MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

9/23/71

GYNECOMASTIA

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Case Protocols

1.) [redacted] [redacted] Gynecomastia of Adolescence.

This 15-year old boy noted the onset of tender bilateral breast enlargement, larger on the left, at the age of 13. Over the course of the next year and a half the right breast enlargement subsided completely. The left breast also decreased somewhat in size and became less tender and less subject to irritation from minor trauma and from rubbing clothes. Because of the persistence of the left breast enlargement, however, his parents sought medical advice, and he was ultimately worked up in the [redacted]. By history every other aspect of pubertal development, including body hair, penile growth, voice change, facial hair, and sexual activity were normal for a late adolescent boy. P.E. was normal except for a GII mid-systolic murmur, thought to be physiological, a palpable thyroid gland, and unequivocal left sided gynecomastia with a 2.5 cm disc of breast tissue palpable on that side. Chest X-ray and routine laboratory studies were within normal limits. The family was reassured, and the boy will be followed in the Endocrine Clinic.

2.) [redacted] [redacted] Gynecomastia in a Prepubertal Castrate (Congenital Anorchia).

This 27-year old man was referred here from [redacted], Texas in 1965. He was diagnosed as having bilateral cryptorchidism at 3 years of age, and at age 18 he had undergone an extensive bilateral exploratory operation of the canals at the [redacted] in search of testes; although remnants of the vas deferens were found, no testicular tissue whatsoever was located, and the diagnosis of congenital anorchia was made. No male pubertal development whatsoever occurred in regard to facial hair, body hair, or pubic hair, and the genitalia remained infantile. At age 13 he had noted some subareolar swelling and tenderness. The gynecomastia remained nondescript until about 5 months prior to his admission here when he began to note the development of florid gynecomastia. According to the history he was probably incapable either of ejaculation or erection.

P.E. revealed a 6 foot tall man with a eunuchoid appearance and habitus, striking absence of body and facial hair, the hairline of a child on the forehead, a palpable thyroid, massive bilateral gynecomastia, a small uncircumcised penis with no palpable testes, and no wrinkling of the scrotum. The prostate was not palpable, and the pubic hair distribution was female in character.

The work-up prior to his referral had revealed normal 17-ketosteroid excretion (8.7 mg/day), a male chromatin pattern on buccal smear, a normal 46, XY karyotype, and a PBI of 5.3.

The following special endocrinological studies were performed.

1.) Blood Testosterone 0.06 µg/100 ml (normal 0.5-1.0 µg/100 ml)
Blood Androstenedione 0.07 µg/100 ml (normal 0.05-0.1 µg/100 ml)

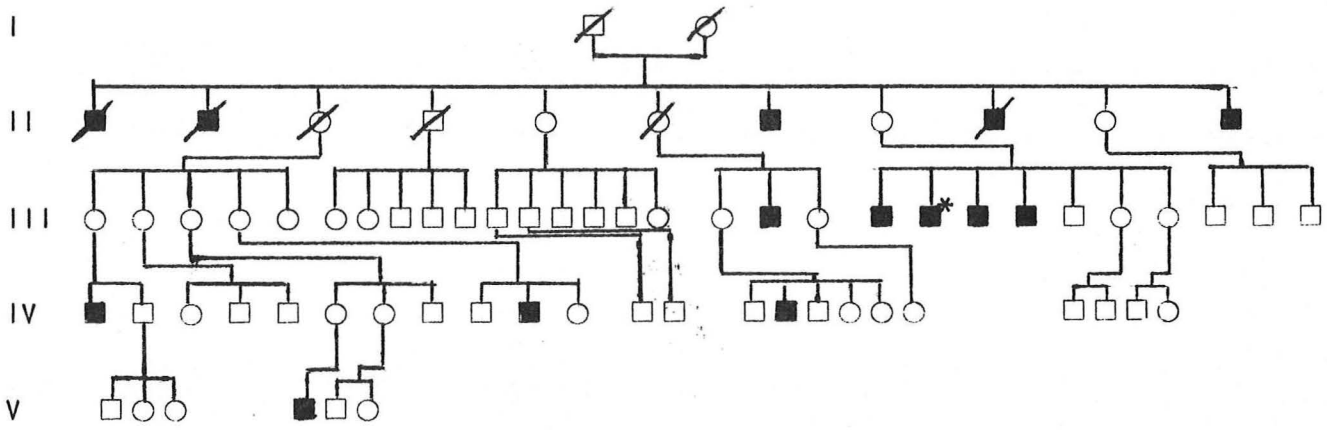
2.) Secretion Rates: Testosterone 0.04 mg/day (N=5-8 mg/day)
Estradiol 57 µg/day (normal)

On the basis of these studies it was concluded that he did not have overproduction of estrogen either from the testes or adrenal gland but that the normal amount of male estrogen was unopposed by testosterone. He refused either to return for a follow-up visit or to undergo a trial of testosterone therapy.

3.) [redacted] [redacted] Male Pseudohermaphroditism (Reifenstein's Syndrome).

This 19-year old boy has had several admissions to the [redacted] and to [redacted] for various procedures as part of a long term plastic repair of a severe hypospadias. He is an affected member of an extensive pedigree of individuals with Reifenstein's Syndrome, a disorder ~~either~~ inherited either as a X-linkted recessive trait or an autosomal dominant, sex-limited defect. Bilateral gynecomastia began at age 14, and he has developed normal male secondary sex characteristics except for scanty facial hair. Findings, in addition to third degree hypospadias in a normal sized adult penis, include azoospermia with thickening and hyaline deposition in the seminiferous tubules of the testes and with grossly normal interstitial cells, and urethrogram revealed a small blind pouch, 0.5 cm deep, proximal to the external sphincter and thought to be a prostatic utricle. The epididymis and vas deferens are rudimentary and end blindly.

Neither he nor any of his affected relatives have agreed to endocrinological work-up. The family have been reported in part (34), and the family tree is shown below:



4.) [redacted] [redacted] Gynecomastia in Postpubertal Failure of the Testes (Bilateral Testicular Atrophy Due to Mumps Orchitis).

This 68-year old man was referred to [redacted] in 1969 because of gynecomastia. He said that he had undergone a normal puberty, and at the age of 18 he had bilateral mumps orchitis, following which both testes became atrophic. Although he never had children he continued to have normal libido until approximately age 45 when he began to develop marked gynecomastia and the onset of a progressive decrease in libido so that for the past 10 years he had been unable to have intercourse. In addition, the frequency of shaving decreased to 2 times a month, and the gynecomastia had continued to worsen so that by the time of his referral he had enormous pendulous breasts. P.E. was otherwise unremarkable except for small 1½ cm, boggy testes with approximately normal sized epididymis, a positive serology, hypertension, and a large lipoma of the shoulder. Routine laboratory studies were within normal limits. The following studies were performed by Dr. Brenner:

Testosterone Secretory Rate 0.84 mg/day (N=5-8 mg/day)
Androstenedione Secretory Rate 2.16 mg/day (normal)

Estradiol Production Rate	37 µg/day
Estradiol Production from T and E_2	40 µg/day
Estradiol Production from Testes	nil

It was concluded that the gynecomastia was the result of testosterone deficiency rather than estrogen excess. Therefore, in [redacted] of 1969 he was begun first on 100 mg testosterone propionate per week and then on 50 mg per week, and finally on 200 mg depo-testosterone every 3 weeks. He immediately noted a striking increase in libido, the frequency of shaving increased to 2 times a week, and his breasts have decreased progressively in size. At present, there is residual breast tissue still palpable bilaterally, but they are probably only about ¼ their maximal size (his bust measurements have decreased 3 inches).

