DRUGS AND HUMAN LACTATION

P.N. BENNETT

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Drugs and Human Lactation

Second Edition

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A comprehensive guide to the content and consequences of drugs, micronutrients, radiopharmaceuticals and environmental and occupational chemicals in human milk

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Preface

In 1985 the European Office of the World Health Organization called together a group of experts with the remit of evaluating and rationalising the rather confused literature on the dangers, real and perceived, of substances in human milk. Over the next two years the WHO Group met in Copenhagen, Bath, Oslo and, memorably, amid the pine and birch trees of a more remote part of Norway, and developed principles for assessing reports and allocating levels of risk for breast-feeding mothers. These principles and their application to the current literature on drugs, radiopharmaceuticals, micronutrients and pollutants comprised the first edition of this book, which appeared in 1988.

It is a pleasure to record the contribution of the European Office of WHO and in particular Graham Dukes in overseeing the original project. In addition, the first edition owed a great deal to the input of Chris van Boxtel, Elisabet Helsing, Per-Knut Lunde, Michael Orme, John Philip, Hans Seyberth, Paivi Soderman and John Wilson; although they are not participating in the new edition, their part in the development of the methodology for the book and its application to individual substances is gratefully acknowledged.

This second edition welcomes the contributions of Evan Begg, Peter Mountford, Margaret Neville and Carol Walsh. New material has been analysed according to the methods established for the first edition, bringing the various subject-areas up to date. The book remains what its sub-title claims: a comprehensive guide to the content and consequences of substances in milk. We hope it will continue to provide a rational basis for making therapeutic decisions in women who seek to breast-feed.

Peter N. Bennett

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Contents

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Drugs and Human Lactation
P.N. Bennett, editor

1. Is breast best? Milk and formula feeds

Lidia J Notarianni

SUMMARY

Breast-feeding has important clinical, economic and sociological consequences. Nursing mothers benefit from drug therapy, as we all do. But when bottle-feeding supplants breast-feeding purely from lack of knowledge of whether a drug will reach the infant in sufficient quantities to cause harm, a mother may unnecessarily deny her child important benefits; these are outlined in this chapter.

INTRODUCTION

Preparation for breast-feeding begins soon after conception. Changes in breast size and the colour of the areola are often the first physical indications of pregnancy noticed by the expectant mother. During gestation some of the energy that will be required for milk production in the first few weeks is stored in the form of fat, typically 2–4 kg. Milk production usually commences within 48 h of birth, although it may precede parturition. Lactating women have been shown to have an increased metabolic efficiency which reduces the overall increase in energy required in milk production (1). Food intake required to maintain milk production is considered to be less than the minimum 500 kcal (2100 kJ) that has previously been recommended (2).

Breast milk is the only nourishment an infant needs for the first 4 months of life, with the possible exceptions of vitamins D and K. Its composition changes from the initial high protein, low fat content of colostrum to that of mature milk in a matter of 2–3 weeks to suit the requirements of the infant. Milk flow is essentially a demand and supply system controlled by the amount of infant suckling; the greater the suckling the more milk is produced. As well as adapting to the needs of the growing child this system allows the successful nursing of twins. Breast-feeding can continue well into the second year of life although supplementation with other foods is necessary from 4–6 months.

USE OF FORMULA FEEDS

Although breast-feeding is associated with a wide range of sociological and health benefits, formula milks have been used throughout this century. The use of diluted cows' milk, and from 1904 'roller-dried' cow milk powder, became popular for reasons of convenience or, as women entered the work force, of necessity. Following the Second World War aggressive marketing techniques associated their use with modern affluent societies and large healthy babies. Formula milks were promoted world-wide and propagated through local health care systems, particularly maternity and baby clinics giving them respectability and the status of medicines. New mothers were frequently given free samples. Early use of these formulae, possibly on a trial basis with the sample packs, could lead to incomplete establishment of lactation and hence 'no turning back' for the mother.

From the 1950s through to the late 1970s, formula milks became widely used not only in the Western world but also in less developed countries where contaminated water supplies, lack of storage facilities and poor hygiene made their use inappropriate. Poverty and high levels of illiteracy meant that the feeds were often not made up correctly. The net result was that in the developing countries, infant mortality, directly related to the use of breast milk substitutes, increased significantly (4, 5).

The issue of the use of these milk formulae in the poorer countries began to receive international attention in the mid-1970s and led in 1981 to the adoption of a resolution by the World Health Assembly recommending member states to implement a World Health Organization (WHO) code of practice for marketing breast milk substitutes (3). The substance of this code was to (a) restrict advertising of

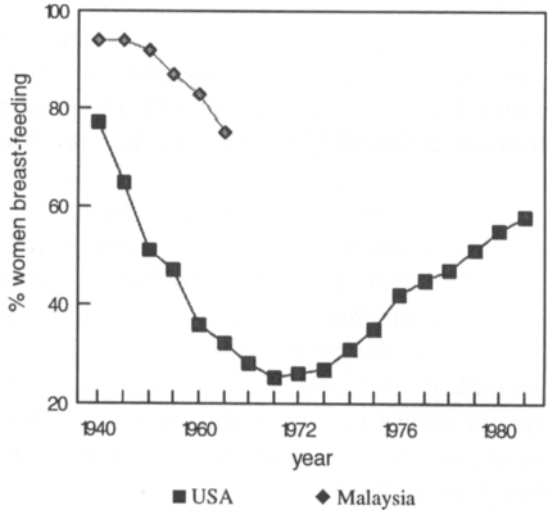

FIG. 1 *Breast-feeding trends in the USA (1936–1980) (68–72) and Malaysia (1936–1965) (63).*

breast milk substitutes directly to the public; (b) prevent personnel paid by manufacturers or distributors of these products from 'educating' mothers via the health care system; (c) stop the distribution of samples to new mothers; (d) eliminate financial inducements to health professionals to promote commercial products; (e) require formula products to contain the necessary information about the appropriate use of the product and the superiority of breast milk; and (f) promote breast-feeding through adequate information and education.

In developing countries a decrease in neonatal mortality and morbidity in breast-fed as opposed to formula-fed infants was demonstrated following the adoption of the WHO code of practice (4, 5). In many Western cultures in the 1970s, breast-feeding rates were slowly increasing for other reasons. Groups were formed to promote and advise on lactational problems as breast-feeding was perceived to be healthier for the child and important in the establishment of the mother–infant bond. The incidence of breast-feeding has subsequently increased in all parts of the globe (Fig. 1, Table 1).

TABLE 1 *Breast-feeding statistics in relation to infant age*

Country	Year	Duration of feeding	% Breast-feeding	Source[a]
Austria	1980	1 week	83.7	a
Austria	1980	3 months	41.2	a
Austria	1980	6 months	17.0	a
Denmark	1988	1 week	99.5	a
Denmark	1988	6 months	71.0	a
Denmark	1988	9 months	33.0	a
Gambia	1989	6 months	99.5	a
Gambia	1989	7–12 months	98.4	a
Gambia	1989	18–27 months	63.9	a
Iceland	1983	2 months	53.0	a
Iceland	1983	4 months	46.0	a
Iceland	1983	6 months	18.0	a
Mexico	1979	1 months	76.8	b
Mexico	1979	6 months	52.4	b
Mexico	1979	15 months	29.0	b
Norway	1993	3 months	84.0	a
Norway	1993	6 months	65.0	a
Norway	1993	9 months	40.0	a
Sweden	1992	1 week	97.0	a
Sweden	1992	3 months	78.0	a
Sweden	1992	9 months	58.0	a
Thailand	1978	1 month	69.0	b
Thailand	1978	2 months	16.0	b
Thailand	1978	6 months	2.0	b
USSR	1984	3 months	76.0	a

[a]Includes mixed infant feeding.

[b]Source a, personal communication from appropriate Ministry of Health or similar authority or data submitted to WHO by member states (67). Source b, from reference (66).

INCIDENCE OF BREAST-FEEDING

Almost all mothers have the capacity to breast-feed (6). Even in times of drought, famine and stress such as captivity or ritual fasting such as Ramadan (although nursing mothers are exempt they often participate), this capacity remains (7). Norwegian statistics show that from 1860 until about 1950 some 75% of mothers breast-fed their infants at 3 months; there was then a sharp decline to 25% participation, followed by a return to the previous level by the 1980s (73). Records on the percentage of mothers suckling their infants from the late 1930s reported 77% of mothers in the USA choosing this method to feed their infants. From the 1940s until the beginning of the 1970s there was a significant downward trend in breast-feeding as the promotion and variety of available formula feeds gathered momentum. In 1972 it was estimated that less than 25% mothers in the USA breast-fed their infants (Fig. 1), not necessary for health or social reasons but rather because the practice was seen as old fashioned. Knowledge that the developed world had apparently abandoned breast-feeding, combined with the promotion of formulae, led to women in less developed nations following their example.

