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Gynecomastia : mammary hypertrophy in the male

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GYNECOMASTIA: MAMMARY HYPERTROPHY IN THE MALE

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I. INTRODUCTION

The first requirement of a systematic study of gynecomastia is a definition of the term. The derivation of the word from the Greek words gyne (woman) and mastos (breast) originally indicated a condition in which the male breast was enlarged to a size grossly resembling that of an adult female. Until recently the gross anatomical characteristic of size was the only criterion for diagnosis (Freeman 1916; Hammett 1920; Gibson 1923).

Within the last several decades, however, careful physiological and pathological studies have resulted in limitation of the term to mean the abnormal physiological hypertrophy of the male mammary gland, with proliferation of glandular tissue as the essential feature of gynecomastia (Menville 1933; Richardson 1943; Maliniac 1943). The latter definition will be used throughout this paper and will be shown to represent a much more complete entity than the former.

Thus, according to strict definition, gynecomastia is not a disease but only an unusual physiological state of the male breast. The microscopic anatomy, clinical aspects, and treatment of this condition are well defined and will be considered only briefly here. By far

the most interesting aspect is the pathogenesis. Nearly every case represents a diagnostic problem, and the causal mechanisms are multiple, as will be shown. They involve a consideration of many features of endocrinology, internal medicine, and genetics.

Gynecomastia is not a common clinical condition, and the usual management of such cases is simple; therefore one may wonder if there is adequate reason for making a detailed study of the subject. The primary reward lies in the absorbing interest of solving an obscure problem through scientific methods. Such a study may also result in saving the life of a patient, since there are several malignant states which present gynecomastia as an early symptom.

The well established knowledge of gynecomastia (history, clinical aspects, and pathology) will be discussed first, then the intricate and still obscure problem of pathogenesis, and finally a brief review of therapy.

II. HISTORY

Gynecomastia has been recognized since ancient times. Aristotle (384-322 B.C.), in "De animalibus historiae", reported that he had seen men with mammae as well developed as those of a woman. In the 7th century A.D. Paulus Aegineta wrote: "Breasts of males also swell to some extent at puberty, but most subside again. But in some cases they go on increasing, owing to the formation of fat below." He also described minutely the surgical excision of such breasts. His findings were preserved and reaffirmed by several Persian and Arabian authors during the Middle Ages.

During the 19th century and the early part of the 20th there were numerous but isolated reports of single cases of gynecomastia. There were at least 160 of these, mostly in the German and French medical literature. Individually these cases contributed very little toward an understanding of male breast hypertrophy. An analysis and summary of 160 reports collected by Deaver and McFarland (1917) illustrates the superficial knowledge and theorizing prevalent before that date. Gynecomastia was defined simply as an enlargement of the male breast. Of 161 cases 78 had been recorded as bilateral in occurence, 19 in the right breast, 27 in the left, and no

data in 37 cases. The mammae were generally described as resembling those of a girl of 15 or 16 years, with a pendulous type observed occasionally. The age of onset was usually unreported. Enlargement was known to persist after an adult size had been reached. Theories of etiology were numerous and all based on unproved premises. Some cases were considered to be atavistic or degenerative phenomena, as supported by claims that the incidence of gynecomastia was high in primitive races, criminals, imbeciles, and insane persons. A few were said to be hereditary in origin because several gynecomasts had been found in one family (Savitzky 1894). 28 of 160 cases were associated with imperfect development of the genitalia, pseudohermaphroditism, or disease of the testis, so sexual abnormality was commonly cited as being related, if not causal, to gynecomastia. Only 7 of the 160 cases reported local trauma to the breast preceding enlargement; these were interpreted as occurring only coincidentally. Most cases of gynecomastia were classified as being of entirely idiopathic origin with no demonstrable cause or accompanying abnormality.

German pathologists of the latter part of the 19th century must be given credit for the earliest descriptions of the histopathology of gynecomastia (Schuchardt 1885; Gruber 1886). They recognized that the

histology resembled that of the normal female breast and that true gynecomastia was therefore a physiological phenomenon. This concept of gynecomastia as a physiological and histological entity was not widely accepted, however, until nearly 50 years later.

No history of male breast enlargement would be complete without mentioning the classical case of Chengwayo, the Zulu chief, whose photograph, showing him in full regalia, including a huge pair of pendulous breasts, appeared in almost every article of 40 to 50 years ago on gynecomastia (Gould and Pyle 1900). He was a tall powerful Negro who maintained his position by his strength and who had 40 wives and 100 children, according to the reports. It was also said that he had the dubious pleasure of helping his wives nurse his numerous offspring. In any case his virility appeared to be well proved.

III. MICROSCOPIC ANATOMY

In the introduction to this paper gynecomastia has been defined as the physiological proliferation of mammary gland tissue in the male. The details of the histological changes will be discussed next.

It has already been mentioned that Schuchardt (1885) and Gruber (1886) were the first men to study the pathology of male breast hypertrophy. They found that the breast enlargement usually resembles a normal female breast both grossly and microscopically, with a marked increase in the number of ducts and tubules, a moderate increase in fibrillar and adipose tissue, and in some cases a few acini.

The most complete and thorough inquiries into the microscopic structure of the male breast thus far have been made by Menville (1933) and Lewis and Geschickter (1934), both working with material from 95 cases of gynecomastia at the Johns Hopkins Hospital. The normal development of the male breast was also studied. It was found that after a slight temporary hypertrophy in the neonatal period both male and female mammary glands remain small, quiescent, and of about the same degree of development during childhood. Then at puberty the female breast rapidly outstrips the male in growth, but the

latter also shows considerable hypertrophy. The epithelium of the ducts becomes hypertrophic and hyperplastic, and two or more rows of nuclei develop. The stroma adjacent to each duct forms a variable amount of loose young connective tissue which contains numerous blood vessels. The ducts are elongated and develop many branches but no alveoli. This puberal hypertrophy is not extensive in the majority of cases. Geschickter later (1938) identified this condition as the gynecomastia of "adolescent mastitis".

Similar changes occur in male breast hypertrophy at all other ages, varying somewhat with the intensity and duration of the stimulating influence. In cases of short duration and intensive stimulation the hyperplasia appears most pronounced. The ductal epithelium becomes several cell layers in thickness, and the cells tend to be cylindrical in form. The duct lumen often contains desquamated cell material. The periductal stroma shows a proliferation of loose embryonic connective tissue containing many young fibroblasts and blood vessels. Immediately surrounding each duct is a lymphocytic infiltration accompanied by plasma cells and a few eosinophils.

If the hyperplasia is present for six or more months, the epithelial proliferation is not as great,

but desquamation is increased. The periductal stroma becomes more dense, and the vascularity decreases. The epithelium may become papillomatous in some cases. Dilatation of the ducts is common, but this may also be present in the normal adult male breast. Acini are absent.

If stimulation and development persist for more than a year, the periductal tissues become the adult collagenous type..But then this condition differs only in a slight degree from the description of fibroadenoma, whether in the male or female breast. Both Woodyatt (1909) and Menville (1933) collected series of cases showing all gradations of changes from the above picture of gynecomastia to fibroadenoma. The only point of differentiation lay in the diffuseness of gynecomastic hypertrophy contrasting with a circumscribed hypertrophy in fibroadenoma (Ingleby 1919). The difficulty experienced in separating these conditions is illustrated by the case of Lewin (1941) in which the hyperplasia of ducts and periductal connective tissue following a teratoma testis resulted in a pathological report of fibroadenoma pericanicular. Neal and Simpson (1930) reported that they found no gynecomastia among 152 enlarged male breasts but that 29.6% represented fibroadenomas characterized by an overgrowth of duct

cells and supporting connective tissues. Such differences in diagnosis are obviously a result of differences in definition and interpretation only. Both Menville (1933) and Lewis and Geschickter (1934) concluded that the so-called fibroadenoma is a further development of gynecomastia and that gynecomastia, fibroadenoma, and virginal hypertrophy of the female breast are all to be classified as phases of the same process.