5.) [redacted] [redacted] Gynecomastia Due to Pharmacological Castration (Spirorolactone-induced Gynecomastia).

The diagnosis of primary aldosteronism was established in this 60-year old man during a 1967 hospitalization at Parkland on the basis of a hypokalemic, hypochloremic alkalosis, increased aldosterone excretion and low plasma renin values resistent to volume depletion. Apparently because of an old hemiplegia (the 1967 chart is missing) it was decided to treat him medically. Therefore, from 1967 to 1969 he was followed in the out patient department on 200 mg aldactone per day together with various combinations of other drugs. Neither hypertension nor hypokalemia was adequately controlled on these regimens, and consequently the spirorolactone was increased to 400-800 mg per day in early 1969, resulting in an apparent improvement both in serum potassium and in his blood pressure. During the two year period of aldactone therapy progressively enlarging gynecomastia was noted, and by the time of his rehospitalization in April of 1969 the breasts were very large. (It is worthwhile noting that he was never treated with digitalis and had normal liver function tests.) The following special endocrinological studies were performed:

Testosterone Secretory Rate 1.95 mg/day (N=5-8 mg/day)
Androstenedione Secretion Rate 0.82 mg/day

Estradiol Production Rate	42 µg/day
Estradiol Production from T and E2	43 µg/day
Estradiol Production from Testes	nil

These findings were interpreted as compatible with the possibility of gynecomastia due to spirorolactone-produced inhibition of testosterone biosynthesis.

He subsequently underwent subtotal adrenalectomy for bilateral adrenal cortical adenomas. The gynecomastia disappeared within months, and when retested, the secretion both of androstenedione and of testosterone had returned to normal.

6.) [redacted] [redacted] Gynecomastia in Klinefelter's Syndrome.

This 18-year old boy was admitted to [redacted] in 1968 for a work-up of gynecomastia. He related the appearance of pubic and leg hair at approximately age 13 but had never developed significant facial hair. At age 16-17 he noted bilateral breast enlargement without tenderness or discharge. He had normal erections and ejaculations by history. On P.E. he was found to be obese and to have very scanty facial and body hair; bilateral gynecomastia was present, the disc of breast tissue being approximately 7 cm in diameter on the left and 5 cm on the right, and there was a spider angiomata on the left anterior chest. The testes were 5 cm in largest axis, and the penis and prostate were those of a normal adult male. Urinary 17-beta-steroids (25.4 mg/24 hours), 17-hydroxy-steroid excretion (13.9 mg/24 hours), and pregnanetriol (4.4 mg/24 hours) excretion were normal, as were the routine laboratory studies. The ejaculate volume was 2.0 ml with 100 million sperm/ml, 70% of which were motile. Karyotyping revealed that he has an XY/XXY/XO mosaicism (10% XO, 60% XY, and 30% XXY) of the WBC, establishing the diagnosis of Mosaic Klinefelter's Syndrome.

Endocrinologic work-up conducted by Dr. Brenner of the OB-Gyn Department revealed the following:

1.) Testosterone Production Rate 8.8 mg/24 hours (normal)
2.) Androstenedione Production Rate 3.8 mg/24 hours (normal)
3.)

Total Estradiol Production Rate	108 µg/day (2 X normal)
Estradiol Production from T and E2	70 µg/day
Estradiol Production from Testes	38 µg/day

Dexamethasone suppression test resulted in no decrease in the production of estradiol by the testes, but testicular estrogen production was abolished completely by Depo-Provera.

Since he had normal testosterone production, normal ejaculate, and normal potentia but incomplete virilization and profound gynecomastia, the therapeutic aim in this patient was to attempt to treat the gynecomastia and to promote the

maturation of the secondary sex characteristics if possible by inhibiting estrogen production by the testes since it was concluded that the increased estrogen production provided an adequate explanation for the gynecomastia. Therefore, he had in succession the following drug regimens:

1.) Testosterone propionate, 100 mg per week for eight months resulted in a slight increase in the frequency of shaving and, if anything, a worsening of the gynecomastia.

2.) Depo-Provera, 400 mg per week for 2 months had no noticeable effect on the gynecomastia, hair pattern, external genitalia, or potentia.

3.) Depo-Provera (400 mg per week) and Testosterone (100 mg per week) for 6 months also had no noticeable effect either on the breasts or on the facial hair.

Therefore, it was elected to discontinue all his medicines and to follow his course. He is now married and has normal libido. He continues to be overweight and to have florid gynecomastia, and the spider angiomata of the chest wall have increased in size and number over the past 3 years.

7.) [redacted] Digitalis-induced Gynecomastia.

This 63-year old man with long standing chronic bronchitis developed such severity of dyspnea and anterior chest pain on exertion that he was virtually incapacitated by 1967. He was told that he had a bad heart and was placed on long-acting nitrates and digitalis at that time. He was also diagnosed as having adult onset diabetes mellitus, which was adequately controlled on Orinase. In 1969 he developed a painful enlargement of the right breast which was biopsied in Fort Worth. The biopsy specimen was interpreted as benign gynecomastia by the pathologist. He subsequently developed a painful swelling of the left breast and was referred to Dr. Robert McClelland and hospitalized on the surgery service at Parkland. P.E. revealed a plethoric man with diffuse rales and rhonchi in both lungs, an emphysematous chest, bilateral tender gynecomastia with an absent right nipple, spider angiomata on the chest wall, and either hepatomegaly or a downward displacement of the liver (liver function tests were WNL). Chest X-ray revealed a normal sized heart and typical changes of pulmonary emphysema.

It was felt that this man's pulmonary symptoms were the result of obstructive pulmonary disease, that he had never been in congestive heart failure, and that the gynecomastia was due to digitalis. The digitalis was discontinued, and he was treated with bronchopulmonary toilet. Within 72 hours the tenderness in the breasts had disappeared, and the gynecomastia subsequently is reported to have disappeared.

Table I

Classification of Gynecomastia

I. Physiological Gynecomastia

A. Newborn Gynecomastia
B. Gynecomastia of Adolescence
C. Gynecomastia of Aging

II. Pathological Gynecomastia

A. Deficient Testosterone Production or Action
1. Primary Testicular Deficiency
a. Congenital Deficiencies of Testosterone Production
1. Congenital Anorchia and Cryptorchidism
2. Male Pseudohermaphroditism
b. Postpubertal Testicular Failure
1. Mumps Orchitis
2. Trauma
3. Castration
4. Myotonia Atrophica
5. Spinal Cord Injury, Degenerative Disease of the Spinal Cord, Friedreich's Ataxia
6. Leprosy and Other Forms of Granulomatous Orchitis
7. Renal Failure
8. Radiation Damage to the Testes
2. Pharmacological Castration
a. Spironolactone Therapy
b. Cyproterone Acetate and Other Anti-Androgens

B. Increased Estrogen
1. Testicular Estrogen Production
a. Klinefelter's Syndrome
b. Testicular Tumors
Sertoli Cell Tumors
Seminomas
c. Embryonal Tumors of the Testes, Particularly Choriocarcinoma
2. Bronchogenic Carcinoma
3. Adrenal Estrogen Production
Feminizing Adrenal Carcinoma
4. Peripheral Estrogen Production
a. Cirrhosis of the Liver
b. Starvation Gynecomastia?
5. Drug-Induced Hyperestrogenism
a. Stilbestrol Therapy
b. Digitalis
c. Amphetamines (Estrogen Contaminant)
d. Gonadotrophins

