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CHAPTER 30

LACTATIONAL PHYSIOLOGY

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THE PROCESS of lactation has been the subject of much research and experimental investigation, particularly in animals. Interesting advances are being made at the present time and it is the aim here to deal in outline with some of these aspects which may have bearing on clinical medicine.

DEVELOPMENT OF THE MAMMARY PARENCHYMA

Experimental development with ovarian hormones

It has long been apparent that the growth of the mammary gland is under endocrine control, neural influences having no effect so far as is known. Most decisive in establishing this conception were experiments involving transplantation, with subsequent growth, of the mammary rudiment (Stricker, 1929). Researches carried out during the last two decades have established the role of the ovarian hormones, oestrogen and progesterone, as agents responsible for the growth of the mammary ducts and lobule-alveolar tissue. More recent ideas about the additional involvement of the anterior pituitary gland, in a role other than as an exciter of the secretion of the ovarian hormones, will be considered in a later section. These classical researches, which fall into two main categories, (a) comparative studies of normal mammary development in various species in relation to different types of oestrous cycle and to pseudo-pregnancy and pregnancy, and (b) direct experimental analysis of the endocrine mechanisms concerned, have been more or less recently reviewed by Petersen (1944, 1948), Folley (1945, 1947a), Richardson (1947), Folley and Malpress (1948a) and Mayer and Klein (1948).

Farm animals

More recent developments of these earlier studies, directed towards elucidation of the relative effectiveness of oestrogen used alone and in combination with progesterone in promoting experimental mammary development in various species, have assumed practical importance in relation to the artificial induction of udder growth and lactation in farm animals and may also prove of significance to the clinician, since clearly the first requisite for successful lactation is the existence of a sufficiency of histologically normal and functionally potent alveolar tissue. Thus, Engel (1947) has pointed out that many cases of hypogalactia in women are probably due to lack of mammary alveolar development, and incidentally has rightly emphasized the necessity, in morphological studies of the mamma, of sectioning the whole gland in order to get a valid picture of the mammary architecture.

The above-mentioned classical work established that in certain species, notably the guinea-pig, oestrogen alone is capable of causing considerable alveolar development in addition to the duct growth which is so characteristic a response to

oestrogen in all forms hitherto investigated, and since 1940 it has become abundantly apparent that the same applies to ruminants of economic importance, such as the cow, goat and sheep. Since the artificial induction of udder growth, followed by lactation, by treatment with synthetic oestrogens was first described in 1940 in the goat (Folley, Scott Watson and Bottomley, 1940), numerous studies on goats and particularly cows, have followed (*see* Malpress, 1947; Folley and Malpress, 1948a and b; and Petersen, 1948) in which the abundant yields of milk produced by artificially developed udders, supported by admittedly rather inadequate morphological studies, testify that the oestrogen treatment had caused considerable alveolar development. More recent confirmation has come from work on the sheep (Peeters and Massart, 1947) and from further work on the cow (Hohlweg and Spierling, 1947; Trautmann and Fauvet, 1947; Marshall and his colleagues, 1948; Peeters, Massart, Coussens and Vandeplassche, 1949).

Intact animals were used almost exclusively in these experiments, thus admitting of the possibility that progesterone of ovarian origin might have contributed to the responses, but in addition to the one or two cases quoted by Folley (1945, 1947a) in which this possibility was excluded because of positive responses obtained in the absence of ovaries, recent and much more extensive unpublished studies, carried out on goats ovariectomized soon after birth, and involving histological evaluation of udders fixed by perfusion and sectioned *in toto*, show beyond doubt that in this species oestrogen alone will evoke extensive mammary alveolar development sufficient to give milk yields not inconsiderable in relation to those expected after pregnancy and parturition (Cowie, Folley and Richardson, 1948).