Gynecomastia has also been confused with inflammatory mastitis. Neal and Simpson (1930) reported that 33.5% of 152 enlarged male breasts displayed "chronic mastitis" characterized by an increase in fibrous tissue, epithelial proliferation, and the presence of inflammatory cells. The authors admitted that this condition was often distinguished only with difficulty from their group of fibroadenomas. This "mastitis" group should probably also be classified as gynecomastia, since the inflammatory cells described were quite possibly the usual periductal infiltration of lymphocytes and plasma cells. The typical histological changes of male breast hypertrophy have been declared to resemble the "chronic cystic mastitis" of women (Sullivan and Munslow 1942). Andrews and Kampmeier (1927) decried the use of the term gynecomastia and claimed that most cases of male breast swelling consisted of

"chronic or adolescent mastitis", yet the authors made no histological studies of this "mastitis". On the basis of fibrotic changes found in two cases of breast enlargement of long duration these writers claimed that "gynecomastic" breasts did not exhibit hypertrophic glands but were merely fibrous tissue proliferations due to chronic irritation. No additional work confirming such conclusions has been forthcoming.

Despite its varied etiology gynecomastia is an entity presenting the same microscopic pathology in all of the associated syndromes. Histological changes similar to those described by Menville (1933) for idiopathic hypertrophy appear with teratoma of the testis (Cairns 1926; Ferguson 1933; Woodham 1933), chorioepithelioma (Gilbert 1940; Bonn and Evans 1942), testicular atrophy (Goodman 1937; Horsley 1939; Lewin 1941; Klinefelter et al. 1942), hypogenitalism (Young 1937), adrenal cortical tumor (Weber 1926), and cirrhosis of the liver (Woodyatt 1909; Edmondson et al. 1939).

IV. CLINICAL ASPECTS

The gross anatomical characteristic of enlargement of the breast is the usual single presenting feature of gynecomastia. The degree of enlargement necessary for diagnosis varies widely, depending mainly on differences in definition of the term. In 1917 Deaver and McFarland, limiting their analysis to cases with breasts of adult female size, described gynecomastia as the presence of mammae resembling those of girls of 15 to 16 years of age, with proportionately enlarged nipples and areolae. These breasts were said to become pendulous in a few cases, and the enlargement would persist when once present. Lewis and Geschickter (1934), in reviewing 95 cases, described the breast as soft or moderately firm in consistency, rarely nodular, and varying widely in size. Menville (1933) admitted that such is the picture of diffuse hypertrophy but added that rubbery, hard, circumscribed nodules may be present in those cases which have progressed to the fibroadenomatous phase.

In detailed reports in 1935, 1937, and 1938 Jung and Shafton, of Northwestern University Medical School, described the appearance of a palpable mass of mammary glandular tissue, which they called the subareolar node,

in every case of so-called adolescent mastitis. These nodes varied in size and in a few cases were found to grade directly into a size classified as gynecomastia. No true mastitis was found in these adolescents, for biopsies revealed only glandular hypertrophy plus a slight hyperemia and round cell infiltration. Nathanson (1942) further described this "adolescent mastitis" as the presence of a well-defined, freely movable, discoid or round, palpable mass of breast tissue, closely associated with the areola. The size of each mass may vary from one to five or more centimeters in diameter, but is usually two to three centimeters. Most of the more recent authors refer to these subareolar glandular masses appearing during adolescence or accompanying definite endocrine disturbances as true gynecomastia (Lewin 1941; Hoffman 1942; Maliniac 1943). This concept of including mammary hypertrophies of any degree within the limits of gynecomastia will be used in further discussions in this paper.

Gynecomastia may be unilateral or bilateral. Reports on the relative incidence of each are conflicting and again vary with the definitions of the word. Deaver and McFarland (1917) found 50% of large male breasts to be bilateral, while Menville (1933) reported only 12.8% as bilateral. No significant difference in inci-

dence between right and left breasts has been discovered in unilateral types. Studying adolescent hypertrophies of milder degree, Jung and Shafton (1937) and Nathanson (1942) noted that both breasts are usually affected, but that the onset is frequently unilateral, with the opposite breast enlarging later or successively. No other series of a significant number of cases has been analyzed in this respect.

The general incidence and age incidence of gynecomastia are difficult to determine. If adolescent mastitis is included, the condition is nearly universal in males at puberty, since Jung and Shafton (1938), after examining 1000 unselected boys and young men, reported that palpable subareolar nodes appeared at some time between 12 and 17 years in nearly 100%. Nodes were palpable in 36% of boys at 13 to 14 years of age, in 90% at 16 to 17 years, but present in only 13% or less after 21 years of age. Jung and Shafton concluded that palpable enlargement of the male mammary gland is an integral part of the process of puberty, but they were unable to show any definite time correlation with puberal accelerations in somatic or genital growth. A temporary exaggeration of this mazoplazia to a size approaching that of female breasts was found in 3 otherwise normal adolescents of the 1000 males. This 0.3%

possibly represents the approximate incidence seen in clinical practice. There are probably a considerable number of gynecomasts, however, who do not seek medical aid but hide their embarassing condition for years. Gynecomastia associated with definite endocrine disease occurs in such isolated instances that the total incidence in difficult to measure.

The age incidence shows wide variations, depending upon the etiological types. "Neonatal mastitis" is a common but only very temporary hypertrophy in most newborn infants, due to the mammogenic influence of maternal hormones during pregnancy. Most cases of gynecomastia without discernable cause have their onsets during adolescence, while those associated with definite endocrine disease are most common in young adult males of 30 to 40 years. A few cases appear before puberty; Ingleby (1919) reported two examples in boys of 7 and 9 years of age.; Menville (1933) found breast enlargement in a patient of 9 years. All of these were unilateral, of marked size, and idiopathic. Gynecomastia is occasionally observed in aged men; Menville (1933) cited 6 instances of idiopathic enlargement in patients over 65 years of age; Mann (1928) reviewed 5 cases associated with prostatectomies in men of about 70 years of age.

No definite racial factors have been noted in gynecomastia. Menville (1933) in Baltimore found 8 negro patients among 88 cases of idiopathic hypertrophy. Earlier authors claimed that a higher incidence appeared in negroid and primitive races, but no proof was offered. Only a few reports have mentioned any tendency to occur in families (Savitzky 1894; Young 1937; Hoffman 1942).

Symptoms other than the enlargement of the breasts are few. Tenderness and occasionally severe pain accompany most cases of puberal hypertrophy during the first month or two, but less than 15% of males at 20 years of age are able to recall the occurrence of any tenderness in the breasts during adolescence (Jung and Shafton 1938). The tenderness is probably equivalent to that found early in the development of the breasts of girls at puberty. Tenderness or pain is very uncommon after an enlargement approaching that of an adult female breast has been reached.

Secretions of any kind are also rare, as would be expected in the absence of well-developed acini. Several reports of lactation in the male, including the case of Chengwayo (Gould and Pyle 1900), have appeared in the foreign literature, but these have not been thoroughly proved to be true milk production.

Bailey (1924) concluded that secretion was exceptional and then only a pseudolactation, producing a colostrum-like substance. A watery milky fluid could be expressed from the nipples in Weber's (1926) and Lisser's (1936) cases of adrenal cortical tumor and in Entwisle and Hepp's (1935) patient with chorioepithelioma. Rarely a very slight secretion has been noted in adolescent hypertrophies (Jung and Shafton 1938).

Psychic disturbances, usually in the form of an introverted personality, have been found in some cases with breasts of adult female size. These tendencies are obviously due to the stigma usually attached to feminine characteristics appearing in the male.

Other signs of a tendency toward femininity may or may not be present. Among these are loss or lack of libido, feminine hair distribution, effeminate emotions, feminine fat distribution, and small genitalia. Such intersexual variations are uncommon in puberal or idiopathic gynecomastia but frequently accompany endocrine tumors and hypogonad states.

The pathological conditions that have been associated with male breast hypertrophy are quite numerous and varied, considering that the breast change is identical in each. They will be listed here and analyzed in more detail in discussion of the pathogenesis. In

the approximate order of their importance they are as follows: testicular atresia, teratoma testis, genital anomalies, chorioepithelioma, adrenal cortical hypertrophy or tumor, hepatic cirrhosis, hyperthyroidism, pituitary tumor, interstitial cell tumor of the testis, and carcinoma of the lung. It should be noted that most of these are endocrine disorders, indicating that a thorough study of the ductless glands is necessary in every case of progressive or persistent gynecomastia. Mammary hypertrophy may be the earliest sign of chorioepithelioma (Gilbert 1940), of carcinoma of the adrenal cortex (Simpson and Joll 1938), and of carcinoma of the lung (Castillo et al. 1941).

