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Preface

The book presents data on peripheral and central mechanisms of regulation of milk secretion and excretion from the alveolar-ductal system of a woman's breast. Worldwide, the number of women wishing to lactate and breastfeed children has increased. A large experimental material indicates that lactation and breastfeeding is a unique state of the female organism, which is an integral part of the reproductive process and has no equal as a way to ensure the ideal nutrition of infants. In addition to exclusive nutritional value, maternal milk has the ability to maintain both active and passive immunity. In this regard, the relevance of the book increases greatly, since these books are the foundation for the development of practical measures to correct the milk productivity of lactating women for effective feeding of infant. The proposed book is the first monograph in the world specifically devoted to the physiology of lactation of women. This book fully collects modern data on the structure and function of the breast of women so that specialists can use this information in the compilation of individual schemes for correcting secretion or excretion of milk in nursing mothers. The book is of interest to researchers, lactation specialists, obstetricians-gynecologists, pediatricians, and students, graduate students, and residents of universities and medical universities.

Contents

Introduction

1

All that is beautiful in human life is from the rays of the sun and from mother's milk.

Russian writer Maxim Gorky

Abstract

Materials on lactation of nursing women in different periods of human society development are presented in a short form. Systematic studies of the physiology of lactation and breastfeeding begun in the 1990s, and since then, the number of experimental works on this topic has been steadily growing. Scientific studies have shown that in addition to ideal nutrition, breastfeeding reduces the number of cases or severity of diseases. Breast milk also contributes to the development of the mental abilities of children. For most women, lactation reduces the risk of breast cancer.

1.1 Brief History of Research on the Physiology of Female Lactation and Breastfeeding

The final stage, the peak of the reproductive cycle in mammals, is the lactation period—feeding the born cubs with mother's milk. This function is performed by the mammary gland that emerged as a result of evolution. Lactation function of the mammary glands consists of two main processes: milk secretion and milk excretion. In the wild, the lactation period appears to be as important for reproduction as pregnancy and childbirth. The lack of milk in the female or the inability to withdraw it due to abnormalities in the structure or function of her mammary glands leads to the death of the offspring. The same harsh situation was evident in the human community at the dawn of its existence. It seems that it is no accident that primitive artists and sculptors, as an ideal, depicted women on rocks or created stone sculptures of women with fairly large mammary glands, thereby emphasizing that such a woman can provide effective breastfeeding of offspring. In the future, as humanity developed and, first of all, economic activity appeared, and relations

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between people in communities improved, ways began to be found to help nursing mothers who had problems with lactation, i.e., with the secretion or excretion of milk from the breast. Thus, with the domestication of wild animals, it became possible to give the child milk from cows, goats, and donkeys as a substitute for breast milk. In addition, the milk of lactating women-nurses who had an excess of milk and could successfully feed their own child and the child of another mother with a lack of milk or the mother who died was used. To date, the scientific literature has a number of reviews (Drake 1935; Caulfield 1952; Wickes 1953a, b, c, d, e; Cowie 1974; Lawrence and Lawrence 1999, 2011; Zakharova and Machneva 2016) on the history of lactation of women—breastfeeding in different countries of the world in different eras. The first printed works on this topic began to appear in Europe (and probably in the world) during the Renaissance. According to available data, the vast majority of women in Europe and America in the sixteenth and nineteenth centuries, despite sometimes great difficulties, tried to maintain lactation and feed children with breast milk because it was noticed that milk mixtures made from milk domestic animals or liquid cereal gruel often had harmful effects on the baby with a fatal outcome. To date, it is known that this is due to the immaturity of the gastrointestinal tract and the immune system of newborns. The use of wet nurse's milk was more favorable, but for material reasons, not all women could hire a wet nurse. At the same time, women from families with high income, despite their ability to feed their children themselves, often hired wet nurses. For centuries, these mothers have put forward a variety of explanations for their reluctance to lactate and breastfeed their child: breastfeeding is not fashionable; it can damage the mother's health, spoil the shape of her breasts and figure, and prevent her from going to balls, going to the theater, etc. (Cowie 1974).

A similar situation with lactation was observed during this period in Russia. The majority of women tried to breastfeed their children. However, some women from families with high income, who have enough milk to feed a child for the abovementioned far-fetched reasons, hired wet nurses. Women from families with low material income in case of lack of breast milk used milk of farm animals for additional feeding of the child. In the second half of the nineteenth century in Europe, surrogates (formula) for feeding infants began to appear which were very simple in composition and received in Russia, for example, a mixture of Bidert, Nestle flour, and Liebig's children's soup (Gundobin 1901; Mother and Child 1901). However, the cost of these mixtures was very high, and their effectiveness did not differ much from the milk of farm animals (Lipsky 1896). Therefore, they were not widely distributed among nursing women. In general, it should be noted that, despite the existing traditional difficulties, the percentage of lactating and breastfeeding women in Russia at the beginning of the twentieth century was quite large. Thus, according to the well-known Russian pediatrician G. N. Speransky (1928) in Moscow in 1926, about 98% of children were breastfed up to a year. Statistical data for other regions of Russia are not available in the medical literature of that time. However, it can be assumed with a high degree of probability that the percentage of breastfeeding for the whole of Russia slightly differed from the metropolitan data. It should also be noted that the religious factor was of great importance for maintaining lactation and breastfeeding in Russian women. According to the provisions of the main confessions of Russia (Christianity, Islam, Buddhism, Judaism), breastfeeding an infant is the highest good for both the child and the mother (Gundobin 1901; Fateeva and Pustograev 2005; Shaikh and Ahmed 2006; Eidelman 2006; Segawa 2008). Given that religion has had and still has a great influence on the way of life of the population, its encouragement of breastfeeding was and is a strong initiating and supporting psychological incentive for lactation of women.

