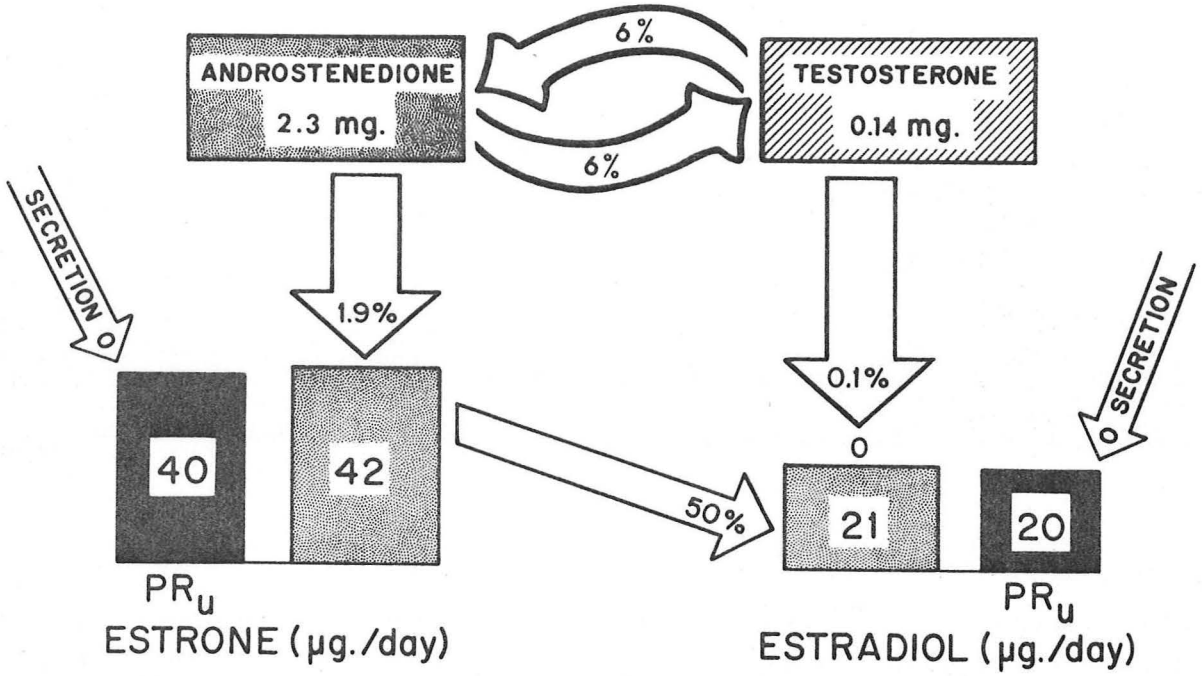


Case 2. Congenital Anorchia with Gynecomastia

JWJ (29-67-46)

This 27 year old man was diagnosed as having bilateral cryptorchidism in infancy. At age 18 he underwent an extensive bilateral exploratory opertion of the inguinal canals at the University of Oklahoma. Although remnants of the vas deferens were found, no testicular tissue was located, and the diagnosis of congenital anorchia was made. No male pubertal development occurred in regard to facial, body, or pubic hair, and the genitalia remained infantile. At age 13 he noted some areolar swelling and tenderness. The gynecomastia remained nondescript until about 5 months prior to his admission here when he noted the development of marked gynecomastia. He was incapable of ejaculation or erection. PE revealed a eunuchoid habitus with absence of body and facial hair, a small uncircumcised penis with no palpable testis, and no scrotal wrinkling. He had a normal 46,XY karyotype and a plasma testosterone of 0.6 ng/ml (normal 5-10). Plasma estradiol values are not available, but his androgen-estrogen dynamics were studied in detail.

FIGURE 8



COMMENT: Both of these subjects have profound testosterone deficiency and low estradiol production. In one (JWJ) all the plasma production of testosterone could be accounted for by peripheral conversion from androstenedione, whereas the other (CSH) secreted small amounts of testosterone (162 µg/dy), presumably from some testicular remnant. We cannot estimate plasma T/E_2 ratios accurately in these men (in one plasma E_2 was not done, in the other it was too

low for accurate measurement), but it is clear that in the subject without gynecomastia, the ratio of T/E_2 production is higher (17) than in the one with gynecomastia (7). This suggests that even small amounts of testosterone production (44-46) may be sufficient to prevent gynecomastia even though not enough to virilize. The results are in general keeping with the concept that the critical factor for feminization is not the absolute level of estradiol but rather some ratio of T to E_2. Presumably, even when remnants of testes are capable of testosterone secretion, they cannot secrete estradiol despite massive elevations of gonadotropins.

2.) Klinefelter Syndrome

49. Gordon, D.L., E. Krompotic, W. Thomas, H.M. Gandy, and C.A. Paulsen. Pathological testicular findings in Klinefelter's syndrome. 47,XXY vs 46,XY/47,XXY. Arch. Intern. Med. 130:726-729, 1972.

50. Paulsen, C.A., D.L. Gordon, R.W. Carpenter, H.M. Gandy and W.D. Drucker. Klinefelter's syndrome and its variants: a hormonal and chromosomal study. In Recent Progress in Hormone Research, New York, Academic Press, 24:321-363, 1968.

51. Becker, K.L., D.L. Hoffman, A. Albert, L.O. Underdahl, and H.L. Mason. Klinefelter's syndrome. Clinical and laboratory findings in 50 patients. Arch. Intern. Med. 118:314-321, 1966.

52. Wang, C., H.W.G. Baker, H.G. Burger, D.M. de Kretser, and B. Hudson. Hormonal studies in Klinefelter's syndrome. Clin. Endocrinol. 4:399-411, 1975.

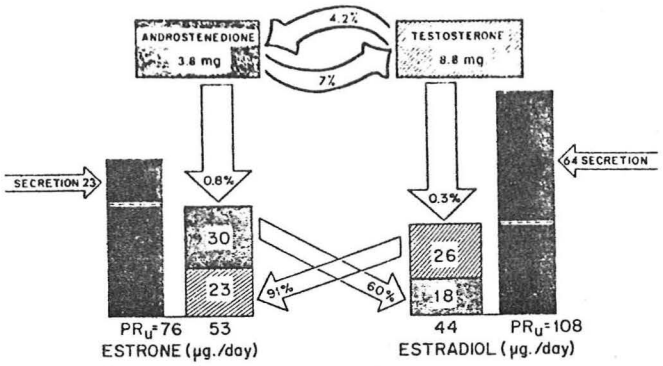
Approximately 50 percent of non-mosaic and a third of mosaic Klinefelter's patients develop gynecomastia after the time of expected puberty. The endocrine abnormalities in this disorder have been characterized in detail. Plasma and urine FSH and LH are high, and the average plasma testosterone is half normal. Many patients have testosterone values that fall within the normal range, however. The variability in plasma testosterone level is the reason for the variable degree of androgenization in this disorder. Another cause is the elevated plasma estrogen. Estrogen metabolism has not been studied in large numbers of patients; in those in whom it has been measured plasma estradiol is elevated (52). The reason for the elevated plasma E_2 was discovered by measuring the androgen and estrogen dynamics in several patients.

