2. Lactation

Lactation is the most energy-efficient way to provide for the dietary needs of young mammals, their mother's milk being actively protective, immunomodulatory, and ideal for their needs. Intrauterine mammary gland development in the human female is already apparent by the end of the sixth week of gestation. During puberty and adolescence secretions of the anterior pituitary stimulate the maturation of the graafian follicles in the ovaries and stimulate the secretion of follicular estrogens, which stimulate development of the mammary ducts. Pregnancy has the most dramatic effect on the breast, but development of the glandular breast tissue and deposition of fat and connective tissue continue under the influence of cyclic sex-hormone stimulation. Many changes occur in the nipple and breast during pregnancy and at delivery as a prelude to lactation. Preparation of the breasts is so effective that lactation could commence even if pregnancy were discontinued at 16 weeks.

Following birth, placental inhibition of milk synthesis is removed, and a woman's progesterone blood levels decline rapidly. The breasts fill with milk, which is a high-density, low-volume feed called colostrum until about 30 hours after birth. Because it is not the level of maternal hormones, but the efficiency of infant suckling and/or milk removal that governs the volume of milk produced in each breast, mothers who permit their infants to feed ad libitum *commonly observe that they have large volumes of milk 24–48 hours after birth. The two maternal reflexes involved in lactation are the milk-production and milk-ejection reflex. A number of complementary reflexes are involved when the infant feeds: the rooting reflex (which programmes the infant to search for the nipple), the sucking reflex (rhythmic jaw action creating negative pressure and a peristaltic action of the tongue), and the swallowing reflex. The infant's instinctive actions need to be consolidated into learned behaviour in the postpartum period when the use of artificial teats and dummies (pacifiers) may condition the infant to different oral actions that are inappropriate for breast-feeding.*

Comparisons of breast milk and cow's milk fail to describe the many important differences between them, e.g., the structural and qualitative differences in proteins and fats, and the bioavailability of minerals. The protection against infection and allergies conferred on the infant, which is impossible to attain through any other feeding regimen, is one of breast milk's most outstanding qualities. The maximum birth-spacing effect of lactation is achieved when an infant is fully, or nearly fully, breast-fed and the mother consequently remains amenorrhoeic.

Introduction

Lactation is a characteristic of mammals alone, and this ability to provide an ideal food for their young, regardless of the season, confers an evolutionary advantage over other species. Even where food is plentiful, lactation is the most energy-efficient way to provide for the dietary needs of the young. In situations of scarcity, the ability of mammals to efficiently utilize low-quality food resources in order to keep the female alive, to provide high-quality nutrition for the infant, and to regulate births is crucial to the survival of both mother and offspring. This is true in humans no less than in other mammals; as an important survival mechanism, mammals have developed many strategies both to optimize lactation's contribution to the development of the young and to reduce the metabolic burden thereby imposed on the female.

Human lactation is a relatively neglected area of scientific research. In fact, less is known about lactation in humans than in commercially exploited animals, and many of the beliefs and practices that sometimes prevent successful lactation in humans have no parallel in animal husbandry. Because there are still so many unanswered questions about the physiology of human lactation, this chapter will require regular up-dating as it is unable to cover many clinically relevant issues.

Development of the female breast

During intrauterine growth and childhood

Intrauterine mammary gland development is apparent by the end of the sixth week of gestation with the appearance of an ectodermal ridge consisting of 4–6 layers of cells at the site of the glands. These layers gradually thicken and invade the underlying mesenchymal tissue in the following weeks, while the smooth muscle of the areola and nipple develops simultaneously.

At about fifteen weeks, the cells invading the mesenchyme bud into 15–25 epithelial strips, which later become the breast segments. Vascularization and formation of specific apocrine glands (Montgomery glands) occur at the same time. By eight months, canalization is complete and differentiation into alveolar structures takes place, accompanied by

increased vascularization and formation of fat and connective tissue. The mammary connective tissue serves as a carrier of blood vessels and supports the smooth musculature of the areola and nipple. The inner layers surround the mammary ducts and support glandular elements.

The early stages of intrauterine mammary development are independent of any specific hormonal effects. Only the main lactiferous ducts are present at birth. Despite this, the placental sex hormones, which entered the fetal circulation in the last stages of pregnancy, may stimulate the neonatal breast to secrete milk ("witch's milk") at 2–3 days postpartum. This secretion subsides spontaneously in the next days or weeks, and should be ignored; manipulation of the infant's breasts can lead to mastitis. Neonatal breast development then regresses into the small mammary disk of childhood and remains at rest for the most part until pre-puberty (*1*).

During puberty and adolescence

With the onset of hypothalamic maturation in the female at 10–12 years of age, the secretion of gonadotrophins (FSH, LH) from the anterior pituitary stimulates the maturation of the graafian follicles in the ovaries and initiates the secretion of follicular estrogens, which stimulate development of the mammary ducts. The volume and elasticity of the connective tissues surrounding the ducts increase, and vascularization and fat deposition are enhanced. These developments become obvious as an enlargement of the breast disc at about twelve years of age. Thus, estrogens are mainly responsible for breast development for the first 2–3 years after the onset of puberty. The complete development of the breasts into their adolescent size and structure requires the combined effects of estrogens and progesterone, as does the pigmentation of the areola. Although the differentiation of the breast tissue takes place during adolescence, changes in the breast continue throughout a woman's life. Pregnancy has the most dramatic effect on the breast (see below), but development of the glandular breast tissue, and deposition of fat and connective tissue continue under the influence of cyclic sex-hormone stimulation.

Anatomy and morphology of the mature breast

In the mature woman the breast contains perhaps 15–25 segments or lobes of glandular tissue, surrounded by connective tissue. Not every lobe is functional in each lactation, or for the duration of any lactation; particular lobes may regress sooner than others. Women can successfully feed a singleton infant with only one functional breast (*2*), or with only parts of both breasts fully functional. This is well documented after surgery of many kinds, including reduction mammoplasty, breast biopsy or enlargement. Successfully breast-feeding more than one child requires a greater amount of functional glandular tissue, and the recorded value of milk produced by wet-nurses and mothers of twins or triplets (*3*) makes it clear that many women never achieve their potential for milk production. With each subsequent lactation, functional glandular tissue generally increases.

The structure of the breast has been likened to a tree with trunk, branches and leaves: the milk ducts form the trunk and branches linked with the tiny, sac-like alveoli, which are the leaves (*4*). Milk is secreted in the alveoli, of which there are 10–100 clusters in each segment enveloped in collagen sheaths. The sheaths, in turn, prolong the small ducts emptying into the main milk duct. Underneath this collagen sheath is a lining of contractile myoepithelial cells, which surrounds the glandular structure. These cells contract under the influence of oxytocin, assisting milk to flow from the alveoli into the ducts (see below).

The main milk ducts are more distensible in the area just beneath the areola. Some milk collects in what are sometimes referred to as the lactiferous sinuses, which are compressed both during suckling and when milk is expressed by hand. Several milk ducts may merge before they reach the nipple, so that the number of openings in the nipple does not correspond to the number of lobes in the breast.

The nipple is located in the middle of the circular, pigmented areola, which probably serves as a visual marker for the infant. The nipple is usually elevated a few millimetres from the skin surface but its size and shape can vary widely between individuals without any loss of function. The areola contains smooth muscle and collagenous connective tissue fibres in circular and radial arrangements. It is usually 3–5 cm in diameter in adult women, but the range is quite wide. Some women have no visible pigmented area, while on others it may occupy half the breast; both groups lactate successfully.

Both the areola and nipple are heavily innervated. The sensitivity of the nipple-areola complex increases during pregnancy and is greatest in the first few days after birth (*5*). The nipple (like the cornea) contains unmyelinated nerve endings, and so is extremely painful when traumatized by an inadequately positioned infant (*6*) (see below). Appropriate stimulation of the nerve endings causes nipple erection and triggers the pituitary reflex mechanisms that release oxytocin and prolactin. The areola also contains structures related to the apocrine Montgomery glands, which probably serve as both lubricating and scent organs during lactation (*7*).

Changes in the nipple during pregnancy

An increase in nipple sensitivity is one of the first signs of pregnancy in many women. The areola surrounding the nipple may increase in diameter during pregnancy, and the Montgomery tubercles, or glands, increase in prominence and begin secreting a sebaceous substance having anti-bacterial properties. Nipple changes during pregnancy have an effect on the infant's later ability to remove milk efficiently. The nipples enlarge and become more protractile, which has been measured by compressing the areola immediately behind the nipple. The more protractile the nipple and breast tissue behind it, the more easily an infant can breast-feed. It is the protractility of breast tissue (rather than the shape and size of the nipple) that determines whether the nipple can be drawn far enough into the infant's mouth to avoid being traumatized by infant oral activity, and whether the infant has a sufficient mouthful of breast to extract milk efficiently (see below). Infants *breast*-feed; the nipple is the conduit through which milk flows, and probably serves as an oral stimulus to initiate feeding behaviour. Extreme, intractable nipple inversion, which often involves tightness and tethering of breast tissue as well, can make breast-feeding difficult or even impossible (see chapter 3); fortunately, this is rare. It is not unusual, however, for nipple inversion to be mistakenly diagnosed when a normal flat nipple is further effaced during breast engorgement.

