2

Endocrine Physiology of the Breast

Endocrine studies emphasize the dependence of postnatal mammary development upon ovarian function. The estrogen secretion of the ovarian follicle plays a major role in adolescent development and, with sexual maturity, both estrogenic and luteal hormones combine to produce physiologic changes. The hormones of the anterior pituitary gland are important not only to stimulate and maintain ovarian function but to activate lactation. Moreover they seem to be essential for the response of the mammary gland to the ovarian hormones. Testicular and adrenal cortical influences may also induce changes in the mammary gland.

Changes produced by endocrine and other physiologic influences are not uniform throughout the breast. Marked differences may be found in different lobes of the same breast (which are independent anatomic units). Response at puberty may differ from that in adulthood, and there are differences between male and female breasts.

POSTNATAL HYPERTROPHY

The early development of the mammary gland in the embryo is apparently uninfluenced by sex hormones. It is possible that the

adrenal acts as a primitive sex gland but there is no experimental evidence to confirm this. Development is the same in both male and female. In marsupials, where the young are born before development is complete, mammary growth proceeds without interruption in the absence of maternal or placental hormones (Bresslau, Hartman). In the rat, where the young are born in a very immature state, mammary growth proceeds through the sixth week at approximately the same rate in males and females in spite of castration performed before the fourth week (Astwood, Geschickter, Rausch).

Infancy. Superimposed upon the embryologic development of the human mammary gland there is an additional growth, occurring about the time of birth[1] which surpasses that seen during childhood. In some infants there is a palpable enlargement of the gland (incorrectly termed "mastitis neonatorum") and after a few days there may be a milk-like secretion microscopically. Such hypertrophy, characterized by expansion of the duct tree and by increased amounts of periductal stroma is assumed to be stimulated by the sex hormones of late pregnancy, maternal and placental in origin.[2] This supposition is based upon the fact that these hypertrophic changes are seen in both boys and girls at a period when both the ovaries and testes are quiescent. Philipp and Brill, independently, found estrogen in the urine of the newborn, Philipp reporting that the hormone rapidly decreased by the fourth day and disappeared by the sixth day. The disappearance of estrogen is followed by secretory changes in the mammary gland, by dilatation of the ducts and by vascular engorgement. The hormonal basis of witch's milk, the secretion of the mammary gland of the newborn, has been discussed by Lyons. He was able to detect pituitary lactogenic hormone in the urine of four newborn babies. One of the babies, a boy who was lactating, had the largest amount of hormone. He concludes that since estrogen has been found in the blood and in the urine in babies for about five days after birth, witch's milk is formed in the infantile breast after successive stimulation by estrogen and lactogenic hormone.

Childhood. The period of quiescence in mammary development during childhood parallels a similar quiescent period in the gonads.

[1] It has not yet been demonstrated whether the hypertrophy of the human mammary gland at birth has its onset during the last few weeks of fetal life, at the time when development is sufficient for the structures to respond to maternal and placental hormones, or whether the hypertrophy begins immediately after birth upon the withdrawal of a preceding and unidentified inhibitory substance.

[2] A review of the hormonal functions of the placenta is given by Newton. Catchpole and Cole, and also Parker and Tenney believe that the estrogens of late pregnancy may be of other than placental origin. However, evidence is overwhelmingly in favor of the placenta as the chief endocrine organ of this period. The ovary of the female infant is quiescent while the uterus and breast show activity.

GROWTH DURING ADOLESCENCE

Adolescent Female Breast and Estrogen Effects

As previously described adolescent growth of the breast in the human being and in laboratory animals is characterized by extension and branching of the mammary ducts, hypertrophy of their lining cells, increase in the size of the lobular buds, and proliferation of the supporting stroma of fat and fibrous tissue. The nipple is enlarged and its epidermal covering thickened. Apparently this adolescent growth is stimulated by ovarian estrogenic hormones.

In girls, a constant and increasingly intense estrogenic stimulus is present throughout adolescence as a result of the ripening of ovarian follicles. This is attested by assays of the urine. While these assays for estrogenic substance show increasing amounts, they probably do not provide a true index of the intensity of stimulation to which the mammary gland is subjected. Mammary growth is rapid in adolescent girls and is definite even in boys at this period. The urine assays for estrogenic substance, however, yield lower values for girls of this age than for normal adult men in whom no mammary growth occurs and are less than those found in the urine of mature cyclic women. Unfortunately, reliable determinations of the estrogen values in the blood or tissues are not available. Recent animal experimentation (Mixner, Lewis and Turner) suggests that a mammogenic factor of the anterior pituitary may play a role in adolescent development.

Estrogen Excretion. Frank gives the following figures for estrogen excreted in the urine of girls before puberty:

> Two international units of estrogen in 500 cc. of urine at 4 years.
> Two international units of estrogen in 250 cc. of urine at 9 years.
> Two international units of estrogen in 30 cc. of urine at 12½ years (one-half adult amount).

Oesting and Webster did not find mensurable quantities of estrogen in urine of girls (or boys) before 10 years but found from 10 to 80 international units per 24 hours in girls between 10 and 15 years, an average of 40 international units in 9 girls. In boys of corresponding ages the values were 10 to 60, averaging 25 international units per 24 hours. Dorfman and Greulich obtained similar values in 18 boys and 5 girls between the ages of 6 and 16.

The adolescent breast of girls responds to estrogen with a growth of both ducts and periductal stroma, but the growth of stroma predominates. The author has never observed lobule formation in the

normal adolescent female breast and is of the opinion that this does not occur before ovulation or pregnancy, that is, prior to the advent of the corpus luteum. The marked stromal growth and absence of lobule formation in adolescence are distinguishing features of the human breast.

Clinical Evidence of Estrogen Effects. Mammary hypertrophy occurring in immature girls having granulosa-cell tumors of the ovary, with estrogen secretion, demonstrates the effect of estrogen on the

FIG. 49 FIG. 50

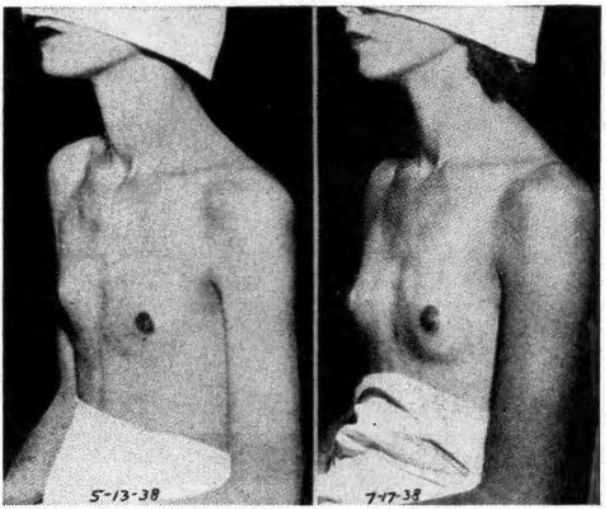


FIG. 49. The effect of estrogen on the human breast (after MacBryde). Patient with hypogonadism before treatment with estrogen ointment applied daily to the mammary region.
FIG. 50. The same patient after eight weeks' treatment with estrogen ointment locally.

development of the human breast. (Chap. 4.) In a case previously reported by the author, infantile hypertrophy in a girl of five followed the administration of 6 mg. estrone over a period of six weeks for the treatment of gonorrheal vaginitis. Kurzrok, Wilson, and Cassidy noted enlargement of hypodeveloped breasts in girls treated with estrogen for primary amenorrhea. MacBryde treated with estrogen three women who lacked mammary development and exhibited other signs of hypogonadism. He was able to demonstrate that active mammary growth could be produced in these patients by the injection of from 150,000 to 350,000 international units of estrone or of estradiol benzoate per week. The mammary enlargement subsided when injections were stopped. It returned when these patients were treated with an estrogen-containing ointment rubbed in for five

minutes each night. (Figs. 49, 50.) The author has obtained similar results in his own patients.

Experimental Evidence. Biopsies of the breast of five adult cyclic women have been studied following the injections of 25,000 to 100,000 international units of estrone over a period of one to two months. Extension of the ducts, increase in the number of their lining cells and proliferation of periductal stroma in these specimens duplicate the histology seen in the normal adolescent female breast. (Fig. 51.)

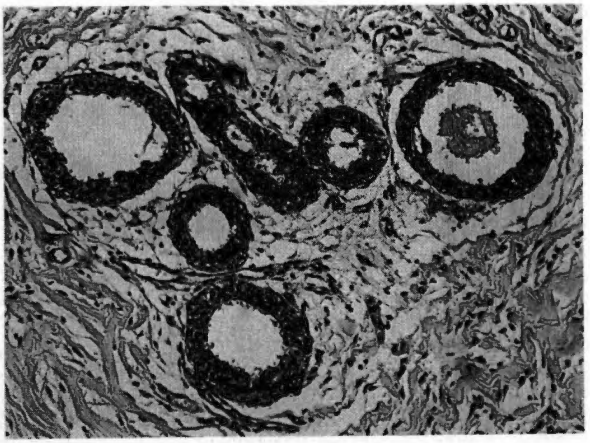


FIG. 51. Mammary response to estrogen. Photomicrograph showing hypertrophy of the duct epithelium and hyperplasia of periductal connective tissue following the injections of 75,000 I. U. of estrone in a woman 42 years old.

Extension of the duct tree during adolescence and in response to estrogen has been demonstrated in monkeys. (Fig. 52.) There is less response in the stroma than is seen in the human breast and lobule formation may occur. Aberle found that the ovary and the mammary gland in the macaque monkey showed a parallel and rapid increase in size during adolescence.

The studies of Gardner and Van Wagenen on prepubertal, spayed female monkeys show that the mammary growth described by Aberle can be produced experimentally with estrogen stimulation. The size of the mammary gland (measured by whole mounts) doubles with estrogenic injections over a period of two to five months. These authors observed lobule formation in response to injections of estrogen. Hartman, Speert, and Geschickter have also reported lobular growth of the monkey breast in response to estrogen. Speert has shown that the growth of the mammary gland in the monkey may be stimulated directly and that the estrogens do not necessarily

stimulate growth through the mediation of the pituitary. He applied the estrogen directly to one breast and not to the other, and obtained