The downward trend in breast-feeding did no harm to infants born to mothers of high socio-economic groups so far as could be established from infant mortality figures, although the incidence of some conditions (allergies, gastrointestinal, respiratory) did appear to be greater in bottle-fed children. The effect of the use of formula feeds in lower socio-economic groups and poorer nations, however, was extremely serious. Rates of infant mortality and serious disease increased with the decline in breast-feeding as did the incidence of post-partum conception due to the loss of the contraceptive effect of lactation. Part of the neonatal mortality was attributed directly to the use of contaminated water or incorrect preparation of the feed leading to dehydration or malnutrition.

As well as the decline in the numbers of infants that were breast-fed, those who were nursed were often suckled for a significantly shorter period and/or mixed feeding (breast and bottle) was practised. These infants may not have derived the full benefit of breast-feeding. Because of these trends, statistics on the number of breast-fed infants are frequently difficult to interpret. Should an infant count as being breast-fed only if s/he were fed exclusively for a minimum period (e.g. 3 months) or did a shorter period qualify? Did mixed feeding qualify as breast-feeding? Any statistics on the percentage of women breast-feeding should clearly define duration and exclusivity. Variation in the criteria applied may yield very different conclusions.

The decline in the number of breast-fed infants rapidly became a cause for concern for various influential groups including health professionals, child psychologists and government agencies. In less developed nations and lower socio-economic groups in richer nations, the return to breast-feeding became appreciated as the safest, most economical way to promote infant health. Consequently, from

the early 1970s there was a conscious attempt to educate, encourage and promote breast-feeding. Surveys were performed to discover why and when women stopped feeding their children and the WHO code of practice was introduced to many countries. The success of this campaign can be judged by the steady increase in the numbers of breast-fed infants in Europe and America while the decline in the developing nations was halted.

Currently the incidence of breast-feeding varies greatly between countries; motivation, necessity, and the socio-economic group of the mother all contribute. In less developed countries, the percentage of women breast-feeding at 3 months is generally over 75% (Table 1). In developed countries, Scandinavia has the highest number of breast-fed infants and also the longest duration of breast-feeding; in 1980 only 2.5% of Norwegian mothers did not breast-feed on discharge from hospital in contrast to 67% in Belfast (8, 9). The numbers of Scottish mothers breast-feeding at 7 days in 1990–1991 varied between 21.1% and 59.1% in different parts of the country (10). In the United Kingdom as a whole in 1985–86, 65% of mothers breast-fed at birth and 22% at 6 months; these figures represented no alteration from the position 5 years before and may herald another decline (11). In the United States the number of women who breast-feed is estimated at 61.4% although marked racial differences exist; 64% of white infants are breast-fed but only 32% of black infants (12). Variation between and within countries of similar social structure may be influenced by the degree of promotion of breast-feeding and support available, and the length and flexibility of maternity leave for working mothers. Additionally, the proportion appears to relate to social group, being 87% for social class 1 (professional) against 43% for class 5 (unskilled) (11). These figures should be taken into account when comparing the merits of different forms of feeding. It is now believed that to increase the number of women nursing their infants in areas and groups where the numbers are low and experience limited, a 'warm chain of breast-feeding' is required, i.e. an investment in education and practical help from experienced health professionals on a one-to-one basis (13).

BENEFITS OF BREAST-FEEDING

The benefits of breast-feeding are varied and range from sociological benefits through to improved health for the young infant and eventually the grown person. Some are pertinent to all socio-economic groups whilst others relate largely to less developed nations. A summary of reported advantages of this form of infant feeding appears below:

Clinical benefits

Breast-feeding exclusively for a minimum period of time is now believed to give protection from various conditions, some of which may not appear until middle age.

Allergies

The incidence in children of IgE-associated disorders such as eczema, asthma and allergic rhinitis is increasing (14, 15). Childhood eczema often precedes the onset of asthma which may persist into adulthood. As far back as 1936 Grulee and Sanford (16) reported a sevenfold increase in the incidence of eczema in babies fed cow's milk. Avoiding early exposure to cow's milk as well as to egg, wheat and beef in the diet could reduce the incidence of eczema and asthma in childhood (17, 18) although other studies have found no difference (19, 20) or a delayed onset of eczema in breast-fed infants (21). Other environmental factors such as exposure to cigarette smoke and chemicals, house-dust mite, housing and social conditions are considered to be more potent than food components in promoting allergies (22, 23). It is now generally believed that breast-feeding diminishes the incidence of diet-related hypersensitivity disorders because of its relatively low allergen nature, although breast milk may for some infants still contain sufficient maternally ingested dietary (dairy based) antigens to promote hypersensitivity reactions. Goat's milk and soya-based preparations however, are generally believed to have a low allergenic nature and may be used in the absence of breast-feeding where infants cannot tolerate cow's milk.

Insulin-dependent diabetes mellitus (IDDM)

Both genetic and environmental components contribute to the aetiology of IDDM. Susceptibility to IDDM is highly correlated with specific genes (24) but its development may be precipitated by some factor in the infant diet. Various studies have indicated that infants breast-fed for >3 months have a lower risk of IDDM than those breast-fed for shorter periods (25, 26) although this view is challenged (27, 28); other environmental factors may also precipitate the condition. Bovine milk proteins have been reported as being the trigger initiating antibody production and the initiating of an autoimmune response resulting in IDDM (29, 30). Early cow's milk exposure has been reported to increase the risk of Type I diabetes by approximately 1.5 in susceptible individuals (31).

Cardiovascular disease

Prolonged breast-feeding (>1 year) has been associated with increased low density lipoprotein cholesterol and higher death rates from ischaemic heart disease in adult life (32), although other studies have been inconclusive (33). Breast-feeding elevates plasma cholesterol which is maintained until weaning (34), throughout childhood (35) or even throughout adult life (32). Additionally the HDL/LDL cholesterol ratio is higher in formula-fed than in breast-fed infants at 2 and 6 months of age (36). A possible explanation for this observation is that the infant absorbs thyroid hormones from breast milk and, through hormonal imprinting, the point of thyroid homeostasis is permanently set at a higher level (37).

Neurological status
Children who were breast-fed for a minimum of 3 weeks after birth appeared to have a small but significantly improved neurological status 9 years later compared to children who had been formula-fed (38). Breast milk contains longer-chain polyunsaturated fatty acids which are absent from formula milk and it has been proposed that these are essential for brain development. Other studies suggest that the method of feeding has a long-term effect on cognitive development (39,40)

Weight
Breast-fed infants are reported to weigh less at 3 and 12 months compared to weaned infants although body length is not different. Statistical data on weight and body length suggest that bottle-fed infants are overweight rather than that breast-fed infants are underweight (34). The difference in weight rapidly disappears after weaning.

Immunity
Maternal antibodies, immunoglobulins and other protective agents are transferred to the infant in milk. Agents such as secretory IgA, lactoferrin, interleukin-6, memory T-cells, PAF-acetylhydrolase, lysozyme and antibodies are not produced until some months after birth (41), and their passage to the infant in breast milk complements the agents transferred while in utero.

Sudden infant death syndrome(SIDS)
Over the past 25 years 11 studies have reported an increased incidence of SIDS in bottle-fed infants while another 7 found no effect. A recent study (42) found full bottle-feeding not to be a significant independent risk factor for SIDS but that bottle-fed babies are more likely to have mothers who smoke, to be born preterm and to come from poorer families. The issue of risk from bottle-feeding appears to remain unresolved.

Sociological benefits

These may be summarised as follows: (a) rapid establishment of infant-mother bond is believed to be invoked whilst breast-feeding; (b) demand feeding is more practical and successful when breast-feeding; (c) the infant obtains the right nutritional balance since milk composition changes both with time and on a circadian rhythm; (d) intelligence quotient at 8 years of age is reported to be increased by eight points in children who breast-fed as infants, particularly premature infants (43), although this finding is in contention with results attributed to other social factors (44, 45). An increased rate in learning disorders has been reported among formula fed infants which may relate to minor neurological dysfunction in these children (46).

Additional benefits pertinent to less developed nations and poorer communities

(a) Breast-feeding is convenient and low cost, and avoids problems of contamination of feed with polluted water and inadequate sterilisation facilities. Additionally, breast-feeding negates problems that may be associated with the making up of a feed to the correct strength. (b) Onset of ovulation is delayed thereby allowing children to be 'spaced' when other forms of contraception are not available, particularly when demand feeding is practised. (c) Breast-feeding protects against environmental infections especially in the gastrointestinal and respiratory tracts. Mortality and morbidity rates are higher among bottle-fed infants living in unfavourable and/or disadvantaged conditions. Specific reports, for example, have shown protective effects of breast milk against *Campylobacter jejuni* diarrhoea (milk contains IgA antibodies which neutralise bacterial surface antigens) (47) and *Escherichia coli* and salmonella infections (48). In countries with a moderate or high infant mortality rate, babies fed on formula milk are at least 14 times more likely to die from diarrhoea than are breast-fed children, and 4 times more likely to die of pneumonia. Even in countries where infant mortality is low, formula fed infants require hospital treatment up to 5 times more often than those who are fully or partly breast-fed (49).