Changes in the breast during pregnancy and after delivery

During pregnancy intensive lobular development occurs under the influence of placental lactogen, as well as the luteal and placental sex steroids. Prolactin is increasingly released and contributes to breast development. Ducts and alveoli multiply and develop so rapidly that already at 5–8 weeks in many women the breasts are visibly enlarged and feel heavier, pigmentation of the areola is intensified, and the superficial veins become dilated. However, as glandular development proceeds, fat stores in some women may be mobilized and removed from the breasts, with the result that there is little noticeable change in breast volume, although these women subsequently lactate successfully. After delivery, the volume of each breast grows by an average of about 225 ml (*8*) due to a doubling of blood flow, increased secretion, and development of glandular tissue, partially filled with colostrum, sometimes from mid-pregnancy. Colostrum may leak from the breast, depending on such varied factors as ambient temperature and the tone of the sphincter muscles that control spontaneous outflow. In all these developments there is normally wide variation between individuals but none of these factors is predictive of success or failure in breast-feeding.

During the early months of pregnancy, ductular sprouting is pronounced owing to the influence of estrogen. With an increase in progesterone levels after three months, development of the alveoli exceeds duct formation, and the progressive increase in prolactin stimulates glandular activity and the secretion of colostrum, the earliest milk. The point at which the breasts develop the capacity to synthesize milk constituents is referred to as lactogenesis I (*9*). Larger-volume milk production is inhibited by placental sex steroids, particularly progesterone. This inhibition is so powerful that even small fragments of retained placental material can delay lactogenesis II, or the time when more copious milk secretion begins after birth. The preparation of the breasts for lactation is so effective, however, that lactation could commence even at 16 weeks if pregnancy were discontinued.

Lactation

Onset of lactation

Milk synthesis in the alveoli is a complex process involving four secretory mechanisms: exocytosis, fat synthesis and transfer, secretion of ions and water, and immunoglobulin transfer from the extracellular space. These are of little direct clinical relevance and are reviewed elsewhere (*10*).

Following birth, placental inhibition of milk synthesis is removed, and a woman's progesterone blood levels decline rapidly. The breasts fill with milk, which is colostrum until about 30 hours after birth. At between 30 and 40 hours (*11*) there is a rapid change in milk composition as the amount of lactose synthesized increases and milk volume thus rises, lactose being the most osmotically active milk component. This rise in milk volume usually occurs before a woman notices any breast fullness and engorgement or other signs of the uncomfortable subjective experience that is often described as "milk coming in".

Mothers who permit their infants to feed *ad libitum* commonly observe that they have a large volume of milk by 24–48 hours after birth, but experience no engorgement. It is now thought that the event described as "milk coming in" marks the shift from lactation driven by endocrine control to lactation under autocrine control (*12*), when it is the removal of milk from the breasts, in a continuing favourable hormonal milieu, which governs milk

production. Some mothers may experience this transition from endocrine control to autocrine control as a sensation of fullness and increased warmth in the breasts, as the build-up of intramammary pressure accompanying the build-up of suppressor peptides in the glands begins to down-regulate the volume of milk produced to that required by the baby (i.e., equal to the amount that is being removed from the breasts). Increasing fullness occurs when inefficient milk removal, combined with increased blood flow to the breasts, creates lymphatic oedema, which in turn can contribute to limiting the milk outflow, permitting the accumulation of suppressor peptides, and eventually decreasing the milk secretion (see below).

Because lactation is an energy-intensive process, it makes evolutionary sense that there should be in-built safeguards against wasteful over-production as well as mechanisms to permit a prompt response to increased infant need. Recent research has confirmed that such mechanisms exist in humans as in other mammals. It is not the level of maternal hormones, but the efficiency of infant suckling and/or milk removal, which governs the volume produced in each breast. Both breasts are subject to the same hormonal influences, but the volume each produces corresponds to that removed by the infant. Many women successfully breast-feed from one breast only; in such cases the unused breast involutes.

Maintenance of lactation

Maternal reflexes. The two maternal reflexes involved in lactation are the *milk-production* and *milk-ejection* reflex. Both involve hormones (prolactin and oxytocin, respectively), and both are responsive to lactation's driving force, which is suckling. Stimulation by the infant of nerve endings in the nipple-areola complex sends impulses through afferent neural-reflex pathways to the hypothalamus, resulting in the secretion of prolactin from the anterior pituitary and oxytocin from the posterior pituitary. Other hormones (cortisol, insulin, thyroid and parathyroid hormones, and growth hormone) also support lactation (*13*). Prolactin is a key lactogenic hormone, stimulating the initial alveolar production of milk; it induces messenger- and transfer RNA for milk-protein synthesis, and influences alpha-lactalbumin, and hence lactose synthesis, in the alveolar cells. Other functions of prolactin include water and salt conservation through the kidneys and, possibly, prolongation of postpartum amenorrhoea through its effect on the ovaries; both these functions reduce the metabolic stress of lactation.

As distinct from its role in initiating lactation, the importance of prolactin in sustaining lactation is the subject of considerable scientific debate (*14*). Serum prolactin levels in non-pregnant women are about 10 ng/ml; its concentration gradually increases during pregnancy but decreases sharply after delivery. At four weeks postpartum the mean is about 20–30 ng/ml in lactating women, and 10 ng/ml in non-lactating women. However, the basal serum level of prolactin, at which satisfactory milk production is reached and can be sustained, varies widely between women after the early postpartum period (*15*). Some women lactate successfully with basal prolactin levels equivalent to those of non-lactating women. In early lactation suckling induces a surge of prolactin to about ten times the basal pre-suckling levels after about 20–30 minutes. By three months this response is markedly decreased, and by six months it has virtually disappeared in most women. Yet suckling and the removal of milk allow milk production to be sustained on a supply and demand basis, catering to the infant's needs. For reasons not yet understood, maternal malnutrition is associated with considerable elevation of basal prolactin levels (*16*).

As well as inducing the release of prolactin from the anterior pituitary, the infant's feeding also excites cholinergic fibres in the hypothalamus and stimulates the release of oxytocin from the posterior pituitary. Oxytocin has a short half-life and is secreted predominantly in short pulses. Since it is very difficult to assay (*17*), little is known about the levels of oxytocin in pregnant, non-pregnant, and lactating women. However, it is estimated that about 100 mU oxytocin are released in ten minutes of breast-feeding (*18*). It is not known whether this is affected by the large doses of oxytocin that are used to augment labour. Oxytocin contracts the myoepithelial cells, forcing the milk out into the ducts. The force of the contractions can initially be very strong and painful for some women, and the milk can be ejected many centimetres from the breast; more usually it simply drips from one breast as the infant drinks from the other.

Mothers may experience this milk-ejection reflex, or milk "let-down", as a warm and tingling sensation in the breast, or as a feeling of pressure, or they may not notice it at all unless they watch the baby's feeding rhythm. Intramammary pressure does rise, and increased blood flow is obvious with thermography. Contractions in the uterus are also induced; this assists speedy and complete uterine involution, but can be extremely painful, particularly for multigravid mothers, for some days after delivery (*19*). These women may need explanation and reassurance and, in severe cases, some form of pain relief.

The importance of oxytocin to milk release varies according to the mammalian species. Traditional dairy animals have large lactiferous sinuses, or

cisterns, which allow for up to 50% of milk to be obtained independently of the milk-ejection reflex. In species not so equipped—including rats, rabbits, pigs, dogs and humans—very little milk can be obtained in the absence of the milk-ejection reflex. However, serious defects in this reflex are clinically rare. It seems to be most sensitive to disturbance during the early neonatal period, which underlines the importance of allowing women to breast-feed under conditions that they find comfortable.

The milk-ejection reflex responds not only to tactile stimuli but can be triggered by visual, olfactory, or auditory (*20*) stimuli (particularly in the early days of lactation); it can also be conditioned (*21*). Physical closeness to, or thinking about, an infant can trigger milk ejection in some women through a contraction of the myoepithelial cells. This can occur in some women years after lactation has ceased, even though ejection is not possible in the absence of milk. Conversely, this reflex can be temporarily inhibited by the effects of adrenalin (*22*), e.g., in some women subject to sudden, extremely unpleasant, or painful physical or psychological stimuli.

Minor or chronic stress has not been shown to affect the milk-ejection reflex other than to delay it slightly. Some women do experience a genuine inability to release milk even when their breasts are obviously full. The most usual explanation for this is not psychological but physical; owing to limited suckling their breasts are overfull, and the resulting extreme back-pressure prevents oxytocin from contracting the myoepithelial cells. Warmth, pumping, or skilful hand-expression of some milk can decrease this pressure and enable the reflex to operate. Temporary inhibition, or simple delay in milk ejection, is relatively common. It can be readily overcome by cajoling the infant to persevere for the minute it may take for the suckling stimulus to operate. Unfortunately, in cases where women are subjected to negative messages about their capacity to lactate, this temporary inhibition of milk ejection is frequently misinterpreted as a sign of "milk insufficiency"; the introduction of supplementary feeds only contributes to making the feared insufficiency a reality (see chapter 3).

The responsiveness of the milk-ejection reflex explains why successful breast-feeding has been described as a "confidence trick". If a mother truly believes that she can provide milk for her infant, she will encounter few problems with milk let-down, even in the stressful conditions and overwork experienced by most of the world's lactating women. Research from the Gambia confirms this (*2*). If, on the other hand, a woman believes that modern life is incompatible with full breast-feeding, she may be more inclined to interpret any difficulties encountered—ironically, even those arising from producing too great a volume—as being due to too little milk. Women need basic information about the mechanics of breast-feeding and the reliability of lactation; as a survival mechanism it is not easily disturbed except by powerful physiological forces, or interference with its basic mechanism, appropriate suckling.

