TUMORS OF THE BREAST RELATED TO THE OESTRIN HORMONE

CHARLES F. GESCHICKTER, M.D., DEAN LEWIS, M.D., AND CARL G. HARTMAN

(From the Departments of Surgery, Surgical Pathological Laboratory and Carnegie Laboratory of Embryology, Johns Hopkins Medical School, Baltimore, Maryland)\(^1\)

I. GYNECOMASTIA, VIRGINAL HYPERTROPHY, AND FIBRO-ADENOMA

A pathologic study of 95 cases of gynecomastia, 25 cases of virginal hypertrophy, and 450 cases of fibro-adenoma (1, 2) recorded in the Surgical Pathological Laboratory of the Johns Hopkins Hospital, emphasizes the similarity of these lesions. The histologic changes which occur normally in the breast during embryonic life and at puberty are quite similar to those found in the conditions just mentioned (Figs. 1 to 4). In late embryonic life and at puberty the lactiferous tubules become longer, the epithelium of the ducts undergoes hypertrophy, and the periductal connective tissue increases in amount. This characteristic fibro-epithelial growth is a developmental response occurring in both male and female under both normal and abnormal conditions. Its mechanism is most easily demonstrated in gynecomastia, since this form of hypertrophy is apparently independent of hormones derived either from ovarian or placental tissue.

Gynecomastia

Gynecomastia occurs most frequently in males of the white race between the ages of thirty and forty years. The lesion is more frequently unilateral than bilateral. The affected breast is soft or moderately firm, frequently tender, and rarely nodular on palpation. The breast affected may vary in size, and enlargement may recur after subsidence. In about 15 per cent of the cases the enlargement begins at puberty, or shortly thereafter. Malignancy has not been observed in gynecomastia. In our series this benign enlargement of the breasts is about twice as common as cancer in the male. (Fig. 5.)

Clinical observations extending over a number of years have definitely indicated that there is a relationship between altered function of the gonads and glands of internal secretion and gynecomastia. Association of enlargement of the male breast with hermaphroditism, pseudohermaphroditism, and imperfect development of the sex organs has been noted for years, having been recorded almost a century ago by Beau, Polaillon and others (cited by Menville). Atrophy of the testicle, with or without injury, or following orchitis and associated with varicocele, has also been recorded in cases of gynecomastia. Such findings have been interpreted as supporting the theory of Moszkowicz (3) that testicular secretion inhibits the growth of the male breast. At variance with this theory, on the other hand, is the frequent coincidence

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of gynecomastia and teratoma testis, as pointed out by Kriss (4), and more recently by Bailey (5), Cairns (6), Heidrich (7), Ferguson (8), Hamburger (9), and others. Herzenberg (10), in particular, has emphasized the relationship between chorionepithelioma of the testicle

![Figures 1-4 showing the similarity of the histologic picture in early puberty hypertrophy (1), gynecomastia (2), virginal hypertrophy (3), and fibro-adenoma (4)](image)

The specimen in Fig. 1 (Path. No. 52730) was removed at autopsy on a colored girl of eight years, dying of tuberculous meningitis. There are hypertrophy of the duct epithelium and hyperplasia of the periductal connective tissue. The specimen in Fig. 2 (Path. No. 39909) is from a man of forty-five; that in Fig. 3 (Path. No. 18146) from a white girl of seventeen years, with virginal hypertrophy beginning four years previously, two years before menstruation. The specimen of fibro-adenoma (Path. No. 35109) in Fig. 4 is from a woman of twenty-six.

and gynecomastia. The chorionic tissue of the placenta may elaborate the hormones prolan and oestrin. Such tissue present in teratomas and chorionepithelioma of the testicle may secrete the hormone which stimulates the breast to growth, resulting in the hypertrophy known as gynecomastia.
In atrophy of the testicle there may be a hyperplasia of the interstitial cells. Lower and Johnston (11) have shown that a marked increase of interstitial cells occurs in rats in which an atrophy of the tubules has been brought about by small doses of x-rays. Roth (12) and Moehlig (13) have reported cases of hypophyseal tumor with enlargement of the male breast, and Mathias and Weber (cited by Menville) have described a malignant tumor of the suprarenal cortex in a man with gynecomastia. A similar hyperplasia of the interstitial cells of the testis as a result of stimulation by the hypophysis or adrenal may be the active mechanism in these cases.

Chorionic tissue in a teratoma of the testicle would thus seem to stimulate the breast, either directly, by virtue of hormone secretion, or indirectly through action on the interstitial cells of the opposite testis, such stimulation leading to hypertrophy, recognized clinically as gynecomastia. Similarly abnormal stimulation of the interstitial cells of the testicle by the secretion of the anterior lobe of the hypophysis or of the cortex of the adrenal may be followed by enlargement of the male breast.

The clinical and experimental data to follow seem to support the conclusion that the common factor in endocrine disorders causing gynecomastia is a high secretory level of the female sex hormone (oestrin or theelin), and that this hormone may be secreted in high concentration or large amounts by chorionic tissue in teratoma testis, over-active interstitial cells of the testicle, and ovarian tissue in cases of hermaphroditism.

Beginning at birth and extending over a period of two to four months, cystic dilatation takes place in the ducts which have undergone
hypertrophy during the last third of pregnancy. After this change, the breast tissues in both sexes are relatively quiescent until puberty. In the male renewed hypertrophy, similar to that occurring at birth, occurs at the age of fourteen or fifteen. In females this hypertrophy begins earlier and is much more marked than in the male. Until menstruation is established the hypertrophy is identical histologically with that of gynecomastia (Fig. 8); the ducts are dilated and many branches lined by several layers of cells are added to the duct tree. Lobule formation does not occur until after menstruation, when the corpus luteum appears in the physiological picture. Numerous ripening and

Figs. 6 and 7. Photomicrographs of the Branching Tubules in the Breast (left) and of the Testis (right) in a Premature Stillborn Infant

The pregnancy was of six and one-half months' duration. The cells lining the breast tubules are three to six layers deep and are surrounded by a proliferation of periductal and perilobular connective tissue. The tubules of the testis are widely separated by hyperplasia of interstitial cells. This hyperplasia is apparently related to the development observed in the breast at this period. Path. No. 52772.

atretic follicles lined with theca cells, which secrete oestrin, are found in the developing ovary of the prepuberty period (Fig. 9), and numerous observations have shown increasing amounts of oestrin in the blood at this time. The secretion from the ovary is a response to the gonadal-stimulating hormone of the anterior lobe of the hypophysis. This is related to the chorionic gonadotrophic hormone, prolan, found in the urine during pregnancy. An increasing concentration of this hormone occurs toward puberty.