WHEN BREAST-FEEDING MAY NOT NECESSARILY BE BEST

The composition of formula milk has changed greatly over the years. Prior to the second world war the commonest infant 'formula' was diluted cows' milk to which sugar was added. Available dried formulae were also derived from cows' milk by the addition of fat and carbohydrate, the product being diluted to resemble breast milk in its major components. Dietary supplements such as vitamin D and iron were introduced into formulae although the amount of vitamin D was reduced after 1957 (50). In 1972 attention was drawn to the high incidence of babies with gastro-enteritis and dehydration caused by over-concentrated feeds and the high concentrations of protein and electrolytes in the formulae (51). The UK Department of Health and Social Security (DHSS) consequently commissioned a study to examine all aspects of infant nutrition (52). This found that all the fat in formula milks was butterfat, and manufacturers were directed to change within 2 years the fat content to short chain fatty acids. Further research into the composition of human milk prompted a radical alteration of formula milks after 1977. The lipid component became 90–100% vegetable fat, mainly short chain fatty acids, and the content of protein, electrolytes, water-soluble and trace elements was reduced (53). These alterations in the composition of formula milks after 1974 may diminish perceived risks of disorders such as atherosclerosis associated with the use of the earlier formulations (32). Thus the new generation formula feeds do not neces-

sarily disadvantage infants when circumstances dictate that breast-feeding may not confer advantage or may actually be is inadvisable. Some of these are considered below.

Premature infants

The milk of women delivering prematurely differs from that of mature milk in its energy, protein and sodium content (all greater) and its carbohydrate content (lower). Feeding donated human milk to a very low birth-weight infant may lead to insufficient intakes of protein and energy, since available human milk is likely to be mature rather than colostrum. Premature infants fed milk from mothers delivering prematurely grow significantly better than those fed mature breast milk (55). In such circumstances mature milk may be supplemented with protein, fat and carbohydrate derived from human or cow's milk to improve its nutritional content (56, 57). Mature milk may also contain insufficient vitamin D for such infants (58).

Infectious disease

Human immunodeficiency virus (HIV) can be transmitted in breast milk (59, 60) but the risk of transmission has been difficult to separate from other risk factors such as prior transmission of the virus to the infant in utero. Evidence suggests a 14% additional risk of transmission of HIV by breast-feeding (60, 61).

Contamination of milk

Breast milk may suffer contamination with insecticides, pesticides and other environmental chemicals including heavy metals (see Chapter 00). As exposure to these substances also occurs in utero, there is difficult in establishing the extent to which contamination occurs prenatally or during lactation. Advice issued in Canada encourages women to breast-feed despite the presence of pollutants in milk (54).

Drug utilisation during lactation

Women use a variety of drugs, both prescribed and over-the-counter, in the early stages of lactation. In surveys 90% (9), 99% (8), and 95% (62) of women were taking at least one form of medication in the week after delivery. The number of agents taken in this period reached a maximum of 7 (mean 2.1). Reports from Canada (62), Norway (9), England (63) and Northern Ireland (8, 64) find that the drugs most commonly prescribed are analgesics, laxatives, vitamins, antimicrobials, antiemetics, sedatives and hypnotics. Table 2 indicates the percentages of hospitalised women using some of these agents in the immediate post-partum period. After discharge from hospital drug utilisation declines although some 17% of mothers

TABLE 2 *Drug utilisation by mothers in maternity wards in Norway (9) and Northern Ireland (8)*

	Norway[a] (n = 970)	N. Ireland[b] (n = 2004)
Drug class		
Analgesic	82	78
Hypnotic	85	36
Antimicrobial (systemic)	4	14
Specific drug		
Codeine	54	41
Dextropropoxyphene	25	1
Nitrazepam	60	17
Ergometrine	15	1
Diazepam	4	2
Mean number of drugs	2.1	3.6

[a]98% mothers breast-feeding.
[b]33% mothers breast-feeding.

breast-feeding at 4 months take at least one drug per day. Some 5% of mothers who continued to breast-feed were receiving regular medication for asthma, allergy, hypertension, arthritis, diabetes, epilepsy or migraine (65).

For many years the drugs commonly administered during lactation were either assumed to be safe or to present hazard to the suckling infant without being subjected to a rational process of analysis. Table 3 shows that warnings are given more often about drugs use during pregnancy and childhood than during lactation. Consciousness of possible unwanted effects of drugs transmitted in milk appears to be increasing as caveats or proscriptions on drugs for nursing women listed in the UK Monthly Index of Medical Specialities (MIMS) rose from 22% in January 1985 to 32% in 1994.

It is common practice carefully to assess the case for any drug that is administered to a pregnant woman. Since most drugs will find their way into milk to some extent there is an equal case to make a rational assessment of risk to the infant before prescribing medication to a nursing mother. While the quantities of drug transferred may be small in absolute terms, new-born infants have a low capacity to metabolise and excrete these foreign substances. Now that breast-feeding is again

TABLE 3 *Warnings on the use of medicines*

Users	Contraindicated (%)	Special precautions (%)
Children	35.3 (39)	–
Pregnant women	18.0 (15)	27.6 (22)
Nursing mothers	14.8 (4)	17.3 (18)

Data from MIMS, July 1994. Figures in parentheses refer to MIMS, January 1985.

popular, it is especially important to attempt a rational evaluation of the medicines that may be taken with safety during lactation both to avoid harm to the child and permit the mother to breast-feed with confidence.

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Drugs and Human Lactation
P.N. Bennett, editor

2. Effects of drugs on milk secretion and composition

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SUMMARY

The rate of milk secretion or milk composition potentially can be altered by agents that act in a number of ways: they may act directly on the mammary epithelium affecting its growth or its function; they may affect the hormonal milieu that regulates milk secretion or ejection or they may alter the delivery of nutrients to the lactating mammary cell. After a brief review of mammary development and the mechanisms of milk secretion we discuss the potential effects of drugs on mammary development, focussing on anti-estrogens. During lactation a large number of drugs act through the dopamine receptor on the lactotroph to increase or decrease prolactin secretion. Alcohol and opioids, on the other hand inhibit oxytocin release, interfering with the let-down reflex. A great deal of information is available about the effects of sex steroids on milk secretion from studies of oral contraceptive agents. In general estrogens, particularly at high doses, inhibit milk secretion whereas progesterone appears to have little effect. Other points where drugs might be expected to act are the secretory architecture of the mammary secretory cell and the enzymes of lipid synthesis. More research is indicated to determine whether therapeutic agents, as opposed to environmental chemicals, alter milk secretion by affecting these pathways.

INTRODUCTION

Although the greatest concern about drugs and lactation is rightfully directed toward the secretion of drugs in breast milk and their effects on the newborn, there are also potential effects of drugs on lactation itself, without which no treatise on this subject would be complete. Drugs have the potential of intervening at all stages in the development and function of the mammary gland. In particular drugs may interfere with the following processes:

a. normal mammary gland development;
b. milk secretion;
c. the hormonal milieu of the lactating mammary gland;
d. nutrient delivery to the lactating mammary cell.

The effects of drugs on some of these process have been well-defined. For example, a great deal of information is available on the role of dopaminergic compounds on secretion of prolactin, a major lactogenic hormone. In these instances we will present a concise summary of the available information. In other areas, for example, mammary development, the effects of pharmacological agents can only be suspected as definitive research is lacking. In this realm we can only make suggestions about fruitful areas for further investigation. To set the stage for both types of discussion the first part of this chapter summarises normal mammary development and function.

NORMAL MAMMARY DEVELOPMENT AND FUNCTION

Mammary gland development takes place in several stages known as *mammogenesis*, *lactogenesis* or the onset of copious milk secretion, *galactopoiesis* or sustained milk production and *involution* or dedifferentiation of the mammary gland at the cessation of lactation.

Mammogenesis takes place in several stages. In embryonic life the fat pad into which the alveolar elements must grow is laid down subcutaneously and rudimentary ducts composed of epithelial cells develop below the nipple (1). Little further development occurs until puberty when estrogen stimulates ductile growth (2, 3) into the fat pad in a highly regulated manner that probably involves the local secretion of a number of growth factors. With the onset of the menses progesterone secretion by the corpus luteum stimulates limited development of lobulo-alveolar complexes. By the end of puberty the normal gland is composed of ducts that course throughout the mammary stroma and terminate in small alveolar clusters as shown by the beautiful camera lucida drawing of Dabelow (Fig. 1) (4). Again development pauses until the complex hormonal milieu of pregnancy brings about additional growth and differentiation of the mammary epithelium. Although the specific roles of the hormones of pregnancy are not completely understood, it is clear that the lactogenic hormones prolactin and placental lactogen (also known as chorionic somatomammotrophin) play a role in this process as does progesterone (5). The role of estrogens is more problematic since levels are low throughout most of pregnancy in many species, although not humans. Progesterone probably enhances alveolar development while inhibiting milk secretion. In humans increasing levels of estrogens may also play a role in the inhibition of milk secretion, particularly if the woman is lactating at the onset of pregnancy.