C. Gynecomastia of Uncertain Etiology
1. Graves' Disease
2. Methyltestosterone and DOCA
3. Phenothiazine Therapy
4. Miscellaneous Diseases

Table II

Identifiable Causes of Gynecomastia in Three Large Series of Cases

Reference	(2)	(1)	(5)	Total
Number of Patients	108	92	203	403
Per Cent of Cases Attributed To:				
A. Deficient Testosterone Production	18	9	22	16%
B. Increased Estrogen Secretion	27	16	4	16%
C. Uncertain	56	73	74	68%

Figure 1

REGULATION OF TESTOSTERONE FORMATION IN MEN
HYPOTHALAMIC-PITUITARY-LEYDIG CELL AXIS (14)

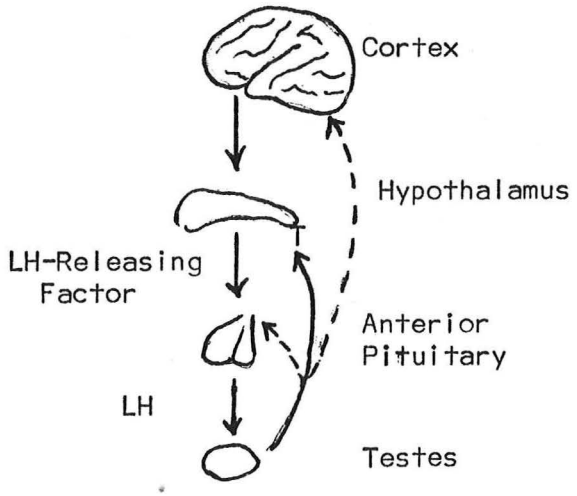


Figure 2

CHANGE IN SERUM LH AND TESTOSTERONE DURING PUBERTY IN BOYS (Ref. 15 and 16)

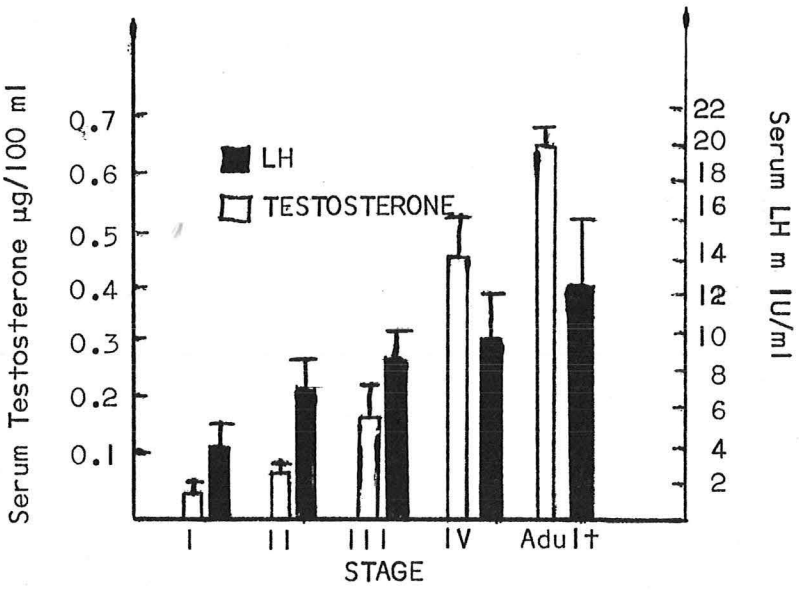


Figure 3

FORMATION OF ESTROGEN IN NORMAL ADULT MEN (Ref. 17)

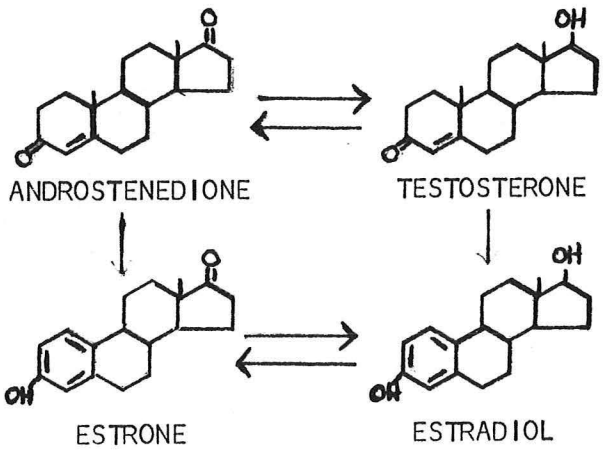
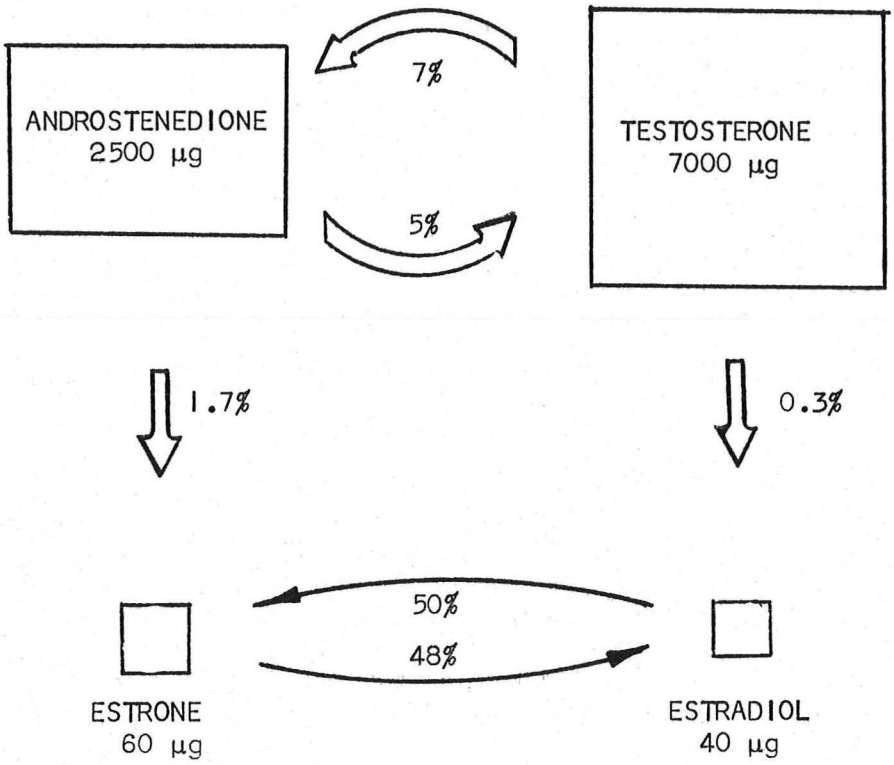


Figure 4

QUANTATIVE ASPECTS OF ESTROGEN FORMATION
IN A NORMAL MAN (17)



REFERENCES

I. GENERAL REVIEWS OF GYNECOMASTIA

1. Wheeler, C. E., E. P. Cowley, H. T. Gray, and A. C. Curtis. Gynecomastia: A Review and analysis of 160 cases. Ann. Int. Med. 40:985, 1954.

