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Hormonal control of lactation

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THE HORMONAL CONTROL OF LACTATION

by

Earl A. Rogers

University of Nebraska College of Medicine. 1935
To my dear friend Dr. Fred Fouts, who has been my inspiration from childhood on, and by whose help I have been able to continue my studies in the profession he has practiced so nobly, this paper is respectfully dedicated.
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INTRODUCTION

The mammary gland is an anatomical structure common to all mammals, and is the medium for the nourishment of the young for a varying period following intrauterine life. To synchronize the development and function of the mammary gland with the development and birth of the young requires a high degree of coordination between ovaries, uterus, pituitary gland and mammary gland, which will be the subject of this paper.

Each mammary gland in a woman is composed of from 15 to 25 individual lobes radiating from the mammary papilla or nipple and separated from each other by layers of connective tissue and adipose tissue. Each lobe is an independent, compound, branched alveolar gland, having a separate opening on the surface of the nipple by means of its excretory or lactiferous duct.

The secreting portions of the gland, the alveoli, consist of a basement membrane, a layer of myo-epithelial cells, (which serve to associate the mammary gland morphogenetically with the sweat glands) and a layer of low col-
ummary epithelial cells. These latter elements secrete the complex product, milk, by diffusion of the constituents from within the cell into the lumen of the alveolus, and, possibly, during strong sucking the portion of the cell which projects into the lumen may be broken off with its contained secretions; hence the gland is of the apocrine type.

The secreting alveoli pass over into excretory ducts lined by cuboidal or low columnar epithelium, which unite with other ducts to form larger ducts in which the epithelium is taller and cylindrical, finally uniting to form the main excretory or lactiferous duct, which is lined by stratified epithelium and which in turn is replaced by stratified squamous epithelium at some distance from its opening on the nipple. Each lactiferous duct is provided with a dilatation, the sinus lactiferous, in the area beneath the areola or pigmented circular area of skin surrounding the nipple.

The primordium of the mammary gland appears in the human embryo of 3 mm. as a paired thickening of the epidermis, the milk line, ex-
tending from the upper limb bud to the inguinal fold. Only a portion of each milk line in the costal region continues to thicken to form a pair of lens-shaped plates, which later become hemispherical or club shaped thickenings projecting into the underlying dermis. These are called mammary buds, and in other mammals a number of such buds may form, or they may develop at different points along the milk line. The mammary buds give rise to a number of cell columns from their lower surface, which project into the underlying connective tissue, and later become lactiferous ducts. In man there are 15 to 25 of these primary sprouts. These give rise to secondary sprouts or cell columns which are the primordia of the excretory ducts. By elongation and branchings the complex duct system of the gland is formed.

At birth the mammary gland is 3.5 to 9 mm. in diameter, and the lactiferous ducts have formed, with a few excretory duct branches. In males there is a regression of the gland, and only the rudimentary nipple remains, with its surrounding areola. In females there is a slow evolution
of the duct system throughout childhood to puberty, when the whole process is speeded up, the gland increases in size due to the deposition of fat, the nipple increases in size, and the duct system becomes complete.

There is no development of secretory portions until the advent of pregnancy. Then there is a rapid multiplication of the epithelium at the ends of the excretory ducts, and the secretory alveoli or lobules are formed. This is especially rapid during the first half of pregnancy, and is accompanied by a loss of fat from the gland to make room for the secreting elements. During the last half of pregnancy multiplication of the epithelial cells slows down, and a secretion is formed in the alveoli, which is colostrum. In the first few days after delivery the colostrum is replaced by milk, which continues to be secreted for the period of suckling of the child. (42, 2)

In other animals the development of the mammary gland at birth, before and at puberty varies somewhat from species to species. For
example, in the ferret there is no duct development even after puberty, while there may be even full lactation in some marsupitals and possibly the dog after oestrus. A full discussion of these differences is given by Turner (2) and may well account for a number of discrepancies in the findings of the various investigators to be discussed later.
THE HORMONAL CONTROL OF LACTATION

In the past half century a great many investigators have directed their efforts toward finding the explanation for the growth, development and functioning of the mammary gland. Much has been accomplished, but there is still much left to be explained. Many discrepancies have arisen between the findings of the various laboratories, all of which cannot be explained on the basis of specie differences, and there is much to be desired in the way of standardization of methods and materials in the various centers of experimentation. Practically all the experimental work has of necessity been done on laboratory animals, and the field of practical applications is still unlimited.

