THE MYOEPITHELIAL CELL: EMBRYOLOGY, FUNCTION, AND PROLIFERATIVE ASPECTS

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I. INTRODUCTION

Myoepithelial cells (or basket cells) were accurately described and illustrated in salivary, lacrimal, mammary, and sweat glands by histologists of the previous century. They lie within the epithelial basement membrane of the secretory and terminal ductular portion of most exocrine glands and display a cytoplasmic organization quite similar to smooth muscle cells. Although the structure of myoepithelial cells is agreed upon, divergent views are held on many functional and developmental facets and their participation in proliferative glandular disorders. These differences of opinion are the result of nonspecific criteria which had been employed during myoepithelial identification and serve to underscore the subjectivity of conventional light and electron microscopic studies. The rapidly developing fields of immunocytochemistry and immunoelectron microscopy invalidated some long-held concepts and facilitated a surge of advanced information on myoepithelial proliferations, especially in the neoplastic state when definition of participating cells becomes difficult. This paper will revise the current status of myoepithelial research, concentrating on pertinent aspects of their development, functions, microscopic identification, and participation in pathologic conditions of exocrine glands. For more detailed information on the structure of myoepithelial cells in salivary, mammary, and sweat glands, readers are referred to other sources.[1-4]

II. EMBRYOLOGY AND FUNCTIONS

A. Salivary Gland Myoepithelium

1. Embryology

It is generally accepted that the major and a significant number of minor salivary glands are of ectodermal origin; the remainder is derived from entoderm. From their respective germ layers, buds of proliferating progenitor cells extend into the adjacent mesenchyme to form a proximal and a distal epithelial cell mass. The proximal cell mass (excretory duct reserve cell) ultimately gives rise to the main excretory duct and the inter and proximal intralobular ducts.

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