Nineteenth century ignorance of these basic physiological facts and of the adverse conditions under which lactation proceeds uneventfully the world over accounts for this same era's traditional insistence that "the secretion of milk proceeds best in a tranquil state of mind and a cheerful manner" (*23*). Relaxed interaction with one's infant is no doubt preferable for a host of reasons, but it is also a luxury that is unavailable to many women. Even the original sudden painful experiments used to demonstrate inhibition of milk ejection under stress showed that the effect was short-lived (*24*) and reduced, rather than prevented, milk transfer.

Both oxytocin and prolactin affect a mother's mood and physical state, and the latter hormone is considered crucial to appropriate maternal behaviour in various species. The effects of bromocriptine or other prolactin-antagonists on mother–infant interaction have not been studied. New research about oxytocin (*25*) suggests that it, too, is a "bonding" hormone, with important consequences for relationships between both sexual partners and mother and child. Recent studies have begun to explore how the chosen feeding method affects a mother's subsequent adjustment to her infant (*26*).

Infant reflexes. The normal full-term human infant at birth is equipped to breast-feed successfully. Like other mammalian newborns, left to their own devices human infants will follow an innate programme of pre-feeding behaviour in the first hours after birth that can include crawling from the mother's abdomen to her breast, coordinated hand-mouth activity, active searching for the nipple while the mouth gapes widely, and finally, attaching well to the breast and feeding vigorously before falling asleep—all this within 120–150 minutes after delivery (*27*). The key to lactation maintenance is appropriate infant-feeding behaviour, which means emptying the breasts efficiently, frequently, and for long-enough periods both to maintain lactogenic hormonal levels and to prevent the build-up in the breasts of compounds that suppress lactation (see below).

A number of complementary reflexes are involved when the infant feeds. The *rooting reflex* programmes the infant to search for the nipple while gaping widely enough to take in a good mouthful of

breast tissue. When the infant's cheek or mouth is touched, the infant gapes and turns towards the stimulus, attempting to grasp it orally. The *sucking reflex* is triggered when something touches the palate. In fact, "sucking" is something of a misnomer for this action, which consists of rhythmic jaw action creating negative pressure, and a peristaltic action of the tongue, which strips milk from the breast and moves it to the throat, where it triggers the swallowing reflex. This feeding action also stimulates the synthesis and secretion of lactogenic hormones that evoke the mother's milk-production and ejection reflexes, and removes the peptides that might suppress alveolar milk synthesis. Recent ultrasound studies have provided excellent illustrations (*28*) of this process of breast-feeding; it differs markedly both from previous verbal descriptions of how infants breast-feed and from printed descriptions of how infants feed from artificial teats.

In the normal neonate, breast-feeding reflexes are already strong at birth. Indeed, evidence now confirms that some infants as young as 32 weeks gestation and as small as 1200 g are capable of breast-feeding efficiently even before they can feed from artificial teats, which are associated with hypoxia and bradycardia in premature infants (*29*). However, these crucial reflexes may be weak or absent in extremely pre-term or very-low-birth-weight (see chapter 5) or sick infants. Cerebral damage, congenital defects, generalized infection (septicaemia), and severe jaundice may also cause feeding difficulties. Physical defects such as cleft lip or palate (see chapter 3) pose individual challenges, depending on the interaction between the defect and the mother's breast. However, the most common causes of decreased efficiency of these reflexes are in fact iatrogenic: obstetrical sedation or analgesia (see chapters 1 and 3), and interference in the process of learning in the period after birth. The infant's instinctive actions need to be consolidated into learned behaviour in the postpartum period. The use of other oral objects, whether teats or dummies (pacifiers), in the neonatal period may condition the infant to different oral actions that are inappropriate for breast-feeding.

In the early postpartum period, lactational reflexes are particularly responsive to changes in suckling frequency, duration and adequacy. To *initiate* breast-feeding successfully, infants should be allowed to breast-feed within an hour of birth, when both their reflexes and their mother's sensitivity to tactile stimuli of the areola and nipple are strongest. To *establish* breast-feeding successfully, factors that decrease the duration, efficiency and frequency of infant suckling should be eliminated as far as possible (*30*). These factors include limitation of feeding time, scheduled feeds, poor positioning, the use of other oral objects, and giving the infant other fluids, e.g., water, sugar solutions, and vegetable- or animal-milk products. The giving of formula milk not only decreases an infant's appetite for breast milk, but also increases the risk of infection and allergy (*31*). Ideally, mothers and babies should be left in close skin contact after an uncomplicated delivery without use of drugs; recent Swedish studies have shown that separation from the mother and analgesia during labour (*32*) were the factors most closely associated with suckling difficulty. Following this early contact, mothers should be encouraged to feed their infants as often and as long as needed. Excessively long feeds or the development of nipple trauma indicate that help is required (*33, 34*). The use of creams, lotions, sprays or other applications for sore nipples has little proven basis and may in fact only create additional problems, which increase the risk of further trauma (*35*) (see Annex 1).

Cessation of lactation

Milk secretion continues for some time after the cessation of suckling. In normal circumstances, lactation will continue in each breast for as long as milk is being removed from it. As the volume of milk decreases, its composition changes; higher levels of fat, sodium and immunoglobulins, and lower levels of lactose are usual (*36*). Although most mammals "dry up" within 5 days of the last suckling episode, the period of involution in women averages 40 days. Within this period it is relatively easy to re-establish full lactation if the infant resumes frequent suckling. In many societies weanling children do revert to full breast-feeding when challenged by disease, and thus a process of gradual involution has obvious advantages for the infant; it also has advantages for the mother. In abrupt weaning, it takes two days for immunoglobulin and lactoferrin levels to rise, which leaves the breast vulnerable to infection. This is undoubtedly part of the reason for higher rates of abscess formation in women with mastitis who stop feeding from the affected breast (see chapter 3).

As discussed earlier, after the initial period the breasts are under autocrine control; it is the build-up in the glandular tissue of inhibiting peptides that brings about the cessation of milk secretion. This makes the management of early lactation, and of mastitis, particularly important. Whenever unphysiological feeding practices prevent the efficient removal of milk, secretion will decrease. Virtually all women initially produce more milk than their infants can consume. The breasts should not be permitted to become over-full, tight and lumpy at any time during

the first week. Women should be shown how to check their breasts for lumpiness (particularly in the axilla and around breast margins); to recognize obstruction of outflow building up in the breast; and to relieve this by gentle hand expression or other means. Otherwise whole lobes of breast tissue may stop secretion, as they will when outflow is impeded by permanent damage such as scar tissue from burns or reconstructive surgery. (In most surgical patients a carefully supervised trial of lactation is advised, as many functional lobes may retain outlets that permit full or partial lactation.) Fortunately, in the normal postpartum woman, the decrease in secretion is likely to be temporary if the infant continues to suckle, and the mother does not supplement with artificial feeds. The milk output seems to be most sensitive in the first weeks to the suckling stimulus and the amount of milk removed, although at all stages of lactation increased suckling frequency will result in increased milk supply, usually after about 48 hours (*37*).

Breast-milk composition

Breast milk and its precursor, colostrum, ensure the neonate's adaptation and successful transition to independent postnatal life. Colostrum is a sticky yellowish fluid which fills the alveolar cells during the last trimester of pregnancy, and is secreted for some days after birth (*38*). Even where a mother has been feeding an older child throughout pregnancy, her milk will go through a colostral phase just before and after the new birth. The amounts of colostrum secreted vary widely, ranging from 10 to 100 ml/day, with a mean of about 30 ml. This secretion gradually increases and achieves the composition of mature milk by 30–40 hours after birth.

Colostrum is a high-density, low-volume feed. It contains less lactose, fat and water-soluble vitamins than mature milk, but more protein, fat-soluble vitamins (including vitamins E, A, and K) and more of some minerals such as sodium and zinc. It is so high in immunoglobulins and a host of other protective factors that it could be described as nature's prescription as well as nature's food. Colostrum is well-matched to the specific needs of the neonate; immature infant kidneys cannot handle large volumes of fluid without metabolic stress; the production of lactase and other gut enzymes is just beginning; anti-oxidants and quinones are needed for protection against oxidative damage and haemorrhagic disease; immunoglobulins coat the immature gut lining of the infant, preventing adherence of bacterial, viral, parasitic and other pathogens; and growth factors stimulate the infant's own systems in ways science is just beginning to understand. Colostrum, like the milk to come after it, acts as a modulator of infant development. To dilute its effects by giving water, or negate them by adding other foreign substances to the infant's gastrointestinal tract, is not easily justified.

Colostrum evolves into mature milk between 3 and 14 days postpartum. Mature breast milk has hundreds of recognized components. It is variable in composition not only between mothers, but also in the same mother between breasts, between feeds, and even during a single feed, as well as over the course of lactation. These variations are not considered random but functional, while the infant's role in determining milk variability is increasingly seen as important. Human milk has the potential to meet an infant's individual needs as does the milk of other mammalian species (e.g., the red kangaroo, which provides two quite different milks from different teats for young of different ages). Women feeding twins who have a consistent breast preference sometimes find that their breasts are producing individually tailored milks. As lactation winds down and the breasts involute, regression milk resembles colostrum in its high level of immunoglobulins, which protect both the weanling and the breast itself.