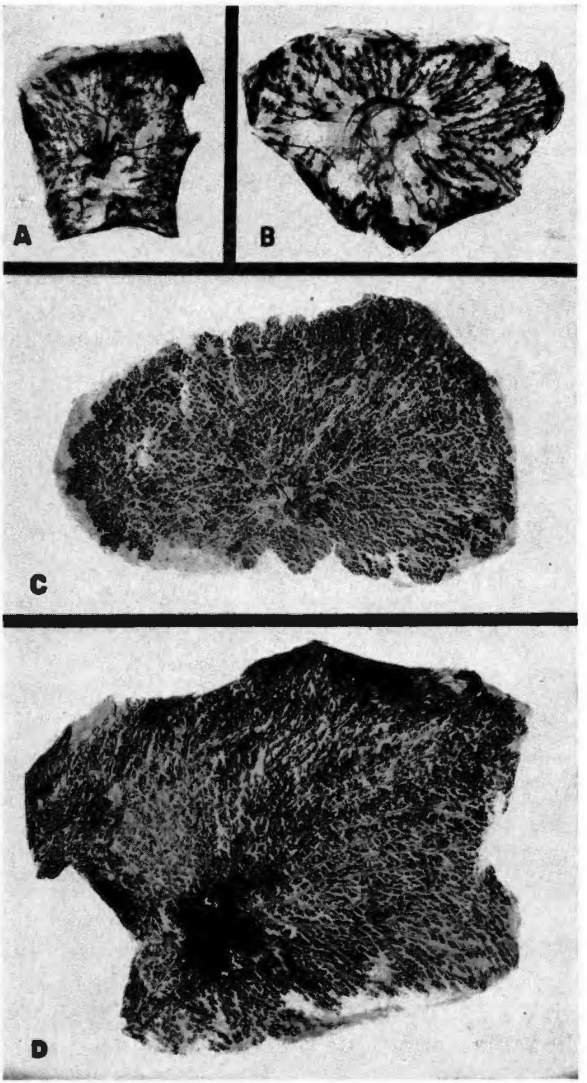
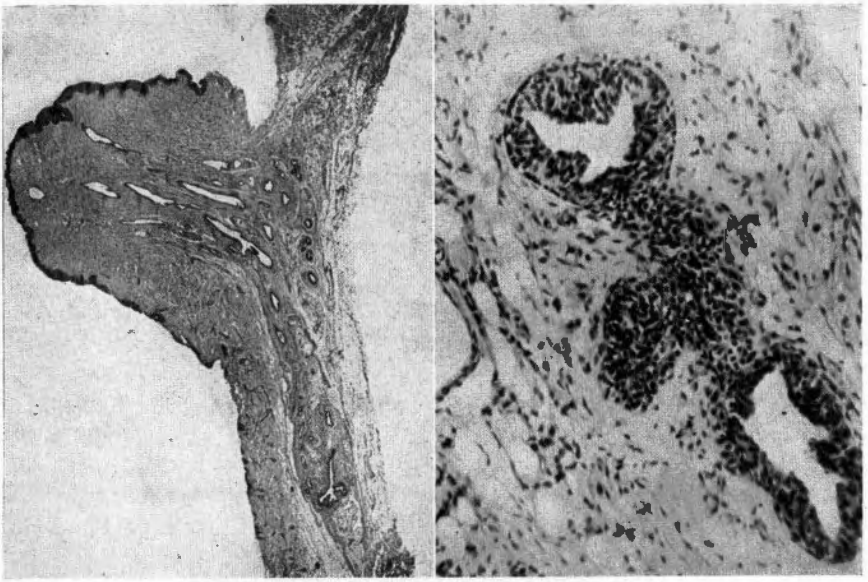


FIG. 52. Growth of the mammary gland of the monkey from puberty to maturity. Whole mounts of the mammary gland of the monkey, showing normal growth. Glands removed at prepuberty (A), puberty (B), toward the end of adolescence (C) and at full maturity (D).

growth only in the treated breast. The author has noted a similar inequality in breast development in a patient who applied estrogen percutaneously in greater amount to one breast than the other.

In the rat, growth of the duct tree is identical in males and females until puberty (sixth week). Castration at three weeks of age does not prevent prepubertal duct growth in either sex, but does inhibit the adolescent growth and causes atrophy of the lobular buds.

FIG. 53 FIG. 54



The Effect of Moderate Doses of Estrogen on the Mammary Gland of the Monkey. There Is Extension of the Duct Tree, Hypertrophy of the Lining Cells and Proliferation of Periductal Connective Tissue.

FIG. 53. Whole section through prepuberty male monkey after 20,000 I. U. of estrone over a period of six weeks. The size of the breast and nipple has doubled. Note the thickening of the epithelium overlying the nipple.

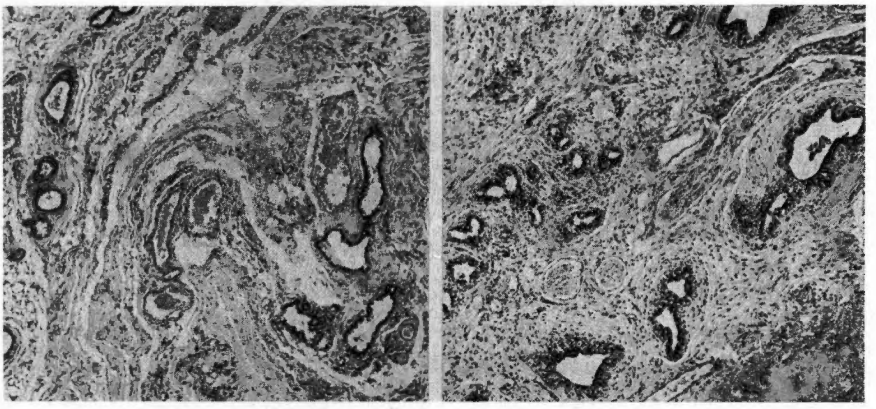
FIG. 54. Photomicrograph of the breast shown in Fig. 53. Hypertrophy of the duct epithelium and increase in periductal fibrous tissue have occurred.

In female rats, castrated at three weeks of age, daily injections of 2 gamma[1] of estrone in oil for three weeks result in an increase of the diameter of the gland from 6 to 13 mm. With 5 gamma of estrone daily over the same period, the maximum diameter measures about 25 mm. (Figs. 57-59). Thus, in castrate female rats, growth of the duct tree may be stimulated at the normal rate or beyond by increasing the intensity of estrogenic stimulation. The physiologic limit of size, however, is reached sooner if larger doses of estrone (5 gamma and over) are given. There is an optimal dosage (less than 10 gamma of estrone daily in the rat) and a period in adolescent

[1] Gamma (γ) or microgram (μgm.) equals one thousandth of a milligram or 10 international units of estrone. It is equivalent to one rat unit or about five mouse units.

mammary development when the gland is most responsive. Estrogenic stimulation beyond physiologic limits (more than 10 gamma) does not result in similar extension of the duct tree but in an abnormal and stunted gland. Premature, enlarged and irregular lobular buds appear at the ends of the mammary tubules with doses of 25 or more gamma of estrone.

FIG. 55 FIG. 56



The Effect of 70,000 I. U. of Estrogen on the Mammary Gland of an Adult Female Monkey. The Monkey Was Castrated Two Years Prior to the Experiment and the Estrogen Given Over a Period of Two Months.
FIG. 55. Microscopic appearance of the gland before estrogen.
FIG. 56. Same gland after estrone injections.

Physiologic Limits. Although estrogen stimulates mammary growth, there is a limit to the amount of growth that can be obtained. The maximum extent of the duct tree is achieved after the end of adolescence. The rate of growth during adolescence is proportional to the intensity of the hormonal stimulus (within physiologic limits), but the maximum extent of growth is controlled by inherent factors. Prolonged estrogenic stimulation after sexual maturity or intense stimulation during pregnancy fails to produce proportional growth in the duct tree after the adult size has been reached. Estrogenic stimulation beyond physiologic limits in adolescence produces stunted growth in the gland and abnormal epithelial changes in the lobular buds. These facts in regard to mammary development stimulated by estrogen have been demonstrated experimentally in the rat (Geschickter and Astwood). For a discussion of these pathologic changes with overdosage of estrogen see Chap. 11.

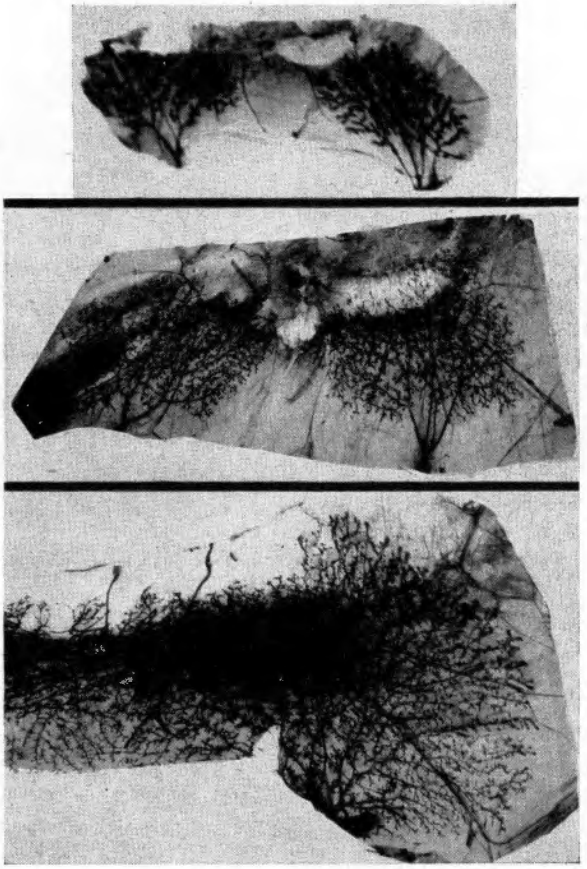
A knowledge of the effects of estrogen on the growth of mammary tissue is important from a clinical standpoint. Estrogenic effects are

responsible for infantile hypertrophy in young girls with granulosa-cell tumors or other estrogen-secreting ovarian tumors, and account for gynecomastia in males with chorio-epithelioma of the testicle. The growth of pre-existing fibro-adenomas during pregnancy is the

FIG. 57

FIG. 58

FIG. 59



Growth of the Female Rat Breast in Response to Estrogen.
FIG. 57. Whole mount of the mammary glands of a normal female rat at 21 days. (× 4).
FIG. 58. Whole mount of the mammary glands of a castrated female rat at 42 days. Animal in Fig. 58 is a litter mate of one in Fig. 57 and was castrated at 21 days. (× 4).
FIG. 59. Whole mount of the mammary glands of a female rat, castrated at 21 days and treated for 20 days with 50 I. U. of estrone daily. (× 4).

result of stimulation by estrogens. Estrogen has been used clinically to promote the growth of the undeveloped breast in cases of hypogonadism. The mammary hypertrophy induced by such treatment, however, tends to regress if estrogen is withdrawn, and it must be borne in mind that prolonged overdosage with this hormone may result in mammary pathology. Estrogen has also been used for the

treatment of painful breasts and other forms of chronic cystic mastitis (see Chaps. 11 and 28).

Adolescent Male Breast and Androgenic Effects

Jung and Shafton believe that the normal enlargement of the human male breast at puberty is due to a hormone from the testes but offer no experimental data. Estrogen as well as androgenic hormone (testosterone) is present in increased amounts and is found in normal male urine (Oesting and Webster). It is still uncertain whether some form of androgenic hormone or estrogen is responsible for the slight increase in the size of the normal human breast in boys during adolescence. Since androgenic hormones stimulate mammary

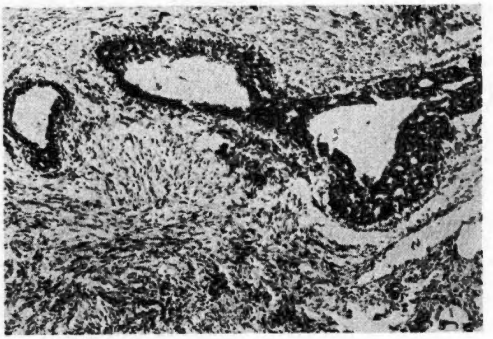


FIG. 60. The effect of estrogen on the human male breast. The patient 40 years old had gynecomastia resulting from the injection of 20 mg. estradiol benzoate given for migraine over a period of three months. (Patient of Dr. C. Dunn of Philadelphia.)

development, it is probable that such secretions from the testicle play a role. Mammary enlargement in men has been observed following the administration of methyl testosterone and also androstenedione. On the other hand, growth of the human male breast is also readily stimulated with estrogen, but the response is not so great as in the female breast.

