PHYSIOLOGICAL ASPECTS

of

MILK EJECTION

A THESIS

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I N T R O D U C T I O N

During the latter part of the last century, a number of physiologists conceived the idea that the functions of the mammary growth and milk secretion were under the control of the nervous system. As a consequence, many experiments were carried out with the object of elucidating the role of the nervous system in lactation; these culminating in the classic experiments of Ribbert. In the year 1898, this man succeeded in transplanting mammary tissue from the inguinal region of the guinea pig to an area behind the ear, thus demonstrating that the mammary gland could grow, and to a limited extent function, independent of nervous connections.

Attention was then focused on the possibility of a purely endocrine control of the mammary gland, a concept that has given rise to much valuable knowledge by virtue of the experimentation it has stimulated. However a third phase in the history of research into mammary gland function is now being entered upon. As with a general tendency of investigations in endocrinology as a whole, integrations are being sought between endocrine and nervous mechanisms.

In 1941 Ely and Petersen postulated the neuro-endocrine theory of milk let-down. This theory suggested that the discharge of milk from the mammary

gland, as distinct from milk secretion, was brought about by the release of a humonal substance from the posterior pituitary into the blood stream, in response to nervous impulses reaching the pituitary from the mammary gland. At this stage there was but limited evidence suggesting the implication of the pituitary gland in such a phenomenon, the nerve supply of the udder was incompletely understood, whilst the existence and mechanism of myoepithelial cell contraction were subjects only for conjecture. In the succeeding ten years, data has accumulated concerning these three points, while increasing recognition has been given to the distinction between milk secretion and discharge. The evidence so adduced has served to support the neuro-endocrine theory of milk let-down.

Petersen (1944) has further suggested that a lack of persistency in milk yield may be related to an imperfect functioning of the neuro-endocrine relationship involved in milk discharge. Petersen's theory, while lacking the support of precise experimental findings, serves to explain many observations regarding the lactational behaviour of both dairy animals and lactating humans, and thus is one that may be capable of directing research into highly profitable fields.

Turner and Cooper (1941) devised an assay technique for the milk ejection hormone, using the lactating rabbit as an assay animal. However, their

assay depended upon minimal responses - a result that does not necessarily indicate normal ejection responses. Ely and Petersen (1941) studied the response of the lactating cow, but this method is unsatisfactory because of the difficulty in interpreting the milk ejection curve of a cow. This curve is determined partly by the sphincter tension and size, and partly by the volume of the milk cistern; complications which obscure the interpretation of the immediate effects of the injected material. The technique of Whittleston (1952) using the lactating sow, allows of a new approach to the problem of milk ejection. The sow has numerous advantages for such a study. It has no expansive milk cistern (Turner 1952), its "sphincter" does not require a marked pressure difference across it before the milk will flow (Turner 1952), it may be handled with ease, and is of small commercial value compared to the larger farm animals.

Using the technique of Whittleston, a study has been made of the phenomenon of milk ejection in the sow with the following objects in view :

(I) To develop the technique to the level of an accurate assay procedure.

(2) To elucidate factors influencing the let-down response.

(3) To further knowledge concerning the efficiency of milking and of milk production in dairy animals, bearing in mind the concept that the milk production of an

animal may be limited by the sub-optimal functioning of the let-down mechanism.

Such a long range object as the last involves a detailed knowledge of the physiology of the posterior pituitary, the mammary gland, and the nervous system which relates them. The first two chapters of this thesis review the literature and summarize the available knowledge in these fields, knowledge without which a critical approach to the problems of milk ejection cannot be readily undertaken. The remaining chapters are an exposition of the experiments performed, and the results and conclusions drawn from them.

P A R T I

A - REVIEW OF LITERATURE

THE MECHANISM OF MILK LET-DOWN

The Development of the Neuro-Endocrine Theory

Among early ideas regarding milk formation, based upon observation only, was the belief that the act of milking resulted in the formation of milk. An illustration of this notion is afforded by a quotation from the text of Judkins College text book (1924) :

> "The udder contains only a small amount of milk, usually between a pint and a quart, when one starts milking. This is found in the four milk cisterns. The enlargement of the udder which occurs before milking is doubtless due to the storing up of the ingredients out of which the milk is to be made. After the first milk is drawn, the cow, by nervous tensions, tightens up the muscles located at the points where the ducts branch off and simply stops making milk until she is ready to do so. When that time comes, the gland lobules and their contents, in some mysterious way, put the stored ingredients together into milk which trickles down the ducts to the cistern, thence it passes to the teat canal & the milker squeezes out. For the most part therefore, milk is really made during the milking process. A cow killed just before milking will be found to have no milk in the udder except that present in the milk cisterns."