Prior to 1895 physiologists believed that the coordination between the developing embryo and the mammary glands was due to direct nervous connection between the uterus and mammary glands. As evidence of this was cited the commonly observed contraction of the uterus following stimulation of the nipples. (62, 2) In 1894 Mirinoff (43) observed that following the complete
severance of these nerves in pregnant animals the gland would continue to develop and would secrete milk after parturition. This was confirmed in 1896 by Goltz and Ewald (23) who completely removed the lumbar cord from a bitch. She subsequently conceived, and gave birth to a litter of puppies which she was able to suckle normally. Houth (57) (1893) observed that complete paraplegia below the level of the sixth dorsal vertebra did not inhibit lactation in man.

The nervous control was also disproven in another way. Hibbert (53) (1893) was able to transplant the mammary gland of a guinea pig into the skin of the ear. During a subsequent pregnancy the gland enlarged as usual, and lactated following parturition. Pfister (52) (1901) repeated the experiment on a rabbit.

On the other hand, it had been shown by Knauer (34) and Halban (24) (1900) that oophorectomy in young animals would cause regression of the mammary glands, and they would not attain normal pubertal size. That this was not due to the severance of nervous connections they demonstrated by grafting the ovaries to the peritoneum
or intramuscularly. When this was done successfully the mammary glands attained their normal pubertal growth.

Therefore it has been generally accepted as true that the source of stimulation to the mammary gland is hormonal, due to a "chemical messenger" (62) rather than nervous. This is true of the growth stimulus; as will be seen later the lactation stimulus is held by some to have a nervous factor in its control. Subsequent investigations have been directed toward finding the nature and origin of the hormones responsible for mammary hypertrophy and lactation.

Lane-Claypon and Starling (36) (1906) were the first to attempt by experimental means to find the hormones responsible for mammary growth and lactation. They injected filtered aqueous extracts of placenta, fetuses, uterine tissue and ovaries, as well as combinations of these into female rabbits. They did not castrate their animals, so the results they obtained were probably due to the rabbits own ovaries, and not the weak extracts they used, especially since their figures show only a duct development, similar
to that observed after reaching puberty. (13)

Frank and Unger (18) (1911) repeated the experiments of Lane-Claypon and Sterling, also with negative results. Other investigators in this period who used aqueous extracts failed to get conclusive results, at best only a slight duct growth. It has since been shown that the tissues they extracted do contain the oestrous producing hormone, but the amounts extracted in aqueous solutions are very small. This fact, together with the fact that they failed to recognize the necessity of removing the ovaries, made what slight results they achieved valueless, since it might easily have been a normal oestrous growth. (2).

Following the report in 1912 by Iscovesco (32) that lipoid extracts of the ovary, corpus luteum and placenta cause distinct changes in the female genital tract and mammary glands, this line of attack was taken up by several investigators. Fellner (21) (1913) obtained duct system growth in normal and castrate male and female guinea pigs and rabbits. Herrmann (29) (1913) (30) (1915) observed
growth of the mammary gland in castrate and normal female rabbits; Frank and Rosenbloom (19) (1915) slight growth in castrate rabbits and rats. It has since been shown that the success of these men was due to their successful extraction of the oestrus producing hormone. (2)

Since the effect of the ovaries on the mammary glands had already been observed by Knauer (34) and Halban (24) it is only natural that these organs should be subjected to considerable study as to a possible relationship to pregnancy development. The experiments just mentioned, with lipoid extracts of the ovaries was a start, but the real impetus to this line of research was given by Allen and Noisy (1) (1923) by the introduction of the rat test unit for the oestrus stimulating hormone of the ovaries, and the determination of the tissues in which this hormone is found in the greatest concentration. This hormone has been named by various investigators "oestrin" "theelin" and "menoformon".