It may be concluded, therefore, from histologic and endocrine studies on the normal male and female breast at birth and at puberty, that the developmental response in mammary tissue at these periods to the female sex hormone, oestrin, is homologous to that in gynecomastia.

By injections of oestrin, varying in amounts from 2,000 to 5,000 rat
units, we have produced in male monkeys a lesion which both grossly and histologically resembles gynecomastia in man. Both *Rhesus macacus* and *cebus* were used in these experiments. The hormone, in corn oil, under the trade name of Amniotin, was supplied through the

courtesy of E. R. Squibb and Sons. Five thousand rat units in doses of 500 units were given to the *cebus* monkeys over a period of ten days, while 2000 units were given to *macacus* monkeys in small doses of from 16 to 64 units daily over a period of six weeks. Better results were obtained with the smaller doses given daily over a long period.
The breasts and nipples of both sides doubled in size after the injections. In the *macacus*, before the injections, the nipple stood out 0.5 cm. beyond the breast, and the breast measured 0.5 cm. from the nipple to the axillary border. After the injections the nipple stood out about 2 cm. beyond the breast, and the measurement from the nipple to the axillary margin was 2 to 2.5 cm. (Fig. 10).²

Microscopically the histologic changes are those of gynecomastia. The ducts have increased in length and have become dilated; there is an increase in the number of layers of epithelial cells and a characteristic proliferation of periductal connective tissue. The perilobular

1 The response in young monkeys is more marked than in adults.
stroma is also definitely increased (Fig. 11). These changes were produced in the breasts of two cebus and five macacus monkeys. Biopsies were made of the breasts in the macacus monkeys before the injections were made, the tissue removed serving as a control. In one monkey the condition was produced after the testicles had been removed. The pituitary and adrenals were intact in all the animals.

The breast enlargement produced by the oestrin injections showed a tendency to regress in three weeks to one month. The number of epithelial layers in the ducts decreased, but the periductal connective tissue, because of its more adult character, remained in excess of normal. Regression was accentuated by castration of the animals.

In four male monkeys (one cebus and three macacus) in which one or both testicles were present, a condition similar to gynecomastia was also produced by the subcutaneous injection of the anterior-pituitary-like hormone (chorionic gonadotropic hormone, prolan) obtained from the urine of pregnancy. Follutein, in powdered form, supplied through the kindness of E. R. Squibb and Sons, was used in these experiments. It was dissolved and suspended in sterile water, and given in doses varying between 7,000 and 22,000 rat units. Grossly, moderate bilateral enlargement of the breasts occurred following the injection. Histologically, hypertrophy of the breast was less evident. A single or double layer of epithelial cells was seen, and less proliferation of the periductal connective tissue than in typical gynecomastia. The hypertrophy in these experiments was due to the effect of the hormone upon the testicle. The testicles were enlarged (increased to two and one-half their normal size in the cebus monkey), and a definite hyperplasia of the interstitial cells occurred. This was accompanied by hypertrophy of the prostate, which in one monkey caused urinary retention and dilatation of the bladder. Hypertrophic changes in the breast were not produced when follutein was injected into monkeys from which the testicles had been removed (Figs. 12-15).

These experiments justify us, we believe, in assuming that gynecomastia is caused by a prolonged hyperstimulation of the breast by the hormone oestrin. Clinically this hormone may, in rare instances, be supplied directly by ovarian tissue, as in hermaphrodites or pseudohermaphrodites; it may be supplied by chorionic tissue in teratoma and choriocarcinoma of the testicle, or its source may be the overactive interstitial cells of the testicle, stimulated in turn by the anterior pituitary or pituitary-like hormone or by a secretion from the cortex of the adrenal. Additional clinical evidence in support of these conclusions is ob-

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3 This testicular-prostatic change is quite similar to that observed clinically by Ferguson in cases of teratoma testis, and produced experimentally by Lower and Johnston. It will be discussed in another paper.

4 The oestrin content of both normal and neoplastic chorionic tissue is known to be high. The human placenta contains from 400 to 700 rat units per kilo of oestrin (Allen, 18). Sigmund (19) has reported 10,000 mouse units of oestrin per liter of cyst fluid in a case of choriocarcinoma of the uterus.
obtained from cases of gynecomastia associated with teratoma of the testicle. In the case studied by Heidrich and his co-workers 250 mouse units of the female sex hormone were obtained from a liter of urine, as well as 35,000 mouse units of gonadotropic hormone. Hamburger found oestrin, as well as gonadotropic hormone, in a patient with a testicular tumor. In a similar case, complicated by gynecomastia, no oestrin was recoverable from the urine. The testicle not involved by tumor was larger than normal at the time the gynecomastia was ob-

Figs. 12–15. Tissues from the breast (12) and testicle (13) of an adult monkey (Cebus) following injection of 7,500 rat units of anterior-pituitary-like hormone (Follutein-Squibb) in four successive doses, and corresponding tissues from another monkey (Rhesus macacus) serving as a control (Figs. 14–15).

The injections were followed by moderate gynecomastia in the breast (Fig. 12), while the testicle (Fig. 13) showed interstitial cell hyperplasia crowding out the tubules. This monkey also had as a result of the injections marked prostatic hypertrophy with urinary retention and dilatation of the bladder. Path. No. 52738.