This idea, was no doubt, based upon the phenomena of "milk let-down" a process whereby the udder enlarges, becomes turgid and shows signs which might be taken as evidence of active secretion.

By 1900, information was available indicating that direct nervous innervation of the mammary gland was not responsible for its physiological function. This fact was well demonstrated by two classic experiments. Routh (1896) observed that lactating women suffering a severed spinal cord exhibited normal lactogenesis, while Galtz and Ewald (1896) severed the spinal cords of various animals without impairing mammary function. Eckhard in 1877 had noted continued lactation from a gland whose nervous supply was severed, while in 1898 Hugo Ribbert succeeded in transplanting two mammary glands of guinea pigs to the skin at the back of the ear of sister animals, where laction was initiated after parturition.

In 1915 Gaines stated that the processes of milk ejection and milk secretion are separate and distinct entities. The conclusion reached by Gaines was based upon the observation that the ejection of milk in a goat was co-incident with a high intra gland pressure, and that low pressure periods occurred between high pressure periods. That pressure is related to the rate of milk ejection was further

demonstrated by Tgetgel (1926). Measuring mammary pressure by manometer readings from the nipple, Tgetgel showed that the pressure gradually increased from one milking to the next as milk accumulated in the cistern. At the beginning of milking however, there was a sudden and very large increase of pressure, and then as milking proceeded the pressure gradually fell (Fig.1.1).

The theory that the sudden increase in pressure was due to a reflex secretion of milk is now discounted, primarily on the grounds that all the milk which is normally obtained at any one milking is already in the udder of the animal before milking begins (Gaines and Sanmann 1927).

Several explanations suggesting the cause of the sharp pressure rise recorded at the time of milking have been offered. Hammond (1936) suggested it was due to an erection of the udder and nipple, caused reflexly by stimulation of the nipple during the act of suckling or milking. This erection was reputed to put pressure on the milk contained in the ducts and alveoli, resulting in a marked increase in the cistern pressure. He suggested that afferent fibres carried the stimuli to a centre in the spinal cord from which the efferent nerves conducted the impulses to smooth muscle fibres, and perhaps the basket cells about the alveoli, running in conjunction