Early in the investigations of the effects of theelin it was observed that one of its effects is on the mammary glands. From that
time to the present this effect has been studied by a great many men, only a few of whom will be mentioned.

Hartman, et al (23) (1926) produced duct system growth in the oppossum by injections of follicular and placental hormones (theelin).

DeJongh and Dingemanse (14) (1931) injecting 200 units of menoformon per day into male guinea pigs produced marked growth of the mammary glands, and if the dose were suddenly reduced to 2 units a day the glands secreted milk.

Turner, et al (66, 67, 63, 1930 & 1931) using castrated immature male and female rabbits and rats were able to produce only duct system growth (pubertal development) by the injection of the oestrogenic hormone, whether obtained from the ovary, placenta, amnionic fluid or urine of pregnancy. In 1932 they used crystalline theelin and theelol (69) and produced significant duct growth but no lobule formation in the mammary glands of male rabbits, castrated female rats and male mice. No difference was observed between the effects of theelin and theelol.
Bradbury (7) (1932) made similar findings in the mouse. He found that the sexually mature gland consisted only of galactophores (primary duct system) and that injections of theelin had no effect on this gland. A similar duct growth could be brought about in castrate immature males and females, however, by the injection of theelin.

From the above experiments it seems clear that the initial development of the mammary gland is under the influence of theelin. This hormone, produced by the ovary, stimulates the pubertal development of the duct system, which may continue to develop during each oestrus cycle. Theelin secreted by the placenta may cause the initial increase in the duct system during pregnancy. This hormone seems to be ineffective in stimulating lobule formation in most species, however. In the guinea pig apparently lobules may be formed by administering large doses of theelin, for secretion is obtained when the dosage is reduced. (14) In other animals a slight lobule may be noted at times. (2, 13) But this slight lobule formation does not begin to
compare with the rapid hyperplasia which occurs during the first half of pregnancy, and therefore an additional hormone has been sought which would stimulate pregnancy hyperplasia.

It is only natural that so prominent a structure as the corpus luteum should be subjected to some study. Starling (62,36) and Frank and Unger (18) used aqueous extracts of this gland, but as has been previously stated their extracts were too weak to have any effect. Iscovesco (32) and Fellner (21) were more successful with lipid extracts, but we have already mentioned that they extracted theelin from the gland, and not the corpus luteum hormone.

The discovery in 1911 by Ancel and Bouin (3) of the condition of pseudopregnancy in the rabbit gave the corpus luteum angle a fresh impetus. The rabbit does not normally ovulate until copulation occurs, hence corpora lutea are not found except in the pregnant condition. By mating does with vasectomized bucks they were able to induce ovulation and corpus luteum formation in the non-pregnant animal. They found that the corpus luteum persisted for about 15 days,
about half the duration of a normal pregnancy. During this time the mammary glands underwent rapid lobule hyperplasia, so they were convinced that the corpus luteum is responsible for the development of the mammary glands during the first half of pregnancy. They ascribed the development of the mammary glands during the latter half of pregnancy to the so-called "myometrial gland". However, Hammond (26) (1917) showed that this structure is not constant, being found in only an occasional rabbit, and not at all in other species. He also pointed out that the corpus luteum persists throughout normal pregnancy, and concluded that the development of the mammary gland during the latter half of pregnancy is due to the same factor which causes its development in the first half, namely the corpus luteum.

In 1930 Corner (13) by using a highly potent extract of corpus luteum, (progestin) was able to carry pregnant does to full term which had been deprived of their ovaries 18 hours after conception, a procedure which otherwise results in abortion. In these rabbits mammary
growth and lactation occurred normally. He reasoned that if the corpus luteum of pregnancy were responsible for mammary gland development, he should be able to produce similar development in spayed non-pregnant does by injections of progestin. He made this test, but could produce no changes in the gland.