Case 3. Gynecomastia in Klinefelter's Syndrome

This 18 year old boy was admitted for a workup for gynecomastia. He described the appearance of pubic and leg hair at age 13, but never developed significant facial hair. At age 16 he noted bilateral breast enlargement. He had normal erections and ejaculations by history. On PE he was obese, and marked gynecomastia was present (7 cm disc on the left and 5 cm on the right). There was a spider angioma on the left anterior lateral wall. The testes were 5 cm in longest axis, and the penis and prostate were normal. Routine laboratory workup was normal. The ejaculate volume was 2.0 ml with 100 million sperm/ml, 70% of which were motile. (He subsequently fathered a child.) On karyotype he was shown to be a mosaic Klinefelter, 10% XO, 60% XY, and 30% XXY. No

gonadotropin values were obtained. Estrogen and androgen dynamics were subsequently measured:

FIGURE 9



COMMENT: In this patient (and in patients with non-mosaic Klinefelter) testicular secretion of estrogen can probably be explained as the result of the increased plasma gonadotropins. Markedly elevated levels of gonadotropins resulted in a steady state concentration of testosterone that is statistically normal. Unfortunately, only a small fraction of mosaic Klinefelter's patients can be diagnosed from a karyotype done on peripheral cells; in most, a testicular biopsy is required. The fact that this patient had gynecomastia despite normal testosterone production suggests that enhanced estradiol is more important as a cause of gynecomastia in Klinefelter's syndrome than is the decreased testosterone.

3.) Androgen Resistance (Testicular Feminization and Reifenstein Syndrome

53. Wilson, J.D., M.J. Harrod, J.L. Goldstein, D.L. Hemsell, and P.C. MacDonald. Familial incomplete male pseudohermaphroditism, Type 1. Evidence for androgen resistance and variable clinical manifestations in a family with the Reifenstein syndrome. N. Engl. J. Med. 290:1097, 1974.

54. Wilson, J.D. and P.C. MacDonald. Male pseudohermaphroditism due to androgen resistance: testicular feminization and related syndromes. In Metabolic Basis of Inherited Disease, J.B. Stanbury, ed. In Press.

55. MacDonald, P.C., J.D. Madden, P.F. Brenner, J.D. Wilson, and P.K. Siiteri. Origin of estrogen in normal men and in women with testicular feminization. Submitted for publication.

56. Griffin, J.E., K. Punyashthiti, and J.D. Wilson. Dihydrotestosterone binding by cultured human fibroblasts. Comparison of cells from control subjects and from patients wtih hereditary male pseudohermaphroditism due to androgen resistance. J. Clin. Invest.

57:1342, 1976.

57. Madden, J.D., P.C. Walsh, P.C. MacDonald, and J.D. Wilson. Clinical and endocrinologic characterization of a patient with the syndrome of incomplete testicular feminization. J. Clin. Endocrinol. Metab. 40:751, 1975.

Hereditary deficiency of the X-linked cytoplasmic androgen receptor protein is the cause for at least three specific syndromes of hereditary male pseudohermaphroditism in which 46,XY patients with testes and male testosterone levels are resistant to their own and to exogenous androgens. When the protein is absent, the syndrome of complete testicular feminization results; when the protein is deficient, incomplete male pseudohermaphroditism results --either the Reifenstein syndrome (hypospadias and gynecomastia) or incomplete testicular feminization. Complete measurement of androgen and estrogen dynamics has been done in six patients with the complete disorder (55), two patients with Reifenstein syndrome (53) and one with Incomplete testicular feminization (57), and it is now clear how the feminization occurs in these disorders.

See FIGURE 10

In each of these disorders, estrone and estradiol production rates are elevated. Plasma gonadotropins are elevated as the result of resistance to the negative feedback of testosterone on gonadotropin production at the hypothalamic-pituitary level. As a result, estrogen secretion by the testis is elevated. It is striking, however, that in these disorders there is no direct relationship between estrogen secretion and the degree of feminization. Two phenotypic men with the Reifenstein syndrome had an average daily estrodiol production rate of 212 µg and testicular secretion rates of estradiol of 160 µg/dy (53), much greater then the observed daily estradiol production rates of 53 to 121 µg/dy in the 6 patients with complete testicular feminization (55). The estradiol production rate in one patient with the incomplete form of testicular feminization was intermediate, 138 µg/dh (57). Nevertheless, testosterone production rates in the three groups overlapped. We conclude that feminization in these three forms of androgen resistance is dependent upon increased estradiol production after puberty but that the degree of feminization is influenced by the severity of the androgen resistance. As we formulate it a ratio of estrogen to effective androgen at some cellular level must be the rate-limiting factor that determines the degree of feminization.

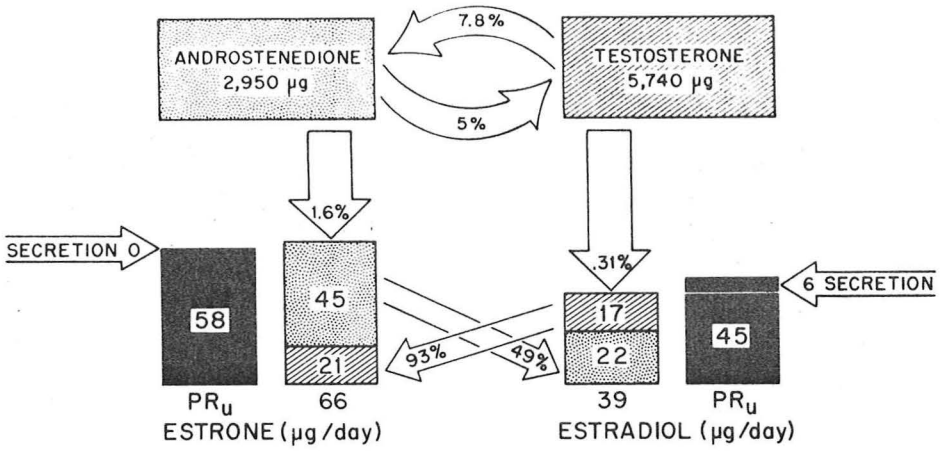
4.) Defects in Testosterone Synthesis

58. Wilson, J.D. and P.C. Walsh. Abnormalities in sexual differentiation. In Campbell's Textbook of Urology, J.D. Harrison, et al. In Press. (Review)