The intensive development of fundamental and applied sciences that began in the twentieth century and, in particular, the improvement of methods of biochemical analysis and synthesis of biologically significant compounds for the human body allowed us to start developing nutritional mixtures for infants whose mothers were not able to breastfeed for various good reasons. As a result of decades of hard work, multicomponent mixtures (formula) have been created that are more or less adapted to infant nutrition. Unfortunately, the advertising activities of companies that produce infant formula were organized in such a way that women who did not have problems with lactation were also involved in using the formula. The reclaim for the formula mentioned two main factors that pushed lactating women to switch to feeding babies with formula from a bottle: the convenience of feeding the baby with formula and the greater nutritional value of these mixtures than the mother's milk. It was really easy and quick to make sure that bottle feeding was simple and comfortable compared to stressful and time-consuming breastfeeding. In addition, the transition to bottle feeding greatly facilitated the work of medical specialists on the nutrition of children in the first months of life, but long-term studies were required to test the second advantage of feeding a child with artificial mixtures. Intensive development of production of relatively cheap multicomponent mixtures has equalized the ability of women from families with high and low incomes not to breastfeed. The spread of formula in the developed world has captured more and more breastfeeding women so that by the early 1970s of the twentieth century, for example, in the United States in the first weeks after birth, only 24% and in Australia 48% of women breastfed their children (Ryan et al. 1991; Hartmann 2007). The attitude of the public in developed countries at that time to breastfeeding and woman lactation is well illustrated by the memoirs of the world's leading lactation specialist, Professor P. Hartman. He wrote:" I have applied to the Australian national health grants Committee for a women's lactation grant. I clearly remember a member of the National Health and Medical Research Council, Grants Committee asking me during an interview why I wanted to do research on these unusual women, i.e., breastfeeding mothers" (Hartmann 2007).

However, at the same time, the scientific literature has accumulated a sufficient amount of experimental data indicating the fallacy of claims that the nutritional value of the formula exceeds or does not differ from the mother's milk. Moreover, research has found that women's milk has active biological properties that are not present in artificial mixtures. Women's milk contains hormones, biologically active substances, immune complexes, and living cells, including stem cells (Hassiotou et al. 2012, 2013; Witkowska-Zimny and Kaminska-El-Hassan 2017), (live cells in 1 ml of milk, 10^4–13×10^6), and has a strong beneficial effect on the child's body, ensuring the normal course of the metabolic process and maintaining resistance to infections and other external adverse factors. All these data pointed to the principal impossibility of artificially producing a formula that completely replaces natural women's milk. This was the reason in the 1970s for a sharp turn toward breastfeeding in all developed countries—the "revolution of the 70s in child feeding" (Wharton 1982), and the practice of artificial feeding of young children was described by the World Health Organization in one of its reports (1981) as "the most widespread uncontrolled experiment in the world." Fortunately, the women of Russia, as well as the women of the Union Republics that were part of the Soviet Union at that time, did not participate in this "experiment." However, the appearance of multicomponent milk formulas in the 1980s in Russia and their corresponding advertising negatively affected lactation and breastfeeding. The percentage of breastfeeding women began to decline, and in the 1990s of the twentieth century in Russia, it was about 40% (Fateeva and Pustograev 2005).

By the beginning of the 1990s, there was an increase in international cooperation aimed at supporting and stimulating women's lactation and breastfeeding children. Here, first of all, it is necessary to note the meeting in 1990 in Italy in the city of Spedale degli Innocenti of representatives of various organizations on the problems of breastfeeding. The famous "Declaration of Innocenti" was adopted, calling on women of all countries to "practice exclusively breastfeeding children from birth to 4–6 months of life, and above this age, breastfeeding with adequate complementary foods up to 2 years and older." This provision was based on numerous scientific data on the exclusive role of breastfeeding for the physical and mental health and development of children, as well as for the health of women themselves, contained in publications, the number of which increased dramatically at the time of the adoption of the Declaration and has steadily increased every year since. Figure 1.1a, b as an illustration shows the distribution of scientific articles starting from the 1950s of the twentieth century by year in the search engine PubMedline for the following keywords: woman's lactation physiology (a) and breastfeeding (b). Despite the fact that not all publications reflect these charts, they largely characterize trends in scientific research on breastfeeding and on various aspects of the physiology of women's lactation.

As a commentary in Fig. 1.1a, b, the statement of one of the world's leading specialists in breastfeeding and physiology of female lactation, Professor R. Lawrence (Lawrence and Lawrence 2009), is well suited. She writes: a thin stream of scientific work on female lactation from the middle of the twentieth century to its end turned into a full-flowing river that went off the banks. It should also be noted that along with the increase in the number of publications in obstetric and pediatric journals, specialized scientific journals devoted to women's lactation and breastfeeding have appeared: The *Journal of Human Lactation* (since 1985), the *International Breastfeeding Journal* (since 2003), and *Breastfeeding Medicine* (since 2006).