Nevertheless, judged by the ultimate test of functional efficiency, there is no doubt from the published results that even the best artificially developed udders are incapable of giving more than about half the yields which would have been given by the same animals had they come into lactation in the normal way, and histological studies indicate that this may be correlated with some degree of morphological abnormality of the alveolar tissue. Mixner and Turner (1943) report that, in the goat, oestrogen alone developed udders often characterized by abnormally large, even cystic, alveoli in which papillomatous outgrowths of the epithelium were frequently seen. The importance of progesterone in normal mammary development in the goat and probably in other ruminants is suggested by the finding that prolonged treatment with oestrogen and progesterone produced alveolar tissue of a more nearly normal type. This preliminary indication has been supported by more extensive comparisons (utilizing more adequate histological methods) at present in progress of the structural features and functional potentialities of udders developed in goats, spayed soon after birth, by treatment with oestrogen on the one hand and oestrogen and progesterone on the other, for periods equal to one half of or to the whole duration of pregnancy (Cowie, Folley and Richardson, 1948). The daily dose of progesterone used in these studies has been chosen on the basis of available evidence of the probable progesterone production by the corpus luteum of pregnancy and, in fixing the gravimetric ratio of the two hormones, the indications of the requirements for optimal alveolar growth provided by American work on the mouse and rabbit (*see* Folley and Malpress, 1948a) have been utilized. The results at the time of writing indicate that the rate of development of the mammary parenchyma under the influence of the combined hormones is slower, but, if sufficient time is given, the resulting alveolar

tissue is comparable in amount to that produced more quickly by oestrogen alone and, moreover, is often more nearly normal histologically and more competent functionally.

Human beings

For obvious reasons, no experimental analysis has been made of the relative roles of oestrogen and progesterone in mammary development in man, though MacBryde (1939) has shown that breast enlargement (if necessary unilateral) can be brought about by percutaneous inunction of natural oestrogens. Such techniques do not, however, appear to have been much utilized clinically for correcting mammary under-development.

Rhesus monkey

Work on the rhesus monkey, more closely related to man than the ruminants considered above, may be of interest as indicating probable relationships applicable to man. Earlier work, reviewed by Folley (1945, 1947a) and Speert (1948), indicated that oestrogen alone would cause development of alveolar tissue particularly in females, but agreement as to the extent and kind of the mammary growth response to oestrogen alone was by no means unanimous, perhaps largely because of lack of sufficient experimental material. Recently, however, an important paper by Speert (1948) has appeared, which, based on much more extensive experimental material than had hitherto been available to previous workers, has done much to clarify the situation. He has shown, more convincingly than earlier workers, that oestrogen alone will evoke complete mammary development in ovariectomized females, so that the monkey can undoubtedly be included among forms in which oestrogen will evoke growth of the mammary lobule-alveolar tissue as well as of the duct system. This study also includes welcome observations on the normal development of the mammary gland in monkeys of both sexes, as well as extending to the monkey previous observations (*see* Folley, 1945, 1947a) on the mammogenic activity of androgens and desoxycorticosterone in other species. Finally, Speert has shown that, in the monkey, as was already known for the rat and mouse (*see* Folley, 1947a), progesterone alone will stimulate growth of the mammary parenchyma, provided large enough doses are given. Here, however, the possible participation of extra-ovarian oestrogen, perhaps from the adrenal cortex, must not be overlooked (in this connexion *see* Fekete, Woolley and Little, 1941).

Conclusions from recent studies

In final comment on these recent studies on the relative roles of oestrogen and progesterone in mammary growth, it may be recalled that Folley (1940) pointed out that experiments in which oestrogen alone was found to grow mammary alveolar tissues in the absence of the ovaries are not conclusive for the point at issue, since progesterone is known to be produced in the adrenal cortex and could thus participate in the response. It is worthy of note that this suggestion, which was further elaborated by Folley and Malpress (1948a) in a discussion of the wide differences in mammary growth and functional responses to the same oestrogen treatment which are so striking and constant a feature of experiments on the artificial induction of lactation in heifers (but *see* Peeters, Massart, Coussens and Vandeplassche, 1949), has since been accepted by Trentin and Turner (1948) who

point out that oestrogen is known to stimulate adrenal cortex activity, and they are inclined to ascribe mammary alveolar growth responses to oestrogen, observed by them, to mammogenic steroids of adrenal origin.