The process of lactogenesis is set in motion with the birth of the young and depends on the presence of a differentiated mammary epithelium, the withdrawal of

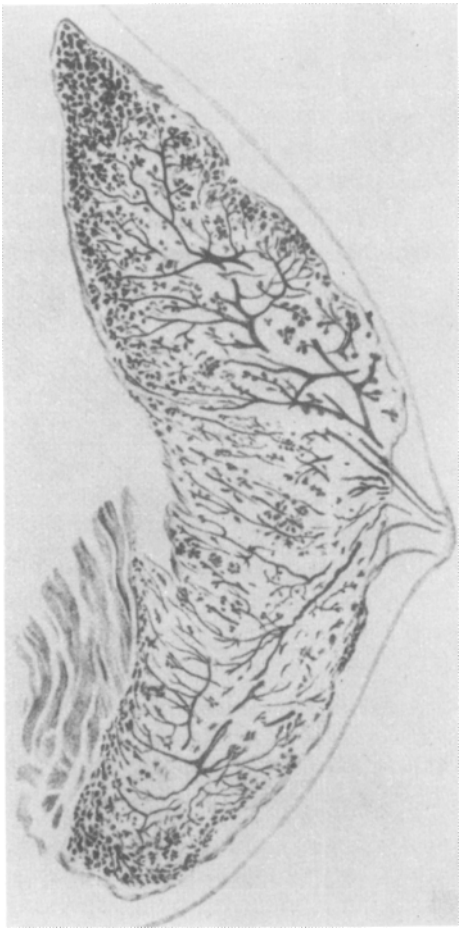

FIG. 1 *Camera lucida drawing of a cross section through the breast of a 19-year-old woman who had never been pregnant. Several ducts coursing from the alveolar complexes at the periphery of the gland are shown terminating on the nipple. From Ref. (4).*

high levels of sex steroids and the maintenance of prolactin secretion. The timing of lactogenesis is thought to depend most directly on the withdrawal of progesterone (6), since the process can be inhibited if progesterone levels are maintained from exogenous sources after parturition. In addition, the timing of lactogenesis across species is temporally related to the fall in progesterone. In humans, unlike most other mammals in which lactogenesis occurs around the time of birth, the onset of lactation is delayed until about 40 h after birth (7, 8). The decline in estrogen and the abrupt fall in placental lactogen are also likely to contribute to lactogenesis, but these effects are as yet poorly defined. Evidence that prolactin must

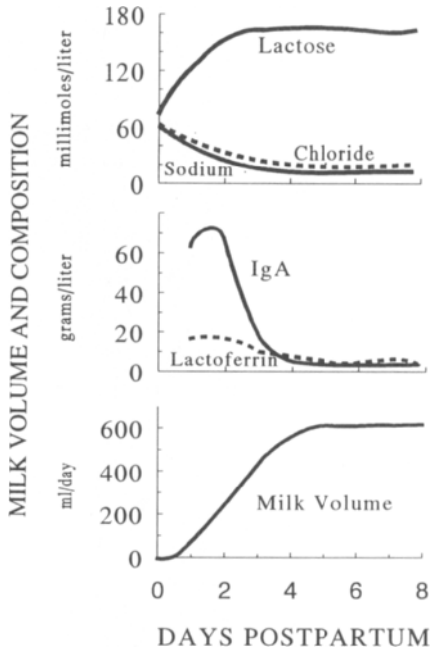

FIG. 2 *Changes in milk volume and composition during lactogenesis. Milk volume increases most rapidly between days 2 and 4 postpartum, thereafter leveling off. Sodium, chloride and lactose concentrations change most rapidly during the first 2 days postpartum as a result of closure of the tight junctions. The total protein concentration of the mammary secretion also decreases rapidly during this period, largely as a result of changes in secretory IgA and lactoferrin concentrations.*

be maintained at high levels for lactogenesis to occur is clear from the repression of lactogenesis by dopaminergic agonists that inhibit prolactin secretion (vide infra).

The composition of the mammary secretion undergoes profound changes during lactogenesis (Fig. 2). Although the product of the mammary gland is commonly termed colostrum during the first 5 days post-partum, its composition is far from constant with profound changes in sodium, chloride and lactose occurring during the first 48 h post-partum and changes in other constituents and milk volume being completed closer to 120 h. The early changes are the result of closure of the tight junctions between mammary epithelial cells that prevent plasma constituents such as sodium and chloride from passing directly from the interstitial space into the milk (8). The process of lactogenesis is normally complete by day 5 in women, although it may be delayed in diabetics for reasons that are incompletely understood (9, 10). Milk removal by the infant becomes necessary by day 2 or 3 postpartum if lactogenesis is to be completed (11). The average amount of milk transferred to the infant per day is about 500 ml by day 5 and continues to increase reaching ap-

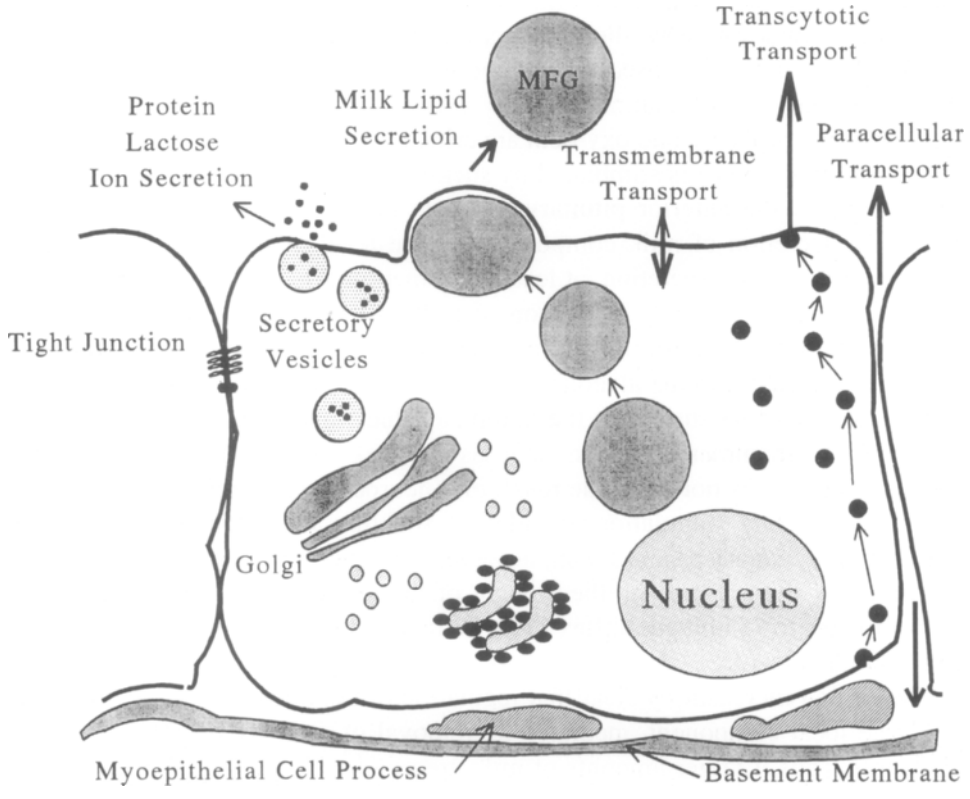

FIG. 3 *Pathways for the secretion of milk constituents. See text for explanation.*

proximately 700 ml at 1 month postpartum and about 800 ml at 6 months (7). The rate of milk secretion declines rapidly if suckling is discontinued for more than about 24 h once lactogenesis is complete.

The secretion of milk is accomplished by the mammary alveolar cell utilizing several pathways and a number of processes unique to the mammary gland (Fig. 3) (12). Most components of the aqueous fraction of milk are secreted via the exocytotic pathway responsible for the secretion of casein and other milk proteins as well as citrate and phosphate. Lactose is synthesized within Golgi vesicles of this pathway and secreted by the same pathway along with sufficient water to maintain an isotonic secretion. Milk lipids, largely triglycerides, are synthesized in the mammary gland and secreted as milk fat globules (MFG) surrounded by plasma membrane. A transmembrane pathway confined largely to monovalent ions and glucose probably keeps these substances equilibrated with the cellular cytoplasm. Finally, a transcytotic pathway is responsible for the secretion of secretory IgA into milk and is probably the route by which most plasma and interstitial proteins including pro-

tein hormones find their way into milk. During pregnancy, involution and mastitis an open paracellular pathway allows direct exchange between the interstitial fluid and milk. This pathway is closed in lactation when milk formation is carried out in its entirety by activities of mammary cells.