Extensive promotion of breastfeeding, actively conducted in the scientific and popular press, as well as on radio and television in the world, has brought positive results. In most cases, women want to breastfeed their newborns, because there is a wealth of scientific evidence that leaves no doubt about the benefits of breast milk. Thus, in addition to ideal nutrition, breastfeeding reduces the incidence or severity of

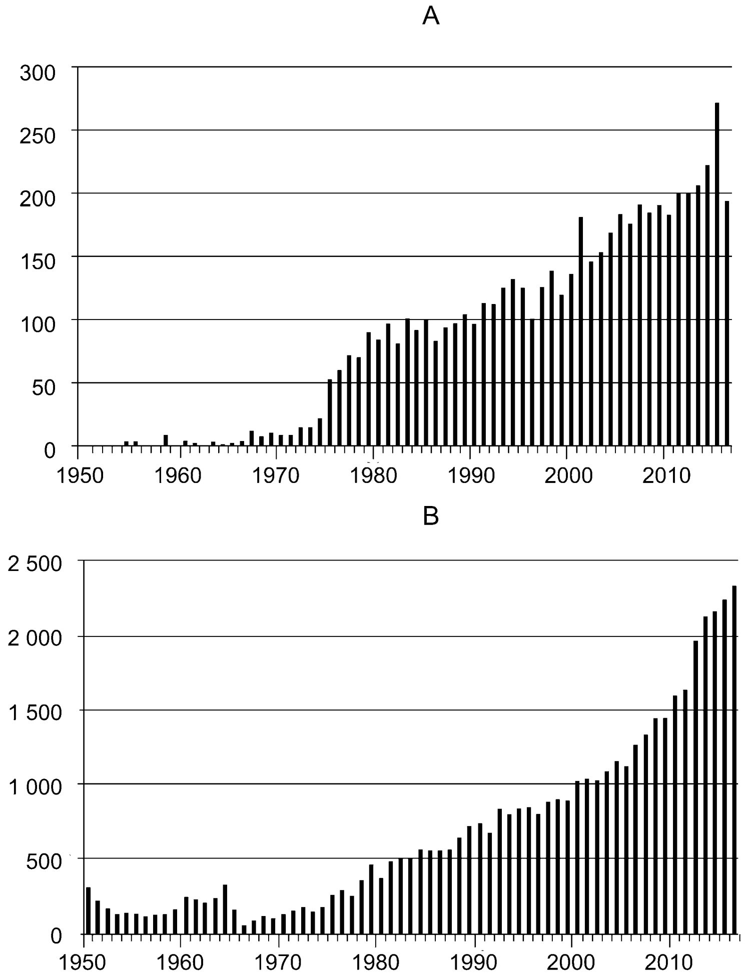

Fig. 1.1 Dynamics of articles output by year on the keyword: woman physiology lactation (**a**) (**b**) in the search engine PubMedline. On the ordinate axis, the number of articles, and on the abscissa axis, the year of publication of articles

a number of diseases, including bacterial meningitis (Istre et al. 1985; Cochi et al. 1986); bacteremia (Istre et al. 1985; Takala et al. 1989); diarrheal diseases (Howie et al. 1990; Popkin et al. 1990; Dewey et al. 1995; Beaudry et al. 1995; Lopez-Alarcon et al. 1997; Bhandary et al. 2003; Kramer et al. 2003); infectious diseases of the respiratory system, including asthma (Lopez-Alarcon et al. 1997; Oddy et al. 1999, 2002, 2003a; Gdalevich et al. 2001; Blaymore Bier et al. 2002; Chulada et al. 2003; Bachrach et al. 2003); infectious diseases of the urinary tract (Pisacane et al. 1992; Marild et al. 2004); infectious diseases of the auditory system (Saarinen 1982; Duncan et al. 1993; Owen et al. 1993; Paradise et al. 1993; Aniansson et al. 1994);

necrotic enterocolitis (Lucas and Cole 1990; Schanler et al. 1999); various forms diabetes (Kostraba et al. 1993; Perez-Bravo et al. 1996; Gerstein 1994; Pettit et al. 1997); lymphoma; leukemia, Hodgkin's disease (Davis 1998; Smulevich et al. 1999; Bener et al. 2001); obesity (Gillman et al. 2001; Singhal et al. 2002; Armstrong and Reilly 2002; Stettler et al. 2002; Toschke et al. 2002; Arenz et al. 2004; Grummer-Strawn and Mei 2004); and sudden infant death syndrome (McVea et al. 2000; Alm et al. 2002). Infants who were breastfed later in adulthood are less prone to alcoholism (Goodwin et al. 1999). Breastfeeding contributes to the development of children's mental abilities (Lucas et al. 1998; Anderson et al. 1999; Jacobson et al. 1999; Reynolds 2001; Horwood et al. 2001; Mortensen et al. 2002; Rao et al. 2002; Bier et al. 2002; Oddy et al. 2003b; Batstra et al. 2003; Feldman and Eidelman 2003; Horta et al. 2018). For most breastfeeding women, the risk of breast cancer is reduced (Newcomb et al. 1994; Enger et al. 1998; Tryggvadottir et al. 2001; Lee et al. 2003; Jernstrom et al. 2004).