However, these rabbits were deprived of oestrin, since they were spayed, and it had been pointed out by Hissau (31) (1929) that the corpus luteum does not exhibit its effects on the symphysis pubis and endometrium without the immediately previous action of oestrin. So Corner used the method of Jares (33) (1930) to subject the rabbit to the continued action of both oestrin and progestin, namely, inducing ovulation and new crops of corpora lutea at of a few days by intravenous injections of 10 c.c. of filtered urine of pregnant women. He found that continued action of progestin even when preceded by the action of oestrin does not induce proliferation or lactation in the mammary gland.

Turner and Frank (67) (1931) found that
injections of progestin in immature male and female castrate rabbits produce no changes in the mammary glands, even when preceded by injections of theelin. Realizing that during pregnancy a large amount of theelin is being secreted by the placenta, they attempted to duplicate this by injecting large doses of theelin in their rabbits simultaneously with their progestin injections. By this method they obtained a full development equal to that during pregnancy.

Bradbury (7) (1932) made similar findings in the mouse. He found that luteinization of the ovaries by means of injections of pregnant women's urine causes mammary hyperplasia, but not if the ovaries are absent.

Selye, et al (58) (1933) confirmed the above findings in the rat. They found that intense luteinization of the ovaries produced by injections of pregnancy urine causes mammary gland growth.

Nelson and Pfiffner, (45, 46) (1930, 1931) found marked hyperplasia in the glands of immature male and female guinea pigs and young male rabbits which were injected with only a
corpus luteum extract. Turner (2) has pointed out, however, that their extracts probably contained oestrin as well as progestin.

At this point it would seem that mammary gland growth in most animals is caused by the action of two hormones, oestrin initiating duct system growth, and oestrin plus progestin causing lobule formation. As we shall see later the corpus luteum problem is not nearly so easily settled as that.

So far we have purposely avoided the problem of secretory activity, for it is in connection with this function that the most important discoveries with regard to the hormonal control of lactation were made. Lane-Claypon and Starling (36) concluded that the substance which gives the growth stimulus to the mammary glands inhibits their secretory activity by direct action upon the secreting cells, for the reason that a cell cannot be both growing and secreting at the same time. This view was held by many of the subsequent investigators.

Evidence supporting this idea, aside from the clinical evidence that these early
investigators based their ideas upon has been put forth by DeJongh and Dingemanse (14) in their work with guinea pigs previously mentioned. Lactation was noted when the amount of oestrin injected was suddenly reduced, just as occurs at parturition following expulsion of the placenta. Also, Selye et al (58) noted lactation in rats following the removal of the ovaries which had undergone intense luteinization under the influence of pregnancy urine, and had been accompanied by mammary gland growth. However, lactation did not occur if the pituitary gland were absent, and that could mean only one thing, that the pituitary has some role in the hormonal control of lactation.

In 1924 Evans (15) had shown that injections of an alkaline extract of the anterior lobe of the hypophysis would cause persistence of pre-existing corpora lutea as well as causing intense luteinization of Graafian follicles without ovulation. Using the method of Evans, Parkes (51) in 1929 injected such an extract in pseudopregnant rabbits and was able to continue the luteal phase beyond the usual 15 day period.
In these animals he obtained a growth of the mammary glands equal to full term pregnancy, and therefore decided that the corpus luteum was responsible. But Corner (13) using the method of Jares (35), that is, pregnancy urine injections, could note no change in the mammary glands although luteinization of the ovaries was produced equally as well as by the anterior hypophysis extracts. He assumed that some other factor must be present in the anterior hypophysis extracts which was responsible for the mammary gland growth obtained by Parkes. He then injected spayed virgin rabbits with alkaline extracts of the anterior pituitary gland, and obtained both hyperplasia and secretion in the mammary glands. His rabbits were mature, but virginal, the mammary glands having reached the pubertal state before the injections.