2. Sirtori, C., and U. Veronesia. Gynecomastia. A review of 218 cases. Cancer 10:645, 1957.

3. Treves, N. Gynecomastia. Cancer 11:1083, 1958.

4. Hall, P. F. Gynecomastia. Ch. in Progress in Endocrinology. New York: Grune and Stratton, 1960, p. 468.

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

These references which summarize the cumulative clinical experience in approximately 2000 cases of gynecomastia are of value only as catalogues of various associated disease states. Since the vast majority of the associations with other disease states are rare and the bulk of the clinical experiences was gleaned prior to the development of quantitative endocrine techniques, it is impossible to be certain what drugs were being taken, whether the liver function tests were normal, whether an underlying endocrinopathy was missed. Therefore, it is impossible to deduce any sort of reliable data as to frequency of underlying endocrinological abnormalities or the pathogenesis of the process from these studies. However, the data shown in Table II have been assembled to represent minimal incidence figures from the three reviews which lend themselves to this type of analysis.

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

This reference is 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.

II. EMBRYOLOGY OF THE BREAST

7. Raynaud, A. Morphogenesis of the mammary gland. Ch. in Milk: The Mammary Gland and Its Secretions. Vol. 1. New York: Academic Press, 1961, p. 3.

8. 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, 1971.

As is true of the other tissues of accessory reproduction, the differentiation of the embryonic mammary gland is regulated by testosterone. In this instance testosterone exerts a negative influence by producing a partial regression of the mammary bud. In the absence of testosterone normal female differentiation takes place whereas in the male fetus testosterone causes a regression of the duct system which connects to the nipple and results in incomplete development of the nipple itself. There are at least three clinical implications of this phenomenon: 1.) Since the development is incomplete in the embryo, later breast development in the usual feminized male falls short of the development seen in the female. 2.) In pseudohermaphroditic states in which fetal testosterone is either deficient or inactive, the usual testosterone-induced regression may not take place, setting the stage for the florid breast development seen in these states. 3.) Most men lack a complete secretory duct system for milk secretion, even if the remainder of the endocrinologic setting were appropriate for milk secretion.

III. ROLE OF ESTROGENS IN BREAST DEVELOPMENT

9. Geschickter, C. F. Diseases of the Breast. Philadelphia, J. B. Lippincott Co., 1945, p. 15.

10. Tindal, J. S., and M. L. McNaught. Hormonal factors in breast development and milk secretion. Ch. in Modern Trends in Endocrinology. New York: P. B. Hoeber, Inc. 1958, p. 188.

11. Cowie, H. T., and S. J. Folley. The mammary gland and lactation. Ch. in Sex and Internal Secretions, 2rd Ed., Baltimore: The Williams and Wilkins Co., 1961, p. 590.

In most species estrogen in remarkably small concentration is the physiological hormone that stimulates the growth and division of the lobule duct system of the breast, and in man the percutaneous injection of estrogen into the breast directly is very effective in this regard. In order to produce true alveolar development at the ends of the duct, however, in most animals the synergistic effect of progesterone is required, usually an estrogen:progesterone ratio of 1:20-1:100 being optimal. Whether testosterone (which under some experimental circumstances can stimulate duct proliferation) does so by a progesterone-like effect or by serving as a precursor for estrogen is moot. In the normal man, following puberty, remnants of a duct system can be seen histologically, but the living cells are atrophic.

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

The formation of milk in the differentiated breast is one of the most complex endocrinological events known, requiring in organ explant systems after the essential roles of the sex steroids is complete, insulin, growth hormone, hydrocortisone, prolactin or placental lactogen, and an epithelial growth factor to get true milk secretion. The complexity of this system (plus the incomplete connection of the duct system to the nipple in many men) probably explains why milk secretion by the male breast is unusual even when the breasts reach enormous size.

IV. REGULATION OF TESTOSTERONE AND ESTROGEN PRODUCTION IN MEN

13. Lipsett, M. B., and S. G. Korenman. Androgen metabolism. JAMA 190: 757, 1964.

14. Lipsett, M. B., C. J. Migeon, M. A. Kirschner, and C. W. Bardin. Physiologic basis of disorders of androgen metabolism. Ann. Int. Med. 68:1327, 1968.

Testosterone secretion in the male arises almost exclusively from the testis and is under control of LH (ICSH); the classical characteristics of a negative feedback system with respect to the Leydig cell pituitary axis have been demonstrated, and it is likely that the major effect is via regulation of a LH-FSH releasing factor in the hypothalamus; and there is good reasons to believe that testosterone affects cerebral cortical and interior pituitary function as well.

15. Fraser, S. D., F. Gafford, and R. Horton. Plasma androgens in childhood and adolescence. J. Clin. Endocrinol. 29:1404, 1969.

16. Johanson, A. J., H. Guyda, E. Light, C. J. Migeon, and R. M. Blizzard. Serum luteinizing hormone by radioimmunoassay in normal children. J. Pediatrics 74:416, 1969.

Plasma testosterone rises during puberty over an extended period of time to reach the normal adult male level, suggesting that the completion of puberty is associated with a slowly increasing testosterone secretion. The increasing testosterone levels correlate well with the rising testosterone levels. It is likely that the pubertal rise is produced by the development of insensitivity to feedback by testosterone at some critical site in the pituitary-CNS axis since prepubertal castration in boys results in a rise in serum LH to values seen in adult castrate men. This suggests that the small amount of testosterone secreted by the immature testis does cause feedback inhibition of LH secretion in the immature state and that following puberty a higher level of testosterone is required to exert this effect.

17. Brenner, P. F., H. T. Hutchinson, P. K. Siiteri, and P. C. MacDonald. The origin of estrogen in normal males and in males with gynecomastia. Program of the Endocrine Society, p. 38, 1969.

In contrast to testosterone which is secreted mainly by the testis, estrogen in the normal adult man arises principally from aromatization of plasma androstenedione and testosterone at some peripheral site(s). In a group of normal men, the daily production of estrone (averaging 60 μg/day) could be accounted for as follows: 42 μg from androstenedione and 18 μg from estradiol. The average daily production of E_2 (40 μg/day) is derived from circulating testosterone (20 μg) and from circulating estrone (20 μg). The rate of this peripheral estrogen formation rises with age in both men and women and is strikingly elevated in cirrhosis of the liver.

18. Leonard, J. M., R. H. Flocks, and S. G. Korenman. Estradiol secretion by the human testis. Proceedings of the Endocrine Society, 1971, p. 99.

19. Jenner, M. R., R. P. Kelch, and M. M. Grumbach. Plasma estradiol and testosterone gradients across the human, simian, and canine testis. Proceedings of the Endocrine Society, 1971, p. 46.

It is clear that the human testis (which contains a complete enzyme machinery for estrogen synthesis) also secretes a small amount of estrogen, but it is likely that this is not a major source of estrogen secretion in man (in contrast to the stallion and boar).

To summarize, in men testosterone secretion is predominantly from the testes and is under precise regulatory control by the hypothalamic pituitary axis. Estrogen formation, however, occurs in the peripheral tissues and is not under known regulatory control; presumably the rate of formation in normal individuals depends upon the amount of substrate available.

V. HISTOPATHOLOGY OF GYNECOMASTIA

20. Karsner, H. T. Gynecomastia. Am. J. Pathology 22:225, 1946.

21. Lenson, N. Enlargement of the male breast in naval personnel. Am. J. Surg. 82:325, 1951.

22. Levy, D. M., J. B. Erich, and A. B. Hayles. Gynecomastia. Postgraduate Medicine 36:234, 1964.

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

Histologic changes in gynecomastia correlate better to the duration rather than to 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 such 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 the 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. Furthermore, although galactorrhea is rare (in virtually all series only 1-3% have secretion from the nipple), on microscopic examination the incidence of secretions in ducts approaches 30% of the cases; this secretion is serous, and in the rare instances in which it is excreted from the nipple it does not resemble colostrum. True galactorrhea in the male is exceedingly rare. Hall (Ref. 4) has emphasized that the changes in the human breast produced by estrogen administration resemble those in clinical gynecomastia both in regard to histologic features and in hyaluronic acid content.