The anterior pituitary gland and mammary growth

One of the most interesting theories yet put forward in the lactational field is the suggestion that the mammogenic activity of ovarian hormones is mediated by the anterior pituitary gland—the "mammogen" theory of Turner. The evidence in favour of this theory has been summarized in research bulletins by Gomez and Turner (1937), Lewis and Turner (1939) and Mixner and Turner (1943). It was originally postulated that oestrogen evokes the secretion by the anterior pituitary gland of a hormone, Mammogen I, which causes growth of the mammary duct system. Later the existence of a second pituitary mammogen, Mammogen II, was postulated, responsible for causing lobule-alveolar growth, the secretion of which was held to be due to the action of progesterone on the anterior lobe. More recently, however, Trentin and Turner (1948) seem inclined to doubt the existence of two distinct mammogenic hormones responsible for the growth of mammary duct and alveolar tissues respectively, and they appear to favour the view that one mammogen excites the growth of both types of tissue.

The main evidence which has been put forward in favour of this theory may be summarized briefly. The mammogen hypothesis first took inception from the failure experimentally to evoke mammary growth in a variety of completely hypophysectomized laboratory animals by treatment with ovarian hormones. Later, it was shown that repeated implants, into hypophysectomized animals, of pituitary glands from oestrogen-treated donors caused mammary growth while implants from untreated donors were ineffective. Finally, it has been claimed that extracts of anterior pituitary gland taken from pregnant cattle exhibit mammogenic activity while extracts from glands of non-pregnant cattle are relatively ineffective.

The mammogen theory, however, is still a matter of controversy. A number of experiments in which mammary growth has been evoked in hypophysectomized animals by steroids have been reported (*see* reviews by Folley, 1947a; Folley and Malpress, 1948a; and Petersen, 1948), and no grounds for discounting them have been advanced. Moreover, experiments in which localized mammary growth has been obtained in response to oestrogen inuncted over certain mammary rudiments, while neighbouring untreated rudiments have either responded to a lesser degree or not at all, testify to a direct action of oestrogen on the mammary gland. Mixner and Turner (1943), however, in rebuttal of this evidence, have attempted an explanation in terms of the mammogen theory. They suggested that the locally applied oestrogen might cause hyperaemia in the mammary stroma, thus resulting in a locally increased supply of already circulating mammogen.

In assessing the present position it seems fair to say that the mammogen theory must for the present remain largely an interesting and perhaps fruitful speculation, though the position would of course be transformed if the postulated mammogenic hormone or hormones could be isolated in pure form as have at least five other anterior pituitary hormones. Nevertheless, the work of a number of investigators not only in Turner's laboratory (for example Cowie and Folley, 1947) leaves little room for doubt that anterior pituitary extracts contain some factor or combination of factors, not necessarily a specific mammogen, which exerts a direct

growth-promoting action on the mammary tissues. It seems probable that this pituitary principle, which may be the lactogenic hormone, prolactin, normally acts synergistically with the ovarian hormones or else, perhaps, it sensitizes the mammary tissues to their growth-promoting action. Various possibilities along these lines have been discussed by Folley and Malpress (1948a).

Role of thyroid gland and adrenal cortex

The thyroid gland is not essential for mammary development (*see* reviews by Petersen, 1944, 1948; and Folley, 1947a) but recent work (Smithcors and Leonard, 1942; Johnston and Smithcors, 1948) indicates that it exerts an influence on the response of the mammary parenchyma to sex steroids. Thus the type of mammary growth promoted in the rat by oestradiol is changed by thyroidectomy; in the absence of the thyroid gland the response of the duct system to oestradiol becomes less prominent and the formation of lobule-alveolar tissue more marked. Chamorro (1947, 1948) has reported that in the intact female rat, thyroidectomy or treatment with anti-thyroid substances leads to mammary alveolar hyperplasia which may become cystic. Here an effect of the thyroid either on the metabolism of, or on the mammary response to, oestrogen may be involved. Further work may serve to clarify the position in this, until now, hardly explored field.