Dunn observed a growth of mammary ducts and periductal connective tissue in a man of 40 years following the administration of 20 mg. estradiol benzoate for the treatment of migraine. (Fig. 60.) He reported a similar hypertrophy in a man treated with the synthetic estrogen, stilbestrol. The author also has produced mammary hypertrophy in a boy of 16 by administering stilbestrol orally in a case of pituitary giantism. In the author's experience, on the other hand, and in that of Vest and Howard, injections of testosterone propionate in adolescent males or adult men, in doses varying from 50 mg. weekly to 10 mg. daily, do not induce noticeable changes in

the mammary gland. Hoffman obtained decrease, not increase, in the size of the male breast in cases of gynecomastia treated with testosterone. Significant microscopic changes were not observed in three cases of gynecomastia in which biopsies were performed by the author before and after injections of testosterone propionate in amounts up to 150 mg. No marked effects were observed in the normal adult female breast after treatment although some increase was noted in the epithelial lining of the ducts (Figs. 61, 62).

FIG. 61 FIG. 62

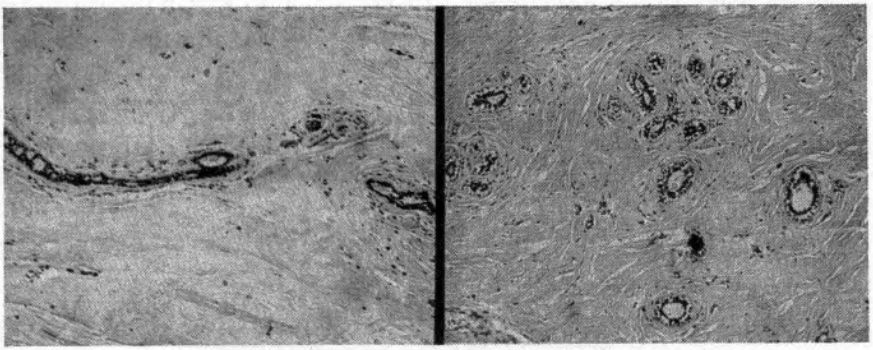


FIG. 61. The effect of testosterone on the human female breast. The patient, 48 years old, had had her menopause two years previously. The atrophy of lobular epithelium and sclerosis of connective tissue before injection are clear.

FIG. 62. Here there is regeneration of the lobular epithelium and a moderate proliferation of periacinar connective tissue. The patient received 215 mg. testosterone propionate over a period of one month.

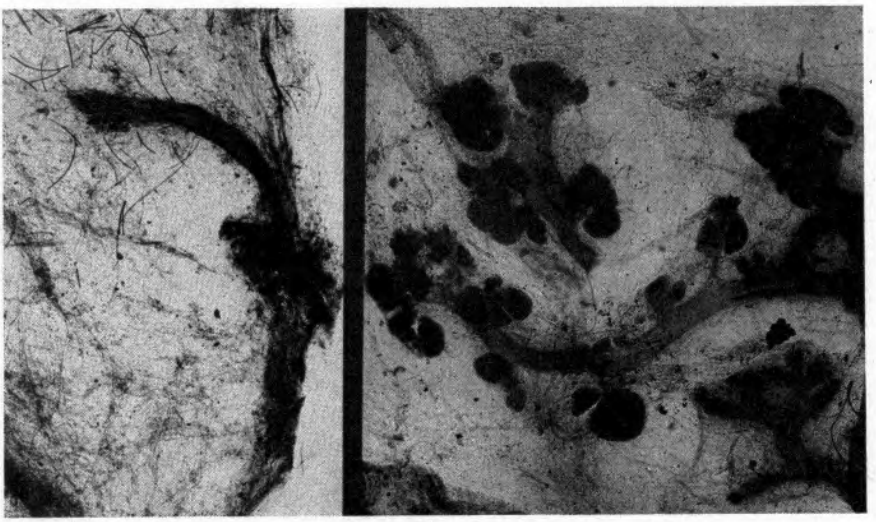
Dunn produced mammary enlargement in a man with injections of androstenedione; in the author's laboratory, lobular growth was stimulated in castrated rats and monkeys with this hormone. McCullagh and Rossmiller observed gynecomastia in 6 of 11 men with hypogonadism treated for four to six weeks with a total of 3 to 8 grams of methyl testosterone.

Animal experimentation suggests that the male mammary gland responds less readily to estrogen than that of the female. Prolonged stimulation with estrogen in castrate rats produces a greater degree of development in the female than in the male (Astwood and Geschickter). Gardner and Van Wagenen found that the male gland of the monkey was more variable in its response to estrogen than the female. The size of the glands in the untreated animal had no correlation with body weight. Injections totaling 36,000 to 88,000 international units over a period of nine to twenty-two weeks caused the gland to double in size. In experiments performed by the author,

the growth of lobular buds in the male monkey is less pronounced than in the female with corresponding doses of estrogen but with high doses lobule formation will occur. (Figs. 63, 64.)

In the mammary gland of the rat or monkey the effect of testosterone propionate is similar to luteal hormones and stimulates lobule formation (Figs. 65, 66) (Geschickter and Astwood, confirmed

FIG. 63 FIG. 64



The Effect of Estrogen on the Mammary Gland of the Male Monkey.
FIG. 63. Prepuberty gland before treatment.
FIG. 64. Gland, showing lobule formation after 50,000 I. U. of estrone daily for six weeks.

by Speert). These androgenic effects are discussed later. At the present writing, specific growth effects produced by androgenic hormones[1] on the male or female human mammary gland have not been established. Inhibitory effects during lactation have been demonstrated (Kurzrok and O'Connell).

MAMMARY GLAND OF MATURITY

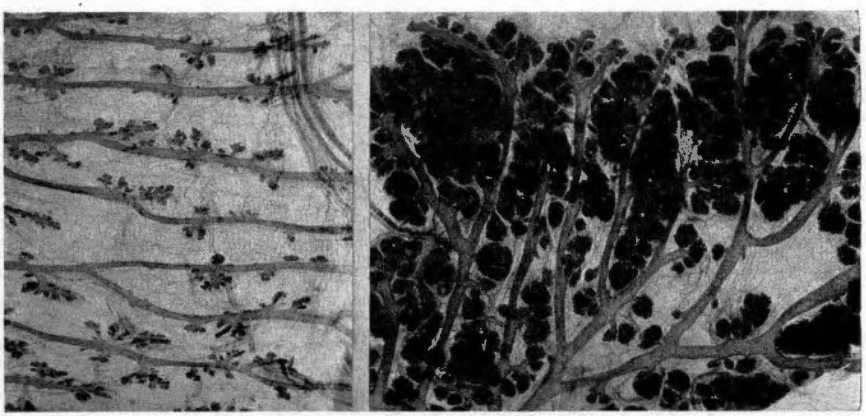
Lobule Formation and Pregnancy Changes in Relation to Luteal Hormones

Prior to Pregnancy. Lobule formation in the human breast is not found in the normal male, and it does not occur in the normal female

[1] The androgenic hormones isolated or synthesized to date including androsterone, androstenediol, androstenedione and the various derivatives of testosterone vary more widely in their mammotropic effects on laboratory animals than the various estrogenic hormones.

prior to the advent of the corpus luteum. These acinar structures appear following sexual maturity in the female and reach their full development during pregnancy. Hormones from the corpus luteum acting in combination with estrogens from the ovarian follicles are apparently responsible for the growth of mammary lobules during the premenstruum in cyclic women.[1] The lobular development found

FIG. 65 FIG. 66



The Effect of Testosterone on the Mammary Gland of the Female Monkey.
FIG. 65. The small lobular buds in a castrate female monkey after 15 days of 100 R. U. daily of estrone. (× 12).
FIG. 66. This shows lobular development 15 days later in the same monkey. The daily injections of estrone have been reduced to 25 R. U. but 50 mg. of testosterone propionate have been injected daily. (× 12). (Courtesy of Dr. Harold Speert).

in pregnancy exceeds, in degree, the development found in the luteal phase of the menstrual cycle. This added development is stimulated by hormones from the placenta.[2]

The size and number of lobules formed in the human breast are proportional to the intensity of the hormonal stimuli. In the majority of women a uniform distribution of well-formed lobules is not seen until after the stimulation of repeated pregnancies (Langer). A definite ratio of estrogen and luteal hormones is necessary to maintain normal lobular structure in cyclic women. Imbalance between these two hormonal functions of the ovary results in irregular epithelial buds at the ends of the mammary tubules (such as is seen in

[1] It has been shown experimentally that lobule formation also results from stimulation by luteal hormones in the absence of estrogens.

[2] Jones and Weil: These authors report a patient in whom the corpus luteum of pregnancy was removed on the 58th day after the last menstrual period. Abortion did not occur. Following this operation the authors measured the urinary content of pregnandiol. Pregnandiol which had been absent since the third day following operation began to increase rapidly. The authors conclude that progesterone is probably produced by the placenta, beginning, in this case at least, at about the end of the second month and probably continuing to the end of pregnancy. Seegar and Delfs have reported a similar case in which abortion did not occur following removal of both ovaries.

cystic mastitis) rather than in normal lobule formation (see Chap. 11). Speert has shown that in the cyclic monkey there is definite lobular growth during the premenstruum and that removal of the

FIG. 67 FIG. 68

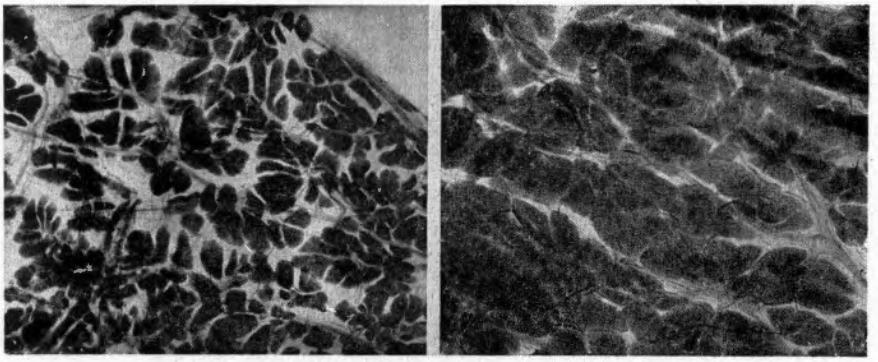


FIG. 67. Lobular growth in the cyclic female monkey. Whole mount showing the size of the lobules on the second day of the menstrual cycle in the normal female monkey. (× 12).

FIG. 68. Whole mount from the same monkey on the 24th day of the cycle. There is premenstrual growth. Small light points in the lobules indicate increased size of the acini. (× 12). (Courtesy of Dr. Harold Speert).

corpus luteum results in rapid involution of the mammary lobules (Figs. 67, 68).

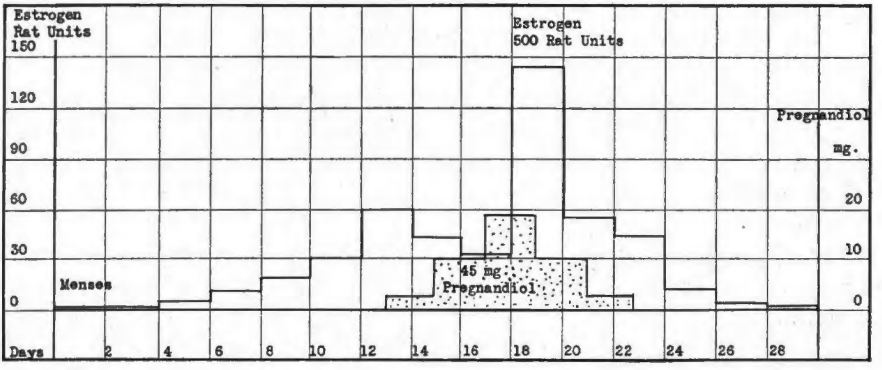


FIG. 69. Chart showing the recovery of estrogen and pregnandiol from the urine in a normal menstrual cycle.