However, in our time, during lactation, some women (sometimes the percentage of such women is quite high) have the same difficulties that were observed in nursing women in the previous centuries. The main ones are associated with a lack of milk secretion and its removal from the breast by the child. Moreover, these problems are most often found at the beginning of a woman's lactation. Therefore, as medical practice shows, the degree of effectiveness of eliminating these problems depends on whether a woman will continue to lactate and breastfeed the child or will switch to an easier way of feeding artificial infant formula from a bottle due to the difficulties encountered. Here, it should be noted that the treatment and correction of the work of any organ is carried out more effectively if the structure and mechanisms of its functioning are known. To date, scientists of various specialties have received quite extensive material on the structure and function, as well as mechanisms, for regulating the work of a woman's breast. However, this information is scattered in various and numerous publications, which makes it difficult to use it in the practice of breastfeeding. Therefore, the purpose of this book is to present up-to-date data on the structure and function of a woman's breast, so that medical professionals, as well as participants in breastfeeding support groups, can use this information when drawing up individual schemes for correcting the secretion or excretion of milk in nursing mothers. In addition, this book can be an indispensable tool for medical students and postgraduates in the study of woman lactation or breastfeeding. It should be noted that the book does not include experimentally and statistically unbiased "anecdotal" data on the structure and function of a woman's breast, which, unfortunately, are sometimes contained in textbooks and manuals on women's lactation.

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2 Origin and Development of the Mammary Glands

Abstract

The chapter presents data on the development of breast structure and function during various periods of a woman's life: in the prenatal period, in the first 2 years after birth, during puberty, and during pregnancy. The onset of breast development, as well as early morphogenesis in the embryo, is due to mesenchymal-epithelial interaction with the help of autocrine/paracrine growth factors. The mammary glands of human fetuses achieve a rather high degree of development in structural and functional relation, by the time of birth. After birth, infant mammary glands for some time begin to function while continuing their development. The most intensive development of the breast begins with puberty and the appearance of a menstrual cycle in girls. The development and functioning of the mammary glands changes during this cycle under the influence of the steroid hormones, prolactin and oxytocin. Final breast development occurs during pregnancy and is highly dependent on reproductive and metabolic hormones.

2.1 Origin of the Mammary Glands

According to paleontological research, mammals are descended from reptilian synapsids (Synapsida), which first appeared about 300 million years ago in the second half of the Carbon period. Synapsids were small lizard-like animal that multiplied by laying eggs. Synapsids were a branch of early terrestrial vertebrates-amniotes, which also propagated by laying eggs. But their eggs were different in structure from those of crocodiles, turtles, dinosaurs, and birds that lived at that time. These eggs, called amniotic (hence the name of the animals), had additional shells that contribute to better gas exchange, utilization of nutrients and waste products of the embryo, as well as water retention. Synapsids were better adapted to land and tree life than other reptiles. Some of the synapsids have become able to remain active in the cold season due to the development of a four-chamber heart and a constant

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body temperature. One of these groups has formed a hairline. As a result of modification of the structure and function of a certain type of skin glands, mammary glands were formed, due to which this group was named mammals. This happened at the beginning of the Triassic period (about 250 million years ago). The first mammals still laid eggs and hatched their young, but they were already feeding the young with milk. An idea of what their mammary glands looked like can be made on the basis of the structure of the mammary glands of an ancient almost extinct group of oviparous mammals that has survived to date, including two families: platypuses and echidnas that live in Australia and its surrounding islands. Their glandular department consists of separate tubular glands (in the amount of 100–200). Each gland has a single duct. The excretory ducts are grouped into bundles and open directly on the surface of the abdominal wall, forming a so-called glandular (milky) field, from the surface of which the baby licks the milk. Subsequently, as a result of the evolutionary process, viviparous mammals appeared, the cubs of which developed before birth in a special organ formed during pregnancy—the placenta. Significant alterations occurred in placental mammals and in the structure of the mammary gland. The structure of the glandular part changed, and special formations appeared on the surface of the skin—nipples containing milk ducts opening outward (Grachev and Galantsev 1973).

The question of the origin of mammary glands and lactation in mammals began to be discussed in the scientific literature from the mid-nineteenth century. Most authors believe that the mammary glands are derived from the skin glands. However, there is no consensus on the type of skin glands. There are several hypotheses, among which there are two noteworthy ones. According to the first hypothesis, the most common, the mammary glands are derived from the sweat apocrine glands located next to the hair follicles. This position is based on the fact that the glandular apparatus of the apocrine sweat glands has a great similarity in structure and function with the tubular glandular apparatus of the mammary glands that currently exist in ancient groups of lower mammals: platypuses and echidnas. According to the second hypothesis, mammary glands, as well as other skin glands (sweat, sebaceous), were descended from nonspecialized skin glands of animallike reptiles, and in phylogeny, the first among specialized skin glands, apparently, were mammary glands. This is indicated by the fact that in embryogenesis in placental mammals, the laying of mammary glands occurs earlier than the sweat and sebaceous ones (Raynaud 1961). It unfortunately, the lack of sufficient paleontological data, does not allow us to present a corresponding series of evolutionary transformations from ancestral forms of skin glands to the mammary glands of modern placental mammals. More information of hypotheses about the origin of mammary glands can be found in the currently available reviews: Grachev and Galantsev (1973), Galantsev and Gulyaeva (1987), Blackburn (1991), Oftedal (2002a, b, 2012), Lefèvre et al. (2010), and Oftedal and Dhouailly (2013).

2.2 Development of the Breast

The main development of the breast occurs in the postnatal period and reaches the final formation in a woman after childbirth in the first days (weeks) of lactation. Before the final stage, there are three main phases in the development of breast structure and function: intrauterine development, development in the first 2 years of life, and development at puberty (Lawrence and Lawrence 1999). A detailed description of the structure of a woman's lactating breast will be presented in Chap. 3. However, for a better understanding of the material presented in this section and subsequent sections of Chap. 2, it is advisable to first present in schematic form (Fig. 2.1) the structure and location of the main structures of the breast of a woman during lactation. It should be noted that due to the dense packaging and different size of the structures that make up the inner part of the gland, it is fundamentally impossible to visually depict all the elements of the breast on any one scale.