Though at least one adrenal cortical steroid, 11-desoxycorticosterone, is known to exert mammogenic effects, there is as yet no evidence that the adrenal cortex plays any considerable role in normal mammary development, though regressive changes in the mammary structure have been reported following adrenalectomy (Cowie and Folley, 1947; Trentin and Turner, 1948). These regressive changes seem at the best to be slight—indeed, none were observed by Chamorro (1946)—so that it seems doubtful whether the adrenal cortex plays a significant role in normal mammary growth. This conclusion is supported by Jacobsohn (1949). Moreover Cowie and Folley (1947) could find no decrease in the mammogenic effectiveness of anterior pituitary extracts in adrenalectomized rats such as would support the possibility that any considerable proportion of the mammogenic action of the pituitary could be ascribed to the action of adrenocorticotrophin.

Researches on these two aspects, in which the mammary changes under study are expected to be small, suffer from lack of objective and quantitative morphological criteria. In this connexion attention may be directed to an attempt by Cowie and Folley (1947) to develop a semi-quantitative method of assay of mammary growth changes, susceptible of statistical analysis, which may be of use to investigators in this field; already it has been found useful by Jacobsohn (1948) in a recent study of the mammogenic effect of the anterior lobe of the pituitary gland.

LACTATION

Initiation of milk secretion (lactogenesis)

The historic discovery by Stricker and Grueter (1928) of the anterior pituitary lactogenic hormone, prolactin, and its subsequent isolation as a pure protein (for account *see* Voss, 1941; Folley, 1945; Li and Evans, 1948) gave a fresh impetus to attempts to explain the initiation of copious milk secretion at parturition, long a subject of speculation. The most recent theory of the mechanism underlying this process has been put forward in 1942 by Meites and Turner who have recently published additional experimental evidence in support (Meites and Turner, 1948a).

This theory, founded on the conception of prolactin as the specific lactogenic hormone, is based on the view that lactation is initiated as a result of an outpouring of this hormone by the anterior pituitary gland evoked by the action of oestrogen, the body levels of which are known to be high in the later stages of pregnancy. These workers have shown in various species that oestrogen, even in huge doses, always increases, never decreases, the prolactin content of the pituitary, an effect which can be suppressed by simultaneous administration of progesterone, and they have interpreted these results as showing that it is progesterone which prevents the initiation of lactation during pregnancy. At parturition the corpora lutea of pregnancy cease to function and the body level of progesterone is thought to fall before that of oestrogen, thus allowing the latter to evoke the secretion of prolactin by the anterior pituitary gland. It is worth noting that this theory is diametrically opposed to earlier theories, such as that of Nelson (1936), which were based on the concept of oestrogen as the factor preventing lactation during pregnancy, since it casts oestrogen in the role of a stimulator rather than of an inhibitor of lactation.

Folley and Malpress (1948b) have advanced various criticisms of the theory of Meites and Turner which, they feel, hamper its unqualified acceptance. The most serious criticisms can be briefly summarized as follows: (1) the theory assumes that lactogenesis is due to the action of a single hormone, prolactin, a view which is open to doubt; (2) an increased pituitary prolactin content does not necessarily mean increased output—it might result from an inhibition of release; and (3) the method used by Meites and Turner of assaying the prolactin content of the pituitary glands of small animals is open to objection. Though additional experiments covering some of the disputed points are reported in the more recent communication (Meites and Turner, 1948a), it appears that even now all the arguments of Folley and Malpress (1948b) have not been disposed of to an extent which will allow unqualified acceptance of what is nevertheless an interesting and perhaps the most successful attempt hitherto made to explain the hormonal mechanism responsible for the initiation of lactation at parturition. In particular, the evidence that the increase in pituitary prolactin content caused by oestrogen is accompanied by an increase in blood prolactin, which if proved would do much to dispose of the second of the above-mentioned points, can still hardly be considered as convincing.

The possibility that a neuro-hormonal mechanism involving the suckling stimulus, rather than a purely endocrine mechanism, must also be considered in relation to the initiation of lactation is implicit in many of the experiments of Meites and Turner (1948a) and was explicitly stated by Petersen (1944, 1948).

Stimulation of established lactation (galactopoiesis)

Anterior pituitary hormones

The discovery and subsequent isolation of prolactin led to hopes that this anterior pituitary hormone might prove to be useful in the treatment of hypogalactia in the parturient woman. Unfortunately such hopes have hardly been realized, clinical results with purified prolactin preparations having been rather variable and, on the whole, disappointing (*see* Riddle, 1940; Voss, 1941, for review), so that prolactin has tended to fall into disuse as far as the clinician is concerned.

