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The magnitude and mechanisms of the uptake of milk precursors by the mammary gland

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The functioning mammary gland is a large organ in all species. Udders weighing 75 kg have been reported in dairy cows but even in rats and mice the empty tissue weighs 5–7% of the body-weight in full lactation and is larger than the liver; the whole economy and metabolism of the animal must be altered quantitatively if not qualitatively to meet the demands of this organ secreting maximally. It had been surmised for a long time, and now has been proved with the aid of isotopes, that the glands synthesize milk from simple substances extracted from the plasma, i.e. glucose, amino acids, fatty acids and minerals. During the last few years the development of improved techniques for studying metabolism of the udder of the goat quantitatively in vivo and in vitro, largely carried out at Babraham, have added to our knowledge of the nature and magnitude of the demands of the mammary glands for substrates. I propose to summarize these new findings because they serve to emphasize that we know something of the needs of the mammary gland itself and what needs to be eaten during lactation, but much less of what goes on in the rest of the body to balance these two processes; this, I believe, is where future research may profitably concentrate.

Improved techniques

Perfusion of the isolated udder. It is now possible to keep goat glands alive and secreting milk for 12 and occasionally 24 h. One can use the animal's own blood, another goat's blood (even a male) or a semi-synthetic perfusate, but to maintain secretion one must continually infuse milk precursors at a rate appropriate to the rate of milk secretion before the experiment (Hardwick & Linzell, 1960). One can produce marked changes in the yield and composition of milk by altering the substrate input (Hardwick, Linzell & Price, 1961) and much has been learnt of the needs of the lactating gland, particularly when using isotopes, but unfortunately at best it only yields $52 \pm 12\%$ (SD) of what it was giving on the animal before the experiment, so that one must be cautious in extending the quantitative results to the normal lactating animal.

Mammary blood flow measurement in vivo. I believe Lintzel (1934) was the first

to make accurate estimates of mammary blood flow. By measuring, in the goat, the arteriovenous differences of a number of milk precursors and comparing these with the quantity of the corresponding products secreted in the milk in a given period he calculated, using the Fick principle, that mammary blood flow was about 450–550 times the rate of milk secretion. Several other groups used this method in cows before the war, but recently mammary blood flow has been measured in conscious undisturbed goats by three different methods (Linzell, 1960*a*, 1966; Rasmussen, 1963; Reynolds, 1965), and Rasmussen's method has been used in cows (Rasmussen, 1965; Kronfeld, Raggi & Ramberg, 1966). One advantage of being able to measure udder blood flow is that arteriovenous difference measurements can be converted into uptake in g/min or, more usefully to a nutritionist, g/100 ml of milk formed, and this has now been done for the major precursors and components of milk in the goat.

Isotope infusions in vivo. A more recent innovation is the measurement of the uptake of nutrients by the mammary gland during the constant infusion of tracer quantities of ^{14}C-labelled milk precursors into the blood stream (Annison & Linzell, 1964; Annison, Linzell, Fazakerley & Nichols, 1967). One can then make a number of important measurements: (1) the total entry of endogenous substrate into the circulation and thus the utilization by the whole animal, from the blood specific radioactivity (sp.ac.) and the rate of infusion of the isotope; (2) the amount of the substrate oxidized, from a comparison of the sp.ac. of the circulating $^{14}CO_2$ with that of the substrate sp.ac.; (3) the amount of the substrate taken up by the mammary glands, from the arteriovenous difference and blood flow; (4) the amount of the substrate oxidized by the mammary glands, by comparing the arterial and the mammary venous CO_2 sp.ac. with that of the substrate sp.ac.

If the isotope is injected into one mammary gland one can decide whether the substance is incorporated into milk directly by the mammary tissue or only after conversion into some other compound elsewhere in the body, because in the former event the sp. ac. of the product will be higher in the milk of the injected gland than in the milk of the other glands. Kleiber and his group (following Kleiber & Luick, 1956) injected their isotopes via the teat canal but Wood and his colleagues (following Wood, Siu & Schambye, 1957) used the mammary artery. The latter is the more physiological route but unfortunately anaesthesia is needed to expose the inaccessible artery and in some of Wood's experiments the milk yield was reduced. Recently this difficulty has been overcome by moving the glands of goats to other parts of the body where the mammary artery can be permanently exteriorized as a skin-covered loop (Linzell, 1963).

Milk precursors

The raw materials used in the synthesis of milk have been identified by analysis of blood entering and leaving the udder of cows and goats and by the transfer of labelled substances into milk. Information is most comprehensive for the goat and results dealt with here will be mainly for it. Barry (1964) gives results for the cow and goat.