The course and duration of gynecomastia is highly variable. Jung and Shafton (1937) found that the subareolar nodes of puberal hypertrophy usually reached a maximum size within a few months, during which time tenderness was noticeable. This size was maintained, with some fluctuations, for about six months, after which there was great diversity of behavior. Most nodes then declined slowly, disappearing in about three years. Some persisted as very small nodules, so that 14% of normal men between 20 and 30 years still had palpable nodes. A few of the subareolar masses progressed to

pronounced enlargement, with the breast tissue reaching a diameter of 5 to 7 or more centimeters. In these the glandular tissue was distributed more diffusely and was softer in consistency. Jung and Shafton (1938) considered that enlargement to this size was only temporary, but almost all other investigators have found that gynecomastia persists indefinitely after a female size has been attained. Young (1937) and Heller and Nelson (1945) have recorded cases of more than 20 years duration. Menville (1933) found an average duration of 14.7 months in patients with moderate hypertrophy, while Nathanson (1942) and Hoffman (1939) state that the usual adolescent "mastitis" regresses spontaneously in one to eight months. Gynecomastia associated with tumors of the endocrine glands generally displays a more acute course, with intense, painful enlargement of palpable glandular tissue for only two to twelve weeks before a physician is consulted. Rapid regression follows removal of the tumor.

Except for the occasional persistence of grossly enlarged breasts the prognosis in mammary hypertrophy of itself is excellent. Only 1 case of malignant change is recorded in all of the English literature; this was a scirrhous carcinoma arising in a pre-existing, bilateral gynecomastia, in a colored man aged 56 (Ge-

schickter 1943) and could well have occurred only coincidentally. The possibility of malignant change has been suggested, however, by the findings of Gardner et al. (1934; 1936) that male mice of a strain in which the females were subject to spontaneous breast cancer also became very susceptible to carcinoma after mammary growth was stimulated by the injection of estrogens. Of course, death due to the endocrine malignancies associated with gynecomastia is frequent, constituting one of the main reasons for a careful study of every case of breast enlargement in the male.

The laboratory findings in mammary hypertrophies have only recently been studied and are incomplete and inadequate at the present time. The urinary excretion of sex hormones has been investigated rather intensively, however, as would be expected in this sexual anomaly. Gonadotropins, as identified by the Ascheim-Zondek and Friedman tests, have been found to be greatly increased in those cases associated with teratoma testis, chorioepithelioma, or interstitial cell tumor of the testis (Ferguson 1933; Gilbert 1940; Hunt and Budd 1939). More recently a moderate increase in gonadotropic levels, as measured by semi-quantitative methods, has been consistently demonstrated in a syndrome characterized by hyalinization of the seminiferous tubules

(Klinefelter et al. 1942; Heller and Nelson 1945); otherwise gonadotropin tests have been generally negative in gynecomastia.

Estrogen and androgen excretion rates have been determined in a few series of idiopathic and adolescent hypertrophies. Glass and Bergman (1938) and Nathanson (1942) reported that there is no consistent increase or decrease in either group of hormones, but that the androgen-estrogen ratio tends to show a shift toward the feminine type, with definitely low androgen levels in some cases. In the syndrome described by Klinefelter et al. (1942) and Heller and Nelson (1945), androgen levels range from normal to decidedly subnormal, and estrogens from normal to slightly subnormal. In all of these series there were a number of gynecomasts with entirely normal hormone levels; these were generally interpreted as having recovered from the endocrine imbalance before the tests were made.

The basal metabolic rate is frequently measured in patients with male breast hypertrophy, and normal readings are found in the great majority. A rate lowered by -10% to -20% is common in those patients with hypogonadism (Horsley 1939; Wernicke 1939), while markedly increased values may appear in those with associated hyperthyroidism (Starr 1935).

Roentgenological examination of the skull for the detection of pituitary tumors and perirenal insufflation with air to outline adrenal tumors are useful aids in the diagnosis of the endocrine neoplasms that may occasionally cause gynecomastia.

Spermatozoa counts have been investigated in only a few instances. Hoffman (1942) reported a low sperm count (2,000,000/mm^3), of which 25% were non-motile, in a boy of 16 years who was otherwise normal except for marked bilateral gynecomastia and low levels of both androgens and estrogens. Heller and Nelson (1945) find that azoospermia is a constant feature of a gynecomastic syndrome characterized by hyalinization of the seminiferous tubules. The degeneration of the tubules has been verified by testicular biopsies, both by these workers and by Klinefelter et al. (1942).

In the differential diagnosis of gynecomastia, breast enlargement due entirely to excess adipose tissue in the mammary region is the condition most often confused with true glandular hypertrophy. This pseudogynecomastia, which may be due to obesity, Froelich's syndrome or eunuchoidism, is nearly always bilateral, soft, pendulous, and readily transilluminated (Lewin 1941; Geschickter 1943; Maliniac 1943). Microscopically it consists of a diffuse hyperplasia of fatty and fibrous

tissue, with few or no glandular elements and no hyperplasia in these.

Carcinoma of the male breast must also be differentiated. Gynecomastia is three times as common as cancer (Geschickter 1943), and diffuse or bilateral enlargement in adolescent boys is almost certainly benign. The presence of any firm, discrete or infiltrating nodule in a middle-aged male, however, requires a biopsy for an accurate diagnosis. Gynecomastic nodules are usually not as hard as carcinomatous masses, nor do they produce dimpling or retraction of the nipple.

Benign swellings of the male breast other than gynecomastia are uncommon. These include dermoid cyst, lipoma, lymphangioma, and infections and may be recognized by the specific characteristics of each.

Hoffman (1942) has made a useful differentiation between the constitutional type of gynecomastia and that due to true endocrine disturbance. He states that the former tends to appear in families, has its usual onset at puberty, and shows no sudden reversal of other sex characteristics. On the other hand endocrine disturbances such as chorioepithelioma may appear at any age, are not familial, tend to show a sudden reversal of several sex characteristics, and usually have a readily demonstrable endocrine neoplasm.

V. PATHOGENESIS

A great number of theories on the mechanisms of development of gynecomastia have been propounded, but it may be stated at the outset that no specific one of these has been completely verified or widely accepted as yet. In short, the pathogenesis is not truly known in most cases, but enough is known to allow rather accurate deductions.

This complexity in etiology is primarily due to the fact that male breast hypertrophy is apparently a disturbance of the endocrine system, the one system of the body with the most complex reactions and interreactions and the system with multiple controlling substances often closely related to each other yet differing in action in many subtle ways.

For purposes of presentation and discussion the etiology of male mammary hypertrophy may be considered under the following headings:

A. Sex Hormone and Pituitary Control.

B. Adrenal Cortex Control.

C. Thyroid Control.

D. Genital Anomalies.

E. Heredity.

F. Miscellaneous.

A. Sex Hormone and Pituitary Control.

Since any physiological breast enlargement is obviously a secondary sex characteristic, gynecomastia has been linked with disturbances in sex hormones since the earliest years of endocrinology, and the sex hormonal mechanisms have the most throughly studied of all the etiological aspects. The control of mammary growth has been a problem of great interest not only to the endocrinologist, but also to the physiologist, gynecologist, obstetrician, surgeon, and even the dairy industry; and men and women in all of these fields have contributed to our present knowledge of the subject.

A thorough review of the experimental studies on the control of breast growth is necessary before the clinical reports and theories of the etiology of gynecomastia can be properly evaluated and analyzed. Fortunately many of the laboratory findings on breast growth are able to be appropiately applied to the problem of male breast hypertrophy because male or immature animals have been the subject material in the majority of the experiments, with breast responses comparing closely to those of human males.

Two Englishmen, Lane-Claypon and Starling (1906), were among the earliest workers to produce mammary growth by means of sex hormones. They injected virgin

female rabbits with water extracts of placentas, fetuses and uteri, eliciting considerable hypertrophy of the mammary glands and ducts. Very little additional data was obtained until more nearly purified hormonal preparations were available; then Hartman et al. (1926) reported palpable enlargement of mammary glands in ovariectomized opossums injected with placental extracts or follicular extracts.