The probable reason for this has become clear as the result of a series of investigations (*see* summaries by Folley and Young, 1947 and Young, 1947) on the galactopoietic action of anterior pituitary extracts in lactating cows. These investigations show that, per unit of prolactin, crude extracts of ox anterior pituitary gland are much more effective than is purified prolactin in stimulating established lactation. Moreover, a study of the galactopoietic potencies of a series of anterior pituitary extracts in relation to their other biological properties revealed little relationship between galactopoietic potency and prolactin content, though there was evidence of a much closer parallelism between the effects of these extracts on milk yield and their action on certain phases of carbohydrate metabolism. These results, which must not be interpreted as necessarily minimizing the importance of prolactin in galactopoiesis, were taken as pointing to the existence of a complex of anterior pituitary hormones responsible for the galactopoietic properties of anterior pituitary extracts, a complex of which prolactin is, as far as present knowledge goes, almost certainly a member, though the indications are that it does not possess outstanding galactopoietic properties by itself. Some of the earlier experiments of Folley and Young pointed to the possible importance of adrenocorticotrophin as a member of the anterior pituitary galactopoietic complex, and subsequent experiments (Folley, Roy and Young, 1947) have indicated that this hormone may indeed exhibit galactopoietic properties under appropriate circumstances, though this needs confirmation. This work, however, gave no reason for the belief that the galactopoietic effects of anterior pituitary extracts could be accounted for solely in terms of their contents of prolactin and adrenocorticotrophin, so that it seems likely that other components of the complex remain to be identified. Purified anterior pituitary growth hormone has recently been shown to exhibit galactopoietic effects in cows (Cotes and his colleagues, 1949).

The important point for the clinician interested in the endocrine treatment of hypogalactia is that, as Folley and Young (1941) have pointed out, prolactin content (as measured by the pigeon crop-gland assay) is not necessarily an indication of the galactopoietic potency of an anterior pituitary extract except perhaps in cases, if such exist, in which a specific deficiency in prolactin output by the anterior lobe is the limiting factor, so that anterior pituitary extracts intended for clinical use should be assayed for galactopoietic potency in mammals.

Other possible causes of hypogalactia may be deficiency of mammary alveolar development, as indicated by the studies of Engel (1947), or possibly a breakdown at some point of the neuro-endocrine mechanism now believed to govern the discharge of milk from the mammary gland. This may help to explain the otherwise rather puzzling failure of Robinson (1947) to elicit improvement in cases of hypogalactia with unfractionated extracts of ox anterior pituitary of the type which uniformly has given good responses in lactating cows.

Thyroid secretion

A relation between the thyroid secretion and mammary gland function was indicated long ago by Hertoghe (1896), who reported a temporary stimulation of milk yield in one cow following the administration of dried thyroid gland. More recent work on the effects of thyroidectomy (reviewed by Folley, 1945; Petersen, 1948), though giving a less clear picture than might be desired, indicated that the

function of the mammary gland depends to some extent on an optimal level of thyroid secretion, a conclusion which has been more positively emphasized by experiments on the administration of thyroid-active preparations to lactating animals. Experiments of this latter type on the cow and goat have uniformly shown that quite considerable increases in milk yield, often accompanied by increases in the content of milk solids, particularly the fat, can be achieved by feeding dried thyroid gland or by injection of thyroxin (*see* reviews by Folley, 1945; Reineke, 1946; Young, 1947). These galactopoietic effects are temporary and subside soon after the termination of the course of treatment, but are of sufficient magnitude to warrant consideration of the use of thyroid-active preparations in practice for increasing the milk yield of cattle over limited portions of the lactation period, particularly in the winter months.