Table 1. *Mammary arteriovenous differences in lactating goats*

(Summary of results collected for twelve Saanen goats at Babraham, 1963–7, during experiments referred to in the text. The animals were surgically prepared to enable udder blood flow to be measured and arterial and mammary venous blood to be collected regularly in the animal house without disturbance. They were in their second to fifth lactations each lasting about 42 weeks, total milk yields 350–1080 l., peak yields 3·1–5·3 l./day. Mean mammary blood flow to milk yield 493 ± 15 to 1. Plasma flow 353 to 1. Mammary RQ 1·4 ± 0·037. Extraction is the arteriovenous difference expressed as a percentage of the arterial concentration. Mean values with their standard errors)

Substance	Arterial concentration (mg/100 ml)	Extraction (%)
	Blood	
Oxygen	11·85 ± 0·8 *	45 ± 1·3
Glucose	45·5 ± 1·5	33 ± 1·4
Acetate	8·9 ± 0·6	63 ± 2
Lactate	6·72 ± 0·51	30 ± 1·5
	Plasma	
β-hydroxybutyrate	5·8 ± 0·22	65 ± 2
Acetoacetate	0·25 ± 0·05	8 ± 8
Trigylcerides	24·6 ± 2·1	45 ± 5
Free fatty acids	8·7 ± 0·4	3 ± 4
Phospholipids	160 ± 19	4 ± 3
Total sterols	104 ± 15	0 ± 8
Glycerol	0·24 ± 0·02	7 ± 7
'Essential' amino-acids:		
Methionine	0·27 ± 0·02	72 ± 9
Phenylalanine	0·70 ± 0·05	63 ± 5
Leucine	2·07 ± 0·08	63 ± 5
Threonine	0·96 ± 0·06	60 ± 2
Lysine	2·13 ± 0·19	49 ± 6
Arginine	2·53 ± 0·11	48 ± 7
Isoleucine	1·79 ± 0·08	47 ± 5
Histidine	1·04 ± 0·12	42 ± 5
Valine	2·79 ± 0·11	37 ± 5
'Non-essential' amino-acids:		
Glutamic acid	1·93 ± 0·11	58 ± 4
Tyrosine	0·95 ± 0·07	39 ± 5
Asparagine	0·89 ± 0·07	37 ± 7
Proline	2·59 ± 0·19	36 ± 6
Ornithine	1·11 ± 0·14	36 ± 7
Aspartic acid	0·28 ± 0·03	33 ± 7
Alanine	1·66 ± 0·10	25 ± 4
Glutamine	3·74 ± 0·27	23 ± 5
Glycine	6·85 ± 0·78	5 ± 2
Citrulline	1·93 ± 0·18	3 ± 6
Serine	1·41 ± 0·12	0 ± 7

*Vol.%.

Milk protein

Ideas as to the precursors of milk protein have wavered over the last 40 years. Early workers considered that plasma amino acid uptake accounted for the protein synthesized, but later glycoproteins were proposed as equally likely candidates. Isotopic evidence came down heavily on the side of amino acids as the source of milk protein synthesized in the udder (see review by Barry, 1964). However, recently column chromatography of all the amino acids in cows (Verbeke & Peeters, 1965) and goats (Mepham & Linzell, 1966) has shown a constant high extraction of some

and negligible or variable arteriovenous differences for others (Table 1). Simultaneous measurement of blood flow and amino acid output in the milk proteins in the goat (Mepham & Linzell, 1966) resolve this by showing that the uptake of all 'essential' and some 'non-essential' amino acids is sufficient to account for the corresponding amino acid residues in the milk protein (i.e. 100% efficient), whilst others (e.g. serine, alanine) are taken up in insufficient quantities and must be partly synthesized in the tissue. The uptake of the non-essential amino acids is more variable than that of the essential ones (Table 1), suggesting that the glands are not completely dependent on plasma precursors for the former. Isotopic evidence is consistent with these findings, in showing that some of the serine, alanine, glutamate and aspartate can be formed from glucose, and serine, proline, glutamate and aspartate from acetate, when these labelled substrates are infused intra-arterially (Linzell & Mepham, unpublished). Unexpected and so far unexplained findings are (1) that in the goat, but not in the cow, arginine is taken up in excess (three to four times) of its requirement and is used for forming urea and proline (Mepham & Linzell, 1967), and (2) that ornithine is taken up in both species. In ruminants amino acids can be formed by microbial synthesis in the rumen and these, together with any residual dietary amino acids, are absorbed in the intestines, but whether the final mixture absorbed is always optimal is not known. Mammals without gastrointestinal microbial symbionts will certainly need all 'essential' and possibly some 'non-essential' amino acids in their diets to satisfy mammary requirements for optimum milk protein secretion.