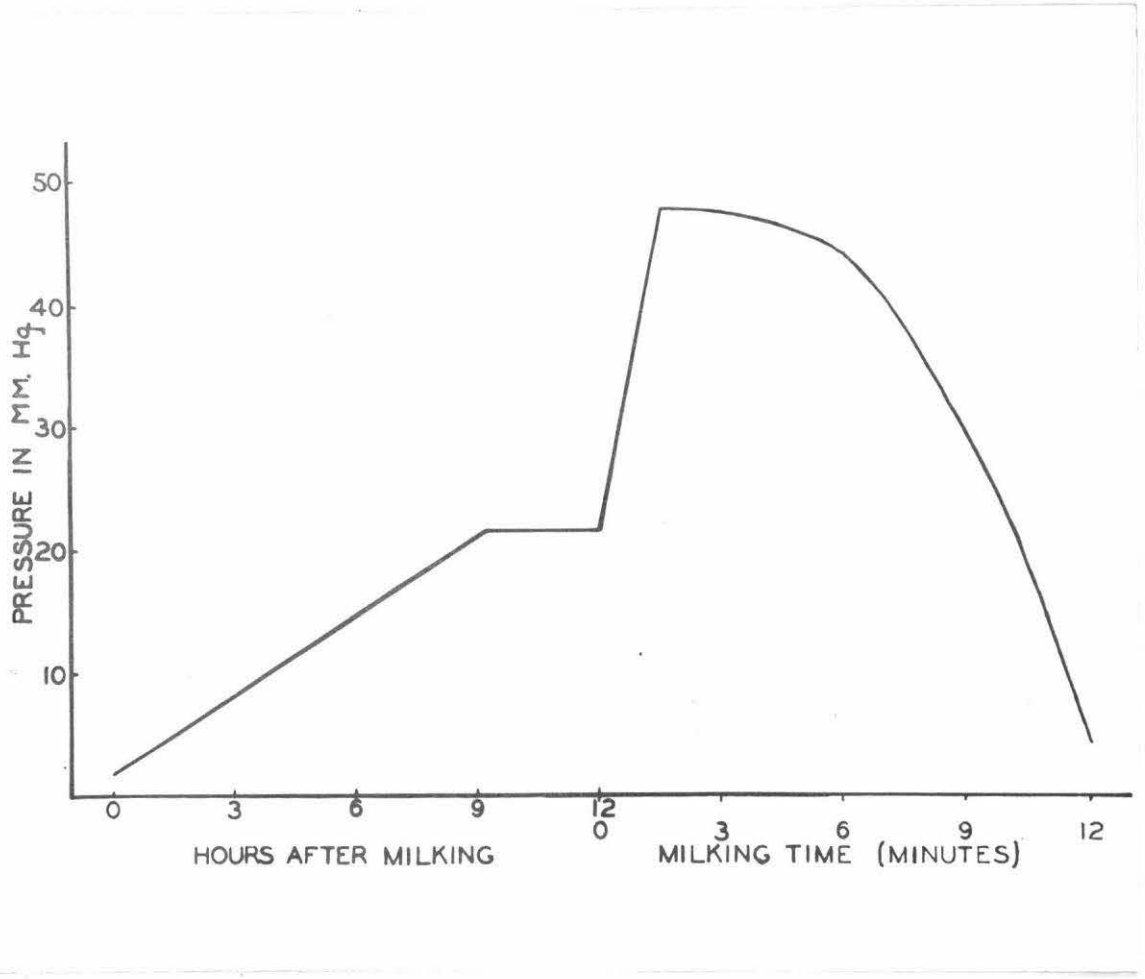


Fig.1.1 - Diagram of Milk Pressure changes in the Udder (from Tgetgel).

with or over veins, and by occluding the latter, caused accumulation of blood in the tissues of the udder and nipples. Gaines (1915) had supposed a reflex contraction of smooth muscle in the glands to be the cause of milk ejection, a view supported by Krupski (1925). Krzwanek and Bruggemann (1931) believed the contraction of "kabzellen" (basket cells covening the alveoli) to be the primary cause.

Meanwhile Ott and Scott (1912) has demonstrated that the injection of an extract of the posterior lobe of the pituitary into a lactating goat caused the discharge of milk from the mammary gland. In 1915 Gaines suggested that "pituitrin" (an extract of the posterior lobe of the pituitary) had a muscular action on the active mammary gland, causing a constriction of the milk ducts and alveoli with a consequent expression of milk. This action took place in the excised gland in the absence of any innervation as well as in the normal gland. Together with Sanmann in 1926 he postulated an hypothesis of milk secretion and discharge involving continuous intracellular milk formation, cellular discharge by membrane rupture to the duct system, and the subsequent removal of the milk by a contractile mechanism set in action by a nervous reflex initiated by the stimulus of milking. Hammond (1936) viewed the action of pituitrin as that of a galactogogue, a

suggestion refuted by Gaines and Sanmann. Turner and Slaughter (1930) showed that the injection of pituitrin permitted the removal from the udder milk that was otherwise unavailable, and were thus "inclined to the theory that pituitrin is not a galactagogue but rather acts on the mechanism normally effective during the milking process."

Thus there was dispute as to the nature of the let-down process. The American workers favoured the view that the phenomena was activated by stimulation of the teats, causing a release of a pituitary factor into the blood, the mammary glands being the target organ, while Hammond propounded the idea that the ejection of milk was brought about by a nervous reflex causing an engorgement of mammary tissue with blood.

Ribbert (1898) and others had previously demonstrated that the nervous system did not exercise a direct control over the combined effects of secretion and ejection. MacKenzie (1911) and McCandlish (1918) tried numerous drugs, several of which might be classed as nerve stimulants, and failed to produce a marked effect on the rate of secretion or ejection of milk. Both however noted that pituitrin produced a marked milk discharge effect. Canon and Bright (1931) sympathectomised a dog, and from its behaviour during lactation concluded that the autonomic nervous system

was essential to this function. They described the effect as a belated one, causing the mother to be indifferent to her young, while viscous creamy material accumulated in her mammae. Inglebrecht (1935) sectioned the spinal cords of ten rats between the last thoracic and first lumbar vertebrae, thus denervating the six posterior glands while permitting the six anterior ones to remain intact. Nursing young died when permitted access only to the posterior six glands, but when two of the anterior glands were suckled, all glands functioned normally. Selye et al (1930) found that nursing caused continued gland function in adjacent glands which were not nursed. Thus, save for the single experiment of Canon and Bright all results could be explained in terms of a sensory nervous system - pituitary interaction.