The hormones prolactin and oxytocin are critical for the maintenance of lactation (5). The secretion of both is stimulated by suckling. Prolactin, however, is secreted by lactotrophs in the anterior pituitary and acts on mammary epithelial cells to stimulate the secretion of milk components. Some level of prolactin is necessary for continuation of milk secretion, at least in women; it does not, however, seem to be responsible for day to day regulation of milk volume. Oxytocin, on the other hand, is secreted by the posterior pituitary and is responsible for the let-down reflex. Milk is secreted into the alveolar lumen where it remains until the network of myoepithelial cells that surrounds the mammary ducts and alveoli contracts, forcing milk into the mammary ducts and sinuses and making it available for the suckling infant. Letdown is normally the result of a neuroendocrine reflex whose afferent arm is the sensory stimulation provided by suckling and whose efferent arm is provided by oxytocin secretion. It can, however, be conditioned; in many women it is stimulated by the cry or even the thought of the infant. Strong emotional states are also thought to inhibit the reflex (13). Without this reflex milk cannot be removed from the alveoli.

It is becoming increasingly clear that regulation of the rate of milk secretion has a very large local component, mediated by removal of milk itself from the mammary alveoli. Thus if larger amounts of milk are required by the nursing infant, increased removal of residual milk from the alveoli stimulates milk secretion. Conversely, if the infant removes less milk because of illness or increased supplementation with other foods, removal of milk from the gland is less complete and milk secretion is down-regulated. A feedback inhibitor of lactation (FIL) (14,15), present in milk, is thought to be responsible for the effects of residual milk in the gland mediating the effects of infant demand on the amount of milk secreted. An understanding of this concept is crucial to the design and interpretation of experiments on the effects of drugs on milk secretion. If, for example, an agent like a combined oral contraceptive partially inhibits milk secretion, its effects can be overcome by increased removal of residual milk by the infant. If this occurs, neither a change in the daily transfer of milk to the infant nor in infant growth may be observed. However, the volume of residual milk will be decreased. For this reason procedures that measure residual milk volume are likely to provide important information about the effects of drugs on milk secretion.

Involution occurs when milk secretion is inhibited either by withdrawal of prolactin or cessation of regular milk removal (5). Although it has not been thoroughly studied, partial loss of the mammary epithelium appears to occur after weaning of the infant with further loss of both epithelium and stroma on withdrawal of sex steroids at menopause.

EFFECT OF DRUGS ON MAMMARY DEVELOPMENT

Estrogens and antiestrogens

Estrogens play an essential role in the pubertal development of the mammary gland, bringing about extension of the mammary ducts throughout the preexisting fat pad. Extensive evidence that estrogen replacement in ovariectomized prepubertal animals brings about ductule development (2) has recently been reinforced by the studies of Silberstein et al. (3) in which a specific estrogen antagonist, ICI 163,438, implanted into the mammary glands of pubertal mice, was shown to inhibit local ductule growth. This experiment constitutes proof that any agent that disrupts the action of estrogen has the potential to inhibit mammary growth. Such observations provide the experimental justification for the administration of antiestrogens such as tamoxifen in patients at high risk for breast cancer (16). Because a wide variety of estrogens and antiestrogens appear to be present in the environment (17, 18), the risk of exposure may not be restricted to the small number of women for whom such agents are prescribed as anticancer agents.

Anti-estrogens can act in a number of ways. The classic mechanism is interaction with the estrogen receptor directly inhibiting the effects of estrogen on estrogen-responsive cells (19). Some compounds, however, like the triphenylene antiestrogens may also bind to membrane-associated antiestrogen binding sites (20). Compounds such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) may enhance estrogen degradation (21) by upregulating estrogen metabolising enzymes. Others such as 6-hydroximinoandrostenedione may inhibit aromatases and thereby suppress estrogen synthesis (22, 23). There is an extensive literature in this area that can be reviewed only briefly here.

Antagonists like tamoxifen and ICI 163,438 bind directly to the estrogen receptor, competitively inhibiting the actions of estrogen as a transcription regulator. Biswas and Vonderhaar (20, 24) showed that tamoxifen and related triphenylene anti-estrogens also bind to the prolactin receptor, inhibiting prolactin binding. This interaction appears to be the basis of the inhibition of prolactin-stimulated casein synthesis in mammary explants by tamoxifen. The effects of tamoxifen and estradiol on mammary growth in prepubertal pigs were compared by Lin and Buttle (25). Tamoxifen, which is a partial estrogen agonist, stimulated mammary growth when given alone but partially inhibited the effect of estradiol when both agents were given together. When the treatment was repeated in pregnant pigs (26), neither mammary development nor the ability to lactate at parturition was affected although mammary progesterone receptor content was lower than the controls at day 90 of pregnancy. The currently available data make it difficult to predict the effects of tamoxifen and its congeners on mammary development and ultimately on milk secretion.

Epidemiological evidence that polychlorinated hydrocarbons exemplified by TCDD decrease growth of mammary epithelial cells was provided by an investigation of the effects of an industrial accident in Seveso, Italy (27). Although high levels of exposure to TCDD were associated with an increase in breast cancer, in this study a significant decrease in breast cancer incidence in a population exposed to chronic low levels of TCDD was found. In vitro TCDD and its congeners have been shown to reduce growth of estrogen-dependent mammary tumors (28, 29) and suppress estrogen-induced growth of MCF-7 breast cancer cells (21) as well as their secretion of tissue plasminogen activator (30). These agents are thought to act at least in part by combining with the Ah (aryl-hydrocarbon) receptor (31), up-regulating such estrogen metabolising enzymes as CYP1A2 (cytochrome P-4501A2). CYP1A2, in turn, catalyses the formation of 2-OH-estradiol and 16-OH-estradiol from estradiol-17β, thereby decreasing the half-life of the active hormone. Although CYP1A2 is thought to be confined to the liver there is experimental evidence (21) that TCDD increases the rate of estrogen metabolism in mammary cells as well. There is also evidence that TCDD decreases the level of estrogen receptor in the mammary gland (31). Chronic exposure of rats to TCDD in vivo has been observed to decrease the incidence of mammary tumours (32).

Another category of compounds may inhibit estrogen synthesis by interfering with the aromatase that converts androgenic precursors into active estrogens. For example, Gervais and Tan (22) have identified a male steroid hormone analogue, 6-hydroximinoandrostenedione, that acts as both an aromatase and growth inhibitor in cultured human T47D breast cancer cells. Kadohama and colleagues (23) found that tobacco constituents, acyl derivatives of nornicotine and anabasine, suppressed estrogen production by breast cancer cell lines.

The possibility does not seem to have been investigated that a crucial time window exists during pubertal formation of the mammary ducts when reductions in estrogen activity might effect a permanent decrease in mammary alveolar tissue. The accumulating evidence that estrogenic and anti-estrogenic compounds are widespread in the environment including cigarette smoke (23, 33), and that activities such as smoking have a deleterious effect on milk production, suggests that much more research is needed to relate the growing field of environmental estrogens and antiestrogens to their effects on mammary development and function.

DRUGS THAT ALTER THE HORMONAL MILIEU THAT SUPPORTS LACTATION

Prolactin

Prolactin is necessary for milk secretion in humans and may also play a role in mammary development. The secretion of prolactin from the anterior pituitary is

regulated primarily by dopaminergic neurons of the tuberoinfundibular pathway with cell bodies in the periventricular and more caudal regions of the arcuate nucleus and terminals in the external layer of the median eminence of the hypothalamus (34). Dopamine released from these neurons diffuses into capillary loops of the hypophysial portal system and is transported to the anterior pituitary. The activity of these neurons is not regulated by dopaminergic feedback loops or autoreceptors; their activity, however, is inhibited by suckling and during lactation these neurons become less responsive to feedback inhibition by prolactin (34). In the anterior pituitary, dopamine interacts with the D_2 subtype of membrane receptor on prolactin-secreting cells or lactotrophs. Activation of these receptors by dopaminergic agonists inhibits prolactin release, in part through G-protein-dependent inhibition of cAMP (35). Signal transduction may be mediated through activation of potassium channels and cell hyperpolarisation, but not by direct inhibition of voltage-gated calcium channels (36).

Pharmacologic agents alter prolactin release by modifying the activity of dopaminergic neurons, by competing with dopamine for its receptor, or by directly activating dopaminergic receptors on prolactin-secreting cells (37). Drugs of therapeutic importance for their ability to decrease prolactin secretion selectively activate the D_2 receptor subtype. Many of these agents are ergot alkaloid derivatives. The prototype, approved in the United States for treatment of hyperprolactinemia, is bromocriptine. This drug has been documented in numerous clinical studies to inhibit postpartum lactation by bringing about a significant reduction in plasma prolactin (38). Bromocriptine is currently the drug of first choice in treating hyperprolactinemia associated with pituitary tumors (39). The drug is typically administered orally twice a day, but is also efficacious by the intravaginal route in women who cannot tolerate oral administration (40). The drug has a markedly longer duration of action when injected in a microsphere formulation by the intramuscular route (41–44). Analogues of bromocriptine which have also been shown clinically to inhibit lactation include dihydroergocristine (45), lisuride (46), terguride (47), pergolide (48), and cabergoline. Cabergoline is unique with respect to its long duration of action after oral administration (49–53). These other agents are not approved for use in the United States, except for pergolide which has other indications. Approval for the use of bromocriptine to inhibit post-partum lactation has recently been withdrawn in the United States because of cardiovascular complications (54, 55).