Allen (1927), attempting to approximate closely the conditions existing in man, chose female monkeys as material for his thorough study of the actions of sex hormones. The adult female monkeys were found to have breasts with well-developed ducts and alveoli; these atrophied shortly after double ovariectomy but showed marked growth of both ducts and alveoli upon replacement injections of placental extract. The results indicated that ovarian secretions are necessary for the maintenance of breast tissue in the female. It was later shown that placental extracts contain both gonadotropic (APL) hormones and estrin; the latter was probably the active fraction in Allen's experiments.

In 1931 Nelson and Pfiffner produced considerable gross and microscopic hypertrophy of the mammary glands of both male and immature female guinea pigs, normal and gonadectomized, with injections of follicular hor-

mone (theelin) and extracts of corpus luteum. They concluded that the ovarian hormones are necessary for the development of the breasts in puberty and early pregnancy but that they do not initiate lactation.

Working with male rabbits, rats and mice, Turner et al. (1932) found that the estrogenic hormones theelin and theelol stimulated the growth of the duct system of the mammary gland but did not result in any proliferation of the lobule-alveolar system. Turner and Allen (1933), at the University of Missouri, injected more than 13,000 rat units of theelin into a mature male monkey over a period of 9 weeks and obtained not only growth of the ducts but also extensive lobule formation. They also noted that the normal adult male monkey has a very small mammary duct system, smaller than that of normal humans. Lewis and Geschickter (1934) made similar but more extensive studies. They injected 7 normal male monkeys and 1 castrated male monkey with 2,000 to 5,000 rat units of estrin in small daily doses over 6 or more weeks. Bilateral breast hypertrophy was obtained in all animals and was interpreted as being clinically and pathologically identical with gynecomastia as observed in human males. Regression started within two weeks after cessation of estrin injections. 7,000 to 20,000 rat units of anterior-pituitary-like

hormone from pregnancy urine were similarly injected into 4 male monkeys, resulting in hyperplasia of the interstitial cells of the testicles and in moderate breast changes toward gynecomastia. It is difficult to prove whether the latter breast changes were due directly to stimulation by the estrogenic fraction or indirectly from the stimulation of the interstitial cells secretion by the gonadotropic fraction of the APL hormone. In any case, the authors decided that gynecomastia, virginal hypertrophy, and fibroadenoma of the breast represented different phases of the same process and that all had the same etiology; namely, hyperestrogenization. This experimental production of gynecomastia in monkeys by estrogenic substances was repeated and confirmed by Van Wagenen in 1938.

In order to rule out the possibility that the pituitary gland might have some affect on mammary growth, Asdell and Seidenstein (1935) and Nelson (1935), working with rabbits and guinea pigs, studied the effects of estrin on the mammary glands of hypophysectomized animals. It was decided then that hypophysectomy had little or no effect on the development of the mammary glands.

In 1936, Nelson, then at Yale University, reviewed the literature up to that year on the endocrine control

of the mammary glands. He reported that male glands normally showed little or no development in the mouse, rabbit, dog, cat, and other common species; a slight development in the guinea pig and monkey; and progressive and quite extensive duct proliferation in the normal male rat and human. He noted that male animals are excellent subjects in which to demonstrate the effects of hormones on the mammary glands and that the male breast has the capacity to respond readily to growth-promoting substances. He concluded that the absence of the female type of development in the normal male breast may be attributed to a deficiency of the ovarian hormones; i. e., estrone and progesterone. It seemed to be well established that estrone caused growth of the duct system in all species and sexes and development of the lobule-alveolar system in some species. Progesterone, in combination with estrone, was considered necessary for complete development of the breast up to the time of lactation. Nelson reaffirmed the statement that there did not appear to be a hypophyseal hormone directly controlling breast development.

Thus it was seemingly settled that the prime mechanism of breast growth depended upon ovarian hormone control, but early in 1936 two articles were published which led to an intensive re-investigation of

the entire subject, lasting up to the present. Nelson and Gallagher (1936) noted that several androgenic substances, particularly androsterone and androstene-dione, caused a remarkable proliferation of the ducts and lobules of the mammary glands in ovariectomized rats, while Lyons and Pencharz (1936) found that they were unable to produce significant mammary growth with injections of estrogens in hypophysectomized male guinea pigs and decided that the presence of the pituitary gland is necessary for growth of the breast. The latter results and conclusion aroused the greater controversy. On one side of the question Gomez, Turner, and Reece of the dairy husbandry department of the Missouri Agricultural Experiment Station have reported numerous experiments tending to uphold their theory of a pituitary mammogenic hormone, while on the other Nelson of Yale and Wayne Universities and Geschickter of Johns Hopkins University have steadfastly maintained that breast growth is due to the direct action of sex hormones.

Reece, Turner, and Hill (1936) confirmed the results of Lyons and Pencharz in being unable to produce mammary growth with estrogen (Progynon-B) in immature hypophysectomized male rats. Howard's (1936) findings tended to support the pituitary mammogen theory when he produced duct and periductal growth in female

rat breasts with acid extracts of the anterior pituitary gland, but these animals were not gonadectomized so that the mammary hypertrophy may well have been indirectly due to a gonadotropic action of the injections on the ovaries.

Gomez, Turner, and Reece (1937) maintained that the action of estrogens in breast growth was indirect, operating through stimulation of the pituitary to produce a mammogenic hormone. They attempted to demonstrate this mechanism by injecting a large number of rats with theelin for 10 to 20 days; then the stimulated (?) pituitary glands from these rats were implanted daily into 3 hypophysectomized male guinea pigs, while a control guinea pig received rat pituitary implants. Only the 3 experimental animals presented extensive duct and alveolar growth. This otherwise perfect experiment had only one flaw: it was not shown that the pituitary transplants did not contain high concentrations of estrogens. The same flaw was present in the report of Gomez and Turner (1938) that anterior pituitary extracts from pregnant cattle stimulated mammary growth in immature castrated female rats and rabbits by means of a mammogenic hormone. Gomez, Turner, Gardner, and Hill (1937) also asserted that the positive results obtained by other workers in attempting estrogen stimulation of

hypophysectomized animals were due to imcomplete hypophyseal removal and that breast response would occur if as little as 2% of the pituitary gland remained. Turner, writing a chapter in Allen's (1939) volume on sex hormones, reviewed the literature on the hormonal control of the mammary glands and concluded that growth was controlled by a mammogenic hormone from the anterior pituitary.

In 1937 Astwood, Gescickter, and Rausch presented strong evidence against the existence of a pituitary mammogen. They decided that Gomez, Turner, and Reece had neglected the factor of the grave nutritional disturbances occurring after hypophysectomy. They showed that cessation and regression of breast growth would occur in the rat despite estrin injections if severe dietary deficiency simulating the effects of removal of the hypophysis were produced. They also noted that large doses of estrin caused a "stunted" mammary growth in the albino rat, with the formation of irregular widened ducts and distorted alveoli, and that progesterone alone, even in large amounts, exerted no demonstrable effect on rat mammary glands. These authors found that the injection of gonad-stimulating substance (prolan) into immature male rats resulted in the development of small dense mammary glands composed of clumps

of acini, resembling the glands of the adult male rat. They concluded that it was erroneous to say that certain hormones such as estrin act through the pituitary just because they are ineffective in hypophysectomized animals. Nathanson et al. (1939) added purified growth complex to estrogen injections into pituitaryless rats and found that the growth and development of the mammary glands closely corresponded to weight gain or loss but in no instance approached the degree of development in animals with intact pituitary glands. These workers decided that nutrition was an important factor in the results noted in hypophysectomized animals treated with estrogens but that it was probable that the pituitary gland exerted some direct influence on the breast.

In the meantime Lewis and Turner (1938) were able to show that the mammogenic effect of pituitary extracts from pregnant cows was not due to estrogen content, so Riddle (1940), in reviewing the literature, concluded that estrogens (plus progesterone in some species) are the principle direct cause of mammary gland development but that some growth may be due to a mammogenic hormone, which can be quite definitely demonstrated in the pituitary of the cow. That the

action of the estrogens is dominant has also been supported by the findings that local application of estrogenic substances in ointments or solutions to one breast caused marked growth of that breast in women, male rabbits, male monkeys, and male guinea pigs (MacBryde 1939; Lyons and Sako 1940; Speert 1940; Nelson 1941). A slight systemic absorption was also observed during these experiments by minimal responses in opposite breasts and by estrogenic types of vaginal smears. These investigators agreed that a pituitary mammogenic function, while still possible, was unlikely and of little importance in most animals.