The position regarding the role of the posterior pituitary was rather confused. Smith (1932) and Houssay (1935) removed the posterior pituitary of the rat and dog respectively and found no inhibition of lactation after parturition. Yet in 1939 Gomez reported that lactating hypophysectomized rats could be maintained in lactation only by replacement therapy with both anterior and posterior pituitary extracts. Without the posterior lobe therapy the young seemed unable to obtain milk present in the gland.

By 1928 Kamn and his co-workers had effected a fairly complete separation of two active constituents

of the posterior lobe. They found one fraction to have an oxytocic action, and named this preparation "Pitocin". The other fraction was found to cause an increase in blood pressure - to this substance they gave the name "Pitressin".

Using Kamm's oxytocic preparation, and a cow in which the afferent nerve fibres to one half of the udder had been cut, Ely and Petersen (1941) found that let-down could be evoked by milking, or by posterior pituitary extracts, or conversely inhibited in both halves alike by adrenalin or fright. On the basis of these results Ely and Petersen suggested that the let-down of milk involved a neuro-hormonal arc. The theory was postulated that palpation of the teat, and possibly other external stimuli, were sources of sensory impulses reaching the central nervous system which in turn stimulated the posterior lobe to secrete "oxytocin" into the blood. This factor was thought to cause the observed increase in intraglandular pressure. In a similar manner fright, causing an inhibitory reflex, stimulated the production of adrenalin by the medulla of the supra-renals.

In the same year Turner and Cooper (1941) found pitocin to have approximately five times the let-down activity of pitressin. They suggested the presence of a separate milk ejection hormone present in both preparations, for the milk ejecting activity of pitressin was somewhat greater than could be

accounted for on the basis of oxytocic contamination of the pressor principle.

The presence of a milk ejecting principle in the blood of a cow stimulated to let down, was demonstrated independently by Petersen and Ludwick (1942), and by Peeters, Massart and Coussens (1947), a finding which lent considerable weight to Ely and Petersen's theory.

In a paper presented to the N.Z. Dairy Science Association in 1948, Whittleston reported that MacFarlane, in a private communication, had clearly demonstrated the existence of a network of myoepithelial cells surrounding the alveoli and ductules; entities which might well be responsible for the physical act of ejection. On this basis Whittleston rejected the hypothesis of Hammond that milk let-down was due to an erectile tissue mechanism, for MacFarlane's sections showed no evidence of the blood vessels necessary for this hypothesis. In 1949 Richardson was able to clearly identify these basket-like cells about the alveoli and ductules, so confirming MacFarlane's communication. Linzell (1952) published a paper reaffirming the conclusions postulated by Richardson regarding the identity, contractility and participation of these myoepithelial cells in the let-down reflex. Fig.(1.2).