The ratio of estrogen to corpus-luteum hormone necessary to promote normal lobular development in cyclic women has been esti-

mated from assays of the urine. Determinations based upon methods of extraction for total estrogen show between 10 and 60 rat units per 24 hours of output; the average total output for a normal cycle is variously stated as between 400 and 600 rat units (4000 to 6000 international units) by Frank, Mazer, Smith and Smith, and Palmer.

The corpus-luteum–hormone function during the menstrual cycle has been measured by determining the quantity of pregnandiol (an excretion product of progesterone) in the urine. Following ovulation values varying from 2 to 10 mg. per 24 hours are obtained, and for the total menstrual cycle between 15 and 60 mg. depending upon the method of extraction (Browne and Venning; Stover and Pratt; Hamblen, Ashley and Baptist; Bucher and Geschickter). The curves of both estrogenic and luteal hormones excreted in the normal menstrual cycle are shown in Fig. 69. The values shown provide a fairly reliable standard for the comparison of the normal with the abnormal if the same methods of assay are used for both.[1]

During pregnancy when larger and more numerous lobules are developed, correspondingly higher values for estrogen and corpus-luteum hormones are obtained, as high as 10,000 rat units per 24 hour output of urine for estrogen and as high as 100 mg. of pregnandiol (Fig. 70).

Clinical Evidence of Luteal-Hormone Action. The influence of the corpus-luteum hormones on the growth of mammary alveoli and on lobule formation was first suggested by Ancel and Bouin in 1911. These authors based their conclusions on observations made during pseudopregnancy or the first half of pregnancy in the rabbit, where the formation of corpora lutea is accompanied by a rapid proliferation of mammary alveoli. However, the relation of luteal hormones to lobule formation has been difficult to establish experimentally because of species differences and because the various corpus-luteum preparations available are not equally effective. The quantity of the hormone, the absence or presence of simultaneous estrogen stimulation and the length of time over which the hormone is administered are important factors.

No reports describing the effects of corpus-luteum–hormone injections on the human mammary gland, which are supported by histologic studies, have appeared in the literature except those herein reported. MacBryde combined high doses of estrogen with relatively

[1] In the Surgical Pathological Laboratory, the estrogen and pregnandiol determinations are both made on the same 48-hour specimen of urine. The total specimen is acidified to pH 6 and incubated until it is pH 8. This liberates the estrogens and the pregnandiol from their respective complexes, and they are then extracted with butanol. The butanol is distilled off, and the dry residue treated with acetone and aqueous sodium hydroxide. The pregnandiol precipitates, is filtered off, purified and weighed. The acetone–sodium-hydroxide filtrate contains the estrogens; it is neutralized and assayed on castrate female rats.

small doses of progesterone in the treatment of underdeveloped breasts and observed that the mammary tissue was more nodular to palpation than when estrogen alone was given.

Case Reports. The author administered progesterone (Progestin-Roche-Organon) to a girl, 20 years old, who had functional amenorrhea from

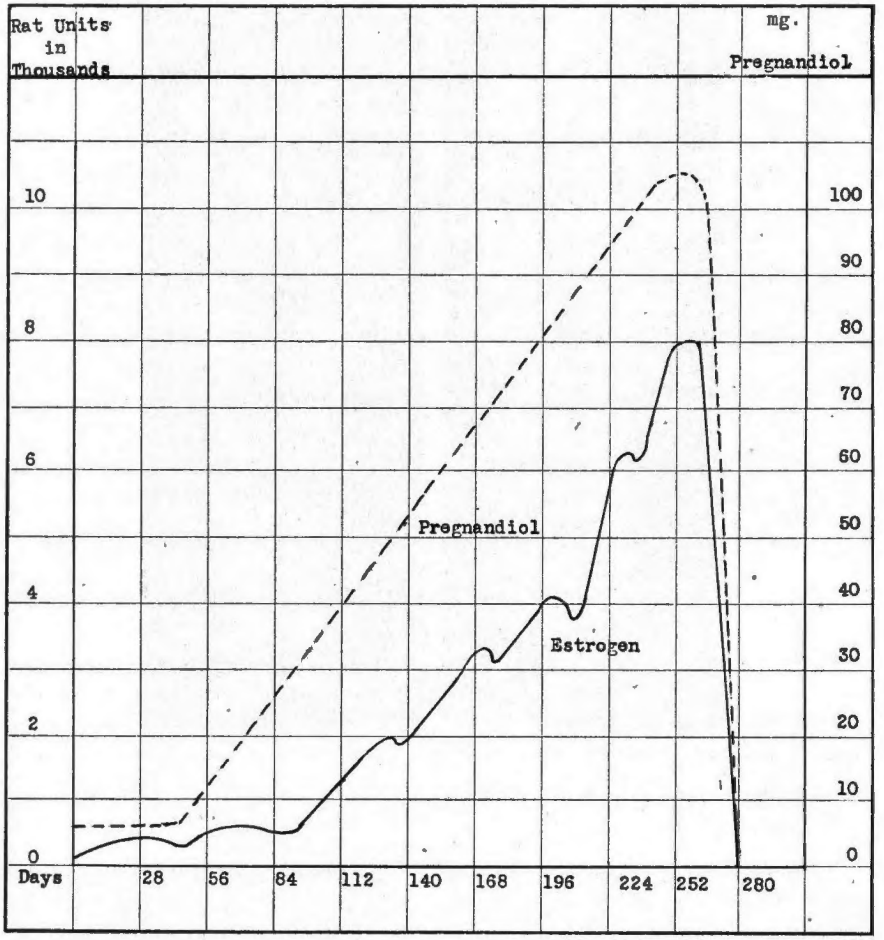


FIG. 70. Chart showing estrogen and pregnandiol values from the urine in normal pregnancy (diagrammatic).

January, 1935, to January, 1938. Urine assays showed an occasional trace of estrogen. The breasts were adipose and pendulous (Fig. 71). A control biopsy was done; it showed a few small rudimentary lobules scattered in sclerotic fibrous tissue. The number of alveoli comprising the lobules varied from two to six (Fig. 73). Following the biopsy, 145 mg. progesterone was administered over a period of six weeks. The patient men-

struated twice during this treatment. A bilateral plastic operation was then performed on the breasts. The tissue excised showed numerous well-developed lobules containing 10 to 20 alveoli and pale-staining intralobular connective tissue. The number of lobular capillaries was increased (Fig. 74).

FIG. 71 FIG. 72

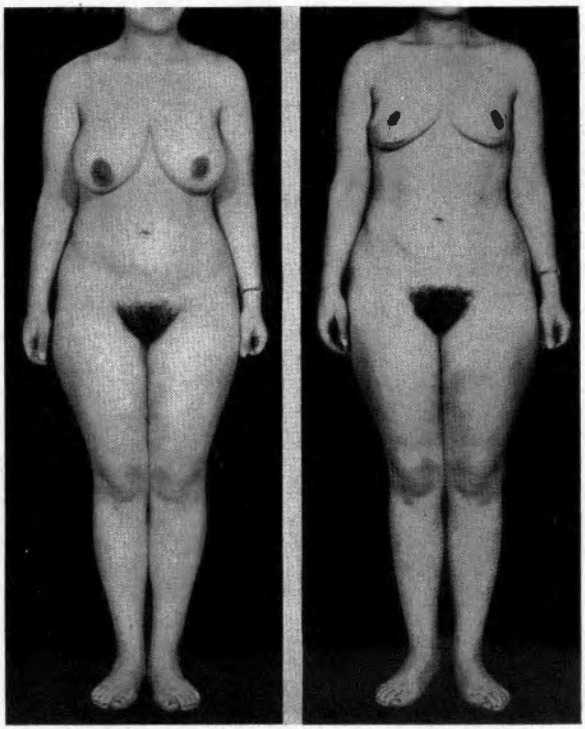


FIG. 71. Functional amenorrhea treated with progesterone. Patient before treatment. (See Fig. 73.)

FIG. 72. Patient after progesterone therapy and plastic surgery of the breasts. (See Fig. 74.)

In a girl of 15 who had normal breast development but had never menstruated, the urine assays were positive for estrogen in excess of 20 rat units per 24 hours of output. A biopsy of the breast showed adolescent development without lobule formation. Menstruation was not established and lobule formation was not induced although the patient received 246 mg. progesterone (including 15 units of progestin, Upjohn) over a period of two months. The endometrium remained atrophic.

Thus, progesterone may stimulate lobule formation in the human breast. The extent of maturity in the duct system prior to the administration of progesterone may be a possible controlling factor and during adolescence estrogen may be present in inhibiting amounts.

Experimental Evidence. In the mammary gland of prepubertal, female, castrate monkeys prolonged estrogen stimulation alone results in the formation of lobules (Figs. 75, 76) but lobular development is enhanced if corpus-luteum hormone is administered in combination with estrogen. In adult female monkeys in which castration has been performed a year or more previously the lobules disappear and the duct system atrophies. Estrogen in moderate amounts

FIG. 73 FIG. 74

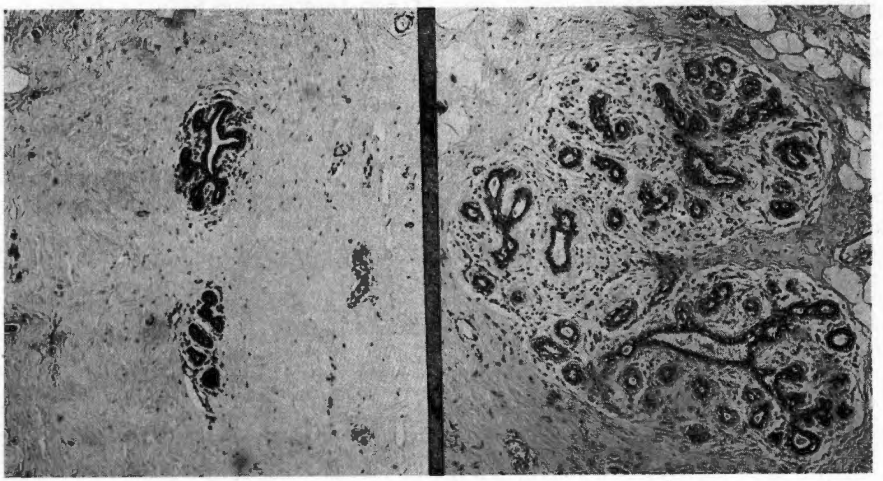


FIG. 73. Biopsy of breast before progesterone injections showing atrophic lobules and sclerotic fibrous tissue.

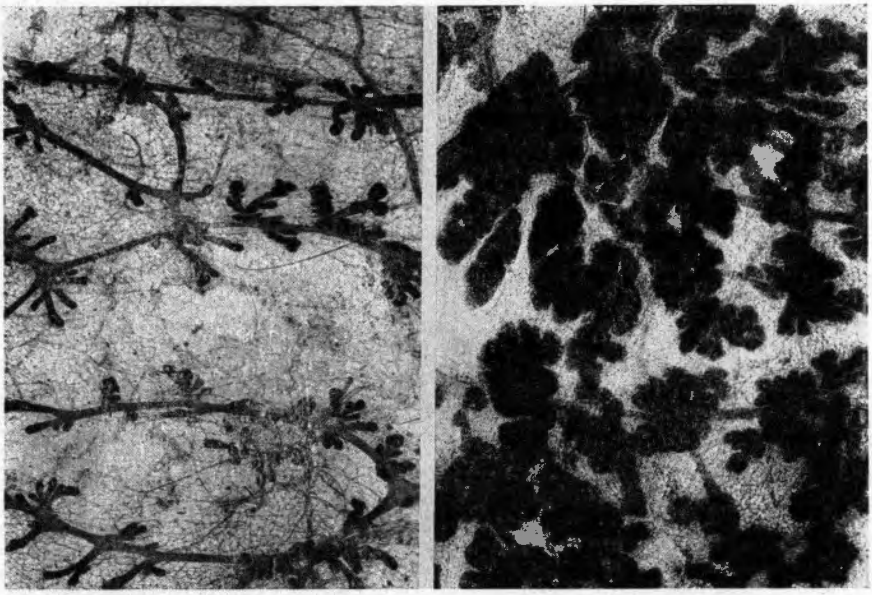
FIG. 74. Biopsy after six weeks of progesterone injections totalling 145 milligrams. Lobule development is marked and there is proliferation of intralobular connective tissue. Figs. 73, 74 are the same magnification.

does not restore lobule formation although it promotes the growth and regeneration of the duct system. On the other hand, progesterone alone restores lobule formation. (Figs. 77, 78.)