Gardner and Van Wagenen (1938) have recently reaffirmed the experimental production of gynecomastia in male monkeys by means of estrogenic injections but found that large doses throughout 22 weeks were required to reproduce full female size and structure, showing development of both ducts and lobules. Van Heuverswyn et al. (1939) noted that synthetic estrogens such as triphenylethylene, stilbestrol, and dibenzanthracene compound caused greater mammary growth in young male mice than the so-called natural estrogens.

In 1939 Dunn made the first report of experimental gynecomastia in the human male. Using a series of injections of 2,000 to 5,000 rat units of estradiol ben-

zoate in the treatment of migraine, he noted clinical and histological evidence of gynecomastia in some patients. Biopsies of these breasts revealed the typical estrogenic response of mammary tissues. He also found marked gynecomastia accompanying the treatment of two hypersexual males with 5 mgs. of stilbestrol daily with the purpose and result of depressing their hyperactive anterior pituitary gonadotropic functions (Dunn 1940; Dunn 1941). The breast hypertrophy in these males took the typical course of an acute gynecomastic swelling, showed a pronounced increase in ductal epithelium and periductal connective tissue, and regressed upon cessation of therapy.

The report that some of the androgenic substances were also able to stimulate proliferation of the mammary ducts and lobules (Nelson and Gallagher 1936) produced less controversy than the mammogen problem but probably contributed more toward an understanding of the pathogenesis of gynecomastia. Selye et al. (1936) found that synthetic testosterone had the amazing action of producing a marked milk secretion with only a slight growth of mammary tissue in immature male and female rats, both in the presence or in the absence of the gonads. Reece and Mixner (1939) confirmed the lactogenic action of testosterone in rats and correlated it with

their mammogenic theory by claiming that testosterone also acted indirectly through the pituitary stimulation of mammogen, as evidenced by a 40% increase in the lactogen content of the hypophysis after injections of the androgen. They also noted that testosterone induced an extensive development of the lobule-alveolar system of the breast but little or none in the ducts. They made the poorly supported suggestion that mammary gland hypertrophy in males might be due to excessive androgens, overlooking the fact that they had demonstrated alveolar growth while true gynecomastia consists of duct hypertrophy. Astwood et al. (1937) also found that testosterone stimulated the acini of rats to some extent, thus distinctly differing from the action of estrin. They inferred that the palpable mammary glands in boys during puberty were probably due to male hormone from the developing testes.

Bottomley and Folley (1938) have introduced the most reasonable experimental concept of idiopathic gynecomastia that has been made up to the present time. They showed that certain androgenic substances, particularly delta-5-trans-androstendiol, testosterone propionate and 17-methyltestosterone, stimulated the mammary ducts of immature male guinea pigs but produced very little alveolar development. All of these

compunds were found to be chemically unsaturated, while the saturated androgenic substances did not stimulate the mammary glands. These investigators concluded therefore that abnormal mammary development in the male might be due to the production of large amounts of estrogens, but that it appeared to be more likely that gynecomastia is the result of the pathological formation by the body of unsaturated androgens such as delta-5-trans-androstendiol.

After injecting young male mice with approximately equal amounts of various androgenic substances, Van Heuverswyn et al. (1939) found that nearly all of these materials produced some degree of breast growth, but a differentiation between duct and alveolar growth was not made. The overlapping of the actions on the mammary glands of androgens and estrogens has been reasonably attributed to their chemical similarity (Allen 1939; Riddle 1940).

McCullagh and Rossmiller (1941) reported the first gynecomastia in human males due to experimental injections of androgens. They noted that tender, nodular masses appeared bilaterally beneath the areolae in 6 of 11 males treated for hypogonadism over periods of 30 to 110 days with 75 to 200 mgs. per day of methyl testosterone given orally. Biopsies were not performed.

The swellings regressed upon cessation of therapy. There was no secretion noted in any of the cases. The hypogonadism appeared to contribute to the results since gynecomastia occurred in only 1 of 7 males given similar treatment for functional impotence. Moreover, large doses of testosterone have been found to be necessary to produce breast growth because Escamilla and Lisser (1941) noted no gynecomastia in 7 cases of hypogonadism treated with 10 to 75 mgs. of methyl testosterone orally, amounts which were adequate to reproduce male secondary sex characteristics.

In summarizing the experimental data on sex hormone control of breast growth in the male, it may be said (1) that chronic dosage with estrogens produces mammary hypertrophy remarkably similar to clinical gynecomastia, (2) that progesterone is effective only as an adjuvant to the estrogens in stimulating the lobule-alveolar system, (3) that there may be a mammogenic hormone from the anterior pituitary gland but its action is subordinate to the estrogens, (4) that certain unsaturated androgens may, like estrogens, produce breast growth closely resembling gynecomastia, and (5) that gonadotropins have an influence on the growth of the mammary glands, but probably only indirectly through stimulation of the gonads.

The clinical investigations of gynecomastia have not entirely kept pace with the advances in experimental knowledge. The earlier theories on the sex hormone etiology were only theories and without any substantiation at all, while the more recent hormone studies have been too few, too inadequate, and often too late to record the endocrine changes throughout the development of gynecomastia.

Noting that gynecomastia was often associated with puberty or with defective genitalia, Hammett (1920) was one of the first authors to state that a disturbance of the internal secretory functions of the male sex glands could be the chief contributing factor. He was unable to make hormone analyses and hesitated to say whether a perversion of the male hormone-producing tissue was present or whether functioning ovarian endocrinal tissue might be found in the gynecomast.

Nearly all other clinical studies of sex hormone disturbances may be classified according to their various conclusions reached concerning the mechanisms of the production of gynecomastia: (a) the theory of deficient testicular secretion, (b) the theory of testicular tumor secretion, (c) the theory of hyperestrinism, (d) the theory of androgen-estrogen imbalance, which grades into (e) that of perverted secretions, and (f) idiopathic.

The theory of deficient testicular secretion was suggested by Bailey (1924) and Mosckowicz (1926), who noted a high incidence of gynecomastia among hypogonad males and quickly jumped to the conclusion that the normal testicular hormone inhibits breast development in the normal male. The fact that castrated males almost never develop a true gynecomastia was overlooked. Kriss (1930) castrated 20 male guinea pigs and found that the absence of the testicles resulted in no detectable change in the microscopic structure of the glands from that of normal control animals. No hormonal analyses supporing this theory have been made, but it has persisted as an explanation of gynecomastia by several authors (Goodman 1937; Woodham 1938).

The theory of testicular tumor secretion arose from the observation of Cairns (1926) that 2 patients out of 78 cases of teratoma testis or chorioepithelioma developed marked bilateral hypertrophy of the breasts. Bailey had earlier (1924) reported breast enlargement in a case of malignant teratoma testis. Ferguson (1933) found hypertrophy of the male breast in 5 of 117 cases of teratoma testis, all of whom showed an extraordinary excess of prolan excreted in the urine. He noted that the normal male does not excrete any appreciable amount of gonadotropins and that at autopsy the pituitary

glands in these patients with malignancies resembled the "adenomas of pregnancy". Entwisle and Hepp (1935) also found bilateral gynecomastia, positive Ascheim-Zondek (gonadotropin) tests, and pregnancy changes in the pituitary in a fatal case of chorioepithelioma. Horsley (1939) and Bonn and Evans (1942) reported similar examples. In 1940 Gilbert reviewed 46 cases of choriogenic gynecomastia and stated that all had high urinary titers of choriongonadotropic (luteinizing, Prolan B) hormone and of folliculin (estrone). The presence of an excess of the latter hormone, probably produced by the tumor cells, gives an adequate explanation of the breast hypertrophy in these cases. Hunt and Budd (1939) reported a case of gynecomastia associated with the very rare interstitial cell tumor of the testis, in which the Zondek test was highly positive. No other analyses were made, so that this may be a case in which estrogenic substances were also present as in chorioepithelioma, or androgenic substances may have been perverted by the tumor cells to a mammogenic form.