Milk fat

The precursors of milk fat vary with the species and the amount and nature of the diet. In the goat there are large net extractions from the plasma of low-density lipoproteins, chylomicra, acetate and β-hydroxybutyrate but little or no arteriovenous differences of sterols, phospholipids, free glycerol or free fatty acids (FFA) (see Table 1).

The uptakes of acetate and β-hydroxybutyrate are associated with the high circulating levels found in ruminants, for arterial concentrations are low and mammary uptake is negligible in pigs (Linzell, Mepham, Annison & West, 1967). In the goat about half the acetate taken up by the udder is oxidized (Annison & Linzell, 1964) and the remainder of it and β-hydroxybutyrate are extensively used to form milk fatty acids up to chain length C_{14} and part of C_{16} (Popják, French & Folley, 1951; Popják, French, Hunter & Martin, 1951; Annison *et al.* 1967; Linzell, Annison, Fazakerley & Leng, 1967). These acids form about 40% by weight of milk fatty acids in ruminants and balance results suggest that they are chiefly formed from acetate and β-hydroxybutyrate.

In non-ruminants such as the pig, the smaller number of short-chain milk fatty acids are probably formed from glucose (Gutte, Kleiber, Raggi & Black, 1961; Linzell, Mepham *et al.* 1967), but, even in ruminants, the greater part of milk fatty acids is made up of those of chain length of C_{16} and longer and these are largely derived directly from plasma fatty acids.

The means by which the mammary glands can extract 50% of such large particles as chylomicra and lipoproteins while blood passes through the glands is an interesting problem in itself. We confirmed the importance of triglyceride (TG) uptake by showing that isolated perfused udders transfer large amounts of radioactivity into milk fat when labelled chylomicra are given. (Lascelles, Hardwick, Linzell & Mepham, 1964). There were two clues as to the mechanism: (1) when radioactive FFA are infused into intact animals there is a marked fall in sp. ac. across the glands and an extensive transfer of radioactivity into milk fat, showing that there is a simultaneous uptake and release of fatty acids (Annison *et al.* 1967), and (2) there is a three- to four-fold increase in lipoprotein lipase in the venous blood leaving the gland (Barry, Bartley, Linzell & Robinson, 1963) and this enzyme has been associated with the capillary wall. When we infused into the mammary artery of conscious goats chylomicra labelled with [^{14}C]glycerol and [^{3}H]fatty acids, we detected the liberated fatty acids and glycerol in the mammary venous plasma and lymph. This suggests that chylomicron triglyceride may be hydrolyzed in the capillaries and that the resulting glycerol and fatty acids pass to the mammary secretory cells (West, Annison & Linzell, 1967*a*,*b*). In fed goats, in which the arterial level of FFA is low, this release of FA from TG is almost equal to that of FFA taken up, so that there is a negligible net FFA arteriovenous difference but in animals fasted for 24 h with high arterial plasma FFA, the release of FA from TG is smaller than the FFA uptake, so that there is then a consistent net arteriovenous difference across the mammary glands in cows (Kronfeld, 1965) and goats (Linzell, 1967*a*,b). It is interesting that in fasting this increased uptake of free (i.e. long-chain) fatty acids about balances the fall in triglyceride and volatile (i.e. acetate) fatty acid uptake, because fat secretion in fasting falls less than lactose secretion (Linzell, 1967*a*,*b*) and the proportion of short-chain milk fatty acids formed from acetate falls.

Milk fat glycerol is derived partly from blood glucose (Popják, Glascock & Folley, 1952) and partly from glycerol released from plasma TG (West *et al.* 1967*b*). Only about 10% is derived from free plasma glycerol (West, Annison & Linzell, unpublished).

Milk lactose

Isotopic evidence is clear that both the glucose and galactose halves of the lactose molecule are largely derived from blood glucose in goats (Barry, 1952; Hardwick, Linzell & Mepham, 1963) and cows (Dimant, Smith & Lardy, 1953).

Other constituents of milk

All minerals in milk must come from the plasma and there is much isotopic evidence to support this conclusion. Citrate is formed in the glands from glucose and acetate in both cows (Kleiber, Black, Brown, Baxter, Luick & Stadtman, 1955) and goats (Hardwick *et al.* 1963). The precursors and source of the many other minor components of milk mostly have not been studied.