Lobule formation was enhanced and secretory globules similar to those seen in the second half of pregnancy were produced in six female, castrate adult monkeys (*Rhesus macacus*) subjected to the combined stimulation of estrogenic and luteal hormones.[1] These monkeys had not been pregnant but had normal menstrual cycles prior to castration. Some received estrone and progesterone, others estrogen, progesterone and testosterone.[1] (Figs. 79, 80.)

[1] The synthetic hormone, testosterone propionate, is closely allied in its formula to hormones present in the corpus luteum of pregnancy and can be substituted for them in the experimental production of mammary lobules in the rat and monkey. The sensitivity of the mammary gland to this otherwise masculinizing hormone is also shown in the normal adult male rat where lobule formation approaches that seen during early pregnancy in the female. Van Wagenen and Folley have reported lobule formation and secretion in the mammary gland of the monkey following injections of 100 to 200 mg. per week of testosterone over a period of 10 to 70 days.

FIG. 75 FIG. 76

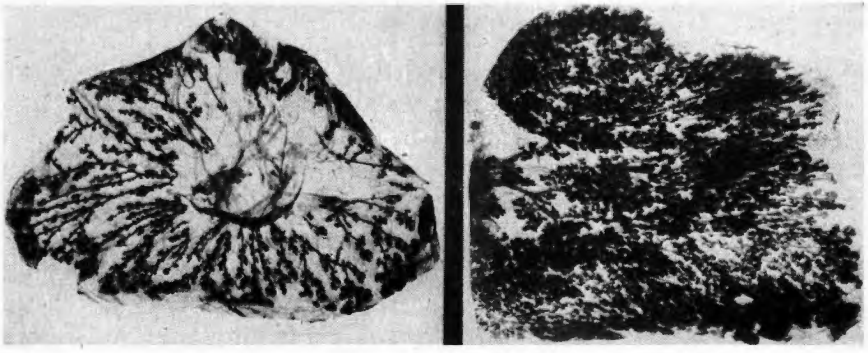


Lobule Formation in the Prepubertal Monkey in Response to Estrone.

FIG. 75. Whole mount of a mammary gland of prepubertal female monkey at the time of castration. There are lobular buds but no lobules. (× 13).

FIG. 76. Whole mount of the opposite breast of the same monkey 34 days later, after the injection of 1,000 I. U. of estrone daily. There is marked lobule formation. (× 13).

FIG. 77 FIG. 78



Comparison of the Effects of Estrone and Progesterone on the Adult Castrate Monkey.

FIG. 77. Whole mount of the mammary gland of an adult female monkey castrated more than a year previously and receiving 60,000 I. U. of estrone over a period of six weeks. There are large lobular buds but very few lobules. (× 2).

FIG. 78. Whole mount of an adult female monkey castrated a year previously and receiving 80 mg. of progesterone over a period of 30 days. There is dense lobule formation. (× 2).

In the mouse, rat and rabbit with intact ovaries, mammary lobules form as a result of follicle ripening and corpus-luteum formation following injections of chorionic gonadotropin. If artificial pregnancy is established in these animals by such injections or if pseudopregnancy by sterile copulation is produced, the lobular formation seen resembles that which is to be found in mid-pregnancy. (Figs. 81-86.)

FIG. 79 FIG. 80

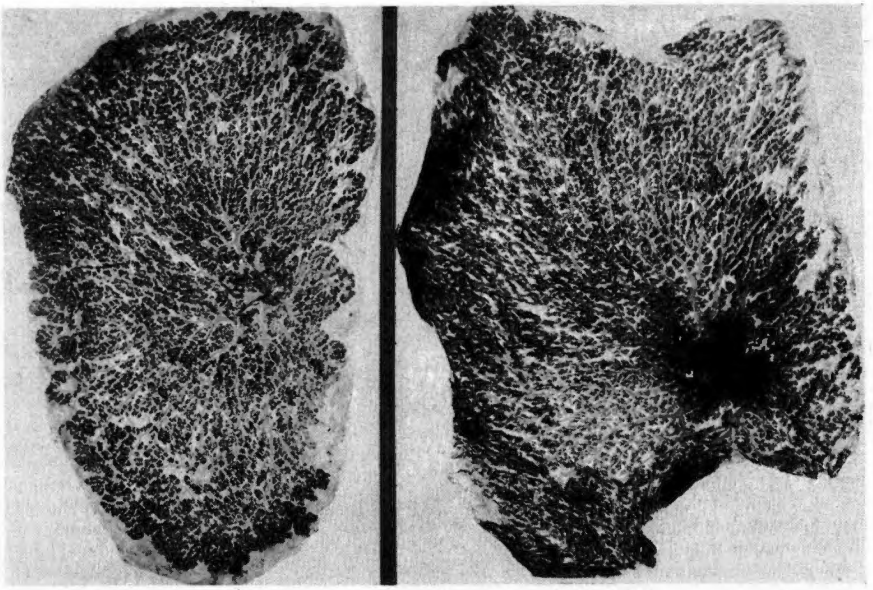


FIG. 79. Whole mounts of an adult castrated female monkey showing lobular development after injections of estrogen combined with injections of progesterone. Mammary gland three weeks after the implantation of one pellet of estrone and six pellets of progesterone. (Each pellet contained 3 mg. of crystalline hormone). (× 2).
FIG. 80. Mammary gland three weeks after the implantation of one pellet of estrone, six pellets of progesterone and four of testosterone propionate. (× 2).

In the mammary gland of the rat, estrogen combined with extracts of the corpus luteum obtained from the ovaries of pregnant cows or pregnant sows produces lobule formation. A ratio of 5 gamma estrone to one unit progestin prepared by extraction by the method of Wintersteiner and Allen produces lobule formation in female castrates, if given daily over a period of three weeks. (Figs. 81-86.) Lobules are formed if the synthetic corpus-luteum hormone, progesterone, is substituted for the natural extracts, but only if the hormone is administered daily for a period of six weeks or more, or

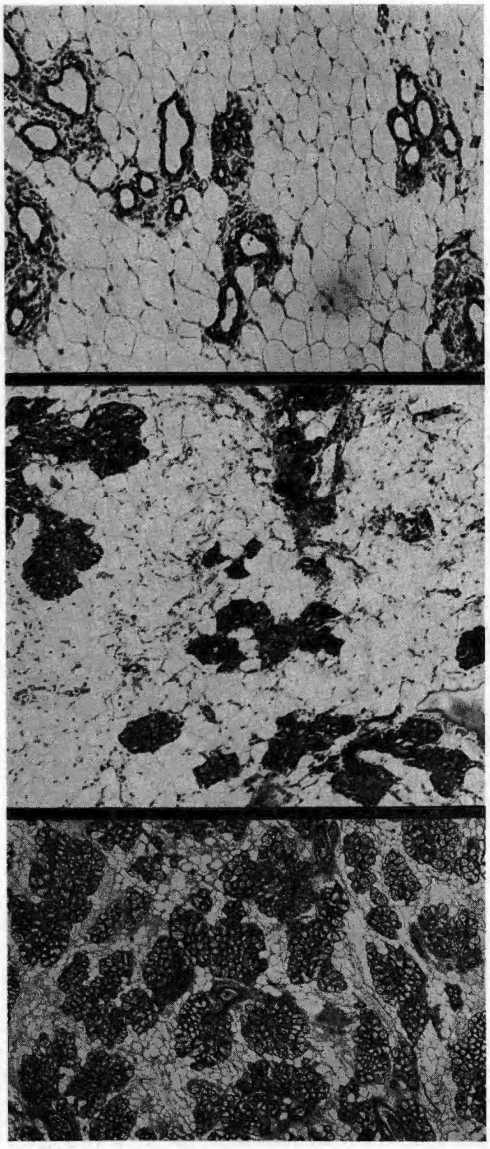


FIG. 81. The effect of five gamma of estrone daily for 21 days in a female rat castrated at 21 days. Lobule formation is absent.

FIG. 82. The effect of five gamma of estrone combined with one unit of progestin (corpus-luteum extract) daily for 21 days (female rat castrated at 21 days). Moderate lobule formation has occurred.

FIG. 83. The effect of 20 rat units of chorionic gonadotropin daily for 30 days on the intact female rat treated from the 31st day of life. Lobule formation resembling that in pregnancy is seen.

Photomicrographs Showing the Effects of Estrone, Progestin and Pregnancy Urine Hormone on the Mammary Gland of the Rat.

when it is implanted in the breast in the form of pellets.[1] This has been recently confirmed by Selye. If the synthetic hormone, testosterone propionate, is given combined with estrogen in a ratio of 5 gamma estrone to 2 mg. testosterone, fairly normal lobule formation results. Astwood has obtained lobule formation in the hypophysectomized rat injected with rat placental extracts.

FIG. 85

FIG. 84

FIG. 86

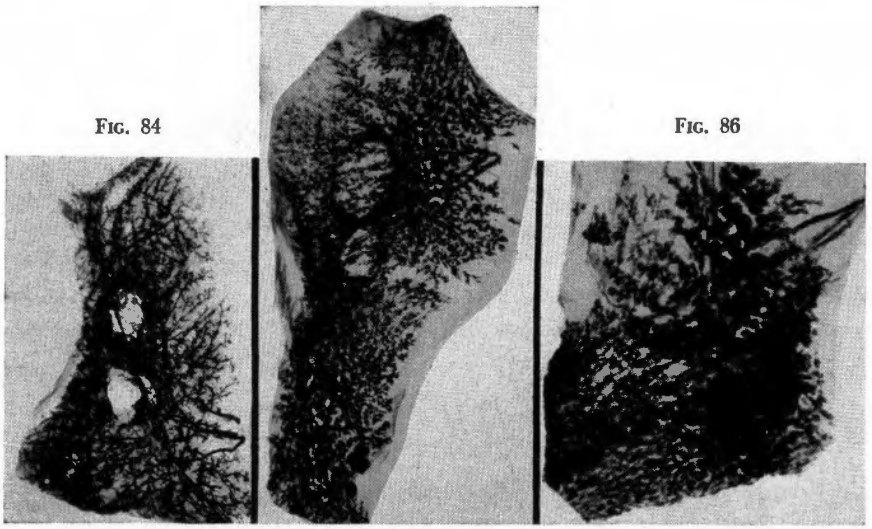


FIG. 84. Whole mount of the mammary gland of the animal in Fig. 81.
FIG. 85. Whole mount from the mammary gland of the animal in Fig. 82.
FIG. 86. Whole mount from the mammary gland of the animal in Fig. 83.

Turner and Frank injected both progestin (natural extract of corpus luteum) and estrogen into castrate male rabbits in order to reproduce normal lobular development experimentally and their observations in the rabbit were later confirmed by Anselmino, MacDonald, and Pallot. Turner and his co-workers repeated these experiments on the rat, mouse, and cat.