Stricker and Grueter (64, 65) (1928 & 1929) had also been able to produce mammary hyperplasia and lactation in rabbits by the injection of an aqueous extract of the anterior hypophysis. They obtained their results first by injections in the latter part of pseudopreg-
nancy. Later they removed the ovaries on the tenth day of pseudopregnancy and were still successful, indicating that the ovaries were not responsible for their results. Still later they learned that it was not even necessary that the animal be pseudopregnant, but it was only necessary that the mammary gland be developed by previous pseudopregnancy or pregnancy. They were successful under these circumstances in producing lactation in rabbits, dogs, hogs, and cattle by their anterior pituitary extracts. They could not induce lactation in virgin rabbits.

Shortly after Corner (13) had published his work, Riddle (54) (1931) and his associates who were studying the physiology of reproduction in birds, found that some of the extracts of the anterior pituitary which they were injecting to determine their effect on the reproductive system of pigeons, also caused an enlargement of the crop glands. These are two dorso-lateral areas in the crop of pigeons and doves of both sexes which normally cannot be differentiated from the rest of the crop mucosa, but which undergo remarkable hypertrophy at the end of the brooding period,
and produce by secretion and desquamation of the mucosa cells a substance called crop milk. This is mixed with partially digested food in the crop and regurgitated to feed the young. This process is analogous to lactation in that it represents a phase of reproduction consequent to ovulation, occurring at a considerable time afterward, and at the time of a new phase of alimentation in the young.

Riddle (54) determined that this growth occurred after previous section of the nerve supply, so it could not be conditioned by nervous control. He was able to produce crop gland growth by injections of anterior pituitary extracts, but not by pregnant urine. He was unable to determine whether it was either of the two known hormones of the anterior pituitary (growth, sex maturity) which was responsible, or a third, unknown hormone. He suggests that the crop gland response might form a convenient means of standardization of the hormone responsible.

A year later Riddle (55) was able to state that the hormone responsible for the crop gland response is a separate hormone, which would
still produce this response when freed of the growth and sex maturity fractions. He gives the method of making such a separation, and proposes the name "prolactin" for the hormone. He found that male and female mature guinea pigs and mature female rabbits would also respond to this hormone by lactation; the males after previous treatment with theelin and progestin. Lactation began 2 to 3 days after beginning the treatment in rabbits, 3 to 5 days in guinea pigs. The term and quantity of secretion were highly variable. In all cases (pigeons, guinea pigs, rabbits) the gonad-stimulating principle and growth principle, when freed of prolactin, failed to give any lactation or crop gland response.

In a subsequent publication (56) (1933) Riddle gives very complete and extensive experimental data which shows that prolactin is a separate hormone; that it is capable of producing the crop gland response in doves and pigeons and the lactation response in guinea pigs, rabbits, rats, oppossum and monkeys; that the growth or gonad-stimulating hormones are incapable of doing this; that prolactin is effective in castrate and hypo-
physectomized animals. He also gives detailed directions for the preparation of prolactin and its assay, using the crop gland response. In a recent article (6) (1934) he has shown that the hormone prolactin is a protein substance, digested by trypsin.

All the investigators who have used prolactin or similar preparations of the anterior pituitary are agreed that it does stimulate lactation under the proper conditions. Here the agreement stops. Some men have held that it not only stimulates lactation, but it also promotes gland growth (lobule formation). There is also a difference of opinion as to whether oestrin only is sufficient to prepare the gland for the action of prolactin, or whether progesterin also is needed. We will first consider the problem of prolactin and gland growth.

This difference of opinion came up in the earliest investigations. It will be remembered that Corner (13) found both hyperplasia and secretion to result from prolactin injections in his rabbits, while Stricker and Grueter (64, 65) were unable to produce lactation in virgin animals,
but only if the mammary glands had been previously developed by pregnancy or pseudopregnancy.