Other dopaminergic agonists have also been demonstrated clinically to decrease prolactin secretion. Examples include ibopamine, a structural analogue of dopamine, and the aminoquinolone quinagolide (CV205-502) both of which have been shown to inhibit puerperal lactation (56, 57). L-Dopa, metabolised to dopamine in the brain, has been shown to inhibit abnormal lactation (58). Indirect-acting agonists such as amphetamine (59) and nomifensine (60) decrease prolactin but have not been used clinically to suppress lactation.

In contrast to dopaminergic agonists, drugs with affinity for the D_2 receptor but no intrinsic activity can inhibit the effect of endogenous dopamine and typically produce hyperprolactinemia in both female and male subjects (37, 61). The effect may be manifested in some patients as galactorrhea or gynecomastia (62). D_2 receptor antagonists, used clinically for their neuroleptic effects, encompass a variety of chemical classes, including phenothiazines such as chlorpromazine, butyrophenones such as haloperidol, benzisoxazoles such as risperidone, and benzamides such as remoxipride and sulpiride (63). There is generally a correlation between their potency in modifying behaviour and in producing hyperprolactinemia (37). There has been concern about the relation between long-term use of neuroleptics and increased risk of breast cancer (64), but this issue is not resolved. The atypical neuroleptic agents such as clozapine are relatively weak D_2 antagonists, do not antagonise dopamine-induced inhibition of prolactin release from pituitary cells in vitro (65) and at most produce a transient rise in prolactin with usual clinical regimens (66).

D_2 receptor antagonists used as anti-emetic or prokinetic agents also can be expected to produce hyperprolactinemia. The benzamide metoclopramide, in a regimen for treating gastric stasis, has been shown to elevate serum prolactin levels (67) primarily the non-glycosylated form of the hormone (68). Use of metoclopramide post-partum has been reported to increase the volume of milk produced by lactating women without changing the concentration in milk of prolactin or sodium (69). Domperidone, another dopaminergic antagonist used in gastrointestinal motility disorders, increases serum prolactin as well (70).

Prolactin secretion is also enhanced by agonists which activate cholinergic, opioidergic, and tryptaminergic receptors in the central nervous system. There is evidence to suggest that these effects are mediated by actions within the dorsal arcuate nucleus that reduce dopaminergic neurotransmission in the tuberoinfundibular pathway (71). The increase in prolactin secretion from cholinergic activation has been demonstrated in unrestrained male rats with nicotine as agonists, this effect undergoes rapid desensitisation (72). Opioid agonists, both alkaloids and peptides, also increase prolactin secretion in part by decreasing dopamine release (35). The opioid-induced increase in prolactin is attenuated during lactation, possibly because of increased secretion of adrenal cortical hormones (73). The role of endogenous opioid peptides in prolactin secretion is unclear, since administration of the antagonist naloxone generally does not alter basal serum levels or hyperprolactinemia from a variety of causes (74). Some studies in animal models, including the cynomolgus monkey (75) and rat (76), suggest that opioids contribute to the rise in prolactin that occurs in response to suckling. It has been hypothesised that endogenous opioids may play a role in amenorrhea in athletes, but studies with the non-selective opioid antagonist naloxone have been inconclusive (77).

Tryptaminergic agonists shown to increase serum prolactin include serotonin (5-HT) (78), tryptophan (the 5-HT precursor) (79), fenfluramine (a 5-HT releasing

agent) (80), fluoxetine (a 5-HT reuptake inhibitor) (81), moclobenmide (an MAO-A inhibitor) (82), the non-selective agonist m-chlorophenylpiperazine (83), and the 5-$HT1_A$ receptor selective agents, buspirone (84) and 8-hydroxy-2-(di-n-propyl-amino)tetralin (71). Serotonin-releasing neurons are believed to contribute to the increase in prolactin which occurs in response to suckling (35).

The release of prolactin is also induced by thyrotropin-releasing hormone (TRH) which acts directly on the pituitary lactotroph (85, 86). The physiological significance of TRH-mediated secretion is not clear (35). A synthetic form of this tripeptide, protirelin, is available for clinical use and has been used diagnostically to evaluate prolactin secretion (68, 87, 88).

Oxytocin

Oxytocin is released in response to suckling as well as certain psychological stimuli such as the cry of an infant. It causes contraction of myoepithelial cells around the mammary alveoli and ducts and brings about milk ejection. The compound is available as a nasal solution containing 40 USP units per ml. The compound is readily absorbed across the nasal epithelium and is prescribed during the first week after parturition to aid the let-down reflex. It has also been used in experimental protocols to produce hourly milk samples that represent complete emptying of the breast (7). As stated above, let-down is essential to milk removal from the breast. In the presence of inadequate let-down milk accumulates in the mammary alveoli, resulting in inhibition of milk secretion.

Ethyl alcohol is a potent inhibitor of oxytocin release. Chronic ethanol ingestion by lactating rats led to both a decrease in milk production and a change in milk composition, with decreased lactose and increased lipid content (89). An elegant, early study in which intramammary pressure was measured in response to suckling by the infant demonstrated that ethanol inhibited milk ejection in a dose-dependent manner (Fig. 4) (90). In this study Cobo found that doses of alcohol up to 0.45 g/kg, doses that produce a blood level less than 0.1%, had no effect on intramammary pressure although they did abolish uterine contractures, suggesting that the myoepithelial cells in the breast are more sensitive to the hormone than is the myometrium or that the effect of alcohol on oxytocin release is attenuated in lactating compared to parturient women. More recently Coiro and colleagues (91) measured the plasma oxytocin concentrations in response to breast-stimulation in non-lactating women and found that 50 ml of ethyl alcohol completely abolished the oxytocin rise. Minor effects of chronic maternal alcohol consumption were observed on motor development of breast-fed infants in a well-controlled study in humans (92). These effects were attributed to alcohol transfer to the infant rather than suppression of milk secretion.

A potent effect of opioids on oxytocin release is suggested by the observation in rats that morphine inhibits the let-down reflex (93, 94) and the mechanism of this

response has been extensively studied in this species. In one carefully done study evidence for involvement of kappa receptors on magnocellular neurons was obtained, whereas morphine, a mu-receptor agonist appeared to depress the mammary response to oxytocin (95) with no effect on oxytocin-secreting neurons. The effects of opioids have not been extensively studied in lactating women. In a single report (91), naloxone, an opioid antagonist, had no effect on oxytocin release but partially abrogated the inhibition produced by alcohol, suggesting both that ethanol acts through an opioid pathway and that oxytocin is not subject to chronic inhibition by opioids during lactation.

Prostaglandins

The effects of prostaglandins on milk let-down were studied in a number of laboratories in the early 1970s with conflicting results (summarised in Ref. 96). Cobo and colleagues (97) found that milk ejection was stimulated in women by $PGF_{2\alpha}$ and McNeilly and Fox (98) found that PGE_1, E_2, $F_{1\alpha}$, and $F_{2\alpha}$ all possessed inherent milk-ejecting ability in the guinea pig. Consistent with a direct effect on prostaglandins on the mammary gland, Batta et al. (99) found that $PGF_{2\alpha}$ caused milk ejection from isolated fragments of lactating mammary gland. In rats, however, $PGF_{2\alpha}$ appeared to interfere with oxytocin release and thus inhibit the letdown reflex (96). In a more recent study prostaglandin E_2 was found to be as effective as bromocriptine in suppressing post-partum lactation in women (100) adding to the general confusion about the effects of prostaglandins on lactation.

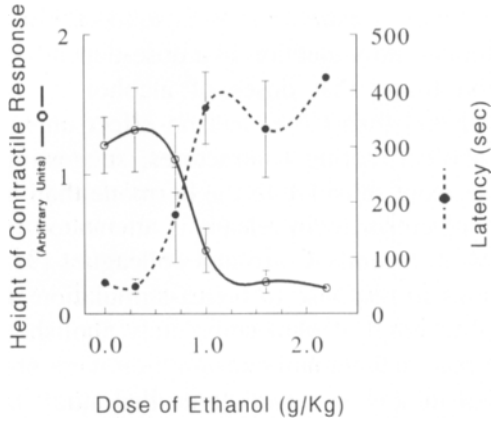

FIG. 4 *Effect of alcohol on the let-down reflex. Intramammary pressure was measured in one breast with a catheter while the infant suckled the other. Control measurements were obtained from each subject prior to ethanol ingestion. All women responded to exogenous oxytocin with increased mammary pressure after ingestion of ethanol, indicating that the inhibition is centrally mediated. Plotted from data in Ref. (90).*

Other hormones

Glucocorticoids have been shown both in vivo and in vitro to be necessary for milk secretion in animal and tissue culture models (101, 102). There are, however, no studies of the effects of chronic glucocorticoid treatment on milk secretion, possibly because breast-feeding is not recommended in women on high doses of glucocorticoids which have the potential to accumulate in milk. Adequate levels of *thyroid hormone* have long been known to be essential for lactation in goats and rats (103–105) and thyroid hormone has been shown to increase milk output in cows with some effects on milk composition (106). Its effects, however, have not been studied in women. Anecdotally, women who are clinically hypothyroid may have difficulty initiating lactation (N. Powers, pers. commun.) but this effect has not received systematic study.