Comparisons of the composition of breast milk and cow's milk, as well as some usual western breast-milk substitutes, are widely available. While they list some of the hundreds of components in milks, they fail to describe the many differences between them. For example, bovine-milk proteins, whether whey or casein, are structurally and qualitatively different from human-milk proteins, and may generate antigenic responses. Bovine lactoferrin may act quite differently in the human infant than it does in the calf; differences in the external carbohydrate structure of the protein may mean that infant receptors for human lactoferrin cannot lock onto, and release, the minerals taken up by bovine lactoferrin. The relative bioavailability of trace minerals (see below) is not obvious from a mere quantitative listing, nor are the qualitative differences between the saturated fats of human milk and atherogenic saturated vegetable fats such as coconut oil (*39*) obvious from tables listing fats by category. Mammalian milks are all fluids of great complexity, uniquely suited to the needs of the young of the species concerned.

Protein

Mature human milk has the lowest protein concentration among mammals. Based on findings from the WHO study concerning the quantity and quality of breast milk (*40*), average protein content is accepted as being 1.15 g/100 ml, except during the first month when it is 1.3 g/100 ml, calculated on the basis of total nitrogen × 6.25 (*41*). There are wide variations

between mothers, however, as in the case of ten mothers whose total protein content on the eighth day postpartum was found to range from 1.13 to 2.07 g/100 ml (*42*). Such differences in milk composition may help explain the equally wide variation in milk intakes observed in thriving breast-fed infants, who are permitted to self-regulate their intake. Some studies have shown that the actual protein content of human milk, when determined on the basis of amino acids, is about 0.8–0.9 g/100 ml (*43*); non-protein nitrogen (mostly urea (*44*)) accounted for the other 25–30% of total nitrogen. Nutritionally available protein may be even less than 0.8 g/100 ml when a correction is made for those whey proteins (the anti-infective proteins such as secretory IgA, lysozymes and lactoferrin) that resist proteolysis and are therefore not absorbed. These low breast-milk protein levels are nevertheless more than adequate for optimal growth in young infants, and result in an appropriately low solute load for the infant's immature kidneys.

In the light of this new information, it is now considered that the total protein content of breast-milk substitutes should be lowered even further. Infants fed artificially, whether on the latest whey- or casein-dominant formulas, have elevated blood urea and amino acid levels, and thus higher renal solute loads (*45*); neither the short- nor long-term metabolic consequences of this finding are known. The high protein and salt content (and consequent renal solute load) of breast-milk substitutes until the 1970s was linked to hypernatraemic dehydration (*46*). While most infants appear to be remarkably capable of adapting in the short term to this unphysiological metabolic stress, little research has been done on its possible relation to adult circulatory or renal disease (see chapter 4).

The whey : casein ratio of human milk is roughly 80:20, that of bovine milk 20:80, while that of breast-milk substitutes varies from 18:82 to 60:40. It is not clear, however, that modifying the bovine protein ratios to the same as human protein will result in improved absorption and serum amino-acid levels that are closer to those of the breast-fed infant (*47*). Some studies have shown that casein-dominant breast-milk substitutes achieve a more physiological plasma profile than whey-dominant substitutes (*47*). Although there are similarities, no bovine-milk protein is identical to any human-milk protein; indeed, they are quite different. The human whey proteins consist mainly of human alpha-lactalbumin, an important component of the enzyme system in lactose synthesis. The dominant bovine whey protein, bovine beta-lactoglobulin, has no human-milk protein counterpart, although it is capable of contaminating the milk of women who themselves drink cow's milk, and provoking antigenic responses in atopic infants (*48*). Human milk's high whey:casein ratio results in the formation of a softer gastric curd, which reduces gastric emptying time (*49*) and facilitates digestion.

Human milk has higher levels of the free amino acids and cystine, and lower levels of methionine, than does cow's milk. Human milk's cystine: methionine ratio is 2:1, which is almost unique for animal tissues and resembles that of plant tissues (*40*). Cystine is essential for the fetus and pre-term infant because the enzyme cystathionase, which catalyses the transulfuration of methionine to cystine, is lacking in the brain and liver (*50*). The level of another amino acid, taurine, is also high in human milk. Taurine is necessary for the conjugation of bile salts (and hence fat absorption) (*51*), in addition to having a role as a neurotransmitter and neuromodulator in the development of the central nervous system. Because infants, unlike adults, are unable to synthesize taurine from cystine and methionine, it has been suggested that taurine should be conditionally considered an essential amino acid for young children (*52*). Breast milk meets this need; taurine has been added to some breast-milk substitutes since 1984. There are many other differences in milk protein quantity and quality, which have been reviewed elsewhere (*53*).

Fat

With few exceptions, the fat content of mature human milk is ideally suited to the human infant, and it evokes a unique physiological response (*54*). Fat concentrations increase from about 2.0 g/100 ml in colostrum to the mature level of a mean of 4–4.5 g/100 ml at fifteen days postpartum; they remain relatively stable thereafter, although there are considerable inter-individual variations both in total fat content and fatty acid composition (*55*). Fat is the most variable of milk constituents (*56*). Circadian fluctuations in fat concentrations occur, with highest concentrations usually recorded in the late morning and early afternoon (*57*). Variations also occur within feeds; in some women fat concentration in hindmilk is 4–5 times greater than in foremilk. The increased fat in hindmilk was believed to act as a satiety regulator, although this could not be demonstrated when infants were bottle-fed milks of varying fat content (*58*). However, because later stages of a feed, when milk volume is lower, may be providing a considerable proportion of an infant's total caloric intake for that feed, there should be no arbitrary time limit on any feed (*59*). Infants are capable of regulating their energy intake by mechanisms not yet under-

stood. Because hindmilk provides a higher energy intake, it is important that a mother who is expressing milk should not simply collect foremilk such as "drip milk" (that collects spontaneously in breast shells worn for the purpose). Such milk would be of inadequate caloric value and particularly unsuitable for preterm infants unless enriched with fat from other batches of human milk (*60*).

Human-milk fat is secreted in microscopic globules that are smaller than those in cow's milk. Triglycerides dominate, with 98% of the lipids enclosed in the globules. The globular membranes are composed of phospholipids, sterols (especially cholesterol) and proteins. The fatty-acid composition of human milk is relatively stable, consisting of about 42% saturated, and about 57% unsaturated, fatty acids (*61*). Although the concentrations of linoleic acid and other polyunsaturated fatty acids are influenced both by maternal diet and by maternal body fat composition, all human milk is rich in long-chained polyunsaturated fatty acids, which are important in brain development and myelinization. Most breast-milk substitutes contain little or none of these (*62–64*), although in 1989 some manufacturers planned to add them. Cow's milk has higher concentrations of short- and medium-chained fatty acids which, in the 1960s and 1970s, sometimes combined with the higher casein content of earlier breast-milk substitutes to form insoluble soaps responsible for milk bolus obstruction and intestinal perforation in term infants. Regrettably, this problem has recently re-emerged in sick preterm infants being fed high-density breast-milk substitutes (*65*, *66*).

Among the polyunsaturated fatty acids, arachidonic and linoleic acids are particularly important. Arachidonic acid is considered essential during infancy because linoleic acid *in vivo* is not as readily convertible into arachidonic acid. The content of these two fatty acids is about four times higher in human than in cow's milk (0.4 g and 0.1 g/100 ml, respectively). Prostaglandins, whose synthesis is dependent on the availability of these essential fatty acids, are widely distributed in the gastrointestinal tract (*67*). They affect a variety of physiological functions that enhance digestion as well as the maturation of intestinal cells, and thus contribute to the overall host defence mechanisms. Human milk can contain significant quantities of prostaglandins (*68*); breast-milk substitutes contain none. Human milk also contains other lipid-associated antiviral compounds.

While glucose is the fetus' main energy source, the infant is highly dependent on fats for energy; breast milk provides 35–50% of daily intake in the form of fats. The infant begins to consume this high-fat diet at a time when both pancreatic lipase secretion and the efficiency of bile salt conjugation are immature (*69*). Their immaturity is partially compensated for by lingual and gastric lipases, but the presence of a non-specific lipase in human milk is particularly significant. This enzyme is activated by bile salts in the duodenum and thus contributes to the infant's fat digestion, which is a feature that is absent from most other milks. In fact, humans and gorillas are the only two mammals that provide their offspring with both a substrate and its enzyme in the same fluid. When fresh breast milk is the main source of fat, it is estimated that the bile salt-stimulated lipase will contribute to the digestion of 30–40% of triglycerides within 2 hours. This process proceeds *in vitro* as well as *in vivo*. It is particularly important in the feeding of preterm infants, whose bile salt and pancreatic lipase production is even more depressed (see chapter 5). However, unheated breast milk should be used since milk lipase is destroyed by heating (*70*). Lipase is only one of dozens of enzymes present in human milk (see below), and it acts as a metabolic modulator for the infant in ways that no other food can mimic.

Human milk is uniformly rich in cholesterol, the importance of which is still not understood. There is conflicting evidence from laboratory animals which suggests that early exposure to cholesterol may affect adult handling of this important lipid. It is not known whether the presence or absence of bovine cholesterol in breast-milk substitutes is an advantage to the artificially fed infant. Without further research in this area, reliable dietary guidelines for children under two years of age cannot be formulated, despite accumulating evidence suggesting that dietary factors in infancy are involved in the later development of cardiovascular disease (*71*) (see chapter 4).

