Histology of breast development in early life

J McKIERNAN,* J COYNE,† AND S CAHALANE‡

**Paediatric and †Pathology Departments, Regional Hospital, Wilton, Cork, and ‡Pathology Department, The Children's Hospital, Temple Street, Dublin*

SUMMARY Histological examination of the breasts of 26 infants and young children who died suddenly between the ages of 3 weeks and 2 years was performed. The glands were composed of well formed lobules surrounded by dense interlobular stroma, while within the lobules there was looser connective tissue. The lobules contained ducts, many of which were dilated and contained secretions. Foci of extramedullary haematopoiesis were found, and in the older infants, fat was prominent within the connective tissue of the breast. Myoepithelial cells were regularly present. No sex differences in breast development at this time were noted. Newborn breast development did not regress rapidly after birth and secretory activity continued for many months in both sexes. This study shows that the human mammary gland remains active for many months after birth and may continue to grow and secrete. The findings are not consistent with the current view that breast development in infancy results from stimulation from 'pregnancy hormones.' It is more likely that the infant's own gonadal secretions are responsible.

The human mammary gland has a number of well recognised phases of growth and development. In late pregnancy the fetal breast (in both sexes) is highly developed, and at birth it often secretes milk.¹ Then at puberty the growth of the breast is usually the first sign of secondary sexual development in girls, and at this time gynaecomastia is not uncommon in boys.² The breast reaches its maximal development during pregnancy in preparation for lactation. There is, however, another ill recognised phase of development of the human mammary gland in the first year or two of life long after the influences of pregnancy have been removed. Contrary to what has been stated³ the infant's breast does not regress rapidly after birth. Careful clinical study has shown that it often persists as a firm discrete nodule in many boys and girls during the first year of life and it may be more prominent by the age of 6 months than earlier and it is only later in infancy that the first sex differences in breast size appear: the gland being bigger then in girls.¹ In prematurely born infant girls this phase of development may be even more prominent.⁴ After the first two years the breast bud usually remains small and barely palpable until puberty.

The histological appearances of the breast in the fetus, at birth, in puberty, and pregnancy have been well described,^{5 6} but there are few reports on breast histology in infancy after the immediate newborn period. Also it is likely that the specimens

of breast tissue that were subject to histological examination were from infants who had died in hospital after chronic illnesses. To obtain information on the natural history and histological appearances of the breast in healthy children it was decided to examine the glands of previously well infants and young children who had died suddenly.

Materials and methods

The breast bud and surmounting ellipse of nipple containing skin was excised from a total of 22 cases of sudden infant death at necropsy; the infants were aged 3 weeks to 6 months. Three infants showed evidence of mild tracheobronchitis and no pathological abnormalities were found in the others. Breast tissue from four additional cases taken at necropsy was examined: a 2 month old girl who died from hydrocephalus and acute pyelonephritis, a 5 month old boy with hydrocephalus and pneumonia, an 18 month old boy with peritonitis due to gastric perforation, and a 2 year old girl who died from shock secondary to trauma. After fixation in formal saline and paraffin embedding sections were stained by haematoxylin and eosin and examined.

Results

On gross appearance the breast gland consisted of a subareolar nodule of firm white tissue up to 1 cm in

diameter. No age or sex differences in size were noticed. On histological examination the glands consisted of well formed lobules surrounded by dense interlobular stroma. The lobules contained a number of ducts (fig 1) and the larger ducts seemed to disrupt the lobular pattern. The connective tissue within the lobules was looser and more delicate than elsewhere but in two cases this also was condensed. The definite lobular pattern was rarely absent after the age of 5 weeks. All the breast specimens contained recognisable ducts. Fat was prominent after the first 2 months of age and was invariably of the adult type. Islets of fat cells were often found within the connective tissue of the breast bud.

In the younger infants (aged 3 weeks to 3 months) the ducts were usually large and dilated and often contained secretions (fig 2). In general the dilated ducts had a single lining of flat epithelial cells (active epithelium) and contained secretions. Desquamated cells were usually present in the duct lumen at all ages, but definite secretion was often seen especially in the first three months, and at this time there were often cytoplasmic buds typical of apocrine secretion (fig 3).

After the first months the ducts were usually smaller, had a double lining of cuboidal epithelium (resting epithelium), and contained little secretion. There was, however, great variation—a single lining was seen as late as 6 months of age, and the dilated ducts of a 10 week old girl had a double lining. Also a double lining layer with eosinophilic secretion was seen in some glands from children over the age of 6 months and large dilated ducts, assuming a papillary appearance were present in the glands of one 18 month old boy. Double epithelial layers were more likely to be found in the embryologically more mature ducts in the subareolar areas.

Fig 1 Section of breast of 4 week old girl (sudden infant death) showing the lobular pattern with interlobular and intralobular connective tissue (haematoxylin and eosin $\times 40$).

Fig 2 Large dilated ducts containing plentiful secretion from a 10 week old girl (sudden infant death) (haematoxylin and eosin $\times 80$).