Nelson (46) (1931) suggests that the ovarian factors (oestrin and progestin) are responsible for the early growth of the mammary glands, and that the profound growth during the latter part of pregnancy is controlled by the anterior pituitary.

Asdell (5) (1932) found that potent lactogenic extracts are without effect in immature rabbits. He produced full mammary development in ovarietomized rabbits which were just mature.

Catchpole et al (36) (1933) found that the mammary glands of rabbits respond to the lactation hormone by both duct and alveolar growth, and lactation.

Weichert (70) (1934) found that the ovarietomized rat does not respond to the lactogenic hormone, but when the ovaries are present, respond by both growth and lactation.

On the other hand, Riddle (56) (1933) states that "we have become fully convinced that prolactin has not in the least favored the growth and development of mammary tissue in the
individuals with which we have worked". (Guinea pigs and rabbits.)

The latter view is held by Turner and his associates. Garner and Turner (22) (1933) could produce no growth of the mammary glands by prolactin injections in young ovariectomized rabbits. Turner (2) cites unpublished data by Garner, in which they not only failed to get duct growth in immature glands, but also they failed to get lobule formation where ducts only were present. His explanation of the apparently positive results of others is a logical one. He thinks that in all cases where lactation is produced by injections of prolactin, lobules were already present, and the apparent hyperplasia is only a distention of the lobules by secretion. It has been shown that in some mature animals a few lobules may be present. This would explain the onset of lactation in such animals. In immature animals and males lobules would not be found, and in these no one has been able to produce lactation without previous treatment with ovarian hormones. Lyons, et al (37, 9, 39) Nelson et al (45, 46, 47, 48, 49, 50) Bradbury (7) Asdell (5) Evans (17).
Some such explanation as given by Turner is necessary, for certainly in the normal pregnant animal secretion and growth do not occur simultaneously, but rather in sequence. Nelson (50) has suggested that perhaps the anterior lobe hormone acting together with the ovarian hormones promotes growth, but lowering the oestrin level (removal of the placenta) allows the anterior lobe hormone to stimulate secretion. This would apparently be refuted by the normal development (but failure to lactate) of mammary glands in hypophysectomized pregnant animals. Selye et al. (59, 71)

In considering the preparation needed before the mammary gland can be stimulated to lactate by the action of prolactin, we find a considerable controversy over the role played by the corpus luteum.

Corner (13) thought that the corpus luteum is unnecessary, since he used spayed virgin rabbits in which he thinks it highly unlikely that corpora lutea ever existed. Stricker and Grueter (64, 65) thought previous sensitization by the corpus luteum is necessary, since they could not
produce lactation in virginal rabbits. De Jongh and Dingsemanse (14) produced lactation by injections of oestrin in male guinea pigs, so evidently progestin is unnecessary in that animal. Nelson (49) did the same, except that he followed the oestrin injections with prolactin in order to obtain lactation, instead of reducing the dosage of oestrin. It would therefore seem that the corpus luteum is not necessary in the guinea pig. Catchpole and Lyons (8) found that no previous corpora lutea are necessary in rabbits, but that lutein sensitization makes them more reactive to prolactin. They suggest that the ovaries which do not show evidences of corpus luteum formation do contain theca lutein cells which normally go to make up the corpus luteum, and think that these cells may be a factor in preparing the gland. Asdell (5) found that the corpus luteum is not necessary for the lactation response in the rabbit and state that a goat which had never been in heat was made to lactate by prolactin injections.

On the other hand, Bradbury (7) finds that in the mouse the lactation hormone is not effective unless alveoli formation has been produced by
luteinization of the ovaries by means of pregnancy urine. Also, Evans and Simpson (16) find that in spayed mature virgin rats it is impossible to produce mammary gland growth and secretion by means of prolactin injections, even if progestin also is given. Weichert et al (70) confirmed these findings, but were able to produce gland growth in the absence of the ovaries by properly proportioned injections of ovarian hormones (oestrin and progestin). They point out that this is a distinct species difference. That there is a distinct species difference in the necessity for the previous sensitization by progestin is also pointed out by Nelson (50) and Selye et al (71).