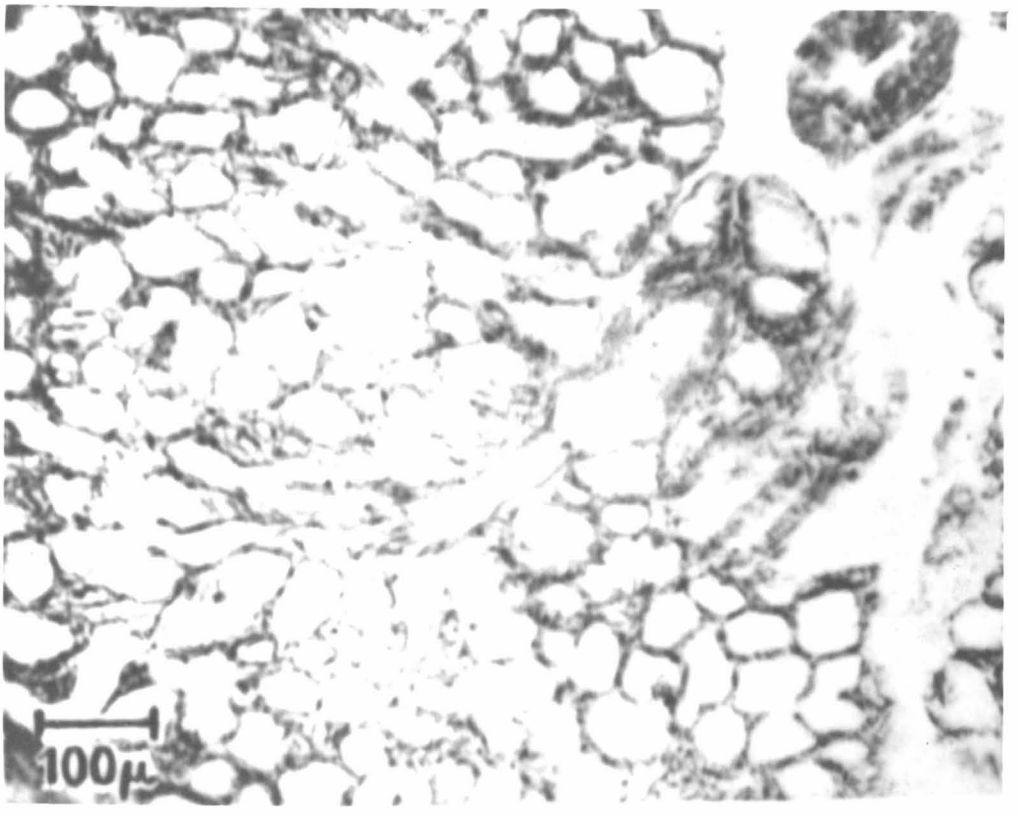


Fig.1.2 - General low power view showing abundance of myoepithelium. Background unstained. Tissue from a cat gland. Carvoy. Frozen section. (from Linzell)

The myoepithelial cells have been seen to run along the walls of the small ducts as well as about the alveoli. The significance of this fact is problematical in the recurring controversy concerning the active participation of the ducts in let-down. In support of the view that the contraction of myoepithelium might cause an opening and closing of these ducts are three pieces of evidence :

1. The obvious enlargement of duct size at let-down (Linzell 1952) (Fig.1.3).
2. Let-down in the sow and its cessation are rapid and valvelike in action.
3. If in the cow mammary pressure is built up by intraduct injections of saline until it exceeds the normal let-down pressure value, and posterior pituitary extract subsequently injected, there is a fall in pressure. If only alveoli were involved no change in pressure, in a negative direction at least, would be expected (Whittleston 1951).

Five important links in the chain of events leading to milk ejection have thus been established. In summarized form these are -

1. Pitocin is capable of eliciting a milk ejection response in both the normal and perfused gland.
2. The blood of a cow stimulated to let-down, contains a substance capable of evoking milk ejection in a perfused udder.

Fig.1.3a - Normal appearance of a distended gland showing evenly distributed alveoli as white dots and white milk filled ducts.

(From Linzell)