The theory of hyperestrinism gained prominence after Allen (1927) and Nelson and Pfiffner (1931) reported that estrin appeared to be the most important hormone in the control of breast growth. Menville (1933) first proposed hyperestrinism as an explanation of idio-

pathic gynecomastia but presented no clinical proof. Lewis and Geschickter (1934) also attributed breast hypertrophy to hyperestrogenization, on the basis of their experiments on monkeys, and by the structural relationship to virginal hypertrophy of the female breast, a condition well proved to be due to excess estrogens. The well known urologist Young stated in 1937 that he was convinced that gynecomastia was the result of estrogen stimulation, but he offered no proof of his statement. Birnberg et al. (1938) evidently considered hyperestrinism as a causal mechanism of gynecomastia because they measured only the estrone levels in their case of breast hypertrophy in a boy of 14 years. They found 4 rat units of estrone per day in his urine, but this result is difficult to evaluate because rat units have not been standardized. Geschickter (1938) was one of the last authors who even mentioned hyperestrinism as causal in idiopathic gynecomastia, and then he was unable to present any substantiating data.

Kenyon et al. (1937), comparing the androgenic and estrogenic excretion rates in various endocrine states, were able to present reasonable evidence for a theory of androgen-estrogen imbalance in gynecomastia. In 4 cases of male breast hypertrophy they found that

an excess of estrogens was excreted by none (5 to 15 gammas per day), that the androgens excreted variedfrom none at all to normal amounts (0 to 37 I.U. per day), and that the most significant finding was the shift of the androgen-estrogen ratios toward the feminine level. These results were interpreted as being unable to bring support to the hyperestrinism theory, but the authors cautuiously stated that the findings were not entirely conclusive because (1) samplings of urine over only a few days were used, (2) increased estrogen production was known to evoke only a limited increase in urinary excretion, and (3) the gynecomastia may have been established before the tests were made.

The presence of hormonal imbalances in gynecomasts was confirmed by Glass and Bergman (1938), in describing a "subclinical adreno-genital syndrome" characterized by breast hypertrophy, small genitalia, and other feminine tendencies. Two such males had sex hormone levels within normal limits but presented a definite shift in androgen-estrogen excretion ratios toward a feminine range, and approximating the ratios observed in 28 females with secondary masculine characteristics. A decided increase in prolan excretion to as much as 50 mouse units per day was also noted, while normal males did not eliminate any detectable amounts.

Similar findings for adolescent "mastitis" were offered by Nathanson (1942). He measured the urinary excretion of estrogens, 17-ketosteroids (an androgenic group of substances), and follicle-stimulating hormone in 21 adolescent males with tender, palpable subareolar nodes, and compared the results with those from young males and females without breast complaints. In most cases of so-called mastitis adolescentium there were slightly increased estrogen excretion rates, or a low 17-ketosteroid excretion, or both. In general there was a definite shift of the androgen-estrogen ratio into the feminine range. In a few cases the levels were entirely within normal male limits; these may have been examined when the hormones had already returned to normal ratios and breast regression had begun. The follicle-stimulating hormones were measured in only 11 cases, and an elevated level found in too few to be of significance. The author concluded that adolescent breast hypertrophy is often associated with atypical urinary excretion rates of the sex hormones, probably as a result of sexual metamorphosis. Gynecomastia was found to be better related to disturbed ratios of hormones than to individual rates, and the role of the anterior pituitary was not established.

A remarkable syndrome was discovered by Kline-

felter et al., of the Massachusetts General Hospital, in 1942. Nine males of 17 to 38 years of age were found to have gynecomastia associated with small testes, aspermatogenesis without absence of Leydig cells, and an increased excretion of FSH. The breast tissues showed ductal hyperplasia and extensive proliferation of the periductal connective tissues. Estrin excretion was found not to be increased, while the 17-ketosteroid excretion and the corresponding secondary sex characterisitics varied from normal to definitely subnormal. The FSH excretion was increased to a degree comparable to that found in castrates. Testicular biopsies on 7 of the patients revealed hyalinization of the seminiferous tubules, but the interstitial (Leydig) cells appeared to be normal in structure and number. The authors interpreted these data as supporting the point of view that the testis secretes two hormones; i. e., androgen from the Leydig dells and inhibin from the seminiferous tubules. These hormones were described as analogous to progesterone and estrin, respectively. The increased FSH levels were explained as resulting from a lack of inhibition of the pituitary, following a lack of inhibin due to the degeneration of unknown etiology in the seminiferous tubules. The gynecomastia was not attributed to a disturbance in either the estrogens or

the androgens alone but to an imbalance of these hormones. The authors cited several previously reported cases which would probably have fitted into this syndrome (Hoffman 1942; Bronstein 1939; Hoffman 1939; Horsley 1939; Goodman 1937; Young 1937; Gibson 1923).

Heller and Nelson have recently (1945) expanded and modified the syndrome described above. After a thorough study of 20 cases collected within one year they consider that the constant and essential features are (1) small testes presenting hyalinized seminiferous tubules but containing Leydig cells, some of which are abnormal in appearance, (2) azoospermia, and (3) high urinary levels of gonadotropins. Persistent gynecomastia is listed as a variable feature because it was found in only 13 of the 20 cases having the three essential characterisitics. It varies with the degree of eunuchoidism accompanying the syndrome, being very slight in eunuchoids and pronounced in those with otherwise normal secondary sex characteristics. The gynecomastia consists of hyperplasia of the ducts and the intralobular connective tissue, but the duct growth is less than that seen in the usual puberal breast hypertrophy. The excretion of 17-ketosteroids and estrogens is at normal to very low levels. The 17-ketosteroid (androgen) excretion rate usually correlates well with the presence

or absence of eunuchoid feautures. The usual onset of the syndrome occurs at about the age of puberty. The elevated gonadotropin level is believed to be due to an abnormal sensitivity of the pituitary gland to the presence of steroids in the blood or to failure of the degenerated seminiferous tubules to utilize gonadotropins. The authors do not agree with Klinefelter's theory of inhibin and maintain that the existence of such a hormone has never been demonstrated. In explaining the gynecomastia the theory of perversion of sex hormones is introduced. Noting that the Leydig cells often appear abnormal, function poorly, and fail early, producing male climacteric symptoms in all patients over 25 years of age, Heller and Nelson assert that the breast hypertrophy in this syndrome is very probably due to the mammogenic activity of unsaturated 17-ketosteroid fractions formed by the abnormal Leydig cells.

In addition to being in agreement with the experimental findings of Bottomley and Folley (1938), the theory of perverted secretion of sex hormones is supported by considerable other clinical evidence. A case of interstitial cell tumor of the testis associated with gynecomastia was recorded by Hunt and Budd (1939). Although sex hormone analyses were not made, it seems

probable that the breast hypertrophy here was due to aberrant secretions. Woodham (1938) and Lewin (1941) reported 3 cases of gynecomastia appearing 2 to 18 months after orchidectomy and deep X-ray therapy for teratoma testis. No metastases were found, and the breast enlargement subsided upon the return of libido within a few months. The authors associated the breast hypertrophy with the preceding teratomas, but it appears more reasonable to presume that the interstitial cells of the remaining testis in each man were producing abnormal secretions while recovering from the insult of irradiation.

As mentioned by Nathanson (1942) and Richardson (1943), there are a few cases of gynecomastia in which no sex hormone disturbance or endocrine dysfunction of any kind can be found, even after complete examinations and analyses. These cases belong to the idiopathic group in the sex hormone classification of etiology but are commonly explained as being studied too late to allow the identification of the disturbance.

In summarizing the entire problem of sex hormone control of male breast hypertrophy, it may be stated (1) that estrogens and certain unsaturated androgens will experimentally reproduce clinical gynecomastia, (2) that testicular tumors may cause breast hypertro-

phy, probably by the mechanism of hyperestrinism, and (3) that most of the so-called idiopathic or adolescent gynecomastias present an imbalance of estrogen and androgen levels or possibly an abnormal type of sex hormone secretion. Proof of the latter must await advances in methods of chemical analysis of the various fractions of the sex hormones.