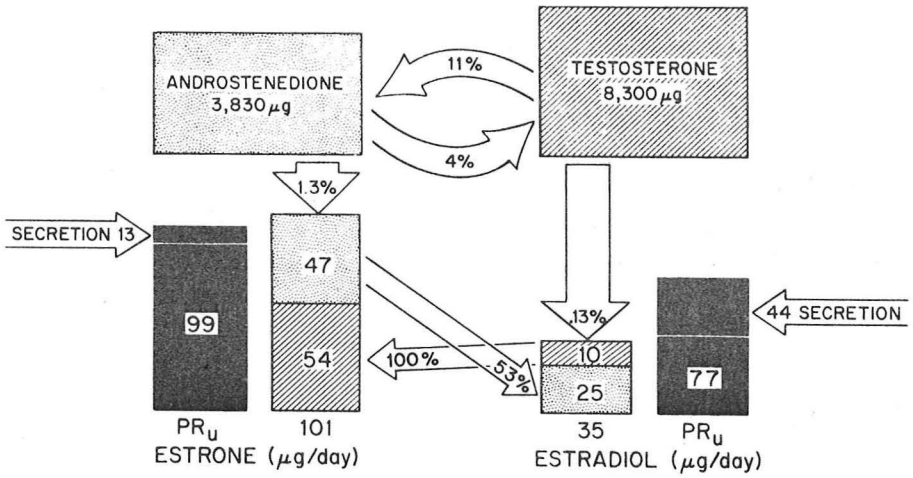
59. Griffin, J.E. and J.D. Wilson. The Testis. In Duncan's Diseases of Metabolism, L.E. Rosemberg and P.K. Bondy, Eds. In Press. (Review)

Five enzyme defects have been described that result in defective testosterone synthesis (and incomplete virilization of the male embryo during embryo-

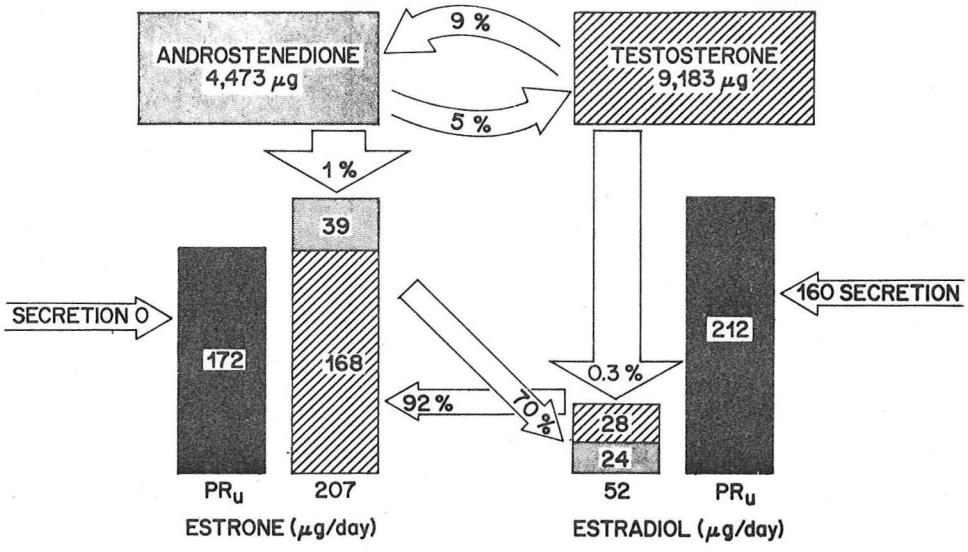
FIGURE 10



NORMAL MEN [4]



TESTICULAR FEMINIZATION [6]



REIFENSTEIN SYNDROME [2]

genesis). Each of the enzymes involves a critical biochemical step in the conversion of cholestrol to testosterone. There is extreme variability in the severity of the blocks and in the clinical manifestations, but in many there is a profound increase in gonadotropin secretion, and gynecomastia may occur in affected males; androgen and estrogen dynamics have not been studied in detail on any patient but presumably gynecomastia results either from diminished androgen production in the face of normal or enhanced estrogen formation. The latter could occur from increased peripheral aromitization of precursor steroids such as androstenedione that accumulate or from increased estrogen secretion from the testis as the result of increased gonadotropin secretion.

b) Secondary Testicular Failure

1.) Viral Orchitis

60. Werner, C.A. Mumps orchitis and testicular atrophy. I. Occurrence. Ann. Intern. Med. 32:1066, 1950.

61. Riggs, S. and J.P. Sanford. Viral orchitis. N. Engl. J. Med. 266:990, 1962.

62. Werner, C.A. Mumps orchitis and testicular atrophy. II. A factor in male sterility. Ann. Intern. Med. 32:1075, 1950.

63. Petersdorf, R.G. and I.L. Bernett, Jr. Treatment of mumps orchitis with adrenal hormones. Report of twenty-three cases with a note on hepatic involvement in mumps. Arch. Intern. Med. 99:222, 1957.

Viral orchitis is the most common cause of testicular failure after puberty, and mumps is the most important etiology, although other viruses are also known to be involved, including ECHO virus, lymphocytic choriomeningitis virus, and group B arboviruses. It is clear that the disease is due to direct effects of the virus in the gland rather than to indirect effects since mumps virus has been isolated from the testis of affected patients.

Orchitis is the most common complication of mumps in adults and occurs in approximately a fourth of affected men. In two-thirds it is unilateral, and in the remainder it is bilateral. It occurs rarely prior to puberty and usually develops within a few days after the onset of parotitis. After the acute phase, the testis gradually decreases in size and may either return to normal or shrink below the normal size. Atrophy is believed to be due either to direct action of the virus on the seminiferous tubules or to ischemia secondary to pressure and edema within the tunica albuginea. The degree of atrophy is not necessarily proportional to the severity of the orchitis; atrophy occurs in approximately a third of all cases of viral orchitis and is bilateral in a tenth. In a survey of 2000 adult men, Werner found atrophy of one or both testes in 2%, half of which was due to mumps. The administration of glucocorticoids is followed by rapid reduction of testicular swelling and pain, but it is not known whether this affects the subsequent development of atrophy.

Very little work has been done on the endocrine changes of mumps orchitis, and the frequency of gynecomastia is uncertain. However, we have had the

opportunity of studying two patients with gynecomastia and bilateral testicular atrophy secondary to mumps.