The formation of the milk occurs in epithelial secretory cells, which with another type of epithelial cells—myoepithelial cells that provide milk excretion—form special hollow structures, alveoli or acinuses, connected by a system of ducts

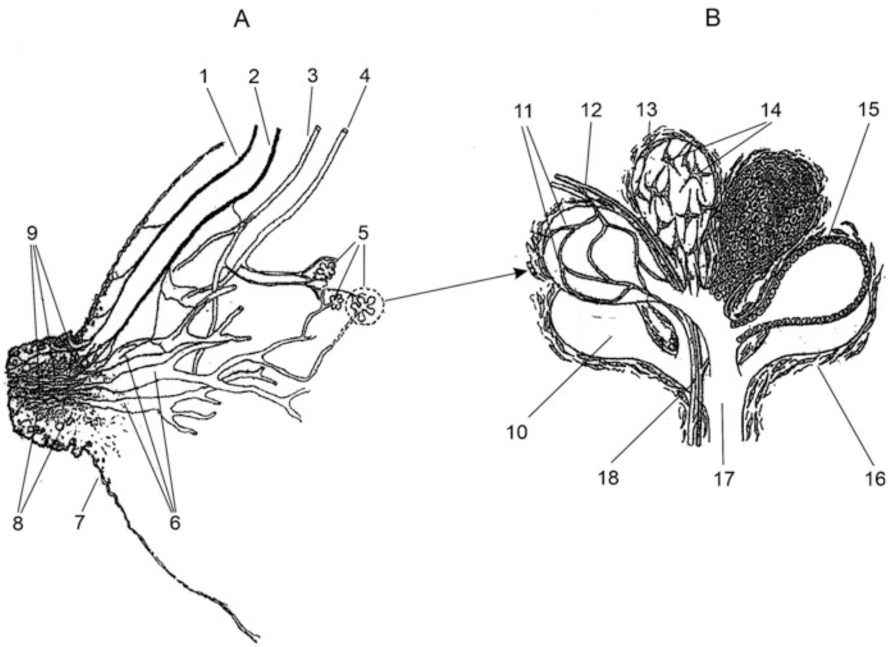

Fig. 2.1 Schematic representation of the general structure of a woman's breast (**a**) and a separate lobule of glandular tissue (**b**). (**a**) 1 nerve trunk containing afferent and efferent nerve fibers of the autonomous nervous system, 2 nerve trunk containing afferent nerve fibers of somatic nervous system, 3 blood vessel, 4 lymph vessel, 5 breast ducts, 6 breast lobes, 7 epidermis, 8 nipple ducts,9 smooth muscles. (**b**) 10 alveolus, 11 blood capillaries, 12 arteriole, 13 interlobular stroma, 14 secretory cells, 15 myoepithelial cells, 16 interlobular stroma, 17 mammary gland duct, 18 venule

(Fig. 2.1b). Here, stem cells are localized, providing the appearance of secretory and myoepithelial cells. A very important structure of the alveolar-ductal system is the basal lamina that covers the alveoli and ducts. The alveolar-ductal system is located under the skin and in addition to the basal lamina is surrounded by a number of connective tissue and cellular structures united by the common name—stroma. Elements of the stroma are extremely important for the normal development and functioning of the breast. Connective tissue structures of the stroma include bundles of various types of collagen and elastin fibers. The stroma cell includes fibroblasts, fat cells, macrophages, lymphocytes, mast cells, Cajal cells, or cells similar to Cajal cells.

Alveoli, united by a single duct, form lobules. Lobule ducts connect to larger ducts to form lobes. The ducts of the lobes of the breast do not just end on the surface of the skin, but pass inside a special skin-muscle formation—a nipple that protrudes above the surface of the skin. The pigmented area of the skin near the base of the nipple is called the areola. When approaching the nipple in the subareolar region, the lobe ducts can join and expand to form the main ducts (Ramsay et al. 2005), the number of which is 4–14. The main ducts have a diameter varying between 1 and 5 mm. Wide, non-branching sections of the main ducts are sometimes called milk sinuses. At the entrance to the nipple, the ducts are largely narrowed and have different diameters along the way in the nipple. The breast nipple and areola do not have hair. The inner part of the gland is abundantly supplied with blood and lymphatic vessels. Blood capillaries pass next to individual alveoli. Somatic afferent nerve fibers in the skin of the nipple and areola of the gland form receptors of various modalities: mechanoreceptors and heat, cold, and pain receptors. Afferent nerve fibers of the autonomic nervous system innervate the walls of broad and medium-sized milk ducts, as well as blood and lymphatic vessels. Efferent nerve fibers of the autonomic nervous system innervate smooth muscle fibers in the breast nipple and in the walls of blood vessels (Eriksson et al. 1996).