In the breast of the control monkey (Fig. 14) note the single layer of duct epithelium and the acellular fibrous tissue. In the testicle (Fig. 15) the tubules are crowded together and interstitial cells can be found only in thin strands. Path. No. 53550.
served. In Ferguson's detailed study quantitative determinations of gonadotropic hormone (prolan) were carried out but the blood and urine were not examined for oestrin. Ferguson did, however, call attention to hyperplasia of the interstitial cells of the testicle occurring in teratoma testis complicated by gynecomastia, but drew no conclusions in regard to the relation of these cells to the breast hypertrophy. Previous observers have extracted oestrin or theelin from the testicle (Fellner, 16; Laqueur, 17). The concentration of oestrin is particularly high in the testis of the stallion.

**Virginal Hypertrophy**

Pathologically virginal hypertrophy in the female is the exact homologue of gynecomastia in the male (Figs. 5, 16, 17). These cases of enlargement of one or both female breasts, however, show a more marked tendency to be related to the prepuberty period. In fifteen bilateral cases recorded in this laboratory, the growth in the breast antedated menstruation by one or two years and was exacerbated at the menarche. The definite relationship to the normal hypertrophy of the breast incident to puberty, and the resemblance under the microscope to gynecomastia, suggest that this diffuse response of the lactiferous ducts and the stroma of the breast is the result of increased stimulation by the hormone oestrin.

Diffuse virginal hypertrophy in one breast is not uncommonly accompanied by the occurrence of a localized fibro-adenoma in the same breast. Ten such cases are recorded in this series. An additional case, the first pathologically described by Bloodgood in this laboratory and reported by Johnston (21) showed tremendous bilateral hyper-
trophies associated with a large, encapsulated fibro-adenoma in the left breast.

Under the microscope the changes in the duct epithelium and in the surrounding fibrous tissue in diffuse virginal hypertrophy are similar

to both gynecomastia and fibro-adenoma. The ducts and periductal connective tissue, however, tend to be surrounded by a tremendously increased amount of adult perilobular fibrous tissue, which may be hyalinized in places. As in fibro-adenoma, the tissue in virginal hypertrophy may show acinar formation after the onset of menstruation due
to the physiological influence of the corpus luteum. In a recent case of unilateral virginal hypertrophy accompanied by a large fibro-adenoma, to be described below, bio-assay of the tissue revealed pathologically high concentrations of the oestrus hormone.

Apparently, localized response on the part of one or more segments of the breast to pathological oestrin secretion leads to fibro-adenoma, whereas a diffuse response leads to unilateral or bilateral virginal hypertrophy. The two types of response may be simultaneous, and with a pronounced local response in the form of fibro-adenoma there is a tendency for the remaining breast tissue to respond more diffusely and less intensely by an analogous hypertrophy. This is microscopically evident in the duct hypertrophy and periductal fibrous proliferation occurring in the breast tissue around the tumor (Fig. 27). It accounts, also, for the familiar clinical observation that fibro-adenoma always occurs in a well developed breast.

### Table 1: Comparative Data on Oestrogenic Tumors of the Breast

<table>
<thead>
<tr>
<th>Data</th>
<th>Gynecomastia</th>
<th>Virginal Hypertrophy</th>
<th>Fibro-adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>95 Males</td>
<td>25 Females</td>
<td>500 Females</td>
</tr>
<tr>
<td>Sex</td>
<td>30–40</td>
<td>11–17</td>
<td>20–25</td>
</tr>
<tr>
<td>Age</td>
<td>1 year</td>
<td>5 years</td>
<td>3 years</td>
</tr>
<tr>
<td>Duration</td>
<td>Diffuse</td>
<td>Diffuse</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Location</td>
<td>12 per cent</td>
<td>60 per cent</td>
<td>7 per cent</td>
</tr>
<tr>
<td>Bilateral</td>
<td>Duct and periductal stroma</td>
<td>Duct and periductal stroma</td>
<td>Duct and periductal stroma</td>
</tr>
<tr>
<td>Structures involved</td>
<td>Doughy; diffuse</td>
<td>Firm; diffuse</td>
<td>Hard; nodular</td>
</tr>
<tr>
<td>Character of tumor</td>
<td>3 per cent</td>
<td>0</td>
<td>3 per cent</td>
</tr>
<tr>
<td>Nipple discharge</td>
<td>Oestrin</td>
<td>Oestrin</td>
<td>Oestrin</td>
</tr>
<tr>
<td>Hormone control</td>
<td>Puberty, decline after maturity</td>
<td>Puberty</td>
<td>Puberty and pregnancy</td>
</tr>
<tr>
<td>Relation to sexual life</td>
<td>Hypertrophy of ducts; hyperplasia of stroma</td>
<td>Hypertrophy of ducts; hyperplasia of stroma</td>
<td>Hypertrophy of ducts; varying degrees of hyperplasia and hypertrophy in the stroma</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>1 per cent</td>
<td>0</td>
<td>10 per cent</td>
</tr>
</tbody>
</table>

Apparently the differences between the moderate breast hypertrophy of gynecomastia, the marked enlargement in virginal hypertrophy, and the localized tumor growth in fibro-adenoma (Figs. 16–18; Table I), are not dependent upon variation in the blood level of oestrin alone. That synergistic action between oestrin and the growth hormone of the anterior pituitary may account for some of these variations is suggested by the relative ease with which breast hypertrophy is produced by injections of oestrin in young animals, as compared to adults. Variations in tissue response must also occur to account for unilateral hypertrophy or localized growth. This is indicated by the fact, demonstrated below, that isolated zones of mammary tissue may show an unusual power to concentrate oestrin.
Fibro-adenoma

Fibro-adenoma is a benign encapsulated lesion of the breast which is relatively common in women during the span of life from early puberty to the menopause. The salient features of a series of 450 cases analyzed were: (1) association with the diffuse enlargement of the female breast known as virginal hypertrophy; (2) slow and prolonged growth over a period averaging three to four years, with a tendency to involve a section of the breast or to give rise to multiple tumors; (3) a tendency to appear during puberty or pregnancy; (4) resemblance of the tumor microscopically to gynecomastia. Histologically fibro-adenoma shows an increase in duct epithelium and in the surrounding periductal and perilobular connective tissue. In many cases there is the same complete absence of acinar formation which is observed in gynecomastia of the male breast.