VI. CLASSIFICATION OF GYNECOMASTIA

A. Physiological Gynecomastia

1. Gynecomastia in the Newborn

24. Bronstein, I. P., and E. Cassorla. Breast enlargement in pediatric practice. Med. Clin. N. America 30:121, 1946.

Also Ref. 4.

The visible enlargement of the neonatal breast that occurs in many normal newborn may be accompanied by the secretion of a thin white fluid (Witches' Milk). This condition probably results from the action of maternal and/or placental estrogens and lactogen. The swelling ordinarily disappears in a few weeks, although it may persist longer in exceptional cases.

2. Adolescent Gynecomastia

25. Jung, F. T., and A. L. Shafton. Mastitis, mastoplasia, mastalgia, and gynecomastia in normal adolescent males. Ill. Med. J. 73: 115, 1938.

26. Nydick, M., J. Bastos, J. H. Dale, Jr., and R. W. Rawson. Gynecomastia in adolescent boys. JAMA 178:449, 1961.

27. Decont, J., M. F. Joyle, and J. P. Massey. Etude de 49 cas de gynecomasties apparemment isolee de l'adolescence. La Semaine des Hopitaux 21:1266, 1962.

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. On the basis of the fact that it is transient in some and occurs earlier in some, 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 as late as 21, and although in virtually all patients it is bilateral at some time, 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. It is interesting that adolescent gynecomastia is said to correlate closely with the presence of adolescent goiter.

The pathogenesis of this feature of puberty has never been elucidated. Any of several possibilities could account for it: 1.) maturation of the peripheral conversion system for estrogen formation (or the availability of androstenedione for substrate) could precede the completion of maturation of the Leydig cell-LH system for testosterone synthesis, resulting in a temporary relative estrogen excess, 2.) the sensitivity of the breast to estrogen stimulation is greater in the immature than in the mature animal, and breast growth in the adolescent might occur temporarily even though the E/T ratios were identical to the adult levels, and 3.) it is possible of course that there is some additional source of estrogen during the disequilibrium state of puberty, either from the testis or adrenal, direct or indirect, which has not been elucidated.

3. Gynecomastia of Aging

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

Also see Ref. 4.

That gynecomastia occurs in otherwise healthy normal men with aging has been known for many years; because it can also be an indication of some serious underlying disease, involutional gynecomastia can only be diagnosed by exclusion. What is remarkable, however, is the frequency; in the only study available of the autopsy incidence of gynecomastia, Williams reported that 40% of aged men have true gynecomastia and that this incidence represents a true rise in frequency with age. A likely explanation for this phenomena is the rise in the peripheral conversion of androgens to estrogens with age (17); in addition, diminution of circulating testosterone with age (controversial and not well documented) may play a part, and no real attempt has been made to correlate the occurrence of involutional gynecomastia with digitalis therapy, liver function, tests, etc., and it is possible that the entity, if it exists at all, is rare.

B. Pathological Gynecomastia

1. Deficient Testosterone Production or Action

a. Congenital Deficiency

1.) Anorchia and Cryptorchidism

29. Howard, R. P., R. C. Sniffer, F. A. Simmons, and F. Albright. J. Clin. Endocrinol. 10:121, 1950.

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

Also Ref. 1.

The exact incidence of gynecomastia in congenital anorchia is uncertain. In four patients (all below the age of 26) Howard et al. did not observe gynecomastia but in the study by Heller, Nelson, and Roth (30) 50% of affected men had gynecomastia. The ultimate pathogenesis of the disorder is uncertain; it is presumed that enough androgen is secreted by the fetal testis to complete differentiation of the external genitalia and male phenotype but that formation of a true testes never occurs. At any rate, the pathogenesis of the gynecomastia in this condition appears to be straightforward (Case 2). In this individual testosterone formation was less than 10% of normal whereas estradiol (ultimately from androstenedione) was normal. It seems reasonable to conclude that feminization occurred because of normal estrogen formation in the presence of failure of androgen secretion.

Gynecomastia has also been well described in cryptorchidism (Ref. 1 for example), although its incidence is uncertain. However, chorionic gonadotrophin administration to cryptorchid males frequently results in gynecomastia, which subsides when the drug is discontinued.

2.) Male Pseudohermaphroditism and Hereditary Gynecomastia

31. Lubs, H. A., O. Vilon, and D. M. Bergenstal. Familial male pseudohermaphroditism with labial testes and partial feminization. J. Clin. Endocrinol. 19:1110, 1959.

32. Gilbert-Dreyfus, S., C. A. Sebooun, and J. Belaisch. Etude d'un cas familial d'androgynoidisme avec hypospadias grave, gynecomastie, et hyperestrogenie. Annales d'Endocrinologie 18:93, 1957.

33. Rosewater, S., G. Gwinup, and G. J. Hamwi. Familial gynecomastia. Ann. Int. Med. 63:377, 1965.

34. Bower, P., C. S. N. Lee, C. J. Migeon, N. M. Kaplan, P. J. Whalley, V. A. McKusick, and E. C. Reifenstein. Hereditary male pseudohermaphroditism with hypogonadism, hypospadias, and gynecomastia. Ann. Int. Med. 62:252, 1965.

35. Donohue, J. P. Hypogonadism in chromatin-negative phenotypic male subjects. J. Urol. 103:645, 1970.

36. Linquette, M., P. Fosseti, J. Lefebrune, M. Decoulx, and J. Dupont-Lecompte. Gynecomastia familiale avec hypospadias: Syndrome de Reifenstein. Ann. d'endocrinologie 28:381, 1967.

37. Wieland, R. G., R. L. Falk, J. N. Taylor, and G. J. Hamwi. Studies of male hypogonadism. I. Androgen metabolism in a male with gynecomastia and galactorrhea. J. Clin. Endocrinol. 27:763, 1967.

In addition to testicular feminization, gynecomastia can occur as a portion of hereditary male pseudohermaphroditism, of which the most common type is the Reifenstein syndrome, which consists of hypospadias and gynecomastia and is typified by Case 3. At least 6 different pedigrees with this disorder have now been reported, all inherited as a X-linked recessive or a sex-limited, autosomal dominant. The pathogenesis of the gynecomastia has never been well studied except in one case (ref. 37) who had a very low testosterone excretion rate and no testosterone production by the testes. Estrogen formation was not measured. If deficient androgen production does turn out to be a characteristic feature of this disorder, then it is reasonable that deficient testosterone production in the fetus could cause incomplete development of the penis and incomplete male regression of the breast bud, thus setting the stage not only for massive breast enlargement in later life but for the occasional galactorrhea reported in ref. 37.

38. Wallach, E. E., and C.-R. Garcia. Familial gynecomastia without hypogonadism. J. Clin. Endocrinol. 22: 1201, 1962.

Familial gynecomastia has also been reported to be inherited as an ordinary autosomal trait. Unfortunately this family was not well studied, and it is possible that 2 of the four individuals had adolescent gynecomastia.