EFFECTS OF SEX STEROIDS AND THEIR CONGENERS ON MILK SECRETION

Much information is available on the effects of sex steroids on milk secretion in women because of the world-wide importance of hormonal contraception. In addition, before the serious side effects of many of these hormones and their congeners were appreciated, very high doses of sex steroids were used to suppress puerperal lactation. While such high doses of drugs have not been used in lactating women for two decades, the effects that were observed in the 1960s and early 1970s provide us with important information about the consequences of high dose steroids on lactation. In this section we review the most important work on the use of steroid hormones to suppress puerpural lactation and discuss the use of combined oral contraceptive agents containing a combination of compounds with estrogen- and progestin-like actions. Finally, the use of progestin-only agents in the lactating woman is discussed.

All extant studies on the effects of sex steroids suffer from inadequate measurements of the rate of milk secretion. Nontheless, some general conclusions can be drawn. In many studies on steroid contraceptive agents a major parameter was the amount of milk that could be extracted from the breast under controlled conditions. This parameter is likely to be sensitive to subtle effects of inhibitory agents because, as discussed above, it includes the residual milk volume. In general changes in duration of lactation tended to parallel changes in extractable milk volume. Infant growth appeared to be much less sensitive to oral contraceptive agents, probably because increased suckling by the infant is able to compensate for partial inhibition of milk secretion. For studies of puerperal lactation suppression, where it was necessary to depend heavily on personal evaluations by the subjects themselves, reliable quantitative data on the inhibition of milk secretion are not available.

Lactation suppression with sex steroids

In several studies doses of steroid hormones, unacceptably high by today's standards, were given to puerperal women under reasonably controlled circumstances for the suppression of puerperal lactation. The parameters investigated included the ability to express milk from the breast and the apparent degree of engorgement and pain. A large, placebo-controlled experiment by Markin and Wolst (107), published in 1960, used five different agents, four of which had their own placebo controls, in about 500 postpartum women. As can be seen from Table 1 all agents, including both a potent estrogen alone (diethylstilbesterol) as well as a number of combinations of an androgen with an estrogen, significantly reduced the signs and symptoms of milk secretion compared to the placebo. Four of the agents were associated with significant rebound milk secretion after termination of daily dosing and for that reason, the clinical impression was that they were no more efficacious than controls. The fifth agent, a high dose of testosterone and estrogen given intramuscularly was not associated with any rebound in this group of patients, possibly because of prolonged absorption of this very large dose from the muscle. Results similar to the effects of diethylstilbesterol were found with the estrogenic agents quinestrel (108) and chlorotriansene (109).

The question of whether estrogens inhibit lactation by suppressing prolactin secretion was answered by a 1975 study (108) in which quinestrol (4 mg immediately after delivery) followed by placebo was compared with placebo alone or with bromocriptine (Fig. 5). It is quite clear that the estrogenic compound increased plasma prolactin levels. Numerous more recent studies confirm a potent stimulation of prolactin secretion by estrogens. From such indirect evidence we surmise that estrogen suppresses lactation by acting locally on the mammary gland. The mechanism is unknown and the finding is, in fact, rather puzzling since studies on the mammary glands of rodents suggest that estrogen neither stimulates formation of progesterone receptors nor binds to chromatin isolated from the lactating gland of mice (110).

It is important to emphasize that sex steroids are now absolutely contraindicated in the post-partum period because they promote blood clotting (111) and thromboembolism, and have been associated with cervical cancer.

Combined oral contraceptive agents and lactation

Tables 2 and 3 summarize data from a large number of studies of the effects of steroid contraceptives on various parameters related to milk secretion. These studies were selected for citation here because they included reasonable control groups. Those parameters that were most often measured were:

a. *Duration of breast-feeding* (112–122). This parameter is best measured by the mean duration of breast-feeding in a population of women who are observed

TABLE 1 *Effect of sex steroids on the initiation of lactation*

Agent	Regimen[a]					*N*		Effects on lactation				Ref.	Year
	Day postpartum					Drug	Placebo	Milk secretion	Engorge-ment	Pain	Rebound secretion		
	1	2	3	4	5								
Diethylstilbesterol	15	15	15	15	15	52	40	↓↓	↓↓	↓↓↓	+	(107)	1960
Dienestrol + methyl testosterone	2.3 45	2.3 45	1.5 30	1.5 30	0.8 15	49	65	↓	↓	↓	+	(107)	1960
Conjugated estrogen, equine + methyl testosterone	7.5 60	5.3 40	2.5 20	1.3 10	1.3 10	49	65	↓↓	↓	↓↓	+	(107)	1960
Testosterone proprionate + diethyl stilbesterol	50 i.m.	50 i.m.	15	15	15	67	0	↓↓↓	↓↓↓	↓↓↓	+	(107)	1960
Testosterone enanthate + estradiol valerate	360[b] 16					42	41	↓↓↓	↓↓↓	↓↓↓	None	(107)	1960
Quinestrol	4[c]					28	27	↓	↓↓	↓↓	None	(108)	1975
Chlorotriansene (progestagen)	125	100	75			94	96	↓	↓	↓	↓	(109)	1975
Testosterone enanthate	360[b]					96	96	↓	↓	↓	↓	(109)	1975
Estradiol valerate	16[b]												

[a]All doses in mg per day given orally unless intramuscular (i.m.) is specified.
[b]i.m., day of birth only.
[c]Oral, day of birth only.

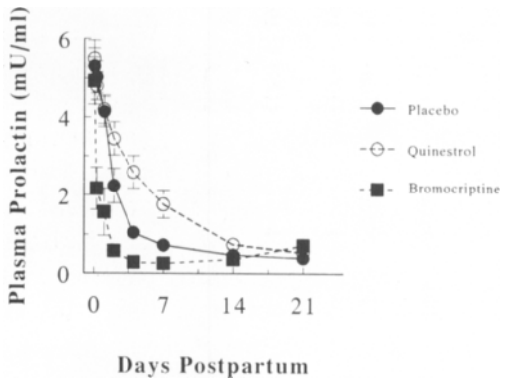

FIG. 5 *The effect of an estrogenic agent, quinestrel, and bromocriptine on prolactin secretion in the puerperium. Quinestrel (4 mg)was given as a single dose on the day of birth followed by placebo (N = 32). Bromocriptine was given orally 2.5 mg twice a day for 14 days (N = 28). Placebo identical in appearance was given on the same schedule (N = 27). Redrawn from Ref. (108).*

throughout the entire period of lactation. In shorter studies it can also be estimated by the number of women who are still lactating at a given time postpartum. In a few studies the use of supplemental feeds has been reported. Supplemental feeds are, however, difficult to quantitate without very intensive observation and, in general, the results in oral contraceptive trials have not been reported reliably.

b. *Milk volume*, as represented by the amount of milk that can be extracted from one or both breasts by breast pump, usually at a defined interval after a feed (112, 113, 118, 123–126). The milk extracted includes residual milk, i.e. milk in excess of that taken by the infant. If studies implicating a local inhibitor of milk secretion are correct (see above), the extracted milk volume may be a better measure of the secretory capacity of the breast than the actual amount taken by the infant.

c. *Milk composition* has been measured in relatively few studies, and then on relatively few parameters (123, 124, 127–129). The mechanism of the few observations of changes in composition is unknown.

d. *Infant growth and development* have been measured either acutely (112, 113, 115–118, 120, 125, 129–131) while the mother is taking the contraceptive agent or much later, after lactation has ceased (119, 121, 132). Changes in growth during contraceptive use are probably more reflective of effects on lactation since 'catch-up' growth may compensate for early growth retardation, at least in well-nourished children.

e. *Other parameters* that have been measured include maternal and infant metabolic state (120, 121, 130, 133), infant morbidity (estimated from clinic visits or school records) (119) and intellectual development (from school records) (119).

Early studies, in the 1970s for the most part, utilised the large dose combined oral contraceptive agents available at the time (112–114, 123, 125, 126) (e.g. those compounds whose labels begin with HD in Table 2). In some cases the estrogenic compound was combined with a progestagen like quingestanol that has some estrogenic or androgenic activity as well. In most of these studies convincing reductions were seen in the duration of breast-feeding, the volume of milk that could be expressed from the breast, and infant growth. Although the effects of these agents on milk production are attributed to the estrogens they contain, in one study where the estrogenic compounds were studied alone (126) in mothers who were expressing all their milk with a breast pump, no effects were observed compared with placebo. With none of the combined agents was a change in composition noted.