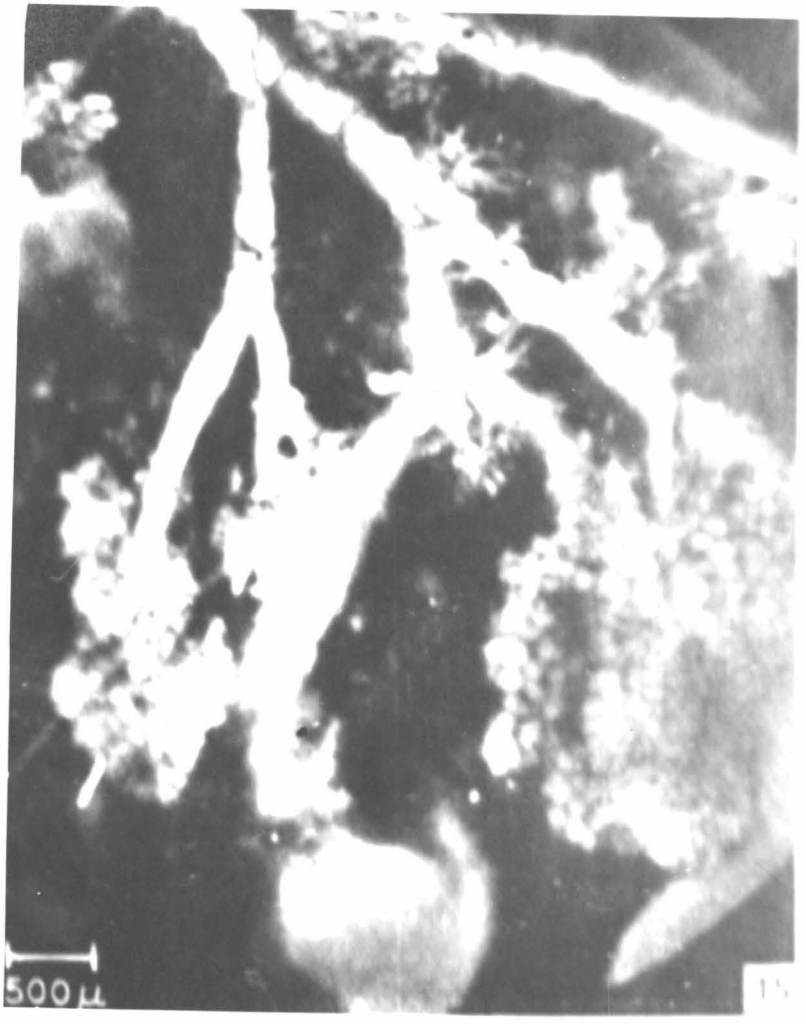


Fig.1.3b - The same field 2 minutes after applying 0.01 unit of Pitocin. Note that the majority of alveoli have been emptied of milk and can no longer be seen, whilst the ducts have become greatly extended.

(From Linzell)

3. The myoepithelial elements of the mammary gland contract under the action of pitocin and cause expulsion of milk.

4. The posterior pituitary appears to be an essential factor in the suggested neuro-endocrine arc.

5. The dennervation of the mammary gland prevents the let-down of milk.

The Role of the Autonomic Nervous System

The contractile elements of the mammary gland respond to a number of pharmacologically active substances, however this fact does not necessarily indicate that such substances are important physiologically. A summary of the effects ofmany of these substances on the milk ejection response and on blood flow is presented in Table I. Of these, particular attention has been focused on the response of the gland to adrenalin and to acetylcholine, since the effect of these drugs may be related to their respective sympathetico and parasympathetico mimetic properties. In view of the fact that the mammary gland is remarkably sensitive to both these drugs, the question of the role of the autonomic nervous system in milk let-down assumes considerable importance, for even if this system does not provide the normal mechanism of let-down, its influence may well be superimposed on, and thus modify the suggested endocrine control.

TABLE - 1

THE EFFECT OF VARIOUS PHARMACOLOGICALLY ACTIVE SUBSTANCES ON MILK EJECTION AND BLOOD FLOW IN THE MAMMARY GLAND

Substance	Amount	Species	Milk ejection response	Vascular response	Reference
Pitocin (oxytocic hormone)	10 units	Cow	Complete ejection	8-20% decrease in blood flow	Petersen, 1942.
	5-10 units	"	" "	No effect	Peeters et al 1952
	3 units	"	Incr. in cistern pressure	-	Peeters, Goussens & Oyaert, 1949
	0.001 unit*	Dog	Ejection	Vasoconstriction	Linzell, 1950
	0.01 " *	Cat	"	"	" "
	0.5 "	Sow	"	-	Whittleston 1952
	1-10 units	"	"	-	Braude & Mitchell, 1950
Pitressin (vasopressor hormone)	10 units	Cow	Partial ejection	40-60% decr. in blood flow	Petersen, 1942
	0.5 unit	Sow	" "	-	Whittleston 1950
	0.01 milli-unit	Dog	No ejection	Vasoconstriction	Linzell, 1950
	0.01 unit	Rabbit	Ejection	-	Cooper & Turner 1941
Adrenaline	50-200 ug	Cow	Partial ejection	50-100% decr. in blood flow	Petersen 1942
	50-200 ug	"	Little or no ejection	-do-	Peeters et al 1952
	0.0001 ug*	Dog	-	Vasoconstriction	Linzell 1950
	0.005 ug*	Cat	-	"	" "
	10^{-6} ug*	Dog	-	"	Linzell & Hebb 1951
	10^{-7} ug*	Cat	-	"	" " "
	10^{-4} ug*	Goat	-	"	" " "
	0.2 ug	Sow	inhibits ejection	-	Whittleston 1952

Table I (Contd.)