Lactose

Lactose is human milk's major carbohydrate, although small amounts of galactose, fructose, and other oligosaccharides are also present. It is a sugar found only in milk, and human milk contains the highest concentrations (an average of 4% in colostrum, increasing to 7% in mature milk). Lactose appears to be a specific nutrient for infancy, since the enzyme lactase is found only in infant mammals. Lactase persists among Europeans and some other populations, but most people do not tolerate lactose after middle childhood; foods containing lactose can thus cause intestinal disturbance.

Lactose furnishes about 40% of energy needs but also has other functions. It is metabolized into glucose (used for energy) and galactose, a constituent of the galactolipids needed for the development of the

central nervous system. It facilitates calcium and iron absorption, and promotes intestinal colonization with *Lactobacillus bifidus*. These fermentative bacteria promote an acidic milieu in the gastrointestinal tract, inhibiting the growth of pathogenic bacteria, fungi and parasites. The growth of *L. bifidus* is further encouraged by the presence in human milk of a nitrogen-containing carbohydrate, the bifidus factor, which is not found in bovine-milk derivatives. Food supplements given in the first days after birth interfere with this protective mechanism (*72*). Ruminant animals require a different gut flora and ecology; artificially fed infants are thus colonized predominantly with coliform and putrefactive bacteria, and their stools have a higher pH value. It is usual to find reducing substances such as sugars in the stools of healthy breast-fed infants; they contribute to maintaining the acid environment that retards the growth of pathogens. In contrast, the delayed gut transit time of industrially prepared milks (*73*) permits almost total metabolism of these sugars.

Primary lactose intolerance is a rare congenital anomaly (see below). Varying degrees of temporary lactose intolerance can occur with any condition that damages the intestinal brush border and results in a loss of lactase (e.g., rotavirus, *Giardia lamblia*, or cow's-milk protein intolerance). Without the enzyme to metabolize it, lactose is fermented by gut bacteria, producing an extremely acid stool, which can itself further damage the brush border. The infant experiences abdominal pain; passes frequent, frothy, liquid stools; and, in extreme cases, may fail to thrive or be at risk of dehydration. Only rarely is it necessary to briefly interrupt breast-feeding; indeed, breast-feeding should almost always continue, and even increase, during periods of diarrhoea (see chapter 6).

Another situation of relative lactose intolerance has recently been postulated, the cure for which is a simple change in breast-feeding management. Mothers may find that they have irritable, unsettled, "colicky" babies whose stools are frequent and liquid, who pass urine and regurgitate frequently, but who are otherwise thriving; they may be gaining weight well or poorly. It is hypothesized that when a mother, who typically has more than enough milk, fails to allow her infant enough time at the first breast and, instead, changes sides after a pre-determined period, the infant may ingest a feed that is too high in lactose and too low in fat (*74*). Lactose intolerance is sometimes resolved within 24 hours if a mother lets her infant "finish" the first breast before offering the second when it is clear that the infant is not satisfied. After a day or two of feeding by choice from one breast, supply will diminish and the infant will insist on feeding from both breasts at each feed, but without the symptoms of apparent lactose intolerance. This theory is supported by the observation that many such unsettled infants have higher than average breath-hydrogen levels (*75*).

Despite the apparent importance of lactose for normal infants, not all breast-milk substitutes contain this carbohydrate. This is understandable in the case of formulas designed for short-term therapeutic use by lactose-intolerant infants. The short- and long-term consequences of feeding lactose-free substitutes to healthy infants from birth are unknown. Likewise, the role of the other oligosaccharides in human milk is under-researched, although they make up 25% of colostrum, and at least one—the carbohydrate known as the bifidus factor—prevents microbial colonization.

Vitamins

Vitamin concentrations in human milk are almost always adequate for infant needs, although they can vary with maternal intake. Given the variability of fat concentrations in human milk, and the relationship of fat to maternal diet, infant intakes of fat-soluble vitamins can differ markedly. The concentration of vitamin A in human milk is higher than in cow's milk except among deficient populations (*76*), and there is twice the amount in colostrum than in mature milk. In the second year of life, vitmin A deficiency is more common among infants weaned early than among those who are still breast-fed.

In the immediate post-partum period the concentration of vitamin K is higher in colostrum and early breast milk (*77*) than in later milk. However, after two weeks vitamin K-supplying intestinal flora will be established in breast-fed infants. Where infants are deprived of colostrum, or of hindmilk, the risk of haemorrhagic disease is greater than in artificially fed infants, unless vitamin K is provided soon after birth. Oral doses are used by some clinicians (see chapter 3); research into their efficacy would benefit those infants in situations where injections are not desirable.

The vitamin E content of human milk usually meets the needs of the infant unless a mother is consuming excess amounts of polyunsaturated fats without a concomitant increase in vitamin E intake.

The vitamin D content of human milk is low (an average of 0.15 μg/100 ml), and for some years it was considered insufficient to meet the needs of the infant, even though exclusively breast-fed infants do not routinely develop a deficiency. Later, the presence of water-soluble vitamin D in the aqueous phase of milk was discovered in concentrations as high as 0.88 μg/

100 ml (*78*). Debate ensued as to the biological significance of this water-soluble vitamin D, and it is now understood that the optimal route for vitamin D ingestion in humans is not the gastrointestinal tract, which may permit toxic amounts to be absorbed. Rather, the skin is the human organ designed, in the presence of sunlight, both to manufacture vitamin D in potentially vast quantities and to prevent the absorption of more than the body can safely use and store. It takes only brief exposure to sunlight to produce sufficient vitamin D; to satisfy a week's requirements for white infants in a midwestern US city the exposure time is 10 minutes unclothed or 30 minutes with only the head and hands exposed (*79*). The only groups at risk of vitamin D deficiency are women and children who do not eat marine oils and who are totally covered and not exposed to daylight.

Variations in water-soluble vitamins can occur, depending on the maternal diet, but levels are generally more than ample in the milk of well-nourished mothers. Case-reports of deficiencies in infants are rare, even among poorly nourished women or vegan women who are more at risk of vitamin B deficiencies. The concentration of vitamin B_{12} is very low in human milk, but its bioavailability is enhanced by a specific transfer factor. Concentration of niacin, folic acid, and ascorbic acid is generally higher than in the milk of ruminants. Special care is required in environments where a deficiency in some vitamins is endemic, for example vitamin A or thiamine (*80*). Long-term users of oral contraceptives may also have lower levels of vitamin B_6 in their milk. Although mothers may fail to demonstrate clinical signs, their milk can still be deficient in these vitamins with adverse consequences for their infants. Improving the mother's diet, which is a priority in its own right, is the most cost-effective way of preventing any vitamin deficiency in the breast-fed infant.

Minerals

The concentration of most minerals in breast milk, e.g., calcium, iron, phosphorus, magnesium, zinc, potassium, and fluoride, will not be significantly affected by maternal diet. Compensatory mechanisms, such as decreased urinary calcium excretion, come into play, and only in extreme cases will a mother's own reserves or tissues be significantly depleted. In these cases the post-lactational recovery period is of great importance. In the case of fluoride, it appears that the breast inhibits passage into the milk of any but trace amounts (*81*).

Mineral concentrations are lower in human milk than in any breast-milk substitute, and are thus better adapted to the infant's nutritional requirements and metabolic capacities. Calcium is more efficiently absorbed because of human milk's high calcium:phosphorus ratio (2:1). The higher phosphorus concentration of cow's milk leads to preferential absorption of phosphorus and is responsible for neonatal hypocalcaemia, which is more common among artificially than breast-fed infants. Calcium availability from cow's milk is decreased even further by the formation of insoluble calcium soaps in the gut, which can cause intestinal obstruction and perforation (see above). The calcium:phosphorus ratio of breast-milk substitutes has generally been modified to improve calcium absorption, although their range is still considerable.

Similarly, the high bioavailability of human-milk iron is the result of a series of complex interactions between the components of breast milk and the infant's body. The higher acidity of the gastrointestinal tract; the presence of appropriate levels of zinc and copper; the transfer factor lactoferrin, which prevents iron from being available to intestinal bacteria and releases it only when specific receptors unlock the lactoferrin molecule—all these factors are important to increase iron absorption. Up to 70% of breast-milk iron is absorbed, compared with 30% in cow's milk and only 10% in breast-milk substitutes (*82*). To compensate, large amounts of supplemental iron have to be added to substitutes, which favours the development of pathogenic gut bacteria.

Iron-deficiency anaemia is extremely rare in infants fed only breast milk during the first 6–8 months of life. Indeed, healthy infants born at term to well-nourished mothers have sufficient hepatic iron stores to meet their needs for the better part of the first year (*83*). Early introduction of other foods in the diet of the breast-fed infant can alter this picture, however (see chapter 4). It has been shown, for example, that pears chelate breast-milk iron, making it insoluble and rendering it unavailable to the infant (*84*). Even supplemental iron may cause problems by saturating lactoferrin, thus decreasing its bacteriostatic effect, and encouraging the growth of pathogens, some of which can cause sufficient gut damage and microscopic bleeding to produce iron-deficiency anaemia (*85*). At the same time, providing additional iron can reduce zinc or copper absorption. While there are specific indications for infant iron supplementation, e.g., extreme prematurity and considerable neonatal blood loss, they are not without risk. See chapter 5.