It would seem therefore, that prolactin is the hormone secreted by the anterior hypophysis which initiates lactation. It probably does not promote lobule formation. It is capable of acting on a gland only if the gland has had lobules previously formed. There is a species difference in the matter of lobule formation. Some animals may form lobules under the influence of theelin alone, others require the action of progestin also. Probably both hormones play a part in normal pregnancy.
We have not as yet considered why lactation occurs only at the termination of pregnancy. It seems to be quite generally accepted that it is the antagonism of theelin that prevents lactation. Nelson (50) as well as Smith and Smith (61) were able to inhibit lactation by injections of theelin. Nelson(50) has shown also that it is the theelin secreted by the placentas which inhibits lactation. He did this by castrating pregnant guinea pigs and having them go to full term, only lactating after parturition. Since mammary gland growth occurred normally there must have been a source of theelin. Removal of the pregnant uterus did not cause lactation, it the ovaries were left, but removal of both resulted in lactation. Removal of the pregnant horn of the uterus and the ovaries leaving the sterile horn resulted in lactation, therefore some factor aside from the uterus was responsible. Removal of the foetuses and ovaries, leaving the placenta did not result in lactation as long as the placenta was retained. Therefore the placenta must elaborate the theelin which inhibits lactation.

That retention of the placenta will in-
hibit lactation has been observed a number of times. Halban (24) Smith and Smith (61) Stimson (63) Transplanted placental tissue will do the same, as long as the grafts are active. Franklin (20)

So then, lactation occurs at the termination of pregnancy because the oestrin or theelin content of the blood falls, due to the loss of a source of this hormone, the placenta. But how does the presence of oestrin inhibit mammary activity? Nelson (50) believes it is by an action on the anterior pituitary, preventing the release of prolactin. When the inhibitory factor is removed, the anterior pituitary secretes prolactin. This is shown by the fact that simultaneous injections of oestrin and prolactin result in lactation in a properly prepared animal. On the other hand, he thinks that large amounts of oestrin may act directly on the mammary gland itself, for if a large amount of oestrin is injected together with a corresponding dose of prolactin, no lactation results. We suggest that this problem could be clarified considerably, as well as the problem of the role of prolactin on mammary development during pregnancy, by some means of
determining the amount of prolactin in the blood of a pregnant animal. The fact that mammary development may continue in an hypophysectomized pregnant animal does not necessarily preclude the possibility of the pituitary being responsible in part, for there are fetal hypophyses which might secrete prolactin.

Another puzzling finding is that of Selye et al (12, 71) who state that pregnant, hypophysectomized rats and mice secrete milk for a few hours after parturition. We would be inclined to attribute this to fetal hypophyseal hormones circulating in the blood of the mother, but they also find (71) that distention of the uterus with paraffin prevents this secretion. They postulate a nervous influence on the hypophysis by the pregnant (or distended) uterus, inhibiting the release of prolactin. They ascribe the secretion of milk for a few hours after parturition in their hypophysectomized animals to a functional stimulus to the mammary gland by the uterus.

Another controversial matter is that of a possible nervous influence on the pituitary by the act of suckling. It would seem that the exper-
iments of Mirinoff (43), Ewald (23), Routh (57) Ribbert (53) and Pfister (52) previously mentioned should be enough to disprove any possibility of a nervous control.

Although Hammond (27) found that when the teats of certain mammary glands of a rabbit were occluded to prevent the young from suckling the corresponding glands would undergo involution, even when adjoining glands were in an active state of lactation; and Nelson (50) found exactly the same to be true, Selye et al (60, 71) found exactly the opposite. They tied the galactophores of a gland, and it remained filled under the stimulus of suckling. Excising the nipple of one gland and allowing the opposit gland to be suckled, they found that the gland which was not suckled due to the absence of a nipple remained in active lactation. They take this to mean that the act of suckling by means of a nervous stimulus to the hypophysis causes the release of prolactin, which continues to stimulate lactation in the mammary gland that is not being suckled. Evidently more work needs to be done to clarify this point. It seems that it would be easy to
settle this question by seeing how long a gland could be kept secreting under the influence of prolactin injections but without being drained. for the whole matter hinges about the question as to whether mere distention of the gland by retained secretions will result in its involution, or whether the absence of prolactin is necessary.