In summary, luteal hormones in combination with estrogen stimulate lobule formation in the mammary gland. The synthetic hormone, progesterone, is active on the human and monkey mammary

[1] Because the mammary gland of the rat does not respond as readily with lobule formation to synthetic progesterone, as it does to natural extracts of corpus luteum (progestin); it is probable that the entire hormonal complex of the corpus luteum of pregnancy is not represented by synthetic progesterone. Fully developed lobules, with secretory changes such as are seen at the end of pregnancy, are obtained more readily in castrated nonpregnant monkeys, when progesterone and testosterone are given simultaneously rather than the progesterone alone.

That synthetic progesterone does not replace corpus-luteum extracts is also indicated by the work of Allen and Heckel who found that corpus-luteum extract (progestin) would maintain pregnancy in rabbits, castrated 18 hours after conception, whereas progesterone would maintain pregnancy following castration only after the eleventh day.

gland but relatively inactive on the gland of the rat. The synthetic hormone, testosterone propionate, resembles progesterone in its action on the mammary gland of the monkey and rat, but to a less extent, if at all, in the human being. The rapid lobule development seen during pregnancy surpasses that obtained experimentally by injecting progesterone and estrogen and it is probable that a hormone supplied by the placenta is a more effective stimulus. This is suggested by the production of mammary lobules in the rat by the injection of rat placental extract. The physiology of lobule formation is further complicated by the fact that in the monkey and guinea pig, lobule formation may be stimulated by estrogen alone.

The forms of mammary dysplasia known as chronic cystic mastitis are intimately related to the physiology of lobule formation in the human breast and to the function of the corpus luteum. Lobule formation is defective in all forms of chronic cystic mastitis and good results in the treatment of this condition have been reported following injections of progesterone (Geschickter). Normal lobule formation is a prerequisite for normal lactation and some cases of deficient lactation are apparently the result of deficient lobule formation.

Relation of Anterior-Pituitary Hormones to Ovarian Function and to Mammary Development

The physiologic effects produced on the mammary gland by estrogen and luteal hormones described above are in turn dependent upon the stimulation or maintenance of ovarian function by hypophyseal activity. Precocious sexual maturity with mammary development is produced in animals by implants and extracts of anterior-pituitary glands (Engle, Zondek, Van Dyke). Separate gonadotropic hormones of the anterior hypophysis are responsible for follicle stimulation and corpus-luteum formation (the follicle stimulation and luteinizing factors) and for corpus-luteum function (luteotrophin, Astwood).

Mediation of Effects. There is no evidence to indicate that the pituitary gonadotropic hormones act directly on the mammary gland since these hormones are without mammary effect in castrated animals. Clinically, patients in whom castration has been performed frequently show increased gonadotropic secretions (as determined by assays on the urine) while studies on the mammary gland show marked atrophy.

Although the mammary effects of the pituitary gonadotropic hormone are mediated through the ovaries, there is experimental evidence to show that the effects of the ovarian hormones, estrogen and

progesterone, may be mediated through the pituitary gland or at least require the presence of an intact hypophysis. Nelson and Tobin reported that estrogen had little effect on the mammary gland in hypophysectomized rats. Lyons and Pencharz reported a similar absence of mammary effect on hypophysectomized guinea pigs and

FIG. 87

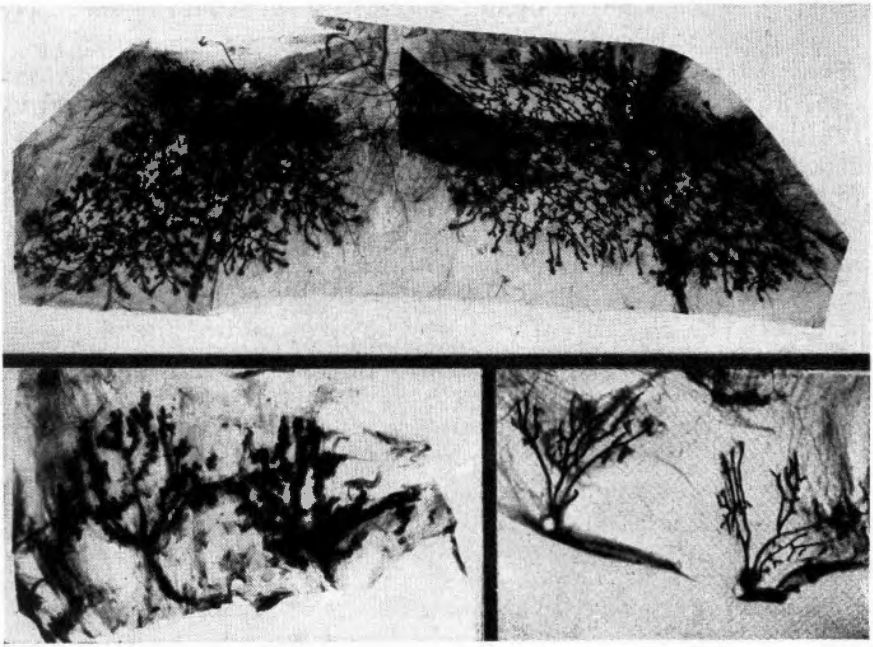


FIG. 88

FIG. 89

FIG. 87. Results of hypophysectomy and starvation on the mammary gland of the rat. Whole mount of two mammary glands of a normal 63-day old male which had received 50 gamma of estrone for eight days. (× 4).

FIG. 88. Whole mount of two mammary glands of a male 63 days old, hypophysectomized nine days previously and treated with 50 gamma of estrone daily for eight days. The extent of regression over the control in Fig. 87 is shown. (× 4).

FIG. 89. Whole mount of two mammary glands of a 35-day old female on a restricted diet treated from 21 days with five gamma of estrone daily. Body weight 28 Gm. Regression has occurred in spite of estrone administration. (× 4).

Gomez and Turner reported that progestin and estrogen were incapable of stimulating mammary-gland growth of male or female rats or guinea pigs after hypophysectomy. In our experiments, estrogen is incapable of maintaining the mammary gland in hypophysectomized rats (Astwood, Geschickter and Rausch).

It has been shown by Zondek, Cramer and Horning and others, that high and prolonged doses of estrogen inhibit the gonadotropic activity of the hypophysis. Makepeace has shown that adequate injec-

tions of progesterone inhibit the gonadotropic function of the anterior pituitary. Recently Geschickter, Hartman, and Speert have demonstrated that, in the monkey, intense treatment with estrogens inhibits the hypophysis.

On the other hand, small physiologic doses of estrogen may stimulate hypophyseal secretion, particularly the luteinizing factor (Wolfe and Wright), and, by causing luteinization of the ovaries, produce lobule formation in the breast. Recently, Turner and Gomez have concluded that the growth of the mammary gland is dependent upon a mammogenic hormone, a protein-like substance secreted by the hypophysis, and that the secretion of this hormone is stimulated by the ovarian hormones. These animal experiments have not been repeated in the monkey and no conclusions in regard to the growth of the human breast may be drawn from them.

It is possible that nutritional deficiencies after hypophysectomy may account for failure of the ovarian hormones to stimulate mammary growth under these conditions (Astwood, Geschickter and Rausch). The majority of authors who have studied the effects on the mammary gland of the ovarian hormones after hypophysectomy are agreed that the hypophysis is essential for their action (Figs. 87-89). Leonard found that estrogen and testosterone would not stimulate the breast of hypophysectomized rats if the hormones were administered more than one week after removal of the pituitary gland, or if the animals were old enough to weigh over 70 grams at the time of hypophysectomy.

Relation of Lactogenic Hormones to Secretory Changes in the Mammary Gland

During lactation, the mammary gland shows actively secreting epithelium, dilatation of ducts and acini, condensation of intralobular and periductal connective tissue and increased vascularity. These changes are influenced by the pituitary lactogenic hormone (lactogen or prolactin) acting upon a gland previously stimulated to full lobular development during pregnancy by estrogenic and luteal hormones. The mechanical stimulus of nursing is necessary to maintain active secretion.

Investigations demonstrating the effects of extracts of the anterior lobe of the hypophysis on mammary secretion have been made by Corner, Nelson and Pfiffner, Gardner and Turner, Riddle, Bates and Dykshorn. These studies have shown that when the mammary glands of rats, guinea-pigs, rabbits and dogs have been stimulated by ovarian hormones, injections of anterior-lobe extracts may initiate secretory changes.

Purified pituitary lactogenic hormones have been prepared by Turner and his associates and by Riddle and his co-workers and by others.

Turner has cited experiments showing that hypophysectomy prevents the appearance of lactation or causes the immediate cessation of milk secretion in lactating animals. In hypophysectomized animals, lactation can be maintained or initiated if lactogenic hormone is combined with pituitary adrenotropic hormone and glucose (Gomez and Turner, 1937).

Lactation is impossible in the absence of development of the duct system, and it is limited if complete lobule development is lacking. Mammary involution caused by castration makes the gland unresponsive to lactogenic hormone. The same is true of senile involution. Turner concluded that immature or involuted female glands and male mammary glands unstimulated by estrogen are incapable of responding to lactogenic hormone. Physiologic doses of estrogen prepare the mammary gland and also stimulate increased lactogen secretion by the pituitary. If large doses of estrogen are given simultaneously with lactogenic hormone, however, lactation is inhibited. Robson obtained inhibition in both normal and castrate guinea pigs by injecting 0.1 mg. of estrone daily.

The lactogenic content of pituitary, blood, and urine may be studied if the specimens to be assayed are injected subcutaneously over the crop gland of pigeons. Increase in the weight of the crop indicates the presence of lactogenic hormone. Reece and Turner studied the lactogenic content of the pituitary and found that animals in estrus had more lactogenic hormone in their pituitary than those in anestrus. The hormone did not increase in pregnancy, but rose markedly following parturition regardless of nursing. Lactogen was higher in the pituitary of dairy cattle than in beef cattle. Injections of 10 cc. blood plasma from a woman five days postpartum gave a positive reaction in the crop gland. Blood of lactating animals gives a positive response. Hoffman, in 1936, found no lactogen in the urine before delivery but obtained positive results on the third and fourth day and thereafter. The urine was negative in seven of eight cases of deficient lactation.

Clinical Evidence of Lactogenic Hormone Effects. Kurzrok and others gave lactogenic hormone to 37 women who had been delivered of normal children. Of these, 29 were thought to have insufficient milk. Twenty-one showed an increase in the amount of milk after the sixth day postpartum, when from 75 to 400 bird units of lactogenic hormone was injected intramuscularly. In eight, the response was unsatisfactory. In eight other women in whom the

secretion was normal, no increase was noted after the use of the lactogenic substance.