Case 4. Gynecomastia after Mumps Orchitis

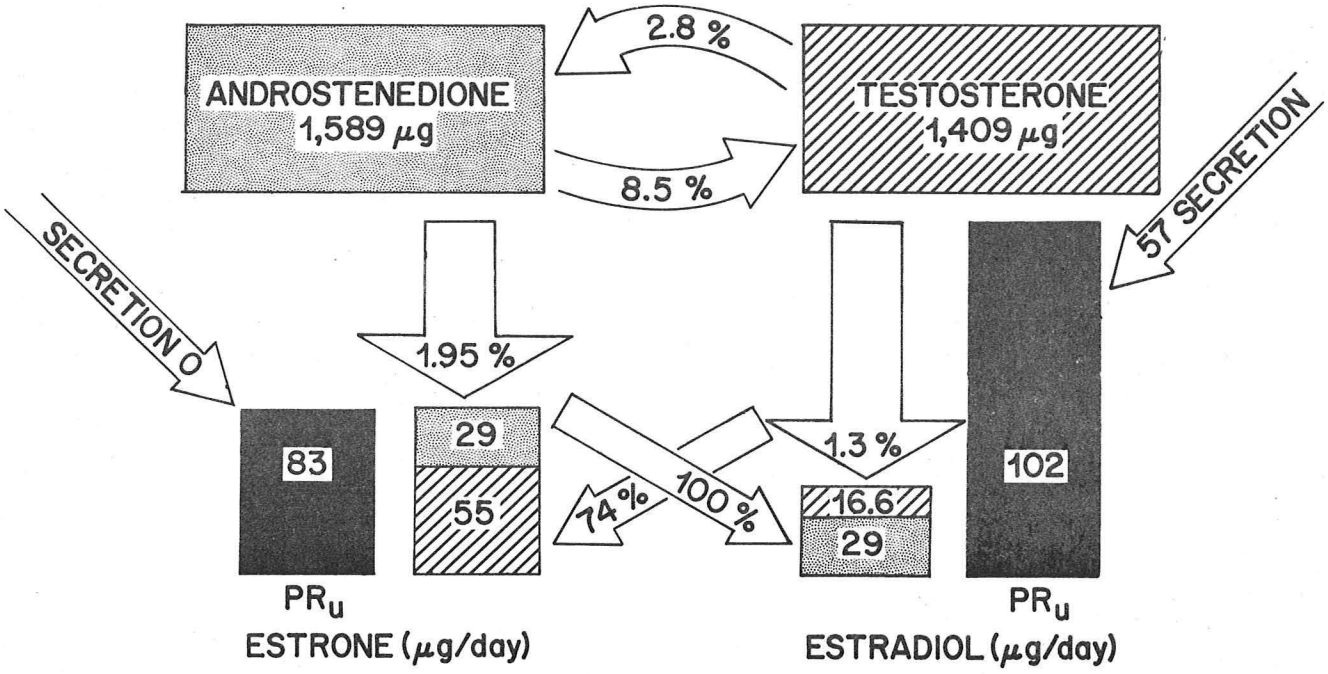
AC (PMH No. 573237)

This 63 year old man had bilateral mumps orchitis at age 27 while in the army. The exact sequencing of ensuing testicular failure is uncertain, but his testes became quite small immediately thereafter, and he had a progressive decrease in libido over the ensuing years so that he has been totally impotent for about 10 years. Approximately 5 years ago he developed left sided gynecomastia, and in the past year he noted development of progressively enlarging gynecomastia on the right. PE was within normal limits except for mild hypertension and gynecomastia.

Testosterone	2.4	ng/ml
E_2	23	pg/ml
LH	80	ng/ml
FSH	>1000	ng/ml

Androgen and estrogen kinetics were measured by Dr. James Aiman:

FIGURE 11



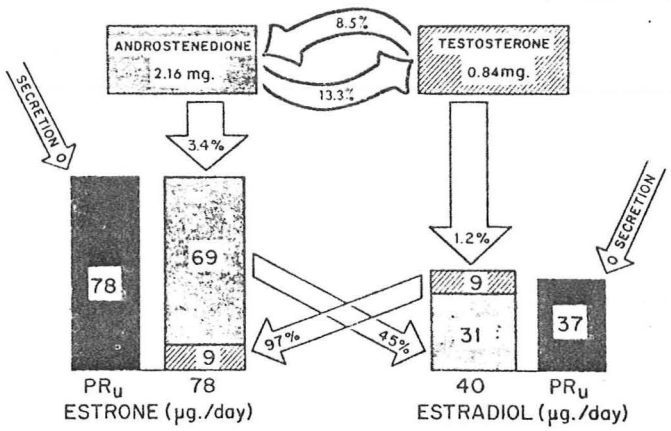
Case 5. Gynecomastia after Mumps Orchitis

CC (10-80-47)

This 68 year old man was referred to Endocrine Clinic because of gynecomastia. At the age of 18 he had bilateral mumps orchitis, following which both testes became atrophic. His libido remained normal until age 48, when he noted the onset of gynecomastia and a progressive decrease in libido. At the time of referral he had enormous pendulous breasts. PE was otherwise normal except for small, boggy testes, obesity, and mild hypertension.

Androgen and estrogen dynamics were measured:

FIGURE 12



COMMENT: On the basis of the findings in these two patients, we offer the following interpretation: As the capacity to synthesize testosterone falls, there is a compensatory increase in gonadotropin levels, and as a result testicular secretion of estradiol rises. Gynecomastia in AC is clearly due to diminished T as well as excess of E_2. However, as testicular function falls still further, the testes loose the capacity to make either T or E_2. In this situation, gynecomastia could either be a residual phenomenon or might be sustained as the result of an abnormal T:E_2 ratio due to diminished T production similar to the sequence in congenital anorchia. Furthermore, in CC an elevated peripheral aromatase (obesity and old age) sustains the production of E_2 via the sequence androstenedione → estrone → estradiol.

2.) Trauma

Trauma is the second most common cause of testicular atrophy in the adult (60). Presumably the endocrine abnormality would be similar to that in mumps orchitis.

3.) Castration

64. Woodham, C.W.B. Hyperplasia of the male breast. Lancet 2:307, 1938.

Gynecomastia is said to follow castration; if so the disturbance in T:E_2 ratio would resemble that in congenital anorchia rather than that in mumps orchitis.

4.) Neurological Disease

65. Clarke, B.G., S. Shapiro, and R.G. Monroe. Myotonia atrophia with testicular atrophy. J. Clin. Endocr. 16:1235, 1956.

66. Cooper, I.S., E.A. Ryanson, A.A. Bailey, and C.S. MacCarty. The relation of spinal cord disease to gynecomastia and testicular atrophy. Staff. Proc. Mayo Clin. 25:320, 1950.

Testicular atrophy occurs in 80% of cases of myotonia atrophica. It is also common among patients with spinal cord lesions and other neurological diseases. Biopsy of the testes reveals atrophy and hyalinization. The nature of the endocrine abnormality is unclear.

5.) Granulomatous Disease

67. Martin, F.I.R, I. Maddocks, J.B. Brown, and B. Hudson. Leprous endocrinopathy. Lancet 2:1320, 1968.

68. Dass, J., K. Murugesan, K.R. Laumas, M.G. Deo, K.C. Kandhari and L.K. Bhutani. Androgenic status of lepromatous leprosy patients with gynecomastia. Intl. J. Leprosy 44:469, 1976.

Testicular atrophy, decreased plasma testosterone, and gynecomastia are common in leprosy; probably direct granulomaous involvement of testis plays a more important role than does the neurological disease. Unfortunately, liver function tests are also deranged in many of the patients with gynecomastia, making interpretation of the endocrinopathy difficult.

6.) Renal Failure

69. Nagel, T.C., N. Freinkel, R.H. Bell, H. Friesen, J.F. Wilber, and B.E. Metzger. Gynecomastia, prolactin, and other peptide hormones in patients undergoing chronic hemodialysis. J. Clin. Endocrinol. Metab. 36:428, 1973.