39. New, M. I. Male pseudohermaphroditism due to 17α-hydroxylase deficiency. J. Clin. Invest. 49:1930, 1970.

In this male pseudohermaphrodite with gross gynecomastia, deficient testosterone secretion was clearly due to a specific enzymatic block in testosterone biosynthesis. Clearly, all hereditary forms of gynecomastia and male pseudohermaphroditism deserve a complete endocrinologic work-up since testosterone replacement may be very effective in preventing gynecomastia when testosterone production is deficient.

b. Postpubertal Failure of the Testes

1.) Mumps Orchitis

40. Weaver, C. A. Mumps orchitis and testicular atrophy. I. Occurrence. Ann. Int. Med. 32:1066, 1950.

41. Weaver, C. A. Mumps orchitis and testicular atrophy. II. A factor in male sterility. Ann. Int. Med. 32:1075, 1950.

Mumps orchitis is the commonest cause of testicular atrophy in this country (about 2 X as frequent as trauma). 5% of all cases of mumps have orchitis, and in a third of these there is a residual atrophy. Thus, one out of every hundred adult men has at least one atrophic testis, and one per thousand has bilateral testicular atrophy on this basis, many of whom do not become androgen deficient. At any rate, testicular atrophy due to mumps orchitis was early recognized as a cause of gynecomastia (Ref. 1-4). See Case 4. In this patient testosterone production was deficient in the presence of normal estrogen production, and the gynecomastia has improved on androgen replacement.

2.) Trauma

3.) Castration

42. Woodham, C. W. B. Hyperplasia of the male breast. Lancet ii:307, 1938.

Gynecomastia clearly may follow castration in the adult male as well as testicular atrophy.

4.) Myotonia Atrophia

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

Testicular atrophy occurs in 80% of cases of myotonia atrophica; although primarily a spermatogenic failure, assays of urine show decreased androgens. Gynecomastia is common.

5.) Spinal Cord Injury, Degenerative Diseases of the Spinal Cord, Friedreich's Ataxia

44. Cooper, I. S., E. H. Ryearson, A. A. Bailey, and C. S. MacCarty. The relation of spinal cord disease to gynecomastia and testicular atrophy. Staff Proceedings of the Mayo Clinic 25:320, 1950.

Mammary gland enlargement and testicular atrophy are common among men who have suffered severe spinal cord injury and in patients who have degenerative lesions of the spinal cord, Friedreich's ataxia, and syringomyelia. Biopsy of the testis revealed atrophy and hyalinization.

6.) Leprosy and Other Granulomatous Orchitis

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

Clearly, gynecomastia in leprosy is due to testicular atrophy, possibly due to involvement of the blood supply or secondary to the neuropathy.

7.) Renal Failure

46. Freeman, R. M., R. L. Lawton, and M. O. Ferring. Gynecomastia: An endocrinologic complication of hemodialysis. Ann. Int. Med. 69:67, 1968.

47. Chen, J. C., D. G. Vidt, E. M. Zorn, M. C. Hallberg, and R. G. Willard. Pituitary-Leydig cell function in uremic males. J. Clin. Endocrinol. 31:14, 1970.

Serum testosterone falls to 30% of normal values in uremia and serum LH is high, suggesting that the testis in this condition cannot respond to a normal LH challenge. In addition, the response to chorionic gonadotrophin is poor. It is likely that this is the cause of the gynecomastia and that dialysis is fortuitous - keeping the patients alive long enough to develop gynecomastia.

8.) Radiation Damage

48. Stokes, J. F. Unexpected gynecomastia. Lancet ii:911, 1962.

It is likely that a significant amount of gynecomastia in cancer (particularly Hodgkin's disease) may be secondary to testicular atrophy resulting from radiation and/or inanition.

2. Pharmacological Castration

a. Spirorolactone Therapy

49. Clark, E. Spirorolactone therapy and gynecomastia. JAMA 193:157, 1965.

This paper (which contains a detailed review of the subject and a complete bibliography on spironolactone-induced gynecomastia) emphasizes that gynecomastia may appear with doses as low as 50 mg per day. In some cases digitalis may also be a factor.

50. Arth, G. E., A. A. Patrhett, R. L. Bugianesi, T. Jefapoulos, L. H. Peterson, L. H. Sorett, E. A. Ham, and N. G. Brink. Steroidal androgen biosynthesis inhibitors. Abstracts III. Int. Cong. on Hormonal Steroids. Excerpta Medica Int. Cong. Series #210, 1970.

51. Arth, G. E., H. Schwann, L. H. Sorett, and M. Glitzen. Aldosterone antagonists 2'3'α-tetrahydrofuran-2-spiro-17-(4-androsten-3-one) and related compounds. J. Med. Chem. 6:617, 1963.

Spironolactones decrease testosterone biosynthesis by inhibiting the 17,20 lyase which converts 17-hydroxyprogesterone to androstenedione. The clinical phenomenon of diminished testosterone due to spironolactone therapy is well illustrated by Case 5 who had normal estrogen production and low testosterone and low testosterone and androstene production rates and whose gynecomastia disappeared when the spironolactone was discontinued.

b. Cyproterone Acetate and Other Anti-Androgens

52. Caplan, R. M. Gynecomastia from a non-estrogenic anti-androgen. J. Clin. Endocrinol. 27:9, 1967.

53. Geller, J., G. Vazakos, B. Fruchtinay, H. Newman, K. Nakao, and A. Loh. The effect of cyproterone acetate on advanced carcinoma of the prostate. Surgery, Gynecology and Obstetrics 127:748, 1968.

Although so-called anti-androgens may in part inhibit the peripheral action of testosterone (and thus cause a functional castration), in fact they probably work primarily by inhibiting testosterone biosynthesis. In the study reported in Ref. 3, a fall in blood testosterone from 0.70 µg% to 0.25 µg% was associated with the development of gynecomastia.

B. Increased Estrogen Production

1. Testicular Estrogen Production

a. Klinefelter's Syndrome

54. Klinefelter, H. F., E. C. Reifenstein, and T. Albright. Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism, and increased excretion of follicle-stimulating hormone. J. Clin. Endocrinol. 2:615, 1942.

55. Nelson, W. O., and C. G. Heller. Hyalinization of the seminiferous tubules associated with normal or failing Leydig cell function. Microscopic picture in the testis and associated changes in the breast. J. Clin. Endocrinol. 5:13, 1945.

56. Federman, D. D. Abnormal Sexual Development. Philadelphia: W. B. Saunders Co., 1967.

As originally described, gynecomastia was an invariable part of Klinefelter's syndrome, in fact only about 80% of affected men develop gynecomastia. In part, the gynecomastia, as the elevated LH secretion, is due to diminished testosterone secretion, and the average value for serum testosterone in Klinefelter's syndrome at the MGH is 0.25 µg% (normal 0.4-0.7 µg%). However, as is illustrated in Case 6, diminished testosterone secretion cannot be the principal cause of gynecomastia in this condition, for this mosaic Klinefelter's had normal testosterone secretion (as do about 20% of typical XXY patients). Instead, the gynecomastia can be explained by abnormal testicular estrogen production.

57. Myhoe, S. A., R. H. A. Ruvalcoba, H. R. Johnson, H. C. Thuline, and V. C. Kelley. The effects of testosterone treatment in Klinefelter's syndrome. J. Pedi. 76:267, 1970.