Werner gave injections of lactogenic substance (220 bird units daily for from four to 14 days) to 10 castrated women, ranging in age from 21 to 35 years. The breasts were prepared by injections of estrogen to which was added the gonadotropic factor from the urine of pregnant women, or progestin in eight cases. All noted enlarge-

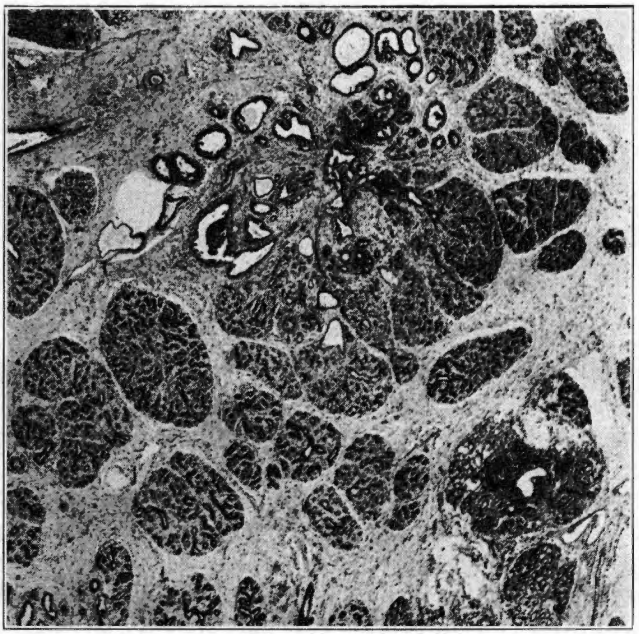


FIG. 90. Lactogenic Effects. Photomicrographs of the mammary gland of a nulliparous woman aged 25, before injection of pituitary lactogenic hormone. (See Fig. 91.)

ment or engorgement of the breasts suggesting the onset of lactation. In no case did lactation occur, however. Ross reported that injections of lactogenic hormone varying from 400 to 1000 units increased the amount of milk and the length of nursing.

In experiments previously reported (Geschickter and Lewis), injections of pituitary extracts were given to 15 menstruating women who had various forms of chronic cystic mastitis but who had not been recently delivered. Small amounts of a watery mammary secretion occurred in eight of the 15 cases after injections of estrogen followed by lactogenic hormone. The mammary changes produced were studied by biopsies taken before and after injections in five cases. Dilatation of acini and secretion were observed but no active lactation (Figs. 90-92).

The results obtained indicate that a lactogenic substance in anterior pituitary extracts may cause mammary secretion in nonpreg-

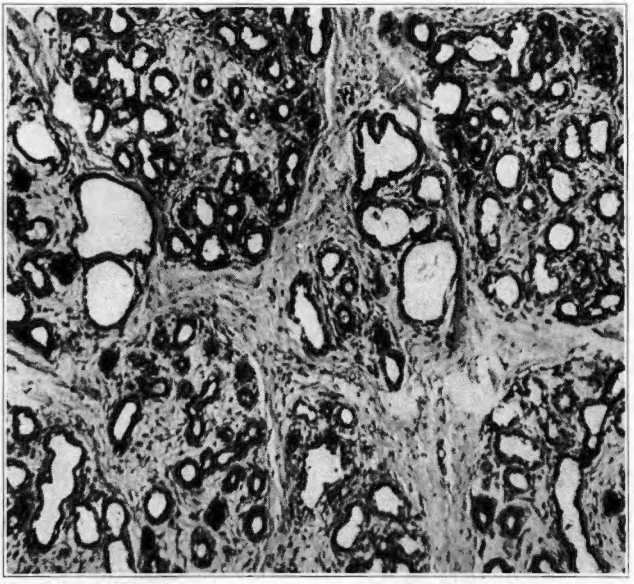


FIG. 91. Lactogenic effects. Photomicrograph of the mammary gland shown in Fig. 90 after injections of 2600 bird units of pituitary lactogenic hormone. The hormone has caused dilatation of and secretion in the acini.

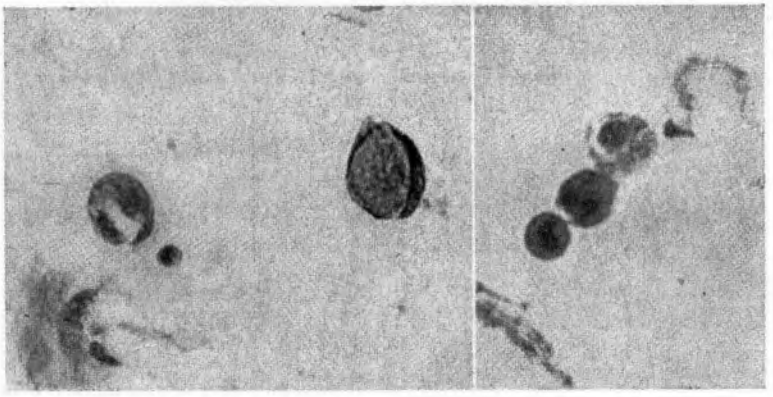
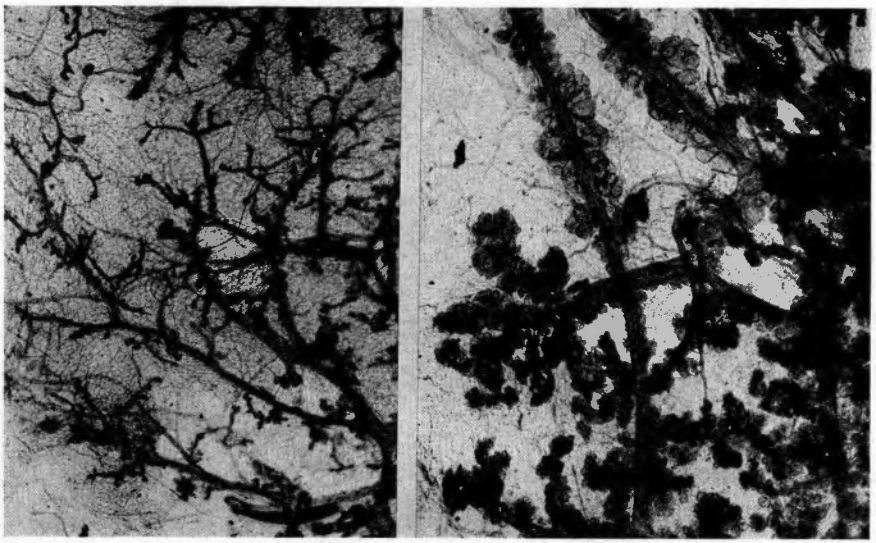


FIG. 92. The microscopic appearance of the secretion of the gland shown in Fig. 91.

nant women when they have been previously stimulated with estrogenic hormone but true lactation does not occur. Secretion was also obtained in two adult men with gynecomastia after injections of lactogenic hormone.

The appearance of secretion was preceded by a feeling of engorgement and heaviness of the breasts and accompanied by an increase in their size. The secretion was creamy white and in no case lasted longer than five days. No more than 10 or 12 drops could be expressed from the nipple at any time. Secretion ceased spontaneously in all cases even when the pituitary extracts were administered after

FIG. 93 FIG. 94



Effect of Pituitary Lactogenic Hormone on the Rat's Breast.
FIG. 93. Control gland from a female rat castrated and receiving 10 gamma of estrone daily for 100 days. (× 14).
FIG. 94. Mammary gland from same rat 6 days later after 20 units of anterior pituitary (complex) hormone injected twice daily for five days. The ducts and lobules are distended by secretion. (× 14).

the secretion appeared and the nipples were stimulated by the patient. Microscopically, the secretion in all the cases resembled colostrum, fatty droplets and desquamated cells being found (Fig. 92).

Experimental Evidence. While recent research tends to emphasize the importance of the pituitary gland in the control of lactation (Figs. 93, 94) and also in the growth of the mammary gland through its interaction with the ovary, metabolic factors and mechanical stimulation in the act of suckling are important.

Van Dyke has summarized the experiments showing that the lactating mammary gland uses glucose extensively (10 to 30 mg. per cent are removed from the blood during each passage through the cow's udder). The metabolism of sugar, believed to be controlled by a "carbohydrate metabolism" hormone from the pituitary, plays an

important role in the level of secretion maintained by the lactating gland.

In a series of papers by Selye and his co-workers, it has been shown that the act of suckling, by stimulating the pituitary through nervous pathways, maintained lactation in rats and mice. Ingelbrecht severed the spinal cord in rats between the dorsal and lumbar vertebrae and inhibited lactation in the glands in the paralyzed region.

Posterior pituitary hormones may be concerned in the discharge of milk in response to suckling. If this mechanism is disturbed by interrupting the nervous pathways, milk stasis followed by mammary involution may result.

Summary. Pituitary lactogenic hormone plays a dominant role in the initiation of lactation. The formation of mammary lobules with differentiation of acini such as those of normal pregnancy is a prerequisite for this secretory activity. The mechanical stimulus of nursing is an added factor. Moreover, the withdrawal of the estrogenic and luteal hormone upon the expulsion of the placenta at childbirth appears to act as a stimulus to hypophyseal secretion of lactogenic hormone.

Women with deficient lactation may be benefited occasionally by injections of lactogenic hormone during the puerperium. The frequency with which a history of inability to nurse is obtained in such conditions as chronic cystic mastitis suggests, however, that the failure of the mammary gland to respond to the sex hormones with normal and adequate lobule formation is a more common cause of deficient lactation.

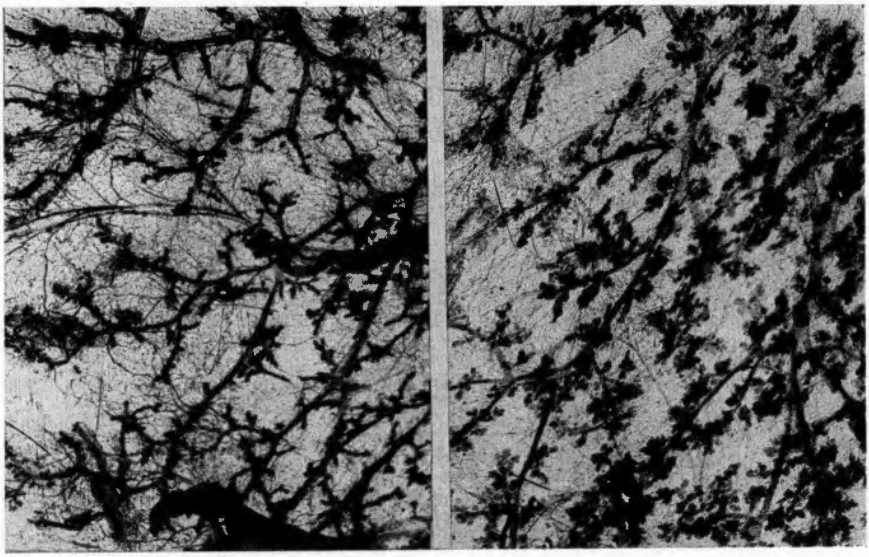
The inhibition of lactation by the injection of high doses of the sex hormones, such as estrogen and testosterone, is important clinically in handling cases of galactorrhea or those in which nursing is impossible because of deformities of the nipple. Abarbanel has reported diminished milk secretion in lactating women after administering large amounts of the synthetic estrogen, stilbestrol, orally. He could not obtain a similar inhibition with injections of large amounts of androgens (testosterone propionate) although painful engorgement on the cessation of nursing was prevented. Beilly and Solomon reported complete inhibition of lactation in 58 per cent of a group of postpartum women receiving three injections of 25 mg. testosterone propionate at 12-hour intervals. It is hard to establish a control for these observations, however, since lactation usually ceases in a few days if nursing is discontinued. (See Chap. 5, p. 138.)

Influence of the Adrenal Cortical and Thyroid Hormones

Adrenal Cortical Hormone Effects. Clinical evidence indicates hyperplasia or tumors of the adrenal cortex may lead to mammary

hypertrophy. Cases of infantile mammary hypertrophy and gynecomastia associated with changes in the adrenal cortex have been reported (see Chap. 4). It is doubtful, however, if hormones peculiar to the adrenal cortex are responsible for the variety of mammary effects observed. It seems more likely that androgenic and estrogenic substances occurring in the adrenal cortex are also active factors and that their action is similar to that discussed above for the sex hormones.

FIG. 95 FIG. 96



Effect of Adrenal Cortical Hormone on the Mammary Gland of the Rat.
FIG. 95. Control gland from a castrated and adrenalectomized female rat 6 months old. (× 14).
FIG. 96. Mammary gland from the same rat 6 days later after 1 cc. of cortin (adrenal cortical extract) given twice daily for five days. There is lobular development. (× 14).