70. Sawin, C.T., C. Longcope, G.W. Schmitt, and R.J. Ryan. Blood levels of gonadotropins and gonadal hormones in gynecomastia associated with chronic hemodialysis. J. Clin. Endocrinol. Metab. 36:988-1973.

71. Freeman, R.M., R.L. Lawton, and M.O. Fearing. Gynecomastia: an endocrinologic complication of hemodialysis. Ann. Intern. Med. 69:67, 1968.

72. Holdsworth, M.B., R.C. Atkins, and D.M. de Kretzser. The pituitary testicular axis in men with chronic renal failure. N. Engl. J. Med. 296:1245, 1977.

73. Schmitt, G.W., I. Shehadeh, and C.T. Sawin. Transient gynecomastia in chronic renal failure during chronic intermittent hemodialysis. Ann. Intern. Med. 69:73, 1968.

74. Gupta, D. and H.D. Burdschu. Testosterone and its binding in the plasma of male subjects with chronic renal failure. Clin. Chim. Acta 36:479, 1972.

Gynecomastia is common in men with renal failure, and approximately half of men with renal failure undergoing hemodialysis develop it. The endocrine changes in renal failure are complex, and those of the pituitary testicular axis are only now being elucidated. In patients with creatine clearance less than 4 ml/min, plasma LH and FSH are elevated (4 times normal), plasma testosterone is depressed (30% of normal), the testes show evidence of spermatogenic damage, and there is a subnormal response of plasma testosterone to chorionic gonadotropin (123). The elevated plasma LH is due both to reduced metabolic clearance and increased secretion (123). Thus, it is possible to explain the sequence as a subnormal response of the testes to gonadotropins with a compensatory increase in gonadotropin secretion. Exactly how this leads to gynecomastia is unclear. In an incomplete study that has been performed on a 27 year old man with diabetes mellitis and renal failure due to Kimmelsteil Wilson's disease (HS) plasma estrone secretion was markedly elevated (179 μg/day), of which only about 60 μg could be accounted for by formation in periphera from circulating androgens. Thus, more than 100 μg was secreted into the circulation, presumably from the testes. This would suggest that the testicular aromatase is not as resistant to gonadotropins as is testosterone synthesis. Thus, in this one patient the development of gynecomastia is almost identical to the sequence in the Klinefelter syndrome.

2. Increased Estrogen Production

a. Testicular Estrogen Production

1.) Testicular tumors

75. Peckham, M.J. and T.J. McElwain. Testicular tumors. Clinics in Endocr. Metab. 4:665, 1975.

76. Gray, S.P., H. Chandler, K.C. Bouskill and N.I. Blaylock. Feminizing interstitial cell tumor of the testis. J. Roy. Nav. Med. Serv. 59:71, 1973.

77. Gabrilove, J.L., G.L. Nicolis, H.A. Mitty, and A.R. Sohval. Feminizing interstitial cell tumor of the testis: personal observations and a review of the literature. Cancer 38:1184, 1975.

78. Ober, W.B., B. Kabalow, and H. Hecht. Malignant interstitial cell tumor of the testis: a problem in endocrine oncology. Bull. N.Y. Acad. Med. 52:561, 1976.

79. Teilum, G. Estrogen producing Sertoli cell tumors of the testis and ovary. J. Clin. Endocr. 9:301, 1949.

80. van Oreem Hansen, G. Malignant testicular androblastoma with gynecomastia. Dan. Med. Bull. 22:33, 1975.

81. Fligiet, Z., M. Kaneko, and E. Leiter. Bilateral Sertoli cell tumor of testes with feminizing and masculinizing activity occurring in a child. Cancer 38:1853, 1976.

82. Cochran, J.S., P.C. Walsh, J.C. Porter, T.C. Nicholson, J.D. Madden, and P.C. Peters. The endocrinology of human chorionic gonadotropin-secreting testicular tumors: new methods in diagnosis. J. Urol. 114:549, 1975.

Testicular tumors produce feminization in two ways. The majority of germinal cell tumors (seminomas, embryonal carcinomas, choriocarcinomas, and teratomas) produce hCG or fragments of hCG which in turn stimulate E_2 and testosterone synthesis by the uninvolved areas of the testes. Stromal cell tumors (Leydig cell and Sertoli cell tumors) may secrete testosterone and estradiol autonomously; in these instances plasma gonadotropin levels are depressed, the uninvolved areas of the testes are nonfunctional, and azoospermia is common. In addition, of course, in choriocarcinoma aromatase activity may be quite high.

2.) Bronchogenic carcinoma

83. Barlow, J.J. and M.J. Krant. Pulmonary hypertrophic osteoarthropathy, spider angioma and estrogen hyperexcretion in neoplasms. Ann. Intern. Med. 70:581, 1969.

84. Becker, K.L., J. Cattrell, C.F. Moore, J.L. Winnacker, M.J. and S. Katz. Endocrine studies in a patient with a gonadotropin secreting bronchogenic carcinoma. J. Clin. Endocr. 28:809, 1968.

85. Charles, M.A., R. Claypool, M. Schaaf, S.W. Rosen and B.D. Weintraub. Lung carcinoma associated with production of three placental proteins. Arch. Intern. Med. 132:427, 1973.

Carcinoma of the lung not only produces an increase in gonadotropin levels but a striking increase in estrogen secretion as well, and the level of gynecomastia clearly correlates with the estrogen production. The exact mechanism of the increased estrogen production has not been elucidated, but it is likely that elevated plasma gonadotropins cause increased testicular estradiol secretion.

b. Adrenal Estrogen Production

86. Wallach, S., H. Brown, E. Englert, and K. Eik-Nes. Adrenocortical carcinoma with gynecomastia. J. Clin. Endocr. 17:945, 1957.

87. Bacon, G.E. and G.H. Lowrey. Feminizing adrenal tumor in a six year

old boy. J. Clin. Endocr. 25:1403, 1965.

88. Gabrilove, J.L., G.L. Nicolis, R.U. Hardsknecht and H.H. Wotiz. Feminizing adrenocortical carcinoma in a man. Cancer 25:153, 1970.

89. Bhettay, E. and F. Bonnici. Pure oestrogen-secreting feminizing adrenocortical adenoma. Arch. Dis. Child. 52:241, 1977.

90. Gabrilove, J.L., D.C. Sharma, H.H. Wotiz, and R.I. Dorfman. Medicine 44:37, 1965.

(See also References 30 and 31)

The etiology of the increased estrogen production in feminizing adrenal carcinoma (which may reach 2-8 mg per day) is not known. The vast majority are associated with massive increases in androstenedione production (and elevated 17-ketosteroid production) and might represent increased availability of substrate for peripheral aromatization. In other instances the tumor itself may secrete estrogen.

91. Maclaren, N.K., C.J. Migeon, and S. Raiti. Gynecomastia with congenital virilizing adrenal hyperplasia (11-β-hydroxylase deficiency). J. Pediatr. 86:579, 1975.