Increased testicular estrogen probably explains why testosterone treatment is relatively ineffective in treating gynecomastia of Klinefelter's syndrome. Rationally, therapy should be addressed either to inhibiting the testicular production of estrogen (ineffective in Case 6) or inhibiting the peripheral action of estrogen or to cosmetic surgery.

b. Testicular Tumors (Sertoli Cell Tumors and Seminomas)

58. Teilum, G. Estrogen-producing Sertoli cell tumors of the human testis and ovary. J. Clin. Endocrinol. 9:301, 1949.

59. Treves, N. Gynecomastia. The origins of mammary swelling in the male: An analysis of 406 patients with breast hypertrophy. Cancer 11:1083, 1958.

(Also Ref. 3)

Estrogenizing tumors of the testis cause profound gynecomastia, impotence, and other evidence of feminization; while the most striking degrees of feminization occur in Sertoli cell tumors, in Ref. 58 it is pointed out that gynecomastia in testicular tumors is more common in seminomas (because seminomas are more common). Although androgen deficiency may play a role, it is very likely on the basis of a variety of types of evidence that the major factor is increased estrogen production. Interestingly, the source of the estrogen has apparently never been elucidated; it could be due to direct secretion by the testes or to increased production of a weak androgenic estrogen precursor such as androstenedione.

c. Embryonal Tumors of the Testis and Choriocarcinoma

60. Gilbert, J. B. Studies in malignant testis tumors: Syndrome of choriogenic gynecomastia. J. Urology 44:345, 1940.

(Also Ref. 3, 58, and 17)

Choriocarcinoma in men causes profound gynecomastia with striking enlargment of the areolae. It accounts for about half of the gynecomastia seen in testicular tumors. Although the increased estrogen production was well known in this condition and presumed to be the consequence of increased gonadotrophin secretion, the site of the increased estrogen production was not clarified until Brenner, Siiteri, and MacDonald (17) demonstrated that the enormous estradiol production (525 μg/day) is due to increased conversion of DHIA sulfate to E_2.

2. Bronchogenic Carcinoma

61. Krant, M. J. Estrogen hyperfunction in patient with non-endocrine cancer. Arch. Int. Med. 115:464, 1965.

62. Becker, K. L., J. Cattrell, C. F. Moore, J. L. Winnaeker, M. J. Matthews, and S. Katz. Endocrine studies in a patient with a gonadotrophin-secreting bronchogenic carcinoma. J. Clin. Endocrinol. 28:809, 1968.

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

64. Barlow, J. J., and M. J. Krant. Pulmonary hypertrophic osteoarthropathy, spider angiomata, and estrogen hyperexcretion in neoplasms. Ann. Int. Med. 70:581, 1969.

Carcinoma of the lung not only produces an increase in gonadotrophin levels in urine and blood but a striking increase in estrogen excretion as well, and the level of gynecomastia clearly correlates with the estrogen excretion. While, as in the case of choriocarcinoma, it is assumed that the hyperestrogenism is the result of gonadotrophin formation as a part of the malignant process, the precise site and mechanism of the hyperestrogenism have not been elucidated. Although some workers have postulated that this may be adrenal in origin, increased formation of estrogen precursors by testis and/or adrenal and increased peripheral conversion seem more likely (17).

3. Adrenal Estrogen Production

Feminizing Adrenal Carcinoma

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

66. Bacon, G. E., and G. H. Lowrey. Feminizing adrenal tumor in a six-year old boy. J. Clin. Endocrinol. 25:1403, 1965.

67. Gabrilove, J. L., G. L. Nicolis, R. U. Hausknecht, and H. H. Watiz. Feminizing adrenocortical carcinoma in a man. Cancer 25:153, 1970.

Although feminizing adrenal carcinoma is rare (only about 40 cases have been reported) it is associated with fantastic feminization and with secretion rates of estradiol of from 2000-8000 µg/day, regressing to normal after resection of the tumor. Testosterone excretion, in contrast, is normal. The source of the estrogen is either direct formation or increased secretion of precursors and consequently increased peripheral formation of estrogen. In contrast, feminization is exceedingly rare in adrenal cortical hyperplasia.

This condition should be easy to diagnose since so far as I have been able to tell this is the only form of gynecomastia associated with increased 17-ketosteroid excretion in the urine, an almost universal finding in these carcinomas.

4. Increased Peripheral Estrogen Production

a. Cirrhosis of the Liver

68. Lloyd, C. W., and R. H. Williams. Endocrine changes associated with Laennec's cirrhosis of the liver. Am. J. Med. 4:315, 1948.

69. Barr, R. W., and S. C. Sommers. Endocrine abnormalities accompanying hepatic cirrhosis and hepatoma. J. Clin. Endocrinol. 17:1017, 1957.

70. Zubiran, S., and F. Gomez-Mont. Endocrine disturbances in chronic human malnutrition. Vitamins and Hormones 11:97, 1953.

The exact incidence of gynecomastia in cirrhosis of the liver is uncertain; in one series (ref. 68) 23 of 55 cases had gynecomastia. One third or more of cases of cirrhosis have testicular atrophy by biopsy - decreased germinal epithelium, complete lack of spermatogenesis, and both small size and decreased number of interstitial cells.

71. Rupp, J., A. Cantarow, A. E. Rakoff, and K. E. Paschkis. Hormone excretion in liver disease and in gynecomastia. J. Clin. Endocrinol. 11:688, 1951.

72. Cedard, L., A. Mosse, and H. P. Klatz. Les oestrogenes plasmatiques dons les gynecomasties et les hepatopathies. Annales d'Endocrinologie 31:453, 1970.

(Also Ref. 17)

However, the major endocrinological change in cirrhosis is almost certainly elevated estrogen production. Whether the elevation of estrogen is due to actual increased formation by the liver or a shunting of estrogen so formed into the peripheral blood rather than into the portal system is unclear, but the net effect is identical, namely an increased secretion of estrogen into the circulation. In Ref. 72 is reported a study in which the degree of gynecomastia correlated well with the level of blood estradiol; while the methodology employed was questionable, there seems little doubt that enhanced estrogen formation rather than defective androgen synthesis is the principal cause of gynecomastia in cirrhosis of the liver. Gynecomastia is much less common in most series than spider angiomata.

73. Kark, R. M., G. R. Money, and C. R. Paynter. Refeeding gynecomastia in cirrhosis of the liver. Am. J. Med. Sci. 222:154, 1951

(Also Ref. 70)

A peculiar feature of the gynecomastia of cirrhosis is that it may appear or worsen during refeeding of the patients in the hospital.

b. Starvation Gynecomastia?

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

(Also Ref. 70 and 73)

Approximately 15% of the American prisoners of war in Japanese prison camps developed gynecomastia. This study contains a very good review of the literature and bibliography on starvation gynecomastia. About a third of the cases developed during refeeding following release and the others developed during imprisonment, frequently associated with temporary increases in the food supply. 70% of the cases were bilateral, and in the vast majority the gynecomastia disappeared within five to seven months. Infectious hepatitis and liver disease may play a role, and a large number of the cases had spider angiomata, suggestive of cirrhosis and fatty infiltration of the liver, although many had normal liver function tests. Although the exact etiology has never been clarified, the similarities to cirrhosis are so striking that it seems reasonable to conclude that increased estrogen formation or decreased turnover may play a role, possibly along with inhibited androgen biosynthesis.