Substance	Amount	Species	Milk ejection response	Vascular response	Reference
Acetyl-choline	4-100 mg	Cow	Complete ejection	No effect	Petersen, 1942
	20-100 mg	"	Partial "	Increased blood flow	Peeters et al 1952
	0.1 ug	Dog	-	Vasodilatation	Linzell, 1950
	0.2 ug*	Cat	-	"	" "
	0.2 g	Sow	Partial ejection	-	Whittleston, 1952
Histamine	0.5-10 mg	Cow	Partial ejection	10-50% decr.in blood flow	Petersen, 1942
	5-100 mg	Cow	" "	Decreased blood flow & capillary dilatation	Peeters et al, 1952
	0.1 ug	Cat & Dog	-	Vasodilatation	Linzell, 1950
	0.4 mg	Sow	No effect	-	Whittleston, 1952
Atropine	2-4 mg	Cow	- prevented	Slight incr.in blood	Petersen, 1942
	2-4 mg	"	- action of	- flow	Peeters et al, 1952
	50 ug	Cat & Dog	- acetylcholine	Varied	Linzell, 1950
Ergonovine	0.2-0.6 mg	Cow	- prevented	10-20% decrease in	
Di-hydro-ergotamine	100 ug	Cat & Dog	- action of adrenaline	blood flow varied	Petersen, 1942 Linzell, 1950
Dibenamine	7 mg/kg	Cow	-	-	Peeters et al, 1952
Neoantergan	40 mg	Cow	Partial ejection	Prevented action of histamine	Peeters et al, 1952
Carbamyl-choline	2-8 mg	Cow	No effect	Slight increase	Petersen, 1942

* - Minimal effective doses. - = No observation available

St.Clair (1940) presented a thesis to the Iowa State College entitled "The Nerve Supply of the Bovine Mammary Gland." His work led him to the conclusion that the bovine udder was innervated by sensory and sympathetic fibres only, these reaching the udder by way of the inguinal nerve, the first two lumbar ventral branches and the perineal nerves. He was unable to find gauglia in the udder, and as a result, he believed that the mammary gland did not have a parasympathetic supply. By cutting the inguinal nerve he caused a vasodilation of the udder, with a resulting increase of local temperature, indicating that the sympathetics were constrictors to the peripheral blood vessels. St.Clair supposed that the sympathetic fibres had a stimulatory effect on smooth muscle elements of the udder, and even though a hormonal influence overshadowed any nervous action the influence of the sympathetic system could not be denied.

Petersen (1942) carried out pharmacological studies on the mammary gland. These led him to believe that the bovine udder was innervated by both a sympathetic and parasympathetic supply, for he argued that a response to acetylcholine and adrenalin indicated a cholinergic i.e. a parasympathetic, and a sympathetic supply.

Peeters, Coussens and Sierens (1949) using a

perfused gland, studied the effect of inguinal nerve stimulation in the presence of ganglionic blocking agents, for parasympathetic innervation is always associated with the presence of nerve gauglia in the tissue supplied. Electrical stimulation of the inguinal nerve led to vasoconstriction, a decrease in milk pressure and the onset of teat contractions, such effects being unaltered by the ganglionic blocking agents employed (nicotine and tetraethyl ammonia). Similar effects to those of nerve stimulation were produced by the injection of adrenalin, and were likewise inhibited by dibenamine. These workers interpreted their results as indicating the absence of a parasympathetic supply. In a further paper Peeters, Genie and Coussens (1951) examined the gland for the release of acetycholine during nerve stimulation using an eserinised perfusion fluid (eserin being a compound that inhibits the activity of choline esterase). They were unable to detect any increase in the activity of leech muscle to this fluid after stimulation. - a result indicating the absence of parasympathetic fibres in the udder, for leech muscle is particularly sensitive to the presence of acetycholine.

Linzell (1950) made a detailed study of the vasomotor nerve supply to the mammary gland of the cat and the dog. He reported vasoconstriction in response to electrical stimulation of the external spermatic and mixed spinal nerves by observing decreased venous

outflow from the isolated gland, increased perfusion pressure, and microscopical examination of living blood vessels. Ergot preparations abolished the vasoconstrictor response, adrenergic stimulants potentiated it. Intra arterial administration of adrenalin completely simulated the effects of nerve stimulation. Although the mammary blood vessels responded to acetylcholine by vasodilation, this observation was not regarded as evidence for cholinergic innervation since the effects of nerve stimulation were unaffected by eserine, atropine or nicotine - all ganglionic blocking agents.