Clinical Features: Solitary fibro-adenomas are most often situated at the periphery of the breast over the pectoralis fascia, in the upper and outer quadrant. The presence of a firm, nodular tumor is usually the only symptom; in a third of the cases the lump is painful or tender. Variation in size with the menstrual cycle is rare, but enlargement during pregnancy is not uncommon. Five per cent of the lesions are tender to pressure, and in another 5 per cent the surrounding breast is lumpy. The breasts in which these tumors appear are usually well

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FIG. 19. FIBRO-ADENOMA OF THE SO-CALLED INTRACANALICULAR MYXOMA TYPE, EXCISED FROM THE BREAST OF A MARRIED WOMAN

The rapid proliferation of periductal connective tissue greatly exceeds the amount of epithelial hypertrophy in the neighboring ducts, resulting in their compression and projection of the fibrous tissue into the lumen. From Oliver and Major: Am. J. Cancer 21: 1, 1934. Path. No. 37880.
developed and of the so-called virginal hypertrophy type. In only one case in our series did cancer develop at the site of a fibro-adenoma, although forty-one cases of related fibrosarcoma have been observed. The sarcomas occurring in this series have been reported elsewhere (22) by Fox, and are discussed below. In about 10 per cent of the cases in which local removal was performed, a similar tumor appeared subsequently in the same or the opposite breast.

The peak of age incidence falls between twenty and twenty-five years, with a duration of symptoms of over three years, indicating onset before the age of twenty. Only 7 patients in our entire series were over fifty years of age. Women who are treated for this condi-

![Typical Fibro-Adenoma](image)

**Fig. 20. Typical Fibro-Adenoma Excised from a Colored Girl Aged Thirteen**

There is a fairly even balance between duct hypertrophy and increase in fibrous tissue, although the latter predominates. Much of the connective tissue has become matured and hyalinized. No acini or typical lobules have been produced in the tumor despite two years' history of menstruation. Path. No. 40305.

... tion near the menopause usually give a prolonged history on careful questioning. In the cases of briefer duration and with a more rapid rate of growth the tumor has the histologic appearance described as intracanalicular myxoma (Fig. 19), with abundant amount of loose embryonic connective tissue surrounding the epithelial structure. Such a tumor is usually subepithelial and confined to the true mammary stroma. In the more protracted cases, to which the term fibro-adenoma is applied (Fig. 20), a more adult stroma surrounds the ducts and tubules and often involves the supporting fascial elements. We believe this to be the only pertinent distinction between the two histologic varieties. Many cases show both types of growth (Fig. 21).

**Histologic Features:** A knowledge of the various types of fibrous tissue in the breast is essential to the understanding of fibro-adenoma
and to the distinction between fibro-adenoma and the sub-variety known as intracanalicular myxoma. Both fibrous tissue and epithelium take part in the new growth. Four forms of fibrous tissue are recognized in the breast. Two of these are fascial in type. One, the enveloping fascia, surrounds the entire breast, and is known as the interlobar connective tissue. The second, or subdividing fascia, separates the gland into lobules, and is known as the interlobular connective tissue. Both of these fascial structures are relatively unimportant in fibro-adenoma. The third and fourth forms of fibrous tissue constitute the true stroma of the breast. One of these surrounds the ducts and acini in concentric fashion and is known as the perilobular con-

![Image](image-url)

**Fig. 21. Whole Section through a Breast with Fibro-Adenoma, Removed from a Girl in the Post-Puberty Period**

Under the microscope the tumor at A showed areas of fibro-adenoma and at B areas of the intracanalicular myxoma type. Path. No. 53554.

nective tissue. The other immediately surrounds the ducts and potential acini and is referred to as periductal and perilacinar.

In most fibro-adenomas there is a definite increase in the periductal and perilobular connective tissue (Fig. 20). In 190 cases young connective tissue with a loose myxomatous appearance (so-called intracanalicular myxoma) predominated. In 150 cases the connective tissue, while somewhat cellular, was of the more adult fibrous type. Only 61 cases showed compact, mature fibrous tissue throughout, indicating an end-stage of the disease.

In fibro-adenoma the normal puberty type of hypertrophy described earlier in this paper is simulated. In 341 of 400 cases there was an increase in the number and size of the ducts, with the piling up of epithelial layers in the ducts. This duct hypertrophy is the characteristic feature of the epithelial changes, as pointed out by Oliver and Major. One hundred and forty-seven cases showed compression of the duct epithelium, indicating more marked growth in fibrous tissue than
in epithelial structures. These cases were usually of the so-called intracanalicular myxoma type. In 130 cases small ducts or acini were prominent, indicating that the menstrual type of hypertrophy had been superimposed upon the puberty type. Many of these 130 cases showed dilated ducts and small cystic areas, pointing to an involutional process, also characteristic of the period of menstrual changes.

These microscopic studies indicate that fibro-adenoma and its histologic variant, intracanalicular myxoma, are essentially exaggerations of the hypertrophy of puberty. The majority of fibro-adenomas show no acinar-like structures, but resemble the hypertrophy of gynecomastia. The other histologic features observed (lobule formation

![Figure 22. Chart showing the secretory levels of the two ovarian hormones, oestrin or theelin and progesterin, in blood and urine during menstrual and pregnancy cycles.](image)


and cystic dilatation of the ducts) may be looked upon as superimposed menstrual phenomena.