In populations where the prevalence of iron deficiency is high there are many women who enter pregnancy already suffering from various degrees of anaemia. In such situations full therapeutic doses of a well absorbed iron salt are obviously needed (*86*). On the other hand, in many developed countries most

women enter pregnancy not only with normal haemoglobin concentrations but also with a reserve of iron of 200–300 mg. The supplementation required in such instances is less, since all that is required is a daily dose of iron sufficient to meet the increased needs of pregnancy, which in the second and third trimesters is about 5–6 mg daily (*86*). More study is needed on the effect of routine iron supplementation during pregnancy of healthy, non-anaemic women; one recent study shows that both folate and iron-folate supplements decreased the maternal serum zinc levels within 24 hours (*87*).

The above recommendations, however, relate exclusively to the iron status of the mother. Most studies, based either on the measurement of ferritin in the newborn (*88, 89*) or the later development of anaemia (*90, 91*) suggest that iron status at birth is little dependent on the iron nutrition of the mother. Similarly, there is no evidence that maternal iron status bears any relationship to the iron-content of breast milk (*83*).

Zinc is essential to enzyme structure and function, growth, and cellular immunity. The amounts of zinc in human milk are small but sufficient to meet the needs of infants without disturbing copper and iron absorption; its bioavailability is high compared with the zinc added to breast-milk substitutes. Human milk is therapeutic in cases of acrodermatitis enteropathica, which is a disease associated with zinc deficiency. Although occasionally reported in breast-fed infants, this condition is far more common among the artificially fed. The level of available zinc varies widely in breast-milk substitutes, and soya formulas have been found to be deficient in this regard (*92*). High zinc:copper ratios have been associated with coronary heart disease; the corresponding ratio in breast milk is lower than that of the usual substitutes.

Trace elements

Once again there are substantial differences between trace elements in human milk and any substitute; only a few can be mentioned in a review of this nature. In general, the breast-fed infant is at little risk of either a deficiency or an excess of trace elements. Copper, cobalt and selenium levels in human milk are generally higher than in cow's milk. Enhanced bioavailability of breast-milk copper results from its binding with proteins of low relative molecular mass. Copper deficiency, resulting in a hypochromic microcytic anaemia and neurological disturbances, occurs only in artificially fed infants (*93, 94*). At three months of age, selenium status is better in exclusively breast-fed than in mixed or artificially fed infants (*95*). Breast-milk selenium levels are slightly lower in areas where soils are selenium-deficient. However, bovine milk selenium is affected even more markedly by dietary intake, varying by as much as 100-fold. There is considerable discussion about the appropriate level of selenium in breast-milk substitutes (*96*). Levels of chromium (*97*), manganese (*98*) and aluminium (*99*) may be up to 100 times greater than in human milk, and some effects on later learning and on bone growth have been postulated. Recently, lead and cadmium have been shown to contaminate formulas still stored in soldered cans (*100*). Dietary lead intake is much lower in breast-fed infants, even where drinking-water exceeds the WHO standard (0.1 μg lead per ml) (*101*). Iodine can be concentrated in milk. In addition, the topical use of iodine (e.g., in skin washes) can affect the breast-fed infant's thyroid function (*102*).

With minerals as with other nutrients, there are many significant differences between human milk and substitutes. Great advances in knowledge about mineral interactions and bioavailability have occurred in the last decade (*103*). It is now recognized that the ability of breast-milk substitutes to provide adequate levels of nutrients cannot be predicted from their compositional analysis alone, and that growth by itself is not a sufficiently sensitive indicator of all possible adverse outcomes due to deficiency or excess. Further study is required on these and other components, including nickel, vanadium, tin, silicon, arsenic and cadmium.

Other substances

Human milk is not only a source of nutrients uniquely adapted to the infant's metabolic capacities; recent research has indicated that it may even exercise a degree of control over metabolism, from the subtleties of cell division to infant behaviour (*104*), as well as over the development and maintenance of breast function. Some hormones (*105*) present in milk have already been mentioned (oxytocin, prolactin, adrenal and ovarian steroids, and prostaglandins). A full list would also include Gn-RH (gonadotropin-releasing hormone), GRF (growth hormone releasing factor), insulin, somatostatin, relaxin, calcitonin, and neurotensin at levels greater than those in maternal blood; and TRH (thyrotropin-releasing hormone), TSH (thyroid-stimulating hormone), thyroxine, triiodothyronine, erythropoietin, and bombesin at levels less than in maternal sera. The evidence that endocrine responses differ between breast-fed and artificially fed infants is reviewed elsewhere (*106*). In addition, hormonal release may be influenced by compounds in milk such as the human beta-casomorphins, which are peptides with opioid activity that may also affect the neonatal central nervous system. Nucleotides (affecting fat absorption)

and numerous growth factors are present in human milk. The latter include epidermal growth factor (EGF), insulin-like growth factor (IGF-I), human milk growth factors (HMGF-I, II, and III), and nerve growth factor (NGF). Their role in the development of the infant is only just beginning to be elucidated (*107*).

The dozens of enzymes in human milk have a multi-functional origin. Some reflect the physiological changes occurring in the breasts; others are important for neonatal development (proteolytic enzymes, peroxidase, lysozyme, xanthine oxidase); still others augment the infant's own digestive enzymes (alpha-amylase and bile salt-stimulated lipase). Many are found in much higher concentrations in colostrum than in mature milk, e.g., lysozyme whose concentration is about 5000 times greater in human than in cow's milk. This enzyme is bacteriolytic against Gram-positive bacteria and may also afford specific protection against some viruses. Other enzymes are believed to have direct immunological functions, while some may be acting indirectly by promoting cell maturation (*108, 109*).

Immunological qualities of breast milk

Human milk is much more than a simple collection of nutrients; it is a living substance of great biological complexity that is both actively protective and immunomodulatory. It not only provides unique protection against infections and allergies (*110–112*), but it also stimulates the appropriate development of the infant's own immune system. In addition, it contains many anti-inflammatory components whose functions are not fully understood (*113*). The most immediately apparent result is decreased infant morbidity and mortality, compared with infants who are artificially fed, the impact of which is particularly dramatic in poor communities (*114, 115*). However, the immunological benefits of breast milk are no less real among relatively affluent populations, (*116, 117*). For example, recent research indicates that there are subtle immunological risks among artificially fed, compared with breast-fed, infants in wealthier communities where there is apparently a greater incidence in childhood of otitis media (*118*), coeliac disease (*119*), Crohn disease (*120*), diabetes (*121*), and cancer (*122*), in addition to problems due to the mechanics of artificial feeding, such as orthodontic defect (*123*). Decreased morbidity among breast-fed infants in industrialized countries has remained constant even during periods when it was the less privileged who breast-fed (*124*).

The methodological flaws of past studies of the protective effect of breast milk in developed countries have served to confuse the issue. Given the importance of gut flora in disease, it is critical to distinguish carefully *inter alia* between infants who have received only breast milk from birth, infants receiving supplementary foods neonatally and only breast milk thereafter, infants who are breast-fed but supplemented from birth with breast-milk substitutes, and infants who are artificially fed from birth (*125*). In studies designed to assess the health effects of infant feeding, all other fluids and solids given to the infant need to be recorded.

A recent study in Dundee, Scotland, followed 674 mother–infant pairs for two years in an effort to overcome these methodological flaws. It was found that the infants who were breast-fed for 3 months or more had substantially less gastrointestinal illness during the first year of life than the infants who were bottle-fed from birth or completely weaned at an early stage. This reduction in illness, which was found whether or not supplements were introduced before 13 weeks, was maintained beyond the point of breast-feeding itself and was accompanied by a reduction in the rate of hospital admission. By contrast, infants who were breast-fed for less than 13 weeks had rates of gastrointestinal illness similar to those observed in bottle-fed infants (*126*).

The protection afforded by breast-feeding is most evident in early life and continues in proportion to the frequency and duration of breast-feeding. The neonate must contend with a number of immediate problems at birth, including colonization of the intestines with microorganisms, the toxins produced by the microorganisms, and the ingestion of macromolecular antigens; all three can cause pathological reactions if permitted to penetrate the intestinal barrier. The intestinal host defence mechanisms are immature at birth; thereafter, the wealth of immune substances and growth factors in colostrum and breast milk protect the intestinal mucosa against penetration, modify the intestinal luminal environment to suppress the growth of some pathogenic microorganisms while killing others, stimulate epithelial maturation, and enhance digestive enzyme production (*127*).

The anti-infective properties in colostrum and breast milk have both soluble and cellular components (*128*). The soluble components include immunoglobulins (IgA, IgM, IgG) as well as lysozymes and other enzymes, lactoferrin, the bifidus factor, and other immunoregulatory substances (*39, 48*). The cellular components include macrophages (which contain IgA, lysozymes and lactoferrin), lymphocytes, neutrophil granulocytes, and epithelial cells. While the concentration of these constituents is very high in colostrum, it decreases in mature milk. However, because decreased concentration is com-

pensated for by increasing milk volume, infant intakes remain more or less constant throughout lactation (see Table 2.1).

Table 2.1: **Distribution of immunoglobulins and other soluble substances in the colostrum and milk delivered to the breast-fed infant during a 24-hour period**[a]

Soluble product	Concentration in mg/day at postpartum:			
	< 1 week	1–2 weeks	3–4 weeks	> 4 weeks
IgG	50	25	25	10
IgA	5000	1000	1000	1000
IgM	70	30	15	10
Lysozyme	50	60	60	100
Lactoferrin	1500	2000	2000	1200

[a] Reference *129*.