Adrenalectomy in animals interferes with lactation. Normal lactation can be restored in such animals by administering the adrenal cortical hormone. Gaunt and Tobin performed such experiments on the rat and Swingle and Pfiffner made similar observations on the dog. Turner believes that the effect of the adrenal cortex is upon the salt-water balance necessary as a precursor to milk synthesis. On the other hand Brownell et al. give the name "cortilactin" to adrenal extracts which would maintain lactation.

In experiments performed by the author in association with Dr. Grollman in the Department of Physiology of the Johns Hopkins School of Medicine, it was found that the adrenal cortical extracts and the synthetic hormone, desoxycorticosterone, had moderate but

definite effect on the growth of the mammary gland in the rat and mouse. (Figs. 95, 96.) Speert confirmed these findings and showed that desoxycorticosterone produced lobule-alveolar growth in the mammary gland of the castrated female monkey.

Thyroid Effects. In cases of hypothyroidism in children, the mammary glands and sexual organs may show delayed development in keeping with underdevelopment of the rest of the body. In such cases, general body growth and the secondary sexual characteristics may develop normally with the administration of the thyroid substance. Specific effects on the mammary gland cannot be demonstrated by feeding desiccated thyroid or by injections of thyroxin; or by combining these estrogen injections. However, Gardner reports increased duct growth in the breasts of male mice fed desiccated thyroid. The effect was an indirect one, since it was not observed in castrated male mice.

Thyroxin augments lactation but its action is indirect. Recent experiments show that lactation will proceed in the absence of the thyroid gland, but the level of secretion is materially reduced. Graham suggested that the action of thyroxin upon lactation is through its effects upon general metabolism, whereas Jack and Bechdel believe that thyroxin stimulates the secretion of lactogen through the pituitary. Turner suggests increased circulation through the mammary glands as a possible cause.

INVOLUTION

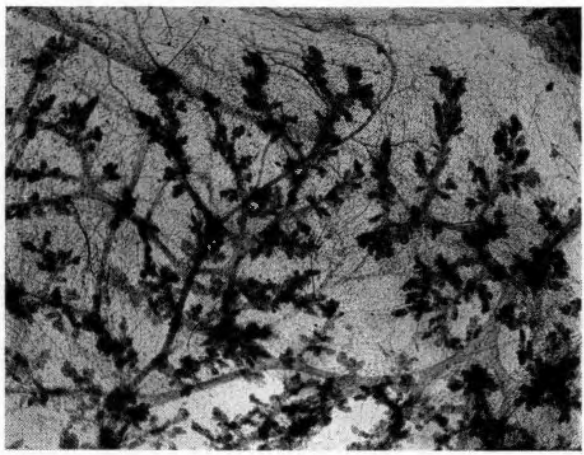
Relatively little attention has been given to the physiology of mammary involution. Regressive changes in the gland occur during menstruation, after lactation, and at or after the menopause. The subject of mammary involution therefore cannot be restricted to the phenomena of castration or senile atrophy.

Menstrual Involution. Microscopic regressive changes in the breast during the menstrual period in cyclic women are due to the fall in the secretory level of the ovarian hormones. These changes indicate that continued hormonal stimulation is necessary to maintain the normal mature developmental state of the gland. Hartman and Speert have confirmed these cyclic changes in the monkey.

Premenopausal involutional changes may appear in the mammary gland about the age of 40 in women who have borne few or no children. Lobular irregularities appear, consisting of cystic dilatation of alveoli or epithelial proliferation of the lobular buds. Similar changes appear in rats maintained over a period of weeks on constant daily doses of estrogen and progressively diminishing doses of luteal

hormones (see Chap. 11). Apparently these changes coincide with the decline in luteal function of the ovary in women approaching the menopause.

Menopausal involutional changes characterized by the formation of minute cysts and cystic dilatation of the mammary tubules must be considered a normal regressive change according to autopsy findings in clinically negative breasts. Certain authors (Borchardt and Jaffe) estimate that approximately 70 per cent of the cases in which the mammary gland of adult women is studied at autopsy show such changes (see Chap. 1). No sharp dividing line can be drawn between the lobular irregularity found in premenopausal involution



Postlactation Involution in the Mammary Gland of the Female Rat.
FIG. 97. Mammary gland following stimulation with estrone (ten gamma daily for twenty days following castration). (× 14.) (See Figs. 98, 99.)

or in the cystic changes of menopausal involution and that in the various forms of chronic cystic mastitis. Apparently the pathologic changes in cystic involution are produced by relatively high and irregular estrogenic secretion at or near the menopause or by diminishing luteal function. These endocrine findings associated with the clinical manifestations of mammary dysplasia have been reported by Bucher and Geschickter and are discussed in Chap. 11. Doses of estrogen beyond physiologic limits (15 to 25 gamma) or high intermittent doses (100 gamma every 10 days) given to castrated rats produce cystic involutional changes similar to those found at the menopause. Cystic changes are accompanied by collapse of the mammary ducts and atrophic changes in other portions of the gland (see Chap. 11). These involutional changes in the breast at or near the menopause or in women with cystic disease result from estrogenic overstimulation when corpus-luteum function is diminished or absent.

Involutional Changes of Castration. Castration is followed by the eventual disappearance of the lobules, collapse of the mammary tubules, involution of the lining epithelium and condensation in the fibrous stroma. It is observed clinically following surgical or roentgen-ray castration in young adults. The same type of atrophy also is found in the senile mammary gland. In monkeys, castration atrophy of the mammary gland begins within a few days after the removal of the ovaries. Concurrent with the atrophic changes, localized nodules of hyperplastic tissue appear and cystic dilatation of

FIG. 98 FIG. 99

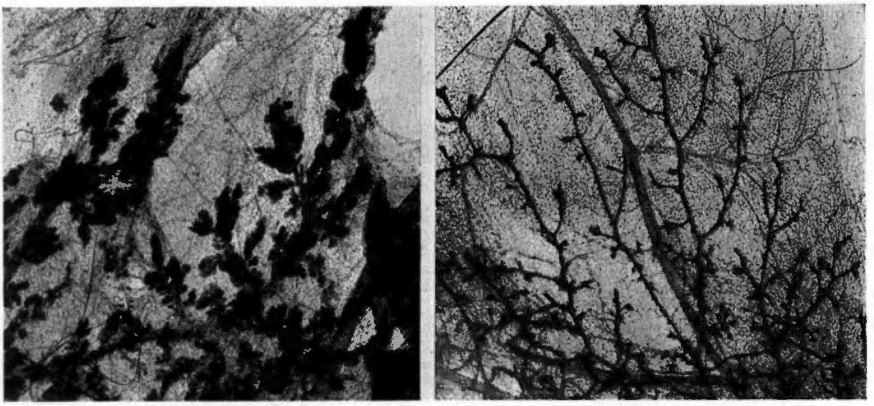


FIG. 98. Mammary gland after lactogenic stimulation (40 bird units of prolactin (Squibb) twice daily for five days.) (× 14).

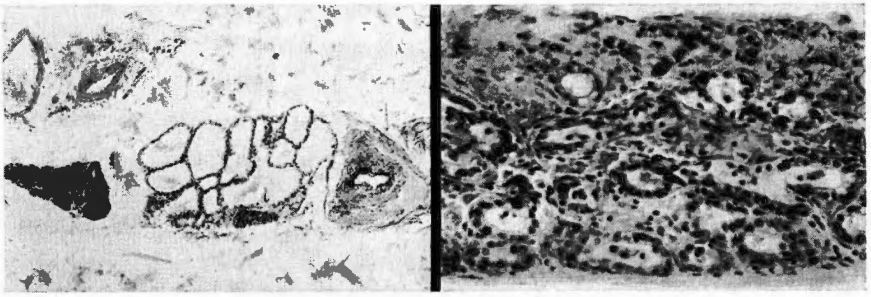
FIG. 99. Mammary gland, 8 days after lactogenic stimulation and 13 days after estrogenic stimulation. Note the rapid shrinkage in the mammary tubules and lobular buds. (× 14).

acini is found (Figs. 100-101). Speert has met these hyperplastic nodules in the mammary gland of the monkey from one to 18 months after castration. They correspond to the presenile involutional changes found at autopsy in the breast of women more than 35 years of age, discussed above; frequently they have been mistaken for forms of cystic mastitis. Speert has shown that these neoformations may be prevented by administering adequate doses of various estrogenic, luteal or androgenic hormones.

Postlactation Involutional Changes. Withdrawal of the estrogenic and luteal hormones of pregnancy is followed by lactation changes in the mammary gland after the third month of pregnancy. Involutional changes appear with the cessation of nursing or in the absence of nursing. Apparently postlactation involution may be accompanied by more rapid regressive changes than are seen following the with-

drawal of ovarian function at castration. During lactation, both of the ovarian hormones and the other mammogenic hormones are probably inhibited. Cessation of lactation therefore leaves the gland in a completely quiescent state. A factor which adds to the effects of postlactation involution is the previous crowding out of the fibrous stroma by the lactating lobules.

FIG. 100 FIG. 101



Lobular Irregularities during Castration Involution in the Mammary Gland of the Adult Female Monkey.
FIG. 100. Cystic dilatation with secretory change 2 months after castration. (× 85).
FIG. 101. Adenomatous nodule 76th day after castration (× 350). (Courtesy of Dr. Harold Speert.)

SUMMARY

Estrogenic hormones stimulate the growth of the duct system and the formation of lobular buds. The extent of such development in response to estrogen has inherent limitations and estrogen stimulation beyond physiologic limits leads to involutional changes. Continued estrogenic stimulation in combination with luteal hormones results in the lobule-alveolar development from the lobular buds and brings about differentiation of the secretory epithelium. During pregnancy luteal hormones of placental origin and possibly a mammogenic pituitary hormone are the most effective stimulants to lobule-alveolar formation. While estrogen stimulates the growth of lobular buds and may initiate the formation of lobules, the combined action of estrogen and luteal hormones is necessary to maintain lobular development. The presence of an intact hypophysis is essential for the mammary effects observed in response to these hormones. The functional activity of the anterior hypophysis also initiates secretion in the mammary alveoli. The mechanical act of suckling is important in maintaining this secretion.

While the differentiation of the duct epithelium is primarily under estrogenic control, the hormonal control of lobular development is more complicated. The lobular buds proliferate during

estrogenic stimulation; differentiate in response to the luteal hormones; and secretion in them is initiated by the lactogenic hormone of the anterior hypophysis. These changes in the mammary epithelium under hormonal stimulation presuppose adequate metabolism and nourishment. This adequacy is apparently lacking in hypophysectomized animals and those subjected to starvation.

The growth of periductal connective tissue is stimulated during the estrogenic phase of development. In the luteal phase, the intralobular stroma becomes increasingly collagenous and vascular. During lactation, vascularity is increased and the stromal elements are compressed or resorbed.

The lobular system is most sensitive to deficiencies of the sex hormones and shows regressive changes following lactation, at or after the menopause and following castration. Lobular atrophy is accompanied by regressive changes in the stroma and in the epithelial lining of the ducts. The earlier phases of involution, at the menopause or following surgical castration, are accompanied by the development of irregular hyperplastic nodules and cystic dilatation of the acini in the mammary lobules, resulting from a withdrawal of ovarian hormones.

In addition to pituitary, ovarian, and placental hormones, the adrenal cortical hormones must be included among the endocrine regulators of mammary physiology. Experiments demonstrate that thyroxin augments lactation, but the effect is probably an indirect one.

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