In the late 1970s low dose combined preparations containing levonorgestrel 150 μg, a progestagen, and ethinylestradiol 30 μg became available and were shown to have very high contraceptive efficacy with few side effects. The effects of these agents on lactation were most carefully studied by the World Health Organization in Hungary and Thailand (118). They were consistently found in this and other studies (115–119, 124, 131) to decrease the duration of breast-feeding and milk volume with little effect on infant growth (Table 2). In one long-term follow-up study in Sweden (119) that was carefully case-controlled, no effects on growth, morbidity, or intellectual achievement could be discerned from school or clinic records.

Progestagen only agents

Progestagens are often used in a long-term injectable form such as depot medroxyprogesterone acetate (DMPA), and were found in some studies to increase the duration of lactation compared to no contraceptive use or use of IUDs, barrier methods or sterilization (114, 121, 122) (Table 3). In one fairly careful study (114), however, there was little difference between the effects of progestagen injections and the use of an IUD on duration of lactation. No consistent effects on milk volume, infant growth or morbidity, or biochemical parameters in mothers and infants have been observed (118, 120, 123, 124, 129, 130, 133), with no effect found in long-term follow-up studies (121, 132). Inconsistent effects on milk composition were observed in early studies (124, 129) but were not reproduced in a more recent investigation (128). In one inquiry (121) where decreased growth, measured as infant weight at 3–4 years old, was observed in infants whose mothers had received DMPA by injection, an apparent decrease in weight disappeared when the statistical analysis was adjusted for breast-feeding duration. Progesterone-containing contraceptives are, therefore, usually recommended as the best means of steroidal contraception in the lactating woman.

The physiologic basis for the lack of responsiveness of the lactating mammary gland to progestins has been shown to reside in a lack of progesterone receptors, at

TABLE 2 *Effects of combined oral contraceptives on lactation*

Variable	Start OC time postpartum	End study	Country	*N*	Drug[a]	Control	Outcome[b]	Ref.	Year
Duration of breast-feeding	2–6 weeks	3 months	US	47	HD1	No OC, placebo	Dec	(112)	1970
	6 weeks	16 weeks	Thailand	20	HD2	No OC	Dec	(113)	1972
	1 months	Weaning	Chile	40	HD4	IUD	Dec 30%	(114)	1974
				81	E3		Dec 40%		
				194	HD5		Dec 67%		
				81	HD6		Dec 67%		
				50	HD3		Dec 52%		
	1 months	3 months pp	Chile	103	LD1	Placebo	Dec	(115)	1983
	2 months	12 months	Chile	103	LD1	No OC	Dec	(116)	1983
	3 months	12 months	Chile	59	LD1	IUD or barrier	NC	(117)	1983
	6 weeks	24 weeks	Hungary, Thailand	86	LD1	IUD, barrier, sterilization, none	Dec	(118)	1984
	2 months	8 years	Sweden	48	LD2	Case control	Dec 20%	(119)	1984
Milk volume[c]	4–24 weeks	8 weeks later	India	62	HD2	No steroid	Dec 25%	(125)	1970
	2 weeks	5 weeks	US	21	HD1	Placebo	NC	(112)	1970
	Not stated; pumping	3 weeks later	Sweden	8	HD7	Placebo	Dec 60%	(126)	1971
				8	E1	(Mothers of hospitalized	NC		
				8	E2	infants)	NC		
	6 weeks	16 weeks	Thailand	20	HD2	No OC	Dec 75%	(113)	1972
				20	HD3		Dec 32%		
	6 weeks	18 weeks	India	34	HD8	Sterilization, barrier	Dec 56%	(123)	1974
				30	HD4		Dec 63%		
	2 months	6 months	India	6	LD3	No OC	NC	(124)	1977
	6 weeks	24 weeks	Hungary, Thailand	86	LD1	IUD, barrier, sterilization, none	Dec 32%	(118)	1984

Milk composition: protein, lactose, lipid, calcium	2 months	6 months	India	6	LD3	No OC	NC	(124)	1977
	6 weeks	24 weeks	Hungary, Thailand	86	LD1	IUD, barrier, sterilization, none	Small changes	(127)	1988
			Brazil	12	LD1	IUD	NC	(128)	1992
				13	LD4		NC		
Infant growth	6 weeks	24 weeks	Bombay	62	HD2	No steroid	Dec 20%	(125)	1969
			US	24	HD1	Placebo	Dec 25%	(112)	1970
	6 weeks	16 weeks	Thailand	20	HD2	No contraceptive	Dec 25%	(113)	1972
			Thailand	20	HD3		NC		
	25–20 days	120 days	Chile	60	LD1	No contraceptive or IUD	Dec 10%	(115)	1978
	1 months	3 months	Chile	103	LD1	Placebo; weight gain	NC	(116)	1983
	2 months	12 months	Chile	103	LD1	IUD; weight	NC	(117)	1983
	3 months	12 months	Chile	59	LD1	IUD, barrier; weight	NC	(131)	1983
	6 weeks	24 weeks	Hungary, Thailand	86	LD1	IUD, barrier, sterilization, none	NC	(118)	1984
	Any	8 years	Sweden	48	LD2	Case control; weight, height	NC	(119	1986
Infant development	Any	8 years	Sweden	48	LD2	Case control; from school and hospital records	NC	(119)	1986

[a]Key to drugs used: *High dose combined agents:* HD1, norethisterone, 1 mg, mestranol, 80 μg; daily; HD2, ethynodiol diacetate 1 mg; mestranol, 100 μg, sequential; HD3, chlormadinone acetate, 2 mg; mestanol, 80 μg, daily; HD4, norethisterone, 1 mg; ethinylestradiol, 50 μg, daily; HD5, quinestrol, 2 mg; quingestanol acetate, 5 mg monthly; HD6, quinestrol, 2 mg; quingestanol acetate, 2.5 mg monthly; HD7, levonorgestrel, 2.5 mg; mestanol, 75 μg; daily; HD8, levonorgestrel, 500 μg; ethinylestradiol, 50 μg; daily. *Estrogens alone:* E1, ethinylestradiol , 50 μg; daily; E2, mestanol, 75 μg; daily; E3, quingestanol acetate, 300 μg; daily. *Low dose combined agents:* LD1, levonorgestrel, 150 μg; ethinylestradiol, 30 μg, daily; LD2, progestin; ethinylestradiol, 50 μg, daily; LD3, norethisterone, 350 μg; ethinylestradiol, 10 μg; daily; LD4, levonorgestrel, 250 μg; ethinylestradiol, 50 μg; daily.

[b]Abbreviations: OC, oral contraceptive; Dec, decrease; NC, no change; IUD, intrauterine device; N.S., not significant.

[c]Methods: (125), 1 feed test weigh; (126), pumping by mothers of hospitalized infants; remainder, defined pumping regimen 2–4 h after previous feed.

TABLE 3 *Effects of progestin only oral contraceptives on lactation*

Effect	Start OC time postpartum	End study	Country	*N*	Drug[a]	Control	Outcome[b]	Ref.	Year pub
Duration of breast-feeding	1–2 days	Wean	Chile	80	IP3	Previous lactation; IUD	Inc. NC	(114)	1974
	1 months	Wean		33	IP3		Inc 20%		
	1 months	Wean		54	IP5		Inc. NC		
	6 weeks	12 months	Finland	29	IUD1	Copper IUD	NC	(120)	1982
				34	IUD2	Copper IUD	NC		
	2 months	3–6 years	Chile	128	IP1	IUD, barrier, sterilization, none	Inc 60%	(121)	1984
	6 weeks	24 weeks	Hungary	85	OP1	IUD, barrier, sterilization, none	NC	(118)	1984
			Thailand	58	IP1		NC		
	2–4 months	Wean	Chile	228	IP1	No contraception, IUD	Inc	(122)	1986
				185	OP2		Inc		
Milk volume	6 weeks	18 weeks	India	30	OP3	Sterilization, barrier	NC	(123)	1979
	2–6 weeks	12 weeks	India	6	IP1	No OC	Inc	(124)	1977
				6	IP2		Dec		
				7	IP7		NC		
	6 weeks	24 weeks	Hungary,	85	OP1	IUD, barrier, sterilization, none	NC	(118)	1984
			Thailand	58	IP1		NC		
Milk composition	6 weeks	18 weeks	India	30	OP3	Barrier, sterilization	NC	(123)	1974
	2–6 weeks	12 weeks	India	6	IP1	IUD, barrier, sterilization, none	Inc (prot)[c]	(124)	1977
				6	IP2		Dec (prot, lip, Ca)		
				7	IP7		Dec (lip, Ca)		
		9 weeks	Brazil		OP4	No OC; Pretreatment values	NC	(128)	1992
		5 weeks			IP1		NC		