The protection afforded the infant is substantial. Calculated on a per/kg body-weight basis, it has been estimated that a fully breast-fed infant receives 0.5 g secretory IgA (SIgA) per day, which is about 50 times the globulin dose given to a patient with hypoglobulinaemia. SIgA is the most important globulin fraction; it is produced by the subepithelial plasma cells of the intestinal tract except during the first 4–6 weeks of life (or even longer in allergic individuals) when infants need to obtain it from breast milk. SIgA is also produced in the mammary gland (*130*). It is resistant to proteolytic enzymes and low pH, and considerable amounts of ingested SIgA can be recovered in an infant's stool (*131*). Soluble IgA covers the infant's intestinal mucosa like "white paint", rendering it impermeable to pathogens. It is believed that the SIgA antibodies bind toxins, bacteria and macromolecular antigens, thus preventing their access to the epithelium. Breast milk also stimulates the infant's own production of SIgA (*132, 133*).

Other breast-milk components also have an immunological role. Lactoferrin is an unsaturated, iron-binding glycoprotein that competes for iron with iron-dependent microorganisms, and is thus bacteriostatic. Like SIgA, lactoferrin is resistant to proteolytic activity. As mentioned earlier, the bifidus factor occurring in fresh colostrum and breast milk is a nitrogen-containing carbohydrate that is easily destroyed by heat (*69*); it promotes intestinal colonization with lactobacilli in the presence of lactose. The resulting low pH in the intestinal lumen inhibits the growth of both *E. coli*, Gram-negative bacteria, and fungi such as *Candida albicans*. A similarly low pH in the stomach may be of particular importance to the premature and low-birth-weight infant (*134, 135*) (see chapter 5). The growth of pathogens in the stomach may lead to the emptying into the intestines of highly contaminated feeds (*136*), and increased risk of potentially fatal disorders such as necrotizing enterocolitis, which occurs only rarely in infants fed only human milk from birth. For example, in a neonatal unit in Helsinki, a study of over 7000 sick infants found only 5 cases, of whom 3 were full-term infants after exchange transfusions. All infants that died were autopsied; all premature infants were radiologically screened (*136*). A neonatal unit in Manila (R. Gonzales, personal communication, 1989) has not had a single case since converting to human-milk feeding; maternity hospitals in Stockholm (*136*) and Oslo (R. Lindemann, personal communication, 1989) report similar findings.

Recent research indicates the presence in human milk of other factors having specific immunological functions. Indeed, it is now clear that there is a broncho-mammary and an entero-mammary circulation, which ensures that every pathogen that challenges a mother stimulates the production of specific antibodies that are present in the milk her infant receives. Breast milk has been shown to be active, *in vitro*, against many pathogens (*137*) (see Tables 2.2 to 2.4) and specific protection against many of these (including rotavirus (*138*) and *G. lamblia* (*139, 140*)) is provided to the infant. Breast milk also contains viral fragments that cannot be replicated, but which stimulate antibody responses in infants, effectively immunizing them before exposure to the active agent, or enhancing their response. Now that PCR (polymerase chain-reaction) tests are available, which can amplify and detect traces of certain viruses, it should be borne in mind that proof of the presence of antigenic fragments reveals little about their function in milk. There has been no study to date of the potential preventive or therapeutic roles of human milk in HIV infection (see chapter 3).

The activity of the cellular components of breast milk is not yet well understood. Macrophages are in highest concentration, followed by lymphocytes and neutrophil granulocytes. These cells help to prevent infection both by phagocytosis and by secretion of immune substances having some degree of specificity for those microorganisms with which the mother is in contact (*130*).

Effects on mothers

Breast-milk quantity

The volume of breast milk varies according to infant demand, the frequency of breast-feeding, the stage of lactation, and glandular capacity. It is only in cases of extreme deprivation that a mother's nutritional status may have an adverse effect on milk volume. In

Table 2.2: **Antibacterial factors found in human milk**[a]

Factor	Shown, *in vitro*, to be active against:	Effect of heat
Secretory IgA	*E. coli* (also pili and capsular antigens), *C. tetani*, *C. diphtheriae*, *K. pneumoniae*, *Salmonella* (6 groups), *Shigella* (2 groups), *Streptococcus*, *S. mutans*, *S. sanguis*, *S. mitis*, *S. salivarius*, *S. pneumoniae*, *C. burnetti*, *H. influenzae* *E. coli* enterotoxin, *V. cholerae* enterotoxin, *C. difficile* toxins, *H. influenzae* capsule	Stable at 56°C for 30 min; some loss (0–30%) at 62.5°C for 30 min; destroyed by boiling
IgM, IgG	*V. cholerae* lipopolysaccharide; *E. coli*	IgM destroyed and IgG decreased by a third at 62.5°C for 30 min
IgD	*E. coli*	
Bifidobacterium bifidum growth z factor	Enterobacteriacea, enteric pathogens	Stable to boiling
Factor binding proteins (zinc, vitamin B_{12}, folate)	Dependent *E. coli*	Destroyed by boiling
Complement C1–C9 (mainly C3 and C4)	Effect not known	Destroyed by heating at 56°C for 30 min
Lactoferrin	*E. coli*	Two-thirds destroyed at 62.5°C for 30 min
Lactoperoxidase	*Streptococcus*, *Pseudomonas*, *E. coli*, *S. typhimurium*	Destroyed by boiling
Lysozyme	*E. coli*, *Salmonella*, *Micrococcus lysodeikticus*	Some loss (0–23%)at 62.5°C for 30 min; essentially destroyed by boiling for 15 min
Unidentified factors	*S. aureus*; *C. difficile* toxin B	Stable at autoclaving; stable at 56°C for 30 min
Carbohydrate	*E. coli* enterotoxin	Stable at 85°C for 30 min
Lipid	*S. aureus*	Stable to boiling
Ganglioside (GMI like)	*E. coli* enterotoxin, *V. cholerae* enterotoxin	Stable to boiling
Glycoproteins (receptor-like) + oligosaccharides	*V. cholerae*	Stable to boiling for 15 min
Analogues of epithelial cell receptors (oligosaccharides)	*S. pneumoniae*, *H. influenzae*	Stable to boiling
Milk cells (macrophages, neutrophils, B and T lymphocytes)	By phagocytosis and killing: *E. coli*. *S. aureus*, *S. enteritidis*. By sensitized lymphocytes: *E. coli* By phagocytosis: *C. albicans*, *E. coli*. Lymphocyte stimulation: *E. coli* K antigen, tuberculin PPD. Monocyte chemotactic factor production: PPD	Destroyed at 62.5°C for 30 min

[a] Reference *137*.

the WHO study concerning the quantity and quality of breast milk (*40*), a "threshold effect", after which breast-milk volume decreased, was observed among rural mothers in Zaire who had less than 30 g/l serum albumin levels (normal levels are 35–45 g/l). Except for this finding, no correlation was established between milk volume and maternal anthropometric characteristics, serum protein and albumin levels, and erythrocyte and haemoglobin counts. However, mothers in Sweden had a significantly higher milk volume during the first four months of lactation. The milk volume per 15 minutes of sucking was also higher among Hungarian and Swedish mothers, two groups enjoying high socioeconomic standards compared to mothers in Guatemala, the Philippines and Zaire.

Milk volume does not correlate with energy content, however; some mothers who are overproducing milk find that once the intake volume is reduced, their infants feed for longer periods at less-frequent intervals and put on more weight. In addition, recent research has demonstrated that, when milk volume drops, the milk tends to become more energy-dense, at the expense of maternal body stores if need be. Data about breast-milk volume demonstrate little about the energy value of the milk provided, however. Infants thrive on widely different volumes and energy intakes.

Table 2.3: **Antiviral factors found in human milk**[a]

Factor	Shown, *in vitro*, to be active against:	Effect of heat
Secretory IgA	Poliovirus types 1, 2, 3. Coxsackie types A9, B3, B5, echovirus types 6, 9. Semliki Forest virus, Ross River virus, rotavirus, cytomegalovirus, reovirus type 3, rubella virus, herpes simplex virus, mumps virus, influenza virus, respiratory syncytial virus	Stable at 56°C for 30 min; some loss (0–30%) at 62.5°C for 30 min; destroyed by boiling
IgM, IgG	Rubella virus, cytomegalovirus, respiratory syncytial virus	IgM destroyed and IgG decreased by a third at 62.5°C for 30 min
Lipid (unsaturated fatty acids and monoglycerides)	Herpes simplex virus, Semliki Forest virus, influenza virus, dengue, Ross River virus, Japanese B encephalitis virus, Sindbis virus, West Nile virus	Stable to boiling for 30 min
Non-immunoglobulin macromolecules	Herpes simplex virus, vesicular stomatitis virus, Coxsackie B4 virus, Semliki Forest virus, reovirus 3, poliotype 2, cytomegalovirus, respiratory syncytial virus, rotavirus	Most stable at 56°C for 30 min and destroyed by boiling
α_2-macroglobulin (like)	Influenza virus haemagglutinin, parainfluenza virus haemagglutin	Stable to boiling for 15 min
Ribonuclease	Murine leukaemia virus	Stable at 62.5°C for 30 min
Haemagglutinin inhibitors	Influenza and mumps viruses	Destroyed by boiling
Milk cells	Induced interferon: virus or PHA Induced lymphokine (LDCF): phytohaemagglutinin (PHA) Induced cytokine: by herpes simplex virus Lymphocyte stimulation: cytomegalovirus, rubella, herpes, measles, mumps, respiratory syncytial viruses	Destroyed at 62.5°C for 30 min

[a] Reference *137*

Of considerable significance are recent findings that thriving infants, who are fed only breast milk by well-nourished mothers, regulate their own intake within a wide range; that this intake volume is well within the lactational capacity of even poorly nourished women; and that the intake volume is relatively stable between one and four months of age (*141*). In contrast, infants fed only breast-milk substitutes increase their intake volume during the same period by an average of an additional 200 ml/day (*142*). The metabolic consequences of this greater intake as well as its possible later significance for such diet-related problems as obesity are unknown (see chapter 4).