2.2.1 Prenatal Development of the Breast

Research on the development of women's breast began in the second half of the nineteenth century (Raynaud 1961; Khizhnyakova 1965; Howard and Gusterson 2000). However, the degree of study of this problem to date is inferior to that of laboratory animals, in particular, in rats and mice. The main reason was and is the limitations associated with the use of methods for the study of a woman's breast. Thus, there are certain ethical and technical difficulties in obtaining histological material in different periods of development of a woman's breast. It was not possible to fully use a number of methods that are successfully used to study the development of mammary glands in laboratory animals. These include primarily methods of immunohistochemistry, molecular genetics, and tissue culture. In addition, great difficulties in studying a woman's breast arise from the fact that the size, shape, and rate of development of the human breast vary significantly between individuals at the macro- and microscopic levels. This is believed to be due to genetic causes, variations in nutrition, and environmental conditions (Howard and Gusterson 2000). However, in laboratory animals, genetic methods allow to breed and maintain lines of animals with certain characteristics while ensuring an appropriate diet and stable environmental conditions. It should be noted here that one of the most important conclusions that has been made on the basis of scientific achievements of recent decades is that the evolutionary process, once stumbled upon an effective version of the structural and functional organization of a system, uses it with varying degrees of modification (sometimes insignificant), both in animals and in humans. Experimental data available to date indicate that this position is also true for the structure and function of the breast (Grachev and Galantsev 1973). Looking ahead, we can note that a comparison of data obtained on the mammary glands of rats and mice and the mammary glands of women reveals similarities in their development, as well as morphofunctional characteristics (Cardiff and Wellings 1999). Therefore, the mammary glands of mice and rats are often used as a model to explain the functioning of women's mammary glands in normal and pathological conditions. However, along with the similarities, as we will see later, there are also noticeable differences (Johnson 2010), which suggests using the mammary glands of mice and rats as a model when studying the breast of a woman with certain adjustments.

In accordance with morphological studies of various authors in the formation of the human breast in the prenatal period, there are several successive stages corresponding to the development of the embryo (human embryo before the ninth week of development) and the human fetus. However, the time of appearance of any breast structure varies depending on the criteria chosen by the authors to determine the age of the embryo or fetus, for example, the time from the beginning of conception, from the last menstrual cycle of a woman in labor, or the length of the embryo and fetus (Howard and Gusterson 2000; Russo and Russo 2004a, b). It is difficult to determine the time with sufficient accuracy based on the first two criteria. More successful was the use of the ratio between the length of the embryo and the development of breast structures (Russo and Russo 2004a, b), proposed by E. Hughes (1950).

While in a pregnant woman, the development of the structure and function of the breast is approaching the final stage in the fetus, who is in the womb, the mammary gland is just beginning to develop. To date, it is an established fact that the final development of the breast during pregnancy is largely dependent on reproductive hormones: estrogen, progesterone, placental lactogen, prolactin, oxytocin, as well as the so-called metabolic hormones, i.e., growth hormone, glucocorticoids, thyroid hormone, and insulin (Neville et al. 2012). This will be discussed in more detail in the following sections of the book. However, the beginning of breast development, as well as early morphogenesis in the embryo, is due to the interaction of ectoderm cells (embryonic epidermis) and mesenchyma (embryonic stromal cells) with the help of known autocrine/paracrine growth factors such as epidermal growth factor (EGF) and transforming growth factor-α (TGF-α), as well as other as yet unknown factors. Moreover, the initial influence is exerted by mesenchyma. This conclusion was made based on the results of experiments on the effect of different combinations of mesenchymal and ectodermal tissue sites on breast development in laboratory animals (rabbits and mice). So in rabbits, before the appearance of the first noticeable signs of mammary gland differentiation, the combination of mesenchyma taken from the area where the mammary gland embryo should occur with the epidermis of the head or neck sections was accompanied by the development of mammary gland structures. At the same time, a similar combination of ectoderm sites, the supposed place of origin of the embryo and mesenchyma of other areas of the embryo, did not lead to the development of mammary gland structures. However, after the first signs of a mammary gland embryo appear, the ectoderm from this site can form the beginnings of the mammary gland when combined with the mesenchyma of other parts of the embryo's body (Robinson et al. 1999; Hovey et al. 2002; Cunha et al. 2004). Similar studies on the mammary glands of human embryos have not been conducted. There are only indirect data indicating that the early development of the human embryo is determined by growth factors. In particular, data from immunohistochemical experiments indicate the presence of growth factors EGF, TGF-α, as well as TGF-β, tenacina-C, and BCL (Osin et al. 1998; Howard and Gusterson 2000).

Analysis of past and current morphological works (Hughes 1950; Raynaud 1961; Grachev and Galantsev 1973; Howard and Gusterson 2000), devoted to the study of prenatal development of the breast of the human embryo and fetus, revealed difficulties in selecting images from microphotographs, which could be sufficiently clearly present simultaneously all the main cellular elements at different stages of breast development. Therefore, for better clarity, when presenting the material, generalized schematic drawings will be provided as illustrations in most cases. The first anatomical structure of the developing breast is the so-called milky strip, which can be seen in a human embryo 4 mm long at the fourth week of the embryo's life (Hughes 1950) (Fig. 2.2). Milky strip are thickening of the ectoderm, consisting of two to four layers of cells and located on both sides of the body from the rudiment of the forelimb in the caudal direction to the inguinal folds. It should be noted here that the milky strip seem to be important not only for the development of the mammary gland but also for other structures of the body, since the milky strip are found in the embryos of reptiles and birds (Howard and Gusterson 2000). In a 7 mm embryo, ectodermal cells appear in the middle of the milky strip in the longitudinal direction, which are slightly larger than neighboring cells and are based on compacted mesenchymal cells. As a result, a narrow ridge is formed in the middle of the milky strip in the longitudinal direction, called the milky line (Fig. 2.2). When the size of the embryo increases to 9 mm, the milky line grows along the entire length of the milk strip (Fig. 2.2). Then the milky line from the caudal side begins to regress so that at the size of the embryo of 10–12 mm, it is observed only in the thoracic region of the embryo. The mesenchyma under the ectodermal cells is differentiated into four layers. On the cross section, the reduced milky line has the form of a biconvex lens or disk (Fig. 2.2) in an embryo of 13–15 mm, and the reduced length of the milky line thickens in the cranial part where the ectodermal cells begin to invaginate into the mesenchyma. As a result, an epithelial thoracic (milky) nodule is formed, which gradually increases in volume. In an embryo at the age of 2 months, having a length of 20–30 mm takes a globular or spherical shape.