General mammary metabolism

Newer methods of measuring mammary blood flow show that it ranges from about 20 in non-lactating to 60-70 ml/100 g tissue per min in fully lactating goats (Linzell, 1960*a*; Rasmussen, 1963; Reynolds, 1965) and cows (Rasmussen, 1965; Kronfeld *et. al.* 1966). These values also confirm older estimates that mammary blood flow is 400–500 times the rate of milk secretion, but also show that this ratio is not constant but increases, at first slightly and later greatly, as the rate of milk secretion declines (Linzell, 1960*a*). Mammary lymph flow has now been measured in conscious goats (Linzell, 1960*b*, Reynolds, 1962) and cows (Peeters, Cocquyt & de Moor, 1963; Lascelles, Cowie, Hartmann & Edwards, 1964) and, as was expected, this also is high, about 2 ml/100 g tissue per h. These figures may be brought into perspective by saying that, per g tissue, mammary blood flow in the goat is at least four times the average for all tissues and mammary lymph flow about ten times. However, blood flow is much less than that through unit weight of liver and heart muscle. These results only begin to be useful when we marry them to the simultaneously measured mammary arteriovenous differences of milk precursors, so that we can then calculate and compare substrate uptake with the output of the corresponding products in the milk. Table 1 gives the arteriovenous differences of the main precursors of milk expressed as a percentage of the arterial level. The most remarkable thing is the magnitude of the extraction of many substances, frequently 60–70% is removed in one passage of the blood through the glands (Table 1). In Fig. 1 the uptake (arteriovenous difference × blood flow) is compared with the output of the corresponding product in the milk, identified by isotopic experiments and expressed per 100 ml of milk secreted. These values are approximate but their general validity may be accepted because of the agreement between the calorific equivalent of the total precursors taken up and that of the milk secreted plus the calorific equivalent of the O_2 consumed. They show that the secreting mammary gland is very efficient in that nearly 80% of the calories taken from the blood are passed to the milk.

The lactating mammary gland of the fed goat derives 30–50% of its energy from the oxidation of glucose and 20–30% from blood acetate. This is in strong contrast to what happens in the whole animal where a similar proportion of the CO_2 is derived from acetate but only 7–11% from glucose (Annison & Linzell, 1964). In the goat fasted for 24 h the main source of energy is FFA (about 25%), with glucose and acetate each contributing about 10% (Annison, Linzell & West, unpublished). The other major sources of energy remain to be determined.

It has been found also that glucose is essential for secretion by the isolated perfused goat's udder; without glucose secretion almost ceases (Hardwick *et al.* 1961), and no other sugar can replace glucose (Hardwick *et al.* 1963). Leaving out acetate or amino acids from the substrates offered does not suppress secretion but merely causes lowering in the milk fat and protein output. This and other evidence shows that the secretion of the milk lactose, fat and protein are to some extent independent of each other.