92. Kadair, R.G., M.B. Block, F.H. Katz, and F.D. Hofeldt. "Masked" 21-hydroxylase deficiency of the adrenal presenting with gynecomastia and bilateral testicular masses. Amer. J. Med. 62:278, 1977.

93. Gabrilove, J.L., G.L. Nicolis and A.R. Sohval. Non-tumorous feminizing adrenogenital syndrome in the male subject. J. Urol. 110:710, 1973.

94. Boyar, R.M. and L. Hellman. Syndrome of benign nodular adrenal hyperplasia associated with feminization and hyperprolactinemia. Ann. Intern. Med. 80:389, 1974.

Feminization can also occur in benign forms of adrenal hyperplasia. Congenital adrenal hyperplasia is a complicated issue (because it can be associated with benign testicular tumors), but the most likely interpretation at the moment is that increased production of androstenedione would result in increased availability of substrate for peripheral aromatase (see below).

c. Peripheral Estrogen Production

Increased peripheral estrogen production can arise from two causes -- increase in the peripheral aromatase enzymes or increased availability of substrate (principally adrenal androgens) for the aromatase reaction.

95. Hemsell, D.L., C.D. Edman, J.F. Marks, P.K. Siiteri, and P.C. MacDonald. Massive extraglandular aromatization of plasma androstenedione resulting in feminization of a prepubertal boy. J. Clin. Invest. 60:455, 1977.

This is a remarkable description of an 8 year old boy who developed a marked feminization syndrome; he converted 55% of his plasma androstenedione to estrone for an estrogen production rate of 780 μg/day - more than 50 times the normal rate of peripheral aromatase activity. In so far as we are aware, this is a unique metabolic abnormality.

2) Liver disease

96. Gordon, G.G., J. Olivo, F. Rafii, and A.L. Southren. Conversion of androgens to estrogens in cirrhosis of the liver. J. Clin. Endocrinol. Metab. 40:1018, 1975.

97. Edman, D.C., D.L. Hemsell, P.F. Brenner, J.M. Grodin, B. Combes, P.K. Siiteri, and P.C. MacDonald. Extraglandular estrogen formation in subjects with cirrhosis. Submitted for publication.

98. Olivo, J., G.G. Gordon, F. Rafii, and A.L. Southren. Estrogen metabolism in hyperthyroidism and in cirrhosis of the liver. Steroids 26:47, 1975.

It has been known for many years that hyperestrogenization is a common feature of cirrhosis of the liver, and it has recently been established that plasma concentrations and urinary excretion of estrogens are both elevated. Gordon et al. (96) reported that the extent of peripheral aromatization of plasma androgens to estrogen is increased in cirrhosis, and Edman et al. (97) have shown that the increased extraglandular formation is largely the consequence of decreased hepatic extraction of androstenedione (7% of the normal rate) and a consequent increased extra-splanchnic metabolism of andro-stenedione, including aromatization.

FIGURE 13

EFFECT OF HEPATIC DISEASE ON THE CONVERSION OF ANDROSTENEDIONE TO ESTRONE (97)

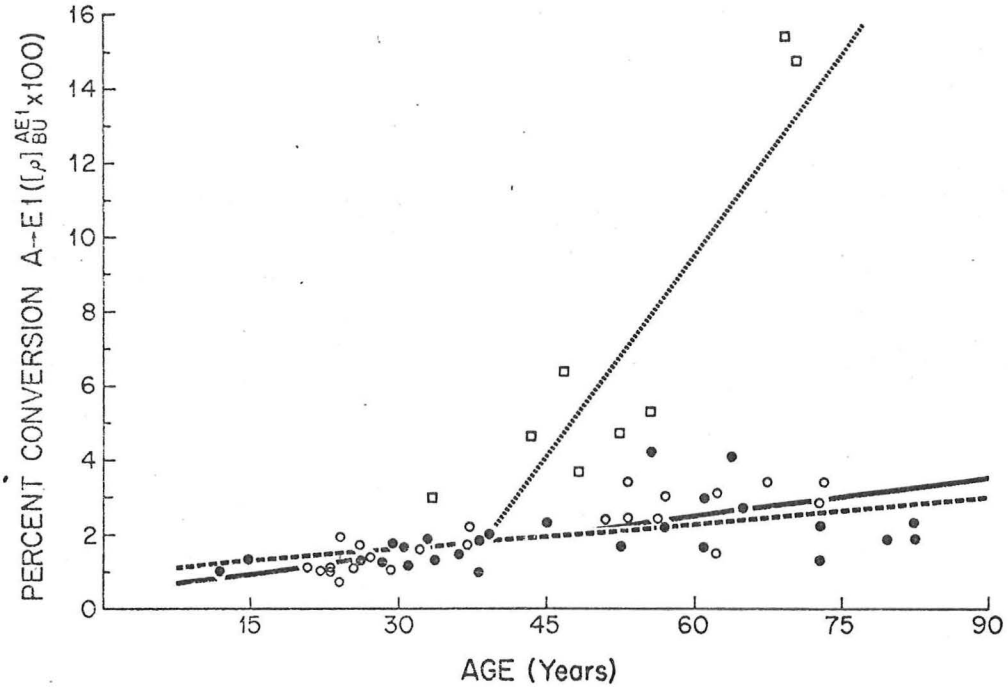
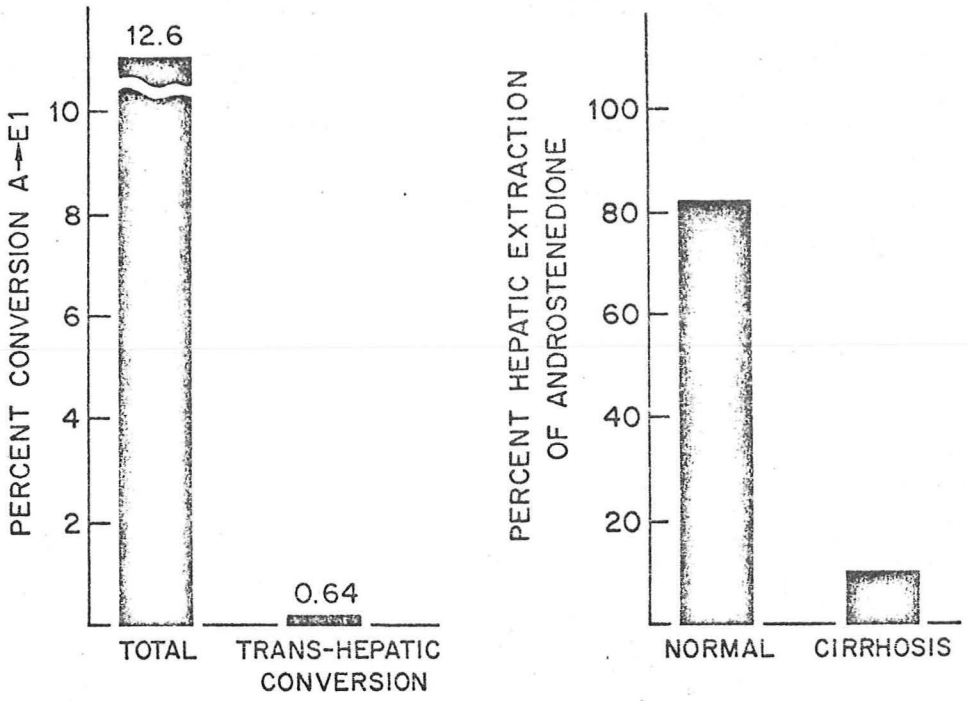


FIGURE 14

EXTENT OF CONVERSION OF ANDROSTENEDIONE TO ESTRONE AND HEPATIC ESTRACTION OF ANDROSTENEDIONE IN A POSTMENOPAUSAL WOMAN WITH CIRRHOSIS (97)



99. Kew, M.C., M.A. Kirschner, G.E. Abrahams, and M. Katz. Mechanism of feminization in primary liver cancer. N. Engl. J. Med. 296:1084-1088, 1977.