Table 2.4: **Antiparasite factors found in human milk**[a]

Factor	Shown, *in vitro*, to be active against:	Effect of heat
Secretory IgA	*G. lamblia* *E. histolytica* *S. mansoni* *Cryptosporidium*	Stable at 56°C for 30 min, some loss (0–30%) at 62.5°C for 30 min, destroyed by boiling
Lipid (free)	*G. lamblia* *E. histolytica* *T. vaginalis*	Stable to boiling
Unidentified	*T. rhodesiense*	

[a] Reference *137*.

Nutritional requirements of lactating mothers

Women's nutritional requirements during lactation vary widely. Energy is needed to cover the energy content of the milk secreted, plus the energy required to produce it. The nutritional cost to the mother in proteins, vitamins and minerals is considerable (*143*), and unless these additional energy and nutrient requirements are met, lactation will take place at the expense of maternal tissues. As previously discussed, changes in metabolic efficiency during pregnancy provide for the anticipated expenditures of lactation. An adequately nourished mother accumulates nutrient stores during pregnancy that are used to compensate for her higher requirements during the first months of lactation.

The extent of those requirements has been the subject of considerable discussion (see chapter 1). Since 1981, much work has gone into the many methodological problems of determining what constitutes a representative breast-milk sample (*144*). First, the estimated average caloric value of breast milk has been progressively revised downwards (from

70 to 65 kcal), which affects the calculation of what energy is required both to replace and to produce breast milk. Second, it appears that the metabolic efficiency of women is considerably improved during lactation, so that maternal food intake is more effectively utilized than normally (*145*).

Studies of women whose milk is their infants' sole source of nourishment, and who have access to as much extra food as they wish, have shown very different patterns of caloric intake during lactation. Almost none met the 1981 guidelines (*146*), including those women whose weight remained stable and whose infants were obviously thriving. Some women do not lose weight despite intakes that are theoretically inadequate to sustain full lactation. Similarly, substantial supplementation (roughly 750 kcal added to a normal daily intake of only 1500 kcal) given to undernourished Gambian women made no difference in their milk output (*2*); mean milk intakes of infants were 750 ml from both Gambian and English mothers of 3-month-old infants, which closely matches data regarding infants in Texas (USA) who were fed only breast milk (*142*). While there may be selective depletion of adequately nourished mothers' nutrient stores during lactation, there is little evidence that this is clinically significant in a range of normal circumstances. Research into the late-lactation and post-lactation recovery of these body stores suggests enhanced uptake at these times and during a subsequent pregnancy; however, more work is required to throw light on the ideal interbirth interval for maternal recovery of lactational losses.

There do seem to be a number of compensatory mechanisms that allow for lactation to continue with much lower energy and nutrient intakes, or even with no caloric increase over the diet of the non-pregnant, non-lactating woman. This does not mean, of course, that lactating women in general do not need to increase their food intakes; rather, it suggests that nutritional status before and during pregnancy plays an important role in lactation performance. However, because of the very wide differences between individuals in nutritional status, metabolic efficiency, and energy expenditure, no universal statement as to maternal nutritional needs can be made. Estimates of "average need" have been revised downwards in recent years (see chapter 1). The amount of physical exertion in a mother's daily routine obviously affects any such calculation.

A mixed and varied diet, which satisfies normal requirements during the non-pregnant and non-lactating period, will usually cover the extra needs for lactation if total intake is increased to satisfy additional energy needs. Monitoring maternal weight provides some guide as to the adequacy of a mother's energy intake. Women around the world breast-feed successfully on many different, and frequently less-than-optimal, diets. Little work has been done to define what would constitute an optimal lactation diet; the key area of interest at present would appear to be the optimal pattern of fatty acid intake.

Greatly increased fluid intake has been frequently stressed in breast-feeding literature. However there is no evidence that either restricting or increasing fluid intake affects lactation success (*147*). Where maternal fluid intake is deficient, the urine will become concentrated and a mother will be thirsty. Women should drink amounts sufficient to satisfy thirst and to keep their urine dilute.

Lactation and contraception

The full importance of lactation as the world's most significant contraceptive (*148*) can only be mentioned briefly in this review of lactation. A consensus statement (*149*) adopted recently summarized what is now known about the conditions under which breast-feeding can be used as a safe and effective contraceptive. The maximum birth-spacing effect is achieved when an infant is fully or nearly fully breast-fed and a mother consequently remains amenorrhoeic. When these two conditions are fulfilled breast-feeding provides more than 98% protection in the first six months postpartum. After six months, or when breast milk is supplemented, or menses return, the risk of pregnancy increases, although it remains low while breast-feeding continues at much the same level. See also chapter 3.

In any discussion of infant feeding, it is important to understand the impact of breast-feeding on the time interval between births and the consequences where providing optimal nutrition for the mother, her infant and any subsequent children are concerned. It is significant that the period of full breast-feeding required to maximize the mother's protection against a subsequent pregnancy, without need for artificial means of contraception, is identical to the period of full breast-feeding required to maximize the infant's protection against allergic and infectious disease. Prolonged amenorrhoea also permits the mother to recover her iron stores, which enhances her immune and nutritional status as well as the prospects for providing adequate nutrition for any future fetus.

Résumé

La lactation

La lactation est le moyen le plus efficace du point de vue énergétique pour satisfaire les besoins

diététiques des jeunes mammifères, le lait de leur mère leur assurant en outre une protection active. Beaucoup de questions sur la physiologie de la lactation chez la femme demandent des réponses. On présente ici un résumé du développement de la glande mammaire depuis le stade embryologique jusqu'à sa complète maturité et l'on insiste sur les changements qui se produisent au niveau du mamelon et du sein lui-même pendant la grossesse et à terme. Il existe en effet une relation entre l'épaisseur des tissus qui entourent le mamelon, la rétractilité de celui-ci et la capacité de l'enfant à bien téter.

Les phénomènes hormonaux qui se produisent pendant la grossesse sont ensuite décrits. Le rôle de la prolactine dans le développement du sein est discuté ainsi que celui des œstrogènes sur le développement des alvéoles. Les différentes phases de la lactogenèse sont décrites ainsi que la séquence selon laquelle prolactine et ocytocine interviennent. Dès la naissance de grandes quantités de lait sont produites et les tétées vont stimuler la sécrétion de prolactine favorisant la lactogenèse. Pour le maintien de la lactation, il est essentiel que la manière d'alimenter le nourrisson respecte certaines conditions. Il faut que le sein soit pris efficacement, fréquemment et pendant des périodes suffisamment longues pour que soit prévenue, entre autres, la constitution de complexes métaboliques peptidiques inhibiteurs de la lactation.

Après la description des réflexes maternels de production et d'éjection du lait, ce sont les réflexes complémentaires existant chez le nourrisson qui sont analysés. Chez le nouveau-né normal tous ces réflexes sont présents dès la naissance et demandent à être consolidés par des comportements acquis dans la période qui suit. Pour initier avec succès l'allaitement maternel il faudrait que les nouveaux-nés puissent prendre le sein dans l'heure qui suit la naissance, au moment où à la fois leurs réflexes et la sensibilité de la mère à tous les stimuli sont les plus forts. Pour maintenir avec succès cet allaitement il faut que tous les facteurs qui pourraient diminuer la qualité de la succion de l'enfant soient, dans la mesure du possible, éliminés.

La composition du lait maternel est décrite en détail depuis le stade du colostrum jusqu'à sa maturation complète. Il s'agit d'un processus qui peut présenter des variations dépendant non seulement de facteurs strictement maternels mais aussi de la relation mère-enfant. D'un point de vue immunologique le lait de la mère non seulement apporte une protection contre infections et allergies mais aussi stimule le développement du système immunitaire de l'enfant.

La morbidité générale a toujours été plus basse chez les enfants nourris au sein dans les pays industrialisés même au cours de périodes où ce mode d'allaitement prédominait parmi les groupes les plus défavorisés. Une étude récente réalisée à Dundee, Ecosse a fait la preuve de la supériorité du lait maternel dans la protection contre les affections gastro-entéritiques dans la population objet de l'enquête. Cette étude a éliminé la plupart des causes d'erreurs qui avaient biaisé les études antérieures les rendant peu concluantes.

La quantité de lait produite varie en fonction de la demande de l'enfant, de la fréquence des tétées, du stade de la lactation et de la capacité de la glande. Ce n'est que dans les cas de privations extrêmes que l'état nutritionnel de la mère peut retentir négativement sur le volume du lait. Des mécanismes compensatoires interviennent qui permettent à la lactation de se maintenir avec des apports énergétiques relativement bas; ce qui explique qu'il est difficile de fixer de manière précise les besoins nutritionnels des femmes allaitantes (voir chapitre 1). Leur état nutritionnel avant et durant la grossesse joue par ailleurs un rôle important.

Enfin l'allaitement maternel en tant que moyen de contraception naturel est mentionné. L'aménorrhée lactationnelle permet un espacement des naissances et l'allaitement maternel assure une protection contre la conception de plus de 98% durant les six premiers mois.

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