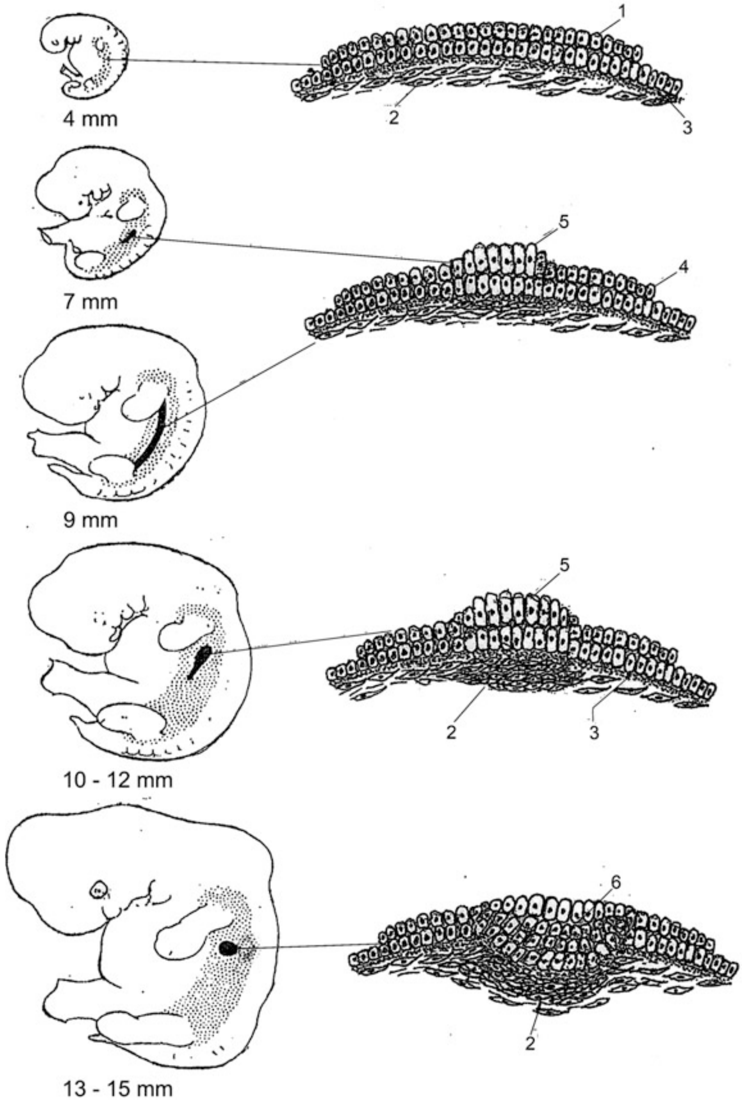

Fig. 2.2 Development of the mammary bud in a human embryo (from Porter J. C., 1974). At the left, the human embryo at different stages of development. Numbers denote embryo length in mm. On the right, mammary glands at different stages of embryo development. 1 milky strip, 2 mesenchyma, 3 basal membrane, 4 ectoderm, 5 milky line, 6 milky nodule

The epithelial cells forming it are located mainly in the radial direction. In parallel with cellular transformations, the milky nodule shifts in the ventral direction.

It should be noted that sometimes the milky line begins to segment, just as it does, for example, in mice or rats. As a result, along the length of the milky line, in

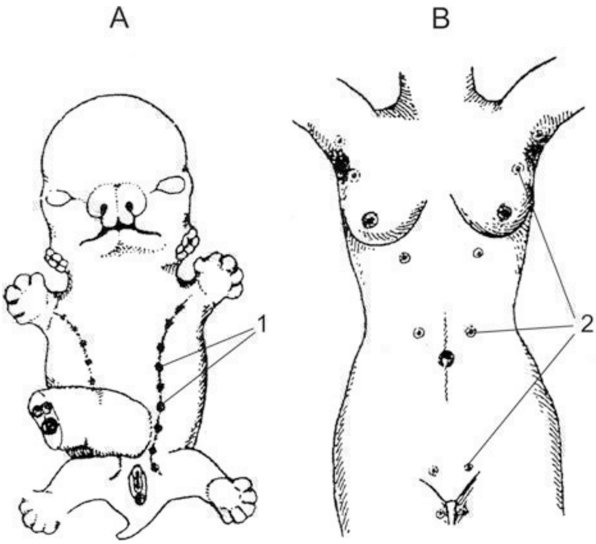

Fig. 2.3 The phenomenon of polythelia in the embryonic period (**a**) and its manifestation in a woman in adulthood (**b**) (from Grachev and Galantsev 1973)

addition to the thoracic pair of milky nodules, several pairs of additional milky nodules are formed, which develop further. The degree of development of additional milky nodules can be different. According to the classification given by Y. Kajava (1915), additional milky nodules can reach the following development: (1) normal mammary glands (polymastia); (2) additional mammary glands that do not have areola region, but the nipple and the glandular tissue are developed; (3) the mammary gland without nipple but with the presence of the areola and glandular tissue; (4) only sections marked glandular tissue (ectopic glandular tissue); (5) the nipple and areola present, but the glandular tissue replaced by fat tissue; (6) there are nipples only (polythelia); and (7) the presence of areola only (polythelia areola). For Fig. 2.3 as an example, the phenomenon of polythelia in the embryonic period (A) and how it manifests in a woman in adulthood (B) are presented. It should be noted that the above abnormalities are most clearly detected during lactation.