The discovery made some ten years ago that iodination of certain proteins, notably casein, yields under suitable conditions iodoproteins possessing thyroid activity which is evinced on oral administration, and the fact that iodocasein can be fairly cheaply manufactured in almost unlimited quantities, has led to numerous experiments, some on a considerable scale, of the use of iodocasein for the purpose just mentioned. These experiments, which have been reviewed by Reineke (1946) and Young (1947), show that the expected galactopoietic effects can be obtained by incorporation of iodocasein in the rations of lactating cows, and though cows receiving doses capable of giving maximal increases in milk yield tend to exhibit symptoms of hypermetabolism, notably losses in body-weight, such undesirable side-effects are negligible with smaller doses, still capable of evoking worth-while galactopoietic effects, provided enough extra food is given to compensate not only for the increased milk production but also to offset the tendency to lose body-weight.

Iodocasein has been preferred to thyroxin mainly because of the high cost of the latter and the belief that its activity by mouth is relatively low, and thus no experiments on the galactopoietic effects in cows of orally administered thyroxin had been carried out in supplementation of the striking results obtained in earlier studies on this hormone given parenterally. Robinson (1947) has, however, reported positive responses in hypogalactia in women who have been given small doses of thyroxin by mouth.

However, the recent development of new methods of synthesis of thyroxin which hold out promise that synthetic thyroxin may eventually become available in quantity at a cost per unit of biological activity which may compete with that of iodocasein, has prompted an investigation of the galactopoietic response to L-thyroxin, given by mouth, in lactating cows (Bailey, Bartlett and Folley, 1949). These workers have shown that a milk yield increase of the same order as that evoked by feeding 15–20 grammes of iodocasein daily (a dose which has been found to be optimal in practice) may be obtained by the daily feeding of approximately 70 milligrams of *l*-thyroxin. Pure thyroxin possesses a number of important advantages over iodocasein for the purpose we are considering. The more important of these are briefly enumerated by Bailey, Bartlett and Folley (1949), and it suffices here to quote one of them, namely, the fact that standardization by biological assay, a very troublesome and uncertain procedure essential with iodocasein preparations, is not necessary with thyroxin since it is a crystalline chemical, the purity of which can be checked by standard chemical procedures. This work

appears to open up the possibility that synthetic thyroxin may replace iodocasein as a galactopoietic agent for use with dairy cattle, and further and more extensive clinical trials of its use *per os* as a treatment for hypogalactia would seem to be worth while.

Effects of oestrogen on lactation

Earlier work on laboratory animals had indicated that oestrogens exert an inhibitory effect on lactation (*see* reviews by Petersen, 1944; Folley, 1945; Folley and Malpress, 1948b), and these experimental indications led to numerous clinical studies of the use of oestrogens for inhibiting lactation in the puerperium (*see* review by Barnes, 1947). Not all clinicians have agreed that the undoubted benefits of oestrogen administration in cases in which it is desired to prevent or terminate lactation are due to a true inhibitory effect of the hormone. Thus Abarbanel and Goodfriend (1940) have suggested that oestrogen does not inhibit lactation if suckling is continued, and that the beneficial effects of the hormone, generally attested by clinicians, may be mainly ascribed to prevention of painful engorgement of the breast. There is thus some confusion in the clinical literature as to whether the effect of oestrogen on the lactating breast is limited to the relief of congestion or whether there is an additional inhibitory effect on milk secretion; further clarification is thus desirable. Moreover, some authors, notably Fauvet (1943) and Meites and Turner (1942), have questioned the reality of the lactation-inhibitory effects of oestrogen observed in small animals, though as Folley (1947b) has pointed out, some of these objections vanish when consideration is given to results obtained in farm animals.

Some authors (for example Barsantini and Masson, 1947) have claimed that oestrogen inhibits lactation only when the ovaries are present, though the true situation seems to be that absence of the ovaries reduces the effect which can still be evoked with high enough doses (Folley and Kon, 1937; Walker and Matthews, 1949). These, however, may be unphysiological, even toxic, as suggested by Fauvet (1943) and more recently by Walker and Matthews (1949) and in any event the contribution which anorexia, due to the oestrogen, makes to the lactational inhibition is worthy of investigation.