B. Adrenal Cortical Control.

It is well known that adrenal cortical tumors lead to sexual precociousness in children and to virilism in adult females, but only a few reports of these tumors occurring in adult males are available. All of these, however, exhibited bilateral gynecomastia as one of the earliest signs of the presence of malignancy. Weber (1926) cited two examples in males of 26 and 27 years of age. Both patients died, and the presence of adenocarcinoma of the adrenal cortex accompanying a true breast hypertrophy was confirmed by autopsy. The rapidly developing gynecomastia was attributed to a functional endocrine activity in the carcinomatous cells. Lisser (1936) reported one case that he had examined and reviewed two others, one of whom recovered after removal of the tumor. In all of these the adrenal neoplasm was demonstrable during life by palpation

or X-ray studies of the abdomen. Metastases to the liver or lungs were early and rapid in growth. The most recent case has been recorded by Simpson and Joll (1938) who made repeated studies of the urinary excretion of sex hormones in their patient. An increase in estrogenic substances to more than 3200 mouse units per liter of urine was found, while only a slight increase above normal was noted for androgens. The Ascheim-Zondek test was negative on two occasions. The authors concluded that the adrenal tumor was directly responsible for the considerable excess of of estrogenic hormone and the resulting feminization. After comparing the tumor tissue with that from females with virilizing tumors, Simpson and Joll reported that there were certain histological differences which might account for the fact that females with this tumor show an increase in androgen excretion while males have an increase in estrogens.

Cahill (1938) reviewed the reports of adrenocortical tumors and classified the gynecomastia in the foregoing cases as part of the adreno-genital syndrome as it appears in the adult male. Then a "subclinical" type of adreno-genital syndrome was announced by Glass and Bergman (1938). They stated that a mild form of sex reversal with a benign course and no demonstrable tumor was much more common than the malignant type. They

offered as evidence the findings that 28 females with masculine secondary sex characteristics and 2 males with gynecomastia, none of whom showed endocrine tumors or hypertrophy, exhibited androgen-estrogen excretion ratios approaching the ranges seen in the opposite sex and a slightly increased excretion of gonadotropins. Although these workers did not establish any proof that the adrenal cortex contributed directly to these disturbances in the sex hormone levels, they concluded that the pituitary, adrenals, and gonads were so intimately interrelated in function that all three were probably disturbed in this syndrome.

At the same time experimental evidence for a mammogenic function of the adrenal cortex appeared. Edwards et al. (1938) reported the case of a man with typical Addison's disease treated with a crude extract of adrenal cortex (eschatin) who developed bilateral gynecomastia with the onset and regression closely related to the course of therapy. In 1939 Van Heuverswyn et al. demonstrated that desoxycorticosterone acetate is as effective as estrogens and unsaturated androgens in producing mammary growth in young male mice. This overlap in physiological activity was ascribed to the close chemical relationships among these steroid compounds. Since then two additional cases of gynecomastia

associated with treatment of Addison's disease with desoxycorticosterone acetate have been recorded (Lawrence 1943; Raleigh and Philipsborn 1944).

Thus it appears that gynecomastia may occasionally be the result of adrenal cortical tumors producing excessive estrogenic substances or some closely related mammogenic substances such as desoxycorticosterone. The existence of a subclinical adrenogenital syndrome with a disturbed function of the adrenal cortex is possible but not proved.

C. Thyroid Control.

Disturbances in thyroid gland function have only rarely been accompanied by gynecomastia. Freeman (1916) reported an example in a 37-year-old male who showed marked enlargement of both breasts, beginning 3 months after the first appearance of symptoms of severe exophthalmic goiter. The further course of the patient was not given. Two cases were submitted by Starr (1935). These were in men of 28 and 45 years who had shown extensive breast enlargement 2 to 10 months after the onset of hyperthyroidism. The breasts rapidly regressed in size after iodine therapy and hemithyroidectomy in each patient, while the older man experienced a recurrence of gynecomastia with a recurrence of the hyper-

thyroid state. Menville (1933) mentioned that hyperthyroidism was present in 1 of his series of 88 gynecomasts. If thyroid hyperfunction is responsible for some cases of breast hypertrophy in the male, no adequate explanation of the mechanisms involved has ever been given. Weichert and Boyd (1934) found that there was an extraordinary increase in breast tissue and early secretory activity in pregnant rats which had been fed desiccated thyroid. These authors gave the farfetched explanation that the increased metabolism of hyperthyroidism caused rapid elimination of estrin, thus relieving the pituitary of the inhibitory effects of estrin and allowing it to produce more lactation hormone.

A moderately diminished basal metabolic rate has been noted in a few case reports of gynecomastia (Moehlig 1929; Menville 1933; Horsley 1939), but these appear to occur only in obese eunuchoid types in which most of the breast enlargement is due to adipose tissue (pseudogynecomastia) while the decreased metabolic rate is the result of hypogonadism.

Thus thyroid dysfunction is only rarely associated with gynecomastia, perhaps only as a coincidence, and no adequate explanation of possible relating mechanisms is known.

D. Genital Anomalies.

It has already been mentioned that Deaver and McFarland (1917) found imperfect development of the genitalia in 28 of 160 gynecomasts (17.5%). That hypospadias, epispadias, atrophic testes, or pseudohermaphroditism are frequently associated with gynecomastia was confirmed by Hammett (1920). In 1937 Young reported 3 cases of greatly enlarged breast accompanying congenital hypospadias. Two of these were brothers. Gynecomastia may also appear as an accompaniment of persistently undescended testicles (Horsley 1939). Atrophic testicles and the resulting hypogonadism appear to be predisposing factors to gynecomastia because methyl testosterone therapy produced breast hypertrophy in 6 of 11 hypogonads but in only 1 of 7 men treated for functional impotence with equal amounts (McCullaugh and Rossmiller 1941). It appears that genital anomalies definitely predispose to gynecomastia, but since these defects tend to be hereditary in origin they are closely associated with the next etiological group.

E. Herdity.

One Russian family in which 4 males were endowed with large feminine breasts was reported by Savitzky (1894). Several other instances of a familial tendency

toward gynecomastia have appeared in foreign reports, but Deaver and McFarland noted that most cases give no history of inheritance of the defect and that those which do may indicate only a peculiar familial excess of the hormones which stimulate the breast. Young (1937) found gynecomastia, hypospadias, and hypogenitalism in two brothers and attributed the breast enlargement to hyperestrinism. Ivanissevich (1941) stated that the probable cause of some cases of gynecomastia was a disturbance during the development of the embryo, while Richardson (1943) ascribed breast hypertrophy to an abnormally vigorous response on the part of the male breasts to normal endocrine stimulation. Both of the preceding ideas reached their acme in the hypothesis proposed by Hoffman (1942). He divided variations in secondary sexual characteristics, such as gynecomastia, into two groups: (1) those due to true endocrine disturbances like chorioepithelioma or adrenal cortical tumor, and (2) those arising from alterations in the germ plasm; i. e., hereditary, chromosomal, or genetic types. He stated that intersexual variations are constitutional in origin in the majority of cases and not any more abnormal than individual variations in types of eyes or noses. He presented the case of a boy who was an entirely normal male except for marked bilateral

gynecomastia and rather low urinary levels of estrogens and androgens. The breast hypertrophy was explained as resulting from chromosomal changes at the time of sex differentiation. Thus the breasts were described as receiving the quality of responding to any female female hormone that might be present, just as in the normal female, while most of the sex characteristics remained masculine. This is an interesting theory but requires more substantiation. It must be shown that the gynecomastic breast is more sensitive to mammogenic substance than the normal male breast. The common occurrence of unilateral gynecomastia lends some support to this idea. Against such a theory is the experimental evidence that the breasts of gonadectomized animals respond equally to estrogenic substances, irrespective of their sex at birth (Nelson 1936).

In summary it may be stated that there is a slight tendency toward a familial incidence of gynecomastia but that there is no adequate evidence for a chromosomal determination of breast growth. Perhaps the explanation for the occurrence of unilateral gynecomastia lies in the genetic or embryonic history of the individual, but this is entirely unknown at present.