In view of this evidence it may be concluded with considerable confidence that the udder has a vasomotor nerve supply of a sympathetic nature, a supply of which probably exerts its vasoconstrictor influence by means of the secretion of an adrenalin like substance. The evidence available indicates the absence of a para-sympathetic supply in the udder.

The Physiology of the Interaction of Pitocin and Adrenalin.

The mechanism whereby adrenalin inhibits the action of Pitocin is an interesting but yet undecided problem. Hebb and Linzell (1951) showed that the sensitivity of mammary blood vessels to adrenalin is dependent upon the rate of blood flow through the gland. Because of the sensitivity of the mammary

blood vessels to adrenalin, it has been postulated that the inhibiting action of adrenalin on the response to pitocin in the mammary gland, reported by many workers (Peeters et al, 1949, 1952, Whittleston 1951,), is due to the vasoconstriction caused by adrenalin preventing the access of pitocin to the contractile elements of the gland.

Observation of the behaviour of smooth muscle "in vitro" in response to adrenalin indicates that adrenalin may act directly upon the smooth muscle causing a marked relaxation (Chapter 8). In view of the fact that myoepithelium and smooth muscle are capable of exhibiting a similar staining reaction (Linzell 1951), and behave in a parallel manner to the action of pitocin, it is not an unwarrantable assumption that adrenalin might well cause a relaxation of myoepithelium similar to that caused in smooth muscle.

If we make the assumption that the action of these drugs is at the surface of the cell, it is feasible to visualize a mechanism whereby a concentration of the molecules concerned, sufficient to stimulate contraction, might arise at a cell surface that exhibits a high degree of specificity.

Adrenalin contains ionizing groups, polar groups and non-polar hydrocarbon groups in its molecule, hence it has an intrinsic capability of

being adsorbed at a surface, and further, when adsorbed, of altering the properties of the surface concerned.

Danielli (1950) furnishes an excellent example of the problem under consideration.

Consider the concentration of adrenalin which may arise at a surface. This is given by Boltzmann's theorem :

$$\frac{Cs}{Cb} = e^{\frac{E}{RT}}$$

where Cs = concentration at adsorbing surface

Cb = bulk concentration

E = energy of adsorption

R = gas constant

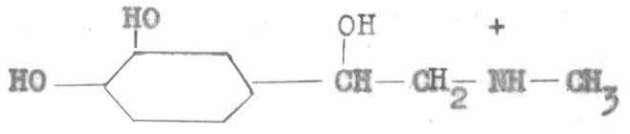
T = absolute temperature

e = the expotential function.

The energy E may be regarded as made up of 3 components, one associated with ionic groups, one with the polar groups, and one with the non-polar groups.

For adrenalin the minimal values of these are -

Ionic	Polar	Non-polar	Total E	$\frac{Cs}{Cb}$
700	3000	3500	7200	2×10^5

Adrenalin 

Thus the concentration of adrenalin which may arise at a surface is seen to be of the order of 10^5 times that which is found in the bulk phase

i.e. the circulating blood.

The surface at which a drug is adsorbed must present an organisation of ionizing groups, polar groups and non-polar groups as specific as that which is to be found in the drug itself. If this criterion is filled the possible energy of adsorption is large - but a group on the wrong position or having the wrong orientation may readily prevent the dove-tailing of the drug and the surface, thus preventing many of the sites of potential adsorption becoming effective.

Considering the mechanism of both adrenalin and pitocin pharmacology in this manner, it is feasible to imagine that the antagonism between them might take the form of adrenalin disrupting the adsorbing surface of the myoepithelial cell preventing the surface uptake of the oxytocic factor, for it is probable that pitocin acts on the muscle cell by this same selective surface adsorption phenomena.

This hypothesis becomes clearer when we consider the functions of enzyme in a muscle cell, for these include the synthesis of substances acting as an immediate source of potential energy, e.g. the synthesis of adenosine triphosphate, and the conversion of this potential energy to mechanical

work, as is seen in muscular contraction.

The possible mode of activity of pitocin in any enzyme system must be purely speculatory, yet it is convenient to think in terms of its action as a prosthetic group of an enzyme, or as a co-enzyme, whereby it rapidly activates a complex metabolic reaction.