The fact that inhibition can be induced by more nearly physiological doses of oestrogen in the presence of the ovaries than in their absence (for example, *see* Barsantini and Masson, 1947), that is, at physiological oestrogen levels there appears to be mediation by the ovaries, suggests a role for progesterone in the inhibitory phenomenon, despite the fact that relatively huge doses of progesterone (15 milligrams daily in the rat) have no effect on lactation (Folley, 1942). In accord with this indication it has recently emerged that in the spayed rat, oestrogen and progesterone in combination effect a marked inhibition of lactation (Fauvet, 1941; Barsantini, Masson and Selye, 1946; Masson, 1948; Walker and Matthews, 1949) while Romani and Recht (1948) have found combinations of oestrogen and progesterone very effective for inhibition of lactation in women.

Folley and Kon (1937), considering the effects of various steroids on the mammary gland, suggested that mammogenic activity goes hand in hand with ability to inhibit lactation. This relationship has since proved not to be absolute in so far as progesterone alone does not inhibit lactation but does promote mammary growth. However, these recent results on the lactation-inhibiting effect of oestrogen-

progesterone combinations do lend support to the general concept, because a similar situation holds for experimental mammary growth, which in most species studied is more effectively evoked by combinations of both hormones than by either separately.

No discussion of the effects of oestrogen on lactation is complete without some mention of the lactogenic and galactopoietic effects of oestrogen. These aspects have been reviewed by Folley (1945), Malpress (1947) and Folley and Malpress (1948b). Though earlier workers had observed mammary growth followed by secretion in small animals given prolonged oestrogen treatment—this was particularly noticed in the guinea-pig in which glands grown by oestrogen secrete milk when the oestrogen dosage is lowered or remitted—the first unequivocal demonstration in large animals was reported by Folley, Scott Watson and Bottomley (1940), who, in experiments on the induction of artificial udder growth in goats with synthetic oestrogens, observed initiation and continuation of lactation while oestrogen administration was continued. For an account of how various groups of workers have extended this work to cattle with spectacular results, the reader is referred to Malpress (1947).

These lactogenic and galactopoietic effects of oestrogen are consistent with the increase in the pituitary prolactin content which is evoked by oestrogen (*see* Meites and Turner, 1948a, for recent experiments as well as for a summary of earlier work), but despite the fact that Meites and Turner have never observed a decrease in pituitary prolactin even following huge doses of oestrogen, there seems little doubt that the galactopoiesis which can be so readily evoked in farm animals with oestrogen eventually gives way to inhibition if the oestrogen stimulus is too intense or unduly prolonged (*see* Malpress, 1947). In this connexion, Mixner, Meites and Turner (1944) also agree that high enough doses of oestrogen will inhibit lactation in the goat. Folley (1941) suggested that the type of effect exerted by oestrogen on lactation depends on the dosage and duration of treatment—generally speaking, low doses for short periods are believed to give lactogenesis or, under appropriate circumstances, galactopoiesis, while high doses over long periods tend to inhibit. This concept has been further elaborated into a "double-threshold" theory which is discussed by Folley and Malpress (1947, 1948b) and accepted by Mayer and Klein (1949).

Neuro-hormonal mechanisms in lactation

Broadly, research on mammary physiology falls into three epochs. At the turn of the century attention was concentrated on the study of neural mechanisms thought to control mammary growth and secretion. Later, with the rise of modern endocrinology, the successes of the endocrinologist were such as to tend to divert attention from neural mechanisms altogether. At the present time a tendency towards redress of the balance is discernible; as in other fields of endocrinology the importance of neuro-endocrine relationships is being increasingly recognized (Mayer and Klein, 1949). These last will now be briefly considered in relation to the two main phases of the lactational phenomenon as defined in the terminological scheme proposed by Folley (1947c) as an aid to clear discussion.

Milk secretion

There is a certain amount of evidence that neural influences arising from the suckling stimulus can effect milk secretion through the agency of a neuro-hormonal

reflex arc involving the secretion of prolactin by the anterior pituitary as its terminal link. The theory that the suckling stimulus can evoke reflex secretion of prolactin by the anterior pituitary gland was originally proposed by Selye (1934) on the basis of experiments on rats, in which he showed that the involution of lactating mammae, the suckling of which was experimentally precluded, was retarded provided suckling of other glands in the same animal was allowed to continue. This theory has since been supported in general principle by a considerable amount of experimental evidence.