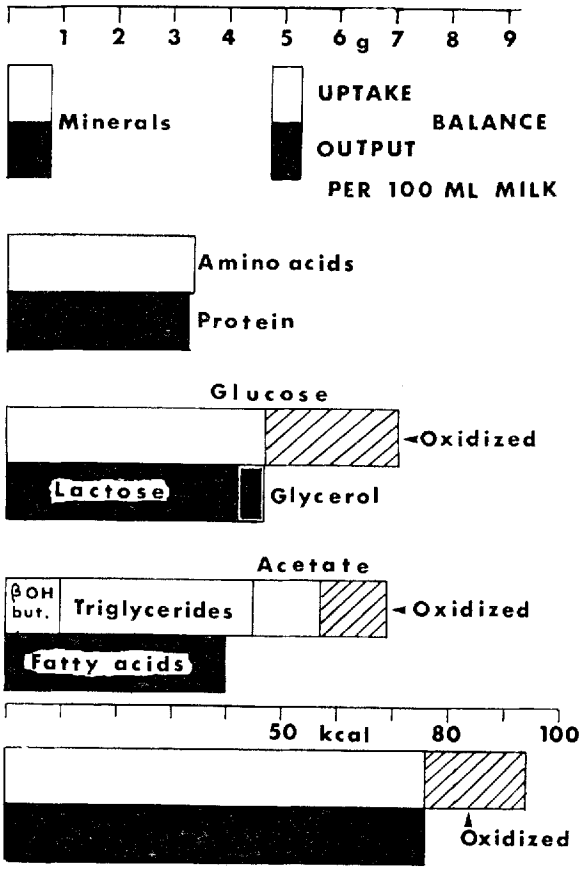

Fig. 1. Balance sheet of metabolic activity of the goat's udder during the secretion of 100 ml milk. The output of the major constituents is compared with the uptake of their chief precursors from the blood. The diagram ignores the uptake and output of minor components and the small degree of overlap between the major ones. The number of calories oxidized is calculated from the O_2 uptake, and the proportion of glucose and acetate oxidized is calculated from $^{14}CO_2$ production in isotope dilution experiments. β OH but. = β-hydroxybutyrate.

It is not entirely clear why glucose is so important for the lactating mammary gland. It is the main source of energy and the precursor of lactose, the chief osmotic constituent of milk which was once thought not to vary in concentration in milk and therefore acted as the controlling factor in the volume of milk secreted. However, lactose secretion rate can vary independently of the rate of milk secretion (Linzell, 1967*a*,*b*) and it may be that glucose is concerned with the passage of water and ions into milk. Of more immediate interest to nutritionists is the evidence, now accruing from experiments on fasted, insulin-treated and high-yielding lactating goats (Linzell, 1967*b*), that the availability of glucose to the udder can be a limiting factor to maximum milk secretion under normal conditions of management. This is

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not surprising for in the high-yielding lactating goat the udder uses 60–85% of the glucose available to the whole body (Annison & Linzell, 1964). In the physiological range the mammary arteriovenous difference of glucose is linearly related to the arterial level in cows (Graham, Jones & Kay, 1936) and goats (Linzell, 1960*a*), and increases in the yield of milk or of lactose after intravascular infusions of glucose have been reported in normal cows (Petersen & Boyd, 1937) and goats (Sopena, 1944; Linzell, 1967*b*). Ruminants are in a special position as regards glucose in that they absorb very little from the diet, but it is probable that the mammary glands of all species will have an absolute requirement for glucose and a high uptake to maintain secretion.

A number of workers have assumed that the lactating mammary gland must take a large part of the cardiac output. Lintzel (1934) guessed 28% in the goat, but measurements have shown that the figure is nearer 10% because the cardiac output itself goes up in lactation (Linzell, unpublished). This has been confirmed by Chatwin, Linzell & Setchell (unpublished) who measured cardiac output and blood flow through all the major organs of lactating and non-lactating rats 12 days postpartum. Not only was the cardiac output 44% higher in the lactating animal but the weight and blood flow per g tissue were higher for the liver and gastro-intestinal tract.

Conclusion

In summary, we may conclude that the main precursors of the major components of milk are now known and that we are beginning to understand the nature and magnitude of the demands that lactation throws upon the mother. The mechanisms controlling mammary substrate uptake are unknown and it is salutary to remember that we cannot yet restore to normal with infused substrates the milk yield of an isolated gland nor of a fasted animal, so that it is quite likely that the mammary uptake of as yet unrecognized factors is important for milk secretion and there is the possibility that the availability of known and unknown substrates to the glands may limit maximal secretion under normal conditions.

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REFERENCES

Annison, E. F. & Linzell, J. L. (1964). *J. Physiol., Lond.* **175**, 372.
Annison, E. F., Linzell, J. L., Fazakerley, S. & Nichols, B. W. (1967). *Biochem. J.* **102**, 637.
Barry, J. M. (1952). *Nature, Lond.* **169**, 878.
Barry, J. M. (1964). *Biol. Rev.* **39**, 194.
Barry, J. M., Bartley, W., Linzell, J. L. & Robinson, D. S. (1963). *Biochem. J.* **89**, 6.
Dimant, E., Smith, V. R. & Lardy, H. A. (1953). *J. biol. Chem.* **201**, 85.
Graham, W. R., Jones, T. S. G. & Kay, H. D. (1936). *Proc. R. Soc.* B **120**, 330.
Gutte, J. O., Kleiber, M., Raggi, F. R. & Black, A. L. (1961). *Z. Tierphysiol. Tierernähr. Futtermittelk.* **16**, 171.
Hardwick, D. C. & Linzell, J. L. (1960). *J. Physiol., Lond.* **154**, 547.
Hardwick, D. C., Linzell, J. L. & Mepham, T. B. (1963). *Biochem. J.* **88**, 213.
Hardwick, D. C., Linzell, J. L. & Price, S. M. (1961). *Biochem. J.* **80**, 37.
Kleiber, M., Black, A. L., Brown, M. A., Baxter, C. F., Luick, J. R. & Stadtman, F. H. (1955). *Biochim. biophys. Acta* **17**, 252.