But that experiment cannot be satisfactorily carried out because of another puzzling finding, namely that continued injections of prolactin are ineffective in continuing lactation, even when increasingly large amounts are injected. Riddle (56) states "it seems, though it is not proved, that initial light dosage with prolactin develops in castrate female guinea pigs a mammary state in which the lactation response is unusually difficult to obtain later either increased and adequate amounts of prolactin."

Nelson (50) "We have never been able to maintain lactation induced by pituitary extracts indefinitely even when increasing amounts were administered." Asdell (5) was able to prevent the normal decline in milk production in goats for only a short time by means of prolactin injections.
Evans (17) made similar observations with goats, but found that after a lapse of 40 days was again able to increase the yield.

Evidently prolactin injections induce in the mammary gland a refractory state, which is extremely difficult to explain, inasmuch as the hypophysis has been shown to be necessary not only for the initiation of lactation but also for its continuation. Collip et al (12) Selye et al (59, 71)

A phase of the lactation problem which has hardly been touched upon is the relationship of the pancreas to the mammary glands. Markowitz et al (40, 41) report three cases in which depancreatized bitches failed to show mammary growth in pregnancy or lactation following parturition, and one case in which a depancreatized bitch suckled two pups for a month following parturition. Chaikoff et al (10, 11) report that five out of six depancreatized bitches kept alive by special diet and insulin failed to lactate when given prolactin in much larger amounts than necessary to produce lactation in normal animals. Also one case in which a depancreatized bitch showed neither
growth nor secretory activity in the mammary glands when she became pregnant 3 months after pancreatectomy. These experiments seem to point to the necessity of the pancreas for lactation, but no further work has been done to prove or disprove this finding.

So far, only a few practical applications have been made with the lactation stimulating hormone. Catchpole et al (9) has produced lactation in virgin heifers, Evans (17) has done the same with virgin goats. Asdell (5) was able to prevent the normal decline of milk production in goats for a short time.

The only work that has been done on human subjects was by Kurzoox et al (35) A series of 37 maternity cases, most of which showed an inadequate milk supply on the 5th or 6th day after parturition, and in the clinical opinion of the obstetrical staff would not improve in their supply, were given 50 to 200 units of prolactin made as described by Riddle (56) in single or repeated doses. Most of the cases showed a gain of from 50 to 400 gm. of milk per day. The failures were easily accounted for on the
basis of insufficient breast tissue; injections given too soon following delivery; or subjects which were already producing the maximum amount. The provisional dosage as shown by their findings is 150 units followed by 100 units in from 12 to 24 hours.
CONCLUSIONS

The mammary gland develops its duct system under the influence of the female sex hormone, theelin or oestrin. A part of this development may be accomplished before or during puberty. In some animals slight lobule formation may occur also as the result of oestrin stimulation at or following puberty. The completion of the duct system, and the lobule formation during pregnancy is due to increased amounts of oestrin secreted by the placenta, and also in some animals supplemented by the secretion of progestin from the corpus luteum. Prolactin, the hormone secreted by the anterior pituitary which is necessary for the initiation and continuation of lactation, is prevented from forming or prevented from acting by the oestrin, but on removing the placenta the oestrin level of the blood falls, and lactation occurs, to continue for a variable length of time if the breast is emptied, but stops if it is not, either because the distention causes involution or because the lack of stimulation of the nipples fails to stimulate reflexly the release of prolactin.
Injections of prolactin cause a refractory state to be created in the gland against the action of prolactin.

The pancreas may be necessary for the development and functioning of the mammary gland.
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