Fig 3 A dilated duct with apocrine secretion showing cytoplasmic globules released in the duct lumen from a 3 week old boy (sudden infant death). Arrow indicates cytoplasmic bud (haematoxylin and eosin $\times 200$).

A cellular infiltrate was often seen within the stroma. Initially this was thought to represent inflammatory change but on more careful examination primitive red and white cells were identified indicating extramedullary haematopoiesis (fig 4). Myoepithelial cells were present at all ages from 4 weeks to 18 months irrespective of whether the gland contained secretion (fig 5).

Fig 4 Extramedullary haematopoiesis in the breast of a 5 week old boy (sudden infant death). Arrow indicates focus of erythroid and myeloid precursors (haematoxylin and eosin $\times 150$).

Fig 5 A duct surrounded by a layer of myoepithelial cells (arrow) with clear cytoplasm is seen in the breast of a 2 month old boy (sudden infant death) (haematoxylin and eosin $\times 150$).

Discussion

From this histological study it is clear that the human mammary gland does not involute rapidly after birth but remains active for a few months often showing typical apocrine secretion. In some cases secretion was still seen many months, and once as late as 18 months, after birth. The histological appearances of the lactating breast in early infancy are, in general, similar to the adult puerperal gland,^{5 6} but it has been noted before that in infancy secretion of milk seems to take place in dilated ducts, and definite alveoli at the ends of ducts are

rarely seen.⁷ In general active epithelium was flattened and had a single lining layer while the resting epithelium had a double lining layer. There was, however, great variation. Definite myoepithelial cells were identified at all ages. Extramedullary haematopoiesis in the newborn breast is not a well recognised phenomenon but has been described before and may be a normal feature.⁸

Previous reports have indicated that the breast becomes inactive soon after birth and remains rudimentary during infancy and early life. A recent clinical study, however, has shown that newborn breast development often persisted.¹ There has been little histological study. Pfaltz found that the breast of a 14 month old boy contained a core of connective tissue with 'underdeveloped' parenchyma but also noted that more branching ducts were present in the first three years than later.⁹ Our finding of histological evidence of breast activity (including secretion) after the first months of life is in agreement with that of Tholen who noted some very dilated ducts with a double epithelial layer and lobular pattern in one 8 month old boy.¹⁰ He also concluded that the gland was not smaller in later infancy than earlier as the amount of stroma and especially dense connective tissue had increased. Berka also commented on the increased amount of connective tissue in a 2 year old child.¹¹ We did not notice any difference in the histological appearance between male and female glands and this was surprising as clinical study had shown that after six months breast nodules were absent in boys but often still present in girls.¹ Another surprising finding was the well formed lobular pattern as it had been suggested that lobules are not formed until much later in childhood.⁵ It has been remarked that one of the characteristics of the mature breast is its variability in size and structure¹² and this certainly also applies to the gland in early life.

We know little of the factors that control breast development in infancy and early childhood. Hormones are thought to regulate breast development at puberty, pregnancy, and the puerperium with oestrogen promoting growth of the duct systems and progesterone that of the alveoli.¹³ High circulating concentrations of prolactin are needed for the initiation of milk secretion.¹⁴ It has been suggested that 'pregnancy hormones' may be implicated in postnatal breast development in the infant but this does not seem possible in view of their short half life and it is more likely that the infant's own endocrine system is responsible. Circulating concentrations of follicle stimulating hormone (FSH) rise after birth in both sexes and especially in girls remain relatively high for the next few years.¹⁵ It has been shown that the ovaries of

girls in the first few years of life are quite active with prominent follicular growth and atresia.¹⁶ Plasma oestradiol concentrations are often higher in girls aged 0–4 years than in later prepuberty.¹⁷ The pattern of hormone secretion seems to differ in boys with an early surge in luteinising hormone and testosterone¹⁸ and lower concentrations of FSH and oestradiol than in girls. We did not attempt to make quantitative measurements of breast size. Nevertheless, our failure to find an obvious difference in the sexes in gland size or development was surprising. Also, while it is known that prolactin concentrations are high at birth and in the first few weeks¹⁹ and may be responsible for the initiation of lactation (neonatal milk secretion), the concentrations then decline rapidly to the normal 'non-lactating range'. There may be other factors implicated in milk secretion, however, because in two infants we have seen definite secretion at the ages of 9 and 18 months long after prolactin concentrations might have been expected to have fallen and lactation to have ceased. It might be argued that the features we have observed are the effects of the acute stressful illness associated with the child's sudden death but this does not seem a plausible explanation.

Our study has confirmed that there is a definite phase of breast development in early infancy and early life and we have shown the histological appearances of the gland at this time. Our findings cast some doubt on current views with regard to the role of hormones in breast growth and development. Pregnancy hormones are not likely to be responsible, but the infant's own gonadal secretions (oestrogen, testosterone) are probably important.

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Correspondence to Dr J McKiernan, Paediatric Department, Cork Regional Hospital, Cork, Ireland.

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