**Relationship of Fibro-adenoma to Puberty and Pregnancy:** The relationship of fibro-adenoma to the physiological hypertrophy of the breast occurring during puberty is substantiated by a study of 220 women with this condition who had not borne children. One hundred and forty-seven of these patients were under the age of thirty when examined, with a duration of symptoms averaging over three years. Of this group, 65 were under twenty and 12 less than fifteen years of age when examined. In the remainder the average age was thirty-six years, with an average duration of symptoms between six and seven years. When the duration of symptoms is subtracted from the pa-
The duct epithelium is also markedly increased as the result of the influence of the hormone, progestin, during the first half of pregnancy. The patient was a white female aged twenty-nine, who had noticed a circumscribed lump in the breast a year before her marriage. At the end of the first half (four-and-a-half months) of pregnancy the lump was excised because of its more rapid growth. Path. No. 46546.
tient's age at examination, and when further allowance is made for the
time that may elapse in these slowly growing tumors before a suf-
ficient size is attained to attract the patient's notice, it seems likely
that the onset of the tumor is most often at puberty, in the decade be-

![Images of slides showing fibro-adenoma](image)

**Figs. 24-27. Fibro-adenoma Occurring in a Colored Girl of Twelve Years before the Onset of Menstruation**

Fig. 24 shows a slice from the mid-section of the gross specimen. The remainder of the specimen was ground and assayed for oestrin and showed a concentration in excess of 5 rat units per gram of tissue. Fig. 25 is a photomicrograph from the specimen shown in Fig. 24, showing a typical fibro-adenomatous area. Fig. 26, another area, shows the connective tissue in the tumor compressing the ducts, which have undergone a marked hypertrophy. Fig. 27 is a photomicrograph of the breast tissue surrounding the tumor. The increased number of cell layers in the duct lining and the increase in periductal connective tissue surrounding the tumor is in response to a higher level of oestrin in the blood. Compare with Fig. 29. Path. No. 57261.

between ten and twenty years, rarely in the following decade, and prac-
tically never after the menopause.

Of 100 women who had borne children the majority were between
the ages of twenty and twenty-five, also indicating an onset of the dis-
ease at puberty. The remaining cases were scattered between the ages
of thirty and forty-five. Of these older women, 34 related the onset
of the tumor to some phase of pregnancy. In 16 cases the tumor was removed during pregnancy or lactation. This group of cases is reported elsewhere by Moran (23). An analysis of the tumors associated with childbearing and of pre-existing fibro-adenomas undergoing rapid enlargement during pregnancy indicates that fibro-adenoma may have its inception or stimulation to further growth in the physiological hypertrophy of pregnancy.

The relationship of fibro-adenoma to the normal physiological hypertrophy of the breast occurring at puberty and in pregnancy suggests that the condition is the result of prolonged and intense stimulation by the follicular hormone oestrin (Fig. 22). In normal females hypertrophy of the breast begins in pre-puberty and extends roughly over a period of five years, from the age of ten to fifteen. During this entire time the breast is under constant stimulation by numerous ripening and atretic follicles in the ovary which secrete oestrin or theelin. In the second half of pregnancy the placenta contains oestrin in high concentration. At this time the size and epithelial differentiation in the ducts are increased. This histologic response to oestrin is complicated by epithelial proliferation and acinar formation in response to "progestin" from the corpus luteum, most marked in the first third of pregnancy. Roughly, however, it may be said that the stimulation of increasing amounts of oestrin through the latter half of pregnancy parallels a more prolonged but less intense stimulation occurring during puberty. At both periods there is marked physiologic hypertrophy of the breast in response to the hormone oestrin and at both periods fibro-adenomatous tumors are prone to occur or to show increase in size (Fig. 23A and B).

Experimental and Biochemical Studies: In the belief that fibro-adenoma, as well as virginal hypertrophy in the female breast and
gynecomastia in the male, is caused by prolonged and intense stimulation by the hormone oestrin, fibro-adenomas removed at operation have been assayed for this hormone. The initial assays, while positive, were weak and variable, but it was soon discovered that the Allen and Doisy test performed on castrated rats and mice was unreliable unless the extract from the tumor tissue was thoroughly detoxified, toxicity tending to inhibit the reaction and give a false negative. Through the cooperation of Dr. Morrell of the Squibb laboratories, a large fibro-adenoma associated with unilateral virginal hypertrophy in a colored girl of thirteen was assayed for oestrin (Figs. 24–27). The preliminary assay of the tissue showed more than five rat units of oestrin per gram of tissue, or more than forty-five times as much oestrin as occurs in the normal hog's ovaries, which are a potent source for this hormone. In other words, the fibro-adenoma occurring in puberty shows in the neighborhood of 2,500 rat units per pound of tissue, whereas a natural source of oestrin yields only 50 to 75 units per pound. The tumor tissue, therefore, shows a marked capacity to concentrate this hormone.

An attempt is now being made to reproduce localized mammary hypertrophy or fibro-adenoma experimentally by the direct injection of oestrin into the breasts of animals. It is too early, however, to report these results at this time. In a white woman aged forty-two, operated on for dilated ducts beneath the nipple, 6000 rat units of oestrin (Amniotin-Squibb) were injected over a period of three weeks preceding a second operation. The histologic response was typical of fibro-adenoma (Figs. 28–31), and not unlike experimental gynecomastia.
Conclusions

The conclusion seems warranted that gynecomastia, virginal hypertrophy, and fibro-adenoma are dependent upon pathological variations in the action of the hormone oestrin upon the duct epithelium and surrounding connective tissue of the breast. That prolonged and uninterrupted stimulation by oestrin rather than brief high concentration is necessary for the production of these conditions is supported by the following facts:

1. This form of hypertrophy is relatively easily produced in male animals, which do not menstruate, when pathologic concentrations of oestrin are present.

![Chart comparing the oestrin levels, in rat units, in the blood in gynecomastia, virginal hypertrophy, and fibro-adenoma with corresponding normal levels in male and female at puberty. The per cent concentration of oestrin in the tissue is also shown. The growth effect of the hormone oestrin is equal to the product of the blood level of the hormone times its concentration by the tissue. The values shown are approximate.](image)

2. The condition is prevalent in the prepuberty period in girls, when the breast is normally under stimulation of small but constantly secreted amounts of oestrin, for a period of three to five years before the onset of menstruation.

3. The condition occurs or is exacerbated during the latter two-thirds of pregnancy, when menstruation is in abeyance and increasing concentrations of oestrin are present.