The whole question has recently been reviewed by Folley (1947c, 1949) and Mayer and Klein (1949). Briefly, it can be said that though there are many gaps in our knowledge of the relation between the suckling stimulus and the secretion of prolactin (particularly as regards possible nervous pathways by which the function of the anterior pituitary may be stimulated), the general principle that the suckling stimulus may be an important, even essential, factor in maintaining the functional and hence the structural integrity of the lactating mammary gland may be taken as well founded.

Milk discharge: the physiology of suckling or artificial milking

It is now well recognized that in addition to the reflex discussed in the preceding section the suckling or milking stimulus reflexly causes discharge of stored milk from the alveolar tissues down into the larger ducts (or, in ruminants, milk cisterns) from which it can readily be drawn off through the teat. This reflex, known in agricultural circles as the "let-down" and by some clinicians as the "draught", was once thought to involve purely neural pathways, but more recent work initiated by Ely and Petersen (1941) indicates that a neuro-endocrine arc is probably involved (*see* also Peeters, Massart and Coussens, 1947; Peeters, Coussens and Oyaert, 1949). The terminal link of this arc is believed to involve the secretion by the posterior pituitary gland of a principle (probably the oxytocic factor) supposed to cause contraction of an effector tissue associated with the mammary alveoli, thus causing the characteristic increase in the intra-mammary pressure which occurs shortly after the beginning of milking, and tending to expel the milk from the alveoli. In this connexion it has long been recognized that injection of posterior pituitary extracts causes expulsion of milk from the mammary tissues (*see* Folley, 1947b). For recent reviews of the physiology of the milking process the reader is referred to Folley (1947c, 1949).

Until recently, one important element of the picture was obscure, namely the nature of the effector contractile tissue responsible for the ejection of the milk from the mammary alveoli. Some workers have caused confusion by speaking of the contraction of "musculature" or "muscle fibres" surrounding the alveoli. However, there is no evidence of the presence of smooth muscle fibres in close association with the mammary alveoli (Richardson, 1947, 1949a). It seems possible that these workers were in reality referring to the myo-epithelial cells which in the mature gland represent the derivative of the outer of the two epithelial layers lining the ducts in the immature gland. These cells, which had been figured in the mammary gland by early histologists, are also present in the salivary glands, where their contractile function had been inferred but never conclusively demonstrated. The occurrence, location and possible function of the myo-epithelial cells in the mammary gland have until recently remained equally obscure.

However, Richardson (1949a and b) has succeeded for the first time in adequately figuring the myo-epithelium in the goat mammary gland by means of a new technique. They are seen as flattened stellate cells lying on the outside of the alveoli between the epithelium and the basement membrane, and their processes so envelop the alveolar surface as to justify the time-honoured designation, "basket cells". Richardson has shown that the numbers and distribution of these cells are sufficient to account for the expulsion of milk from the alveoli by squeezing, provided they can and do contract in response to the suckling stimulus. They are also seen in large numbers round the larger ducts, where their processes are orientated longitudinally, so that on contraction they would tend to shorten and widen the ducts, thus facilitating the egress of milk.

Richardson states that the histological appearance of the myo-epithelium before and after milking is in harmony with the view that these cells actively contract during milking rather than undergo merely passive wrinkling as the distended alveoli collapse. While this evidence is suggestive, nevertheless the experimental contraction of the myo-epithelium in response to oxytocin remains to be positively demonstrated.

Our gradually unfolding knowledge of the physiology of the milking process has served to emphasize the importance to the whole phenomenon of this rather obscure and neglected phase of lactation. It is well known that the milking reflex can not only be conditioned but can be inhibited by unfavourable stimuli arising from fright or inexpert milking technique. The possibility that habitual partial failure of this neuro-endocrine mechanism, resulting in retention of milk, may materially shorten the lactation period in the cow, has been suggested by preliminary experiments of Knodt and Petersen (1944). A similar reflex mechanism governing the discharge of milk is undoubtedly operative in women (Waller, 1947) and since neural and psychological factors must be of special importance in man, the importance to the clinician of further development of the studies just discussed needs no emphasis.

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