In carcinoma of the liver, however, feminization can be the consequence of actual increased aromatase activity in the tumor itself.

100. Klatskin, G., W.T. Saltin, and F.D. Humm. Gynecomastia due to malnutrition. Amer. J. Med. Sci. 213:19, 1947.

101. Zurbiran, S. and F. Gomez-Mont. Endocrine distrubances in chronic human malnutrition. Vit. Horm. 11:97, 1953.

About 15% of American prisoners-of-war in Japanese prison camps developed gynecomastia. About a third of the cases occurred during refeeding following release, and others developed during imprisonment associated with temporary increases in the food supply. 70% of cases were bilateral, and the vast majority disappeared within five to seven months. Infectious hepatitis and liver disease may play a role, and a large number of cases had spider angioma and fatty infiltration of the liver. Although the exact etiology has never been clarified, the similarities to cirrhosis are so striking that it seems reasonable to conclude that the pathogenesis is similar to that of liver disease.

3.) Thyrotoxicosis

102. Ashkar, F.S., W.M. Smoak, A.J. Gilson, and R. Miller. Gynecomastia and mastoplasia in Graves' disease. Metabolism 19:946, 1970.

103. Becker, K.L., J.L. Winnacker, M.J. Matthews, and G.A. Higgins, Jr. Gynecomastia and hyperthyroidism. An endocrine and histological investigation. J. Clin. Endocr. 28:277, 1968.

104. Becker, K.L., M.J. Matthews, G.A. Higgins, Jr. and M. Mohamadi. Histologic evidence of gynecomastia in hyperthyroidism. Arch. Pathol. 98:257, 1974.

105. Chopra, I.J. and D. Tulchinsky. States of estrogen-androgen balance in hyperthyroid men with Graves' disease. J. Clin. Endocrinol. Metab. 38:269, 1974.

106. Chopra, I.J. Gonadal steroids and gonadotropins in hyperthyroidism. Med. Clin. N. Amer. 59:1109, 1975.

107. Bercovici, J.P. and P. Mauvais-Jarvis. Hyperthyroidism and gynecomastia: metabolic studies. J. Clin. Endocrinol. Metab. 35:671, 1972.

108. Chopra, I.J., G.E. Abraham, N. Chopra, D.H. Solomon, and W.D. Odell. Alterations in circulating estradiol-17 in male patients with Graves' disease. N. Engl. J. Med. 286:124, 1972.

109. Southren, A.L., J. Olivo, G.G. Gordon, J. Vittek, J. Brenner, and F. Rafii. The conversion of androgens to estrogens in hyperthyroidism. J. Clin. Endocrinol. Metab. 38:207, 1974.

Although the association of Graves' disease and thyrotoxicosis has been known for many years (102), recent studies have suggested that it is more common than previously realized. In one series about 30% of men had gynecomastia, and a third of those had abnormal liver functions (103). As many as 80% may have histological evidence of gynecomastia (104). It is also clear from Chopra's work that such patients have elevated plasma estradiol values (105-108). Such patients also have elevated androstenedione production rates and consequently form more estrogen in the periphery (despite a normal rate constant (109). Thus, the mechanism of increased estrogen production is probably the same as that in liver disease, namely increased substrate for peripheral aromatization.

3. Drugs

Drugs can cause gynecomastia in any of four ways -- by inhibiting testosterone synthesis or action, by acting as estrogens directly, by enhancing testicular production of estrogens, or by unknown mechanisms.

a. Inhibitors of Testosterone Synthesis and Action

110. Loriaux, D.L., R. Menard, A. Taylor, J.C. Peta and R. Santen.

Spironolactone and endocrine dysfunction. Ann. Intern. Med. 85:630, 1976.

111. Zanner, H.S. and P.M. Black. Unilateral gynecomastia and impotence during low-dose spironolactone administration in men.

112. Clark, E. Spironolactone therapy and gynecomastia. J. Amer. Med. Assoc. 193:157, 1965.

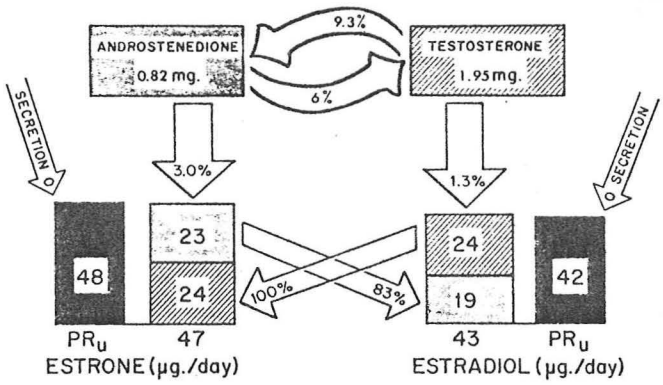
Spironolactone has at least two effects: it inhibits testosterone biosynthesis by inhibiting the 17,20 lyase reaction, and it inhibits the binding of androgen to its receptor. It can cause gynecomastia in doses as low as 50 mg per day -- dosages that apparently do not have any effect on testosterone synthesis. At these dose levels it may cause gynecomastia by inhibiting testosterone binding. At higher doses, however, it clearly inhibits testosterone synthesis as illustrated in the following case.

Case 6. Gynecomastia due to Spironolactone

RB (32-04-40)

The diagnosis of primary aldosteronism was estabished in this 60 year old man on the basis of hypochloremic alkalosis, increased aldosterone excretion, and low plasma renin values. Because of a hemiplegia it was decided to treat him medically, and he was ultimately controlled on 400-800 mg per day for two years. During this time progressively enlarging gynecomastia was noted. He was never treated with digitalis, and liver function tests were normal. Androgen and estrogen dynamics are summarized below:

FIGURE 15



COMMENT: In view of the low production rate for C19 steroids and normal estrogen production, these findings suggest that the gynecomastia is due to inhibition of testosterone synthesis and/or action. The patient subsequently underwent total adrenalectomy for bilateral adrenal cortical adenomas. The gynecomastia disappeared, and when retested, the secretion both of androstenedione and testosterone had returned to normal.