4. Experimental injection of repeated small doses of oestrin into monkeys is more efficacious in reproducing the disease than high doses given over shorter periods.

5. Bio-assay of the pathological tissue demonstrates that it has a marked capacity to concentrate the hormone.
In a general way it may be said that the onset of fibro-adenomatous lesions is incompatible with the menstrual period, although the tumor once formed does not undergo involution under the menstrual influence. Eventually, with repeated menstruation, it may be converted into a cystic fibro-adenoma. The detailed mode of this subinvolution is depicted in cases of cystic disease of the breast.

FIG. 33. CHART COMPARING THE GROWTH RESPONSES AT FOUR AND FIVE WEEKS, IN THE LEFT ABDOMINAL GLAND (A), THE LEFT FIRST INGUINAL GLAND (B), AND THE LEFT SECOND INGUINAL GLAND (C) OF THE WHITE ALBINO RAT

Each of the three breasts depicted has its own degree of response to developmental influences. A comparative study of mammals with polymastia indicates an increasing susceptibility in mammary tissue in certain areas to hormone action, with a regression of susceptibility in other zones. This variability of response to the sex hormones is probably an expression of the evolutionary tendency to concentrate the breast tissue in the pectoral areas. Such a variability in mammary response (or ability to concentrate the sex hormone) is apparently the basis for the formation of circumscribed tumors such as the fibro-adenomas discussed here. After Meyers, J. A.: Am. J. Anat. 19: 353, 1916.

The findings summarized permit a distinction between hypertrophy or hyperplasia and true tumor formation. In hypertrophy, such as gynecomastia in the male and virginal hypertrophy in the female, the etiological factor is an abnormally high concentration of oestrin in the circulation, acting upon apparently normal breast tissue (Fig. 32). On the other hand, in tumor formation, as in fibro-adenoma, the increased amounts of oestrin in the blood are acting upon a hypersus-
ceptible tissue which has the capacity to concentrate the hormone at the site of the tumor. There is much evidence to show that the capacity of the fibro-adenomatous area of the breast to concentrate oestrin is brought about by a basic biological variation in the developmental response in that particular tissue (Fig. 33).

The epithelium of the fibro-adenoma shows a marked tendency to mature in response to oestrin. This hypermaturated epithelium fails to respond in a normal fashion to corpus luteum hormone (progestin), which causes proliferation and acinar formation in the normal epithelial structures of the breast. As a result, many fibro-adenomas fail to show typical lobules and acinar structures (Fig. 36). The same refractory character is manifested by the epithelium in pregnancy and lactation. Here again the epithelium fails to show typical acinar formation and typical lactation. Subinvolution only may occur in lactation (Fig. 35). Such subinvolution is seen also after repeated menstruations giving rise to cystic areas.

The connective tissue in fibro-adenoma shows a marked tendency to proliferate in response to oestrin. It thus stands in reciprocal rela-

Fig. 34. Photomicrograph showing the persistence of cellularity and proliferation in the connective tissue of fibro-adenoma in early lactation

This activity in the stroma of the tumor is a continuation of that seen in the last half of pregnancy (see Fig. 23 A). The tissue was excised from a white woman, aged forty-nine, at the beginning of the third month of lactation. There had been no previous lactations for many years. The tumor occupied an entire hemisphere. The breast was amputated and the patient was reported well twenty-five years later. Path. No. 2168.
tion to the epithelium, which shows maturation and not proliferation. Instead of being refractory to the influences of pregnancy and lactation, the fibrous tissue undergoes marked proliferation (Fig. 23) and may approach sarcoma in its appearance. This same heightened proliferative response may be evident at the menopause, when some 10 per cent of these tumors show a tendency to undergo rapid growth and malignant change.

II. CYSTIC DISEASE AND FIBROSARCOMA

Since both the involutioinal and proliferative responses in the fibro-adenomatous lesions just discussed show abnormalities, it should be possible to relate such reactions to other pathologic conditions of the breast. Our studies indicate that the involutioinal changes in these lesions may give rise to cystic disease and the proliferative changes to fibrosarcoma (Figs. 34 and 35).

**Cystic Fibro-adenoma**

Pathologic study of fibro-adenomas of long standing uncomplicated by pregnancy indicates that when involutioinal changes are superimposed upon the pre-existing tumor, cystic changes are produced. In most of these cases the fibro-adenomas have a typical puberty or post-
TUMORS OF THE BREAST RELATED TO THE OESTRIN HORMONE

Puberty origin but have persisted, with the appearance of one or more tumors during active menstrual life. These patients are usually between the ages of twenty-five and thirty years and childless. In our series 3 were married, with no pregnancies recorded; the remainder were single. The duration of the tumor, as stated in the history, was from one to fifteen years. The progressive change from typical fibroadenoma following puberty to cystic fibro-adenoma observed later in adult life is well illustrated in the following case, shown, also, in Figs. 36-39.

Figs. 36–39. Fibro-adenoma with Multiple Recurrences in an Unmarried White Woman of Twenty-Six

The photomicrograph in Fig. 36 is from the first operation, performed in 1924. Although the patient had been menstruating for nearly ten years at this time, the fibro-adenoma shows no acini or typical breast lobules. The hypertrophic ducts are surrounded by embryonic fibrous tissue of the so-called intracanalicular myxoma type. Fig. 37 is from a recurrent tumor excised in 1931. The fibrous tissue has become adult and hyalinized. Acini or rudimentary lobules have been added to the hypertrophic duct tissue by the repeated corpora lutea at successive menstruations. Fig. 38 shows tissue removed from a second recurrence in 1934. Involution has set in, with edema of the fibrous tissue and cystic dilatation of the ducts. Fig. 39 is the gross specimen from the second recurrence in 1934. Small blue dome cysts were visible. Path. No. 49301.
Recurrent Fibro-adenoma, Bilateral, Three Operations (Path. No. 49301): The patient was a white female, aged thirty-eight. At the age of twenty-six she discovered a small lump in the right breast. By 1924 this tumor had grown to the size of a walnut. It was excised locally, March 12, 1924, and proved to be a typical fibro-adenoma. Hypertrophy of duct epithelium and increase of fibrous tissue of the myxomatous type were prominent in the sections studied. No lobules with acinar-like structures were present, and the appearance was that of gynecomastia in the male. In 1931, a similar tumor appeared just above the scar in the right breast. This was excised April 11, 1931. The microscopic structure was similar to that of the earlier tumor, characteristic lobules with acinar formation were superimposed upon the changes seen in the ducts and fibrous tissue. In 1934, there was a further recurrence, with similar tumors in both right and left breasts. These tumors, excised April 2, 1934, contained numerous cysts the size of a pea, and of a characteristic blue color, embedded in fibro-adenomatous tissue. On micro-