Currently available data indicate that abnormalities in the development of the human breast occur as a result of violations at the genetic level (mutations of the TBX-3 gene), which in turn leads to violations in ectodermal-mesenchymal interactions. Moreover, the abovementioned anomalies can occur as a purely phenotypic, involving only the mammary gland, or as a pleiotropic syndrome, in which there is a violation in the development of the breast, limbs, teeth, and genitals (Bamshad et al. 1997).

The development of the milky nodule from 3 to 5 months is relatively slow (Raynaud 1961). However, at 5 months of life with a fetal length of 120–150 mm, noticeable changes in the structure of the milky nodule begin, leading to the formation of the milky bud, from which the development of the ducto-alveolar system of the future mammary gland is directly carried out (Fig. 2.4). The bud is covered with a basement membrane (shell), which is adjacent to dense layers of

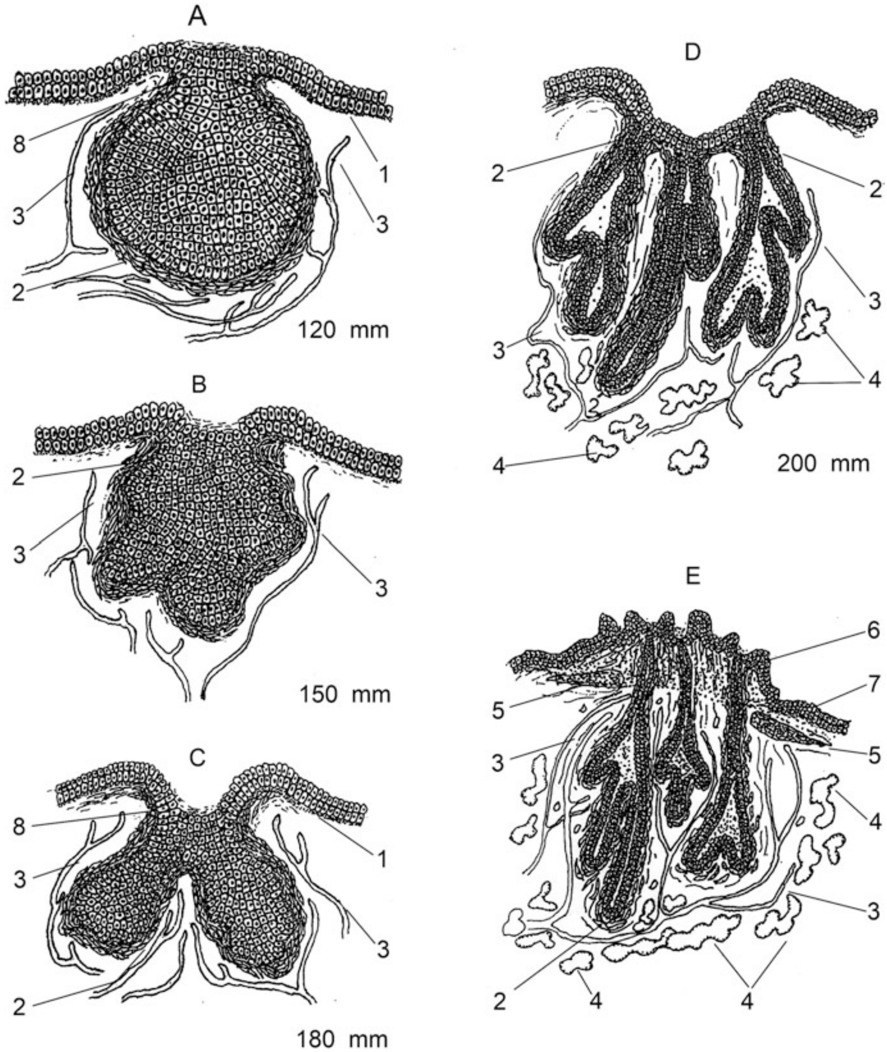

Fig. 2.4 Human fetal breast development. (**a**) Milk bud, (**b**, **c**) the appearance of secondary buds, (**d**) the formation of cell filaments with cavities, (**e**) the formation of the nipple. 1 Basal membrane, 2 layer of fibrocytes and collagen fibers, 3 blood and lymphatic capillaries, 4 adipose tissue, 5 subareolar muscles, 6 breast nipple, 7 epidermis, 8 neck of the milk bud. All the numbers below show the length of the fetus in mm

primary mesenchyma. The bud is attached to the outer epidermis by a short neck formed by epithelial cells and slightly protrudes above the chest surface of the fetus (Fig. 2.4a).

Electron microscopic studies have shown that the cells that make up the bud in the center have a polygonal shape and are connected to each other by thin microvilli and