F. Miscellaneous Conditions Associated with Gynecomastia.

Hepatic cirrhosis occasionally displays the symptom of gynecomastia, particularly in the terminal stages of liver failure. Woodyatt (1909) and Bailey (1924) have each reported a case. In 1939 Edmondson, Glass, and Soll described the breast hypertrophy as similar to that seen after experimental estrone stimulation and as appearing late in the liver disease, after the onset of ascites. A report by Glass, Edmondson, and Soll in 1940 noted that gynecomastia was found in 8 of 14 cases of chronic liver disease and that testicular atrophy appeared in all 14. Based on the findings of Zondek (1934), Israel et al. (1937), and Golden and Sevringhaus (1938) that the normal liver inactivates the sex hormones by combining them with various substances, careful bioassays of both free and combined androgens and estrogens in the urines of these cirrhotic patients were made. It was found that nearly all of the estrogens were in the uncombined form and were slightly increased in amount. Normal males showed no free estrogens. The androgens in the cirrhotic males were considerably decreased in amount, agreeing with the finding of testicular atrophy in all cases. The authors inferred that the free form of the estrogenic substances may be more potent than the combined form and concluded that the

gynecomastia in these cases is due to the high levels of free estrogens resulting from the failure of the cirrhotic liver to inactivate them.

Pituitary tumors have been associated with breast enlargement in a small number of cases, but most of these have actually been the pseudogynecomastia of Froelich's syndrome, and not true gynecomastia (Gibson 1923; Moehlig 1929; Ivanissevich 1941). Bailey (1924) described an anomalous case of a 55-year-old male, in whom autopsy revealed true gynecomastia, an eosinophil tumor of the pituitary, giantism, hypogonadism, hepatic cirrhosis, and subacute bacterial endocarditis. A hyperplasia of the chromophobic cells of the pituitary, resembling the change seen in pregnant women, has been noted in gynecomasts with teratoma testis or chorioepithelioma (Ferguson 1933; Entwisle and Hepp 1935; Gilbert 1940). This increase in the inactive cell forms of the pituitary may be attributed to the high levels of inhibitory estrin present in these conditions.

Traumata have been mentioned by some authors as causal of gynecomastia. Woodyatt (1909) and Deaver and McFarland (1917) reported that breast enlargement was occasionally preceded by local traumata, but the histories and examinations in these cases were not highly reliable. Andrews and Kampmeier (1927), believing gyne-

comastia to be a form of chronic breast inflammation, stated that the cause was chronic irritation. Wernicke (1939) described 4 cases who gave histories of breast enlargement following a single blow to the affected breast 2 to 8 years preceding the examination. It appears likely that the blow merely called attention to the tender or enlarging breast rather than being causal. Sullivan and Munslow (1942) observed that the trauma of wearing a pack resulted in increased size and pain in the breasts of 5 soldiers who had had pre-existing gynecomastia but that an injury was causal in none.

Prostatectomy has been followed in a few instances by bilateral breast hypertrophy in aged males. Mann (1928) reported one case and reviewed four examples from foreign literature. An explanation of the mechanism of breast enlargement in these old men is impossible at present, since the prostate gland has shown no other evidences of an internal secretory function.

A peculiar syndrome consisting of carcinoma of the lung, osteoarthritis, and bilateral gynecomastia was observed in 3 males 37 to 47 years of age by Castillo et al. (1941), of Buenos Aires. All three showed a milky secretion from the breast at some time, and all experienced a marked decrease in libido. The Friedman test was negative for the two men thus tested. The

presence of carcinoma of the lung was verified by biopsy or at autopsy. Breast enlargement was one of the earliest symptoms. The possibility that some types of lung cancer may secrete a substance of feminizing action was suggested by the authors.

VI. THERAPY

The methods of mangement of gynecomastia vary considerably, depending upon the etiology in the individual case, so that an accurate diagnosis is necessary to determine the course of therapy.

In those cases due to teratoma testis, chorioepithelioma, adrenal cortical tumor, carcinoma of the lung, or hyperthyroidism, it is obvious that removal of the underlying cause will result in an early regression of the breast hypertrophy. If metastases have already occurred in a malignant state, an early death will cut short the need for treatment of the gynecomastia. The same prognosis and course holds true for the terminal stages of hepatic cirrhosis.

In the idiopathic and adolescent hypertrophies, conservatism is indicated. Since the vast majority of these undergo spontaneous regression within a few months, Geschickter (1938) advises a period of pure observation for 2 to 3 months. In the few cases that reach feminine size or persist for more than one year, surgical excision is indicated to relieve the embarassment of the patient. Simple mastectomy is all that is required. If the technique of Ivanissevich (1941) is followed, the nipple may be preserved for cosmetic appearances.

Repeated mild X-ray irradiations of the breast were used by Menville (1932) to retard the hyperplasia of the parenchymal and periductal tissues that occurs in gynecomastia. A favorable response was noted in early cases only, and the tendency of these to subside spontaneously has resulted in discontinuance of this method.

The question of endocrine therapy in gynecomastia has become prominent in recent years. Hoffman (1939) has been the chief proponent of sex hormone injections. On the theory that breast hypertrophy might be due to a deficiency of male sex hormone, he injected 28 gynecomasts, mostly adolescents, with testosterone propionate, twice each week for several months. The breast enlargements before injection varied greatly in size and duration. 23 of the 28 showed 75% or more regression within 2 to 5 months and only 2 cases were regarded as absolute failures. Yet 3 untreated cases subsided completely within 2 to 8 months, and the author admitted that it was difficult to evaluate his results in the presence of the strong tendency toward spontaneous regression. Nevertheless he believed that abatement was swifter and surer with testosterone therapy. Wernicke (1939) and Adair (1940) have been the only other investigators to report favorable results, and these were

limited to small series of cases. On the other hand Birnberg et al. (1938), Horsley (1939), Lewin (1941), Sullivan and Munslow (1942), Rea (1942), and Richardson (1943) have all noted no significant responses to testosterone propionate injections. These results are not surprising in view of the facts that experimental evidence indicates that gynecomastia is not due to a lack of androgens and that testosterone may be mammogenic rather than anti-mammogenic (Selye et al. 1936; Van Heuverswyn 1939; McCullaugh and Rossmiller 1941). In short, there are neither convincing results nor a sound rationale to warrant the further use of androgens in the therapy of gynecomastia.

Anterior-pituitary-like hormones were injected into small series of patients by Hoffman (1939) and Wernicke (1939) in the hope of stimulating a normal secretion of sex hormones but nc consistent or encouraging results were obtained.

VII. SUMMARY

1. Gynecomastia is the physiological hypertrophy of the male mammary gland to any appreciable degree.

2. The histological changes consist of hyperplasia of the ducts and proliferation of the periductal connective tissue. The hypertrophy is usually diffuse; it may become localized in the form of fibroadenoma.

3. A tender, firm subareolar mass of glandular tissue is palpable duringthe first few months of the development of gynecomastia. Spontaneous regression within a few more months constitutes the course in the great majority of cases. If the breast attains the size of that of an adult female, the glandular tissue becomes softer, more diffuse, and persistent.

4. A mild degree of temporary breast hypertrophy is nearly universal among adolescent males.

5. Gynecomastia must be differentiated from pseudogynecomastia, carcinoma of the male breast, dermoid cyst, lipoma, lymphangioma, and infections.

6. Some cases of male breast hypertrophy are the result of definite endocrine disease; the great majority are of "idiopathic" origin.

7. Gynecomastia may be an early symptom of teratoma testis, chorioepithelioma, adrenal cortical tumor,

hyperthyroidism, and carcinoma of the lung. It may be a late symptom of cirrhosis of the liver.

8. Estrogens, unsaturated androgens, and desoxycorticosterone have the ability to produce experimental gynecomastia, probably by direct stimulation of the mammary gland. An excess, an imbalance, or a perversion of these hormones is detectable in the majority of gynecomasts. The role of the pituitary secretions is still uncertain.

9. Gynecomastia is occasionally associated with pituitary tumor, prostatectomy, genital anomalies, or trauma. It shows no significant tendency to be inherited.

10. Therapy consists of removal of the underlying cause in the true endocrine disturbances. Observation for several months is sufficient early in the idiopathic types. Surgical excision is indicated for large persistent male breasts.

11. There is no rationale to warrant further use of testosterone therapy in gynecomastia.

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