113. Geller, J., G. Vozakos, B. Fruchtenay, H. Newman, K. Nakao, and A. Loh. The effect of cyproterone acetate on advanced carcinoma of the

prostate. Surg. Gynecol. Obstet. 127:748, 1968.

114. Caine, M., Perlberg, S. and R. Gordon. The treatment of benign prostatic hypertrophy with flutamide (SCH 13521): a placebo-controlled study. J. Urol. 114:564, 1975.

These two experimetal drugs inhibit testoterone binding to the receptor (cyproterone and flutamide) and both cause gynecomastia uniformly.

b. Estrogens or drugs that act like estrogens

115. Hendrickson, D.A. and W.R. Robertson. Diethylstilbestrol therapy. Gynecomastia. J. Amer. Med. assoc. 213:468, 1970.

116. Brandt, N.J., J. Cohn, and M. Hilder. Controlled trial of oral contraceptives in haemophilia. Scand. J. Haemat. 11:225, 1973.

117. Orentreich, N. and N.P. Dur. Mammogenesis in transexuals. J. Invest. Derm. 63:142, 1974.

118. Beas, F., Vargas, L., Spada, R.P. and N. Merchak. Pseudoprecocious puberty in infants caused by a dermal ointment containing estrogens. J. Pediatr. 75:127, 1969.

Estrogens given to men in any form can result in severe gynecomastia.

119. Landolt, R. and G. Murset. Premature signs of puberty as late sequelae of unintentional estrogen administration. Schweitz. Med. Wochenschr. 98:638, 1968.

Young men and boys are more sensitive to estrogens and may develop gynecomastia even with dermal ointments containing estrogens.

120. LeWinn, E.B. Gynecomastia during digitalis therapy. N. Engl. J. Med. 248:316, 1953.

121. Novak, A., L.F. Kass and J.S. LaDue. Estrogen-like activity of digitalis. J. Amer. Med. Assoc. 194:142, 1965.

122. Wolfe, C.J. Gynecomastia following digitalis administration. J. Fla. Med. Assoc. 62:54, 1975.

Although digitalis-induced gynecomastia is well known, the pathophysiology is still poorly understood. LeWinn pointed out that many patients also have abnormal liver function. About 10% of men who have been on digitalis for a year develop gynecomastia. The mechanism is thought to be due either to its role as an estrogen or an estrogen-precursor.

123. Mendelsohn, J.H., J. Kuehnle, J. Ellinboe, and R.G. Babior. Plasma testosterone levels before, during, and after chronic marihuana smoking. N. Engl. J. Med. 291:1051, 1974.

124. Harmon, J.W., and M.A. Aliapoulios. Marijuana-induced gynecomastia: clinical and laboratory experience. Surg. Forum 25:423, 1974.

125. Cicero, T.J., R.D. Bell, W.G. Wiest, J.H. Allison, J.H. Polakowski, and E. Robbins. Function of the male sex organs in heroin and methodone users. N. Engl. J. Med. 292:882, 1975.

126. Mendelson, J.H., J.E. Mendelson, and V.D. Patch. Plasma testosterone levels in heroin addiction and during methadone maintenance. J. Pharm. Exp. Therap. 192:211, 1975.

Heavy use of marijuana and heroin is associated with a high frequency of gynecomastia and depressed androgen levels. The etiology is not clear but has been attributed in the case of marijuana to a direct estrogen effect of tetrahydrocarbaminal.

c. Gonadotropins

127. Naddock, W.O. and W.O. Nelson. The effects of chorionic gonadotropin in adult men. J. Clin. Endocr. 12:985, 1952.

The administration of hCG to children and adults results in gynecomastia, as would be predicted since it causes an increase in estradiol secretion by the testes.

d. Unknown Mechanisms

128. Hall, W.H. Breast changes in males on cimetidine. N. Engl. J. Med. 295:841, 1976.

129. McCallum, R.W., A.F. Ippoliti, C. Cooney, and R.A.L. Sturdevant. A controlled trial of metoclopramide in symptomatic gastroesophageal reflux. N. Engl. J. Med. 296:354, 1977.

A variety of drugs cause gynecomastia by mechanisms yet unexplained. These include busulfan, ethionamide, isonaizid, tricyclic anti-depressants, and on occasion androgens themselves. Most recently, it has been reported that gynecomstia is a common side effect of cymetidine.

VII. DIAGNOSTIC WORKUP

Short of measuring androgen and estrogen kinetics in every patient the evaluation of patients with gynecomastia should probably include the following procedures as a routine:

1. Careful drug history

2. Examination of testes
   a. Both small - Karyotype
   b. Assymetrical - Workup for testicular tumor

3. Evaluation of liver function

4. Endocrine workup
   a. Urinary 17 ketosteroids (elevated in feminizing adrenal states)
   b. Plasma estradiol (helpful if elevated but generally normal)
   c. Plasma LH and testosterone
      1.) If LH is high and T is low, the diagnosis of testicular insufficiency is made (except for those gonadotropin secreting testicular tumors)
      2.) If LH and T are both low, the diagnosis is most likely increased primary estrogen production

Using these various means, we probably reach a satisfactory diagnosis in less than half of patients referred to us for gynecomastia. We believe that many of these undiagnosed patients may represent variant forms of the Klinefelter syndrome, but whether this is in fact the case is unclear. With refinements of plasma E_2 measurements diagnostic accuracy may be improved.

VIII. TREATMENT

A. Surgery

130. Dexter, C.J. Benign enlargement of the male breast. N. Engl. J. Med. 254:996, 1956.

131. Bretteville-Jensen, G. Surgical treatment of gynecomastia. Brit. J. Plastic Surg. 28:177, 1975.

In 228 cases of various etiologies treated conservatively and followed for up to 10 years, no case of carcinoma developed (130). However, there may be a statistically increased chance of carcinoma (27), and indications for surgery include a) psychological disturbances and b) suspected malignancy. Small lesions can be removed through an alveolar incision.

132. Myhre, S.A., R.H.A. Rewalcoba, H.R. Johnson, H.C. Thuline, and V.C. Kelley. The effects of testosterone treatment in Klinefelter's syndrome. J. Pediatr. 76:267, 1970.

The administration of testosterone has little effect when estrogen secretion is elevated, but in profound androgen deficiency states (anorchia, severe viral orchitis) it can have a dramatic effect, on occasion resulting in a melting away of the gynecomastia.

133. Wolf, H., P.O. Masden, and H. Vermund. Prevention of estrogen-induced gynecomastia by external irradiation. J. Urol. 102:607, 1969.

134. Alfthor, O.S. The inhibiting effect of irradiation on gynecomastia induced by estrogen hormone stimulation: an experimental study. J. Urol. 102:905, 1969.

A variety of forms of drug treatments have been tried, including the anti-estrogens clomiphene and the 18-homologue of norethisterone, but unfortunately no suitable control study has ever been performed. The only documented form of

therapy that appears to be any good is irradiation of the breasts prior to the institution of stilbestrol therapy in patients with carcinoma of the prostate. It is effective, and the complication rate is low in this age group.