5. Drug-induced Hyperestrogenism

a. Estrogen Therapy

75. Hendrickson, D. A., and W. R. Robertson. Diethylstilbestrol therapy. Gynecomastia. JAMA 213:468, 1970.

This recent review contains a fairly good and up-to-date review of the stilbestrol-induced gynecomastia that is a constant feature of patients with carcinoma of the prostate treated with estrogens. In addition, this article points out that when progestational agents are used in addition

(delalutin) the breasts may secrete fluid in some instances. This type of gynecomastia along with that seen in adrenal carcinoma and male pseudo-hermaphroditism is probably the most severe gynecomastia described.

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

77. Landolt, R., and G. Murset. Premature signs of puberty as sequelae of unintentional estrogen administration. Schweiz. Med. Wchnschr. 98:638, 1968.

Younger individuals are much more sensitive to estrogens and may develop striking gynecomastia even with dermal ointments containing estrogens, and gynecomastia has been reported in children of workers in a stilbestrol plant who supposedly absorbed the hormone from the father's clothing.

78. Ozsaylu, S., and B. Corbacioglu. Oral contraceptives for hemophilia. Lancet 1:1001, 1967.

This paper serves as a reminder that estrogens given in any form to men may result in striking gynecomastia.

b. Digitalis

79. LeWinn, E. B. Gynecomastia during digitalis therapy. NEJM 248:316, 1953.

80. Harrison, C. E., and N. E. Davies. Unusual reactions to common cardiovascular drugs. J. Med. Assn. Georgia 59: 117, 1970.

Although digitalis-induced gynecomastia is a well known entity, many aspects of it are puzzling. LeWinn (79) pointed out that a large percentage of cases of digitalis-induced, gynecomastia have abnormal liver function tests, implying that this may be a significant factor in the disorder. The incidence has never been studied in detail but in ref. 80, it is stated that 10% of men who have been on digitalis for a year develop gynecomastia, and it is frequently asymmetrical and occasionally unilateral. Case 7 is a typical example of digitalis-induced gynecomastia.

81. Novak, A., L. G. Koss, and J. S. LaDoe. Estrogen-like activity of digitalis. JAMA 194:142, 1965.

At any rate the feminizing effect of digitalis is clearly due to its role as an estrogen precursor. Of 20 post-menopausal women taking digitalis for $>$ 20 years all showed marked estrogenic effects upon vaginal smear.

c. Amphetamines

The early preparations of amphetamines were said to produce gynecomastia as the result of contaminating estrogen in the drug.

d. Gonadotrophins

82. Maddock, W. O., and W. O. Nelson. The effects of chorionic gonadotrophin in adult men. J. Clin. Endocrinol. 12:985, 1952.

(Also Ref. 24)

As might have been predicted from the findings in bronchogenic carcinoma and choriocarcinoma in which increased gonadotrophin secretion is associated with feminization including gynecomastia and increased estrogen secretion, the administration of chorionic gonadotrophin both to children and to adults results in increased excretion of urinary estrogens, increase in size of the Leydig cells, and in gynecomastia. As ia true in hypergonadotrophin secretion of tumors, the mechanism of the increased estrogen secretion is not clear.

C. Gynecomastia of Uncertain Etiology and Importance

1. Hyperthyroidism

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

84. Becker, K. L., J. L. Winnacken, M. J. Matthews, and G. A. Higgins. Gynecomastia and hyperthyroidism. An endocrine and histological investigation. J. Clin. Endocrinol. 28:277, 1968.

Although the association of gynecomastia and hyperthyroidism has been known for many years to occur, recent studies have suggested that it is more common than previously suspected. In this series of 40 men with Graves' disease, 15 were found to have gynecomastia, and approximately a third of these have abnormal liver function tests.

85. Hellman, L., B. Zumoff, and T. F. Gallagher. Influence of thyroid hormone on estrogen metabolism in man. J. Clin. Endocrinol. 22: 389, 1962.

Although the pattern of estrogen degradation changes in thyrotoxicosis, it is not clear what the relation is between this excretory pattern and gynecomastia actually. Some authors have argued that gynecomastia in Graves' disease correlates best with LATS titer.

2. Methyltestosterone and DOCA

86. McCullough, E. P. Methyltestosterone. I. Androgenic effects and the production of gynecomastia and oligospermia. J. Clin. Endocrinol. 1:496, 1941.

87. Lawrence, R. D. Gynecomastia produced by DOCA. Brit. Med. J. i:12, 1943.

Although methyltestosterone and DOCA are listed as causes of gynecomastia in all reviews, in fact this statement is based upon isolated reports from the 1940's in which enormous dosages were given (200 mg of MeT per day) and which may have been contaminated with estrogens. It is also possible of course that these steroids may be converted to estrogens.

3. Phenothiazides

88. Foxworth, D. L., and R. M. Lehman. False-positive frog tests due to promazine hydrochloride. Obstet. Gynecol. 10:385, 1957.

89. Margolis, I. B., and C. G. Gross. Gynecomastia during phenothiazine therapy. JAMA 199:192, 1967.

A variety of tranquilizers, principally phenothiazides, have been reported to cause gynecomastia. The suggestion is made in ref. 89 that they may trigger gonadotrophin release, presumably via the hypothalamus or cerebral cortex.

4. Miscellaneous

90. Kaminsky, H. H. Gynecomastia in patients immobilized in spica casts. JAMA 210:2395, 1969.

91. Kyle, L. H. Gynecomastia in association with chronic ulcerative colitis. NEJM 240:537, 1949.

These two references were chosen among hundreds to illustrate the problem of interpreting isolated reported of association between gynecomastia and various other disease states. In general it can be said that in most such reports, other diseases (such as Klinefelter's syndrome) and possible drug therapy are not adequately excluded. Consequently, most such studies are uninterpretable

VII. TREATMENT

A. Surgery

92. Dexter, C. J. Benign enlargement of the male breast. NEJM 254:996, 1956.

In 228 cases of various etiologies treated conservatively and followed for up to 10 years, no case of carcinoma developed. Indications for surgery include a.) psychological disturbance about the gynecomastia, b.) suspected malignancy, and c.) any lesion which grows progressively.

B. Androgen Replacement

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

Although, as would be predicted the administration of testosterone has relatively little beneficial effect when estrogen secretion is high, in simple androgen deficiency states, testosterone administration may result in dramatic melting away of the gynecomastia.

C. Inhibitors of Estrogen Secretion and Action

94. Greenblatt, R. B., E. C. Jungek, R. A. Pueblo, and M. C. Ward. A new progestogen: The 18-homologue of norethisterone. Clin. Pharm. 7:400, 1966.

This report describes a striking improvement of gynecomastia in patients given this anti-estrogen. Unfortunately, the patients probably had adolescent gynecomastia, and there were no controls; at best it is a promising idea.

Attempts here to inhibit estrogen secretion by inhibiting the secretion of gonadotrophin by the pituitary have not been very impressive (Case 6)

D. Radiation

95. Corvalas, J. G., W. M. Gill, Jr., T. A. Egleston, and A. Rodriguez-Antunez. Irradiation of the male breast to prevent hormone produced gynecomastia. Am. J. Roentgenology 106:839, 1969.

96. Wolf, H., P. O. Mosden, and H. Vermund. Prevention of estrogen-induced gynecomastia by external irradiation. J. Urology 102:607, 1969.

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

98. Malis, I., J. F. Cooper, and T. H. S. Wolever. Breast radiation in patients with carcinoma of the prostate. J. Urology 102:336, 1969.

The only form of therapy which appears to be any good is irradiation of the breasts of patients with carcinoma of the prostate prior to the institution of stilbestrol therapy. It is apparently universally effective, the complications rate is low, and the long term effects of radiation are minimal in this age group.