Kleiber, M. & Luick, J. R. (1956). *Ann. N.Y. Acad. Sci.* **64**, 299.
Kronfeld, D. S. (1965). *Vet. Rec.* **77**, 30.
Kronfeld, D. S., Raggi, F. & Ramberg, C. F. (1966). *J. Dairy Sci.* **49**, 733.
Lascelles, A. K., Cowie, A. T., Hartmann, P. E. & Edwards, M. J. (1964). *Res. vet. Sci.* **5**, 190.
Lascelles, A. K., Hardwick, D. C., Linzell, J. L. & Mepham, T. B. (1964). *Biochem. J.* **92**, 36.
Lintzel, W. (1934). *Lait* **14**, 1125.
Linzell, J. L. (1960*a*). *J. Physiol., Lond.* **153**, 492.
Linzell, J. L. (1960*b*). *J. Physiol., Lond.* **153**, 510.
Linzell, J. L. (1963). *Q. Jl exp. Physiol.* **48**, 34.
Linzell, J. L. (1966). *Circulation Res.* **18**, 745.
Linzell, J. L. (1967*a*). *J. Physiol., Lond.* **190**, 333.
Linzell, J. L. (1967*b*). *J. Physiol., Lond.* **190**, 347.
Linzell, J. L., Annison, E. F., Fazakerley, S. & Leng, R. A. (1967). *Biochem. J.* **104**, 34.
Linzell, J. L., Mepham, T. B., Annison, E. F. & West, C. E. (1967). *Biochem. J.* **103**, 42P.
Mepham, T. B. & Linzell, J. L. (1966). *Biochem. J.* **101**, 76.
Mepham, T. B. & Linzell, J. L. (1967). *Nature, Lond.* **214**, 507.
Peeters, G., Cocquyt, G. & de Moor, A. (1963). *Annls Endocr.* **24**, 717.
Petersen, W. E. & Boyd, W. L. (1937). *Proc. Soc. exp. Biol. Med.* **37**, 537.
Popják, G., French, T. H. & Folley, S. J. (1951). *Biochem. J.* **48**, 411.
Popják, G., French, T. H., Hunter, G. D. & Martin, A. J. P. (1951). *Biochem. J.* **48**, 612.
Popják, G., Glascock, R. F. & Folley, S. J. (1952). *Biochem. J.* **52**, 472.
Rasmussen, F. (1963). *Acta vet. scand.* **4**, 271.
Rasmussen, F. (1965). *Acta vet. scand.* **6**, 135.
Reynolds, M. (1962). *J. Dairy Sci.* **45**, 742.
Reynolds, M. (1965). *Am. J. Physiol.* **209**, 669.
Sopeña, I. (1944). *Revta Fac. Agron. Vet. Univ. B. Aires* **11**, 308.
Verbeke, R. & Peeters, G. (1965). *Biochem. J.* **94**, 183.
West, C. E., Annison, E. F. & Linzell, J. L. (1967*a*). *Biochem. J.* **102**, 23P.
West, C. E., Annison, E. F. & Linzell, J. L. (1967*b*). *Biochem. J.* **104**, 59P.
Wood, H. G., Siu, P. & Schambye, P. (1957). *Archs Biochem. Biophys.* **69**, 390.

The biochemistry of the mammary gland

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As a biochemist I find it useful to think of the mammary gland as a mass of tissue with three principal routes of communication with the outside world: the arterial and venous blood vessels, the afferent and efferent nerves, and the teat orifice. The gland is nourished by components of the arterial blood. Its growth, development and involution are induced by changes in blood composition and rate of flow, by nervous impulses, and by the removal of milk through the teat orifice. Of these routes of communication the blood stream is the most important. Although nervous impulses play a part as, for example, in stimulating the secretion of hormones, nervous connexions to the gland can be severed without disastrous results (Tverskoi, 1957; Linzell, 1960). Also, although the removal of milk through the teat orifice is a factor in stopping and starting milk secretion it is not normally involved in the development of the gland.

Many organic and inorganic compounds, including hormones and metabolic substrates, must be present in the arterial blood for the proper functioning of the gland in all stages of its development. But in this discussion I shall consider only one point: what signals (i.e. changes in blood composition, nervous impulses, etc.) reaching and leaving the mammary gland along the three routes of communication induce its development to full lactation, and then its regression to dryness? This