**Fig. 40. Whole Section through Mid-portion of a Breast with Cystic Disease**

One large and one small blue dome cyst are seen. The entire duct tree is dilated and surrounded by fibro-adenomatous tissue. Path. No. 47478.

scopic examination the breast showed typical cystic fibro-adenoma (Figs. 36–39). For five days prior to the removal of these tumors, the patient received, twice daily, injections of Prolactin, which probably accentuated involution and formation of cystic areas.

A comparison of the histology of the lesions of this case at the three successive operations in 1924, 1931, and 1934, shows the cycle of development in fibro-adenoma. At the first operation the tissue was a typical puberty hypertrophy with embryonic fibrous tissue of the so-called intracanalicular myxoma type surrounding hypertrophic duct epithelium. At the second operation the fibrous stroma was adult, the duct epithelium more markedly hypertrophic, and acinar elements had been superimposed due to the repeated corpora lutea at successive menstruations. At the third operation involution had set in, with edema in the fibrous tissue and cystic dilatation of the ducts.

**Cystic Disease of the Breast**

In a previous report of 600 cases of chronic cystic mastitis (Lewis and Geschickter, 25) evidence was presented to show that these cases comprised two major groups, one dominated by cyst formation and designated cystic disease, the other characterized by epithelial proliferation and termed adenosis of the breast or cystadenoma. In the
pathologic analysis of cystic disease there were found dilatation of the duct lumen, hypertrophic changes in the epithelial lining followed by desquamation, and increased amounts of adult or hyalinized periductal fibrous tissue. As in fibro-adenoma, the pathological changes showed a marked tendency to involve the duct tree, with less striking proliferation in the periductal tissue and a greater tendency for the hypertrophic changes in the epithelium to be carried past the point of maturation toward involution. The hypertrophic and involutional changes in the ducts or lactiferous tubules are apparently responsible for the cyst formation (Figs. 40 and 41).

In contrast to fibro-adenoma, cystic disease of the breast is most common in adult, childless women during the period of life when the level of the ovarian hormones changes repeatedly with each menstrual cycle. The disease occurs after the prepuberty period and, unlike fibro-adenoma tends to disappear rather than to increase with pregnancy. The average age of the youngest child in women with cystic disease who have borne children is over ten years. The disease is characterized by the appearance of one or more circumscribed, freely movable cysts of some size (1 to 3 cm. in diameter) which transilluminate well and may be associated with small palpable nodules (minute cysts) in other parts of the breast. In one-third of the cases small nodules only, or dilated ducts, may be palpated beneath the nipple. The majority of the cysts appear in the mid-zone of the breast.
The clinical appearance of the palpable tumor or cyst is often sudden compared to the slow growth and gradual onset of fibro-adenoma. Pain, when present, is premenstrual. Discharge from the nipple rarely occurs; when it does, it is serous or milky in character. The breasts are usually full, with some tendency to increased parenchyma and, particularly in older women, an increased amount of fibrous tissue. The cysts remain freely movable and may disappear spontaneously only to recur. While forming in the period of active sex life, but not during actual child-bearing, they nevertheless show a tendency to make their clinical appearance toward the menopause or thereafter. The following case is typical.

The patient was a white female, aged fifty-nine, with a lump in the right breast discovered nine days before. She had two children, the youngest aged nineteen; the menopause had occurred at the age of fifty-one. At the age of forty-seven, seven years after the birth of the last child, two cysts were aspirated in the right breast. One year later a cyst appeared in the left breast and then spontaneously disappeared. Six months before the appearance of the present lump the breasts had been examined and found negative for tumor.

On examination a tumor was found in the right breast the size of a silver dollar, about a centimeter above and to the outer side of the areola. The tumor was freely movable and transilluminated clearly. The right breast was otherwise free of nodules, as was the left. Both breasts were large and somewhat adipose. Aspiration of the tumor yielded 8 c.c. of cloudy fluid, which on microscopic examination was negative for epithelial cells. Six weeks after the tumor had been aspirated it refilled and was excised. Pathologic examination showed a typical blue dome cyst with characteristic epithelial lining (Fig. 42).

The resemblance of the hypertrophic changes found in the duct epithelium in cystic disease to those seen in fibro-adenoma, and the tendency for cysts to appear in pre-existing fibro-adenomas of long standing, suggest a relationship between the two conditions. Apparently in cystic disease the breast is also subjected to hyper-stimulation by the hormone oestrin, but the effects of the stimulation are not...
so pronounced and are complicated or diminished by involutional changes. These variations from the basic pattern seen in fibroadenoma are explained by the relation of cystic disease to sex physiology.

Whereas fibro-adenoma is associated with a constant hyper-stimulation of the breast by the hormone oestrin during puberty or the latter half of pregnancy, in cystic disease the higher levels of oestrin in the blood are transient but recurrent with each menstrual cycle, the disease being practically confined to sexually mature childless women or women who have borne no children for a number of years. The action of oestrin on the breast is, therefore, interrupted by involutional changes accompanying recurrent menstruation. As the menopause is approached, these involutional changes are exaggerated and may eventually predominate, leading to spontaneous cure of the disease. During active sexual life, however, the tendency of the increased oestrin stimulation is to lead to sub-involution and cyst formation.

In support of these conclusions we have obtained strong positive reactions for oestrin in breast tissue the seat of hypertrophic changes and early cyst formation. Quantitative bio-assays were not carried out, however, in the case in which a positive Allen-Doisy test was obtained. An attempt has also been made to produce cystic disease

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**Figs. 43 and 44. Photomicrographs of Breast of Monkey (Rhesus Macacus) on the Sixth (Left) and Twenty-Third (Right) Days Following a Course of Ten Injections of Prolactin (Milk-Producing Hormone) Given Twice Daily for Five Days**

This monkey had previously been subjected to an experimental gynecomastia by injections of oestrin during a period of six weeks (Figs. 11 and 29). At the sixth day the epithelium had begun to desquamate (A) and the fibrous tissue to liquify (B). On the twenty-third day (seventeen days after stopping prolactin) cystic dilatation of the ducts had occurred, the excess layers of epithelium had been desquamated and the surrounding fibrous tissue had become acellular, with an adult character. Hormone supplied through the courtesy of Dr. Oscar Riddle, Carnegie Institution of Washington, Station for Experimental Evolution, Cold Spring Harbor, N. Y.
experimentally by the injection of repeated doses of oestrin with intervals of rest. The microscopic changes following the withdrawal of oestrin resembled cystic disease but no actual cysts were formed. These experiments have been varied by following oestrin stimulations with injections of prolactin (the milk-producing hormone obtained from the anterior pituitary gland). The results obtained with prolactin followed by withdrawal of hormone stimulation appeared to duplicate more closely the pathology of cystic disease, but again no gross cysts were formed (Figs. 43 and 44).

**Fibrosarcoma**

In a study of 41 fibrosarcomas of the breast the majority were found to be related to a pre-existing fibro-adenoma or so-called intracanalicular myxoma. This relationship to fibro-adenoma is supported by both the clinical and microscopic findings. Clinically most of the cases appear at the time of the menopause, following upon a fibro-
adenomatous tumor which has shown increasing growth during a period of three to five years. Microscopically all gradations can be found from fibro-adenoma with markedly cellular stroma, without definite signs of malignancy, to rapid proliferating sarcoma of the spindle-cell type (Figs. 45–47; Table II).

FIG. 47. Fibrosarcoma Occurring at the Periphery of a Fibro-Adenoma in a Woman of Forty-Five

The tumor had been present fifteen years and had grown rapidly during the last five months. Amputation of the breast was done in January 1924. The patient remained well over five years. The spindle-cell proliferation can be seen surrounding and compressing the persisting area of fibro-adenoma in the upper right hand corner. Path. No. 34478.

No definite experimental data are at hand to account for the added growth stimulus found in fibro-adenomas undergoing malignant change. The tendency for the sarcomatous change to occur at the menopause, when there is known to be a rise in the secretory activity of the anterior pituitary gland, suggests a synergistic action between a hormone from this source and the oestrin hormone concentrated in the fibro-adenomatous tissue. Such a synergistic action is also suggested by the marked proliferation in fibro-adenomas seen during pregnancy, when high concentrations of the anterior-pituitary-like hormone, prolan, are combined with high concentrations of oestrin (Figs. 23A and 34).

Diagnosis and Treatment

Both new diagnostic procedures and new modes of therapy are suggested by the relationship of gynecomastia, virginal hypertrophy, fibroadenoma, cystic disease, and fibrosarcoma to the ovarian hormone oestrin. Where the nature of the condition is not obvious (as it frequently is in gynecomastia and virginal hypertrophy), the blood level
of the hormone oestrin can be assayed after the method of Frank. The presence of a low metabolic rate—minus 15 to plus 5—suggests increased concentrations of oestrin in the blood. In a small series of cases we have found rates as low as minus 11 and none over plus 5 during active gynecomastia and in recently discovered fibroadenoma. We have determined the depressing effect of the oestrin upon the basal metabolic rate by the administration of the hormone to patients with hyperthyroidism.

**Table II: Oestrogenic Tumors of the Breast with Involutional and Proliferative Changes**

<table>
<thead>
<tr>
<th>Data</th>
<th>Cystic Disease</th>
<th>Fibrosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>500</td>
<td>41</td>
</tr>
<tr>
<td>Sex</td>
<td>Females</td>
<td>Females</td>
</tr>
<tr>
<td>Age</td>
<td>35-45</td>
<td>40-55</td>
</tr>
<tr>
<td>Duration</td>
<td>12 months</td>
<td>5 years</td>
</tr>
<tr>
<td>Location</td>
<td>Mid zone</td>
<td>1 or 2 hemispheres</td>
</tr>
<tr>
<td>Bilateral</td>
<td>17 per cent</td>
<td>0</td>
</tr>
<tr>
<td>Structures involved</td>
<td>Ducts</td>
<td>Stroma</td>
</tr>
<tr>
<td>Character of tumor</td>
<td>Smooth cyst</td>
<td>Hard to fluctuant</td>
</tr>
<tr>
<td>Nipple discharge</td>
<td>3 per cent</td>
<td>0</td>
</tr>
<tr>
<td>Hormone control</td>
<td>Oestrin</td>
<td>Oestrin + anterior pituitary</td>
</tr>
<tr>
<td>Relation to sexual life</td>
<td>Incompatible with pregnancy; may persist after menopause</td>
<td>Puberty, pregnancy, menopause</td>
</tr>
<tr>
<td>Pathology</td>
<td>Differentiation and desquamation of duct epithelium</td>
<td>Proliferation of stroma</td>
</tr>
<tr>
<td>Recurrence</td>
<td>20 per cent</td>
<td>9 per cent recurred; 22 per cent metastasized</td>
</tr>
</tbody>
</table>

We have attempted to bring about the involution of gynecomastia by treatment with the milk-producing hormone, prolactin, and have obtained softening of the breast two months after the injections were discontinued. No comparable results have been obtained with fibroadenoma to date, but it seems not unlikely that a better conception of the physiology of these lesions will lead to the development of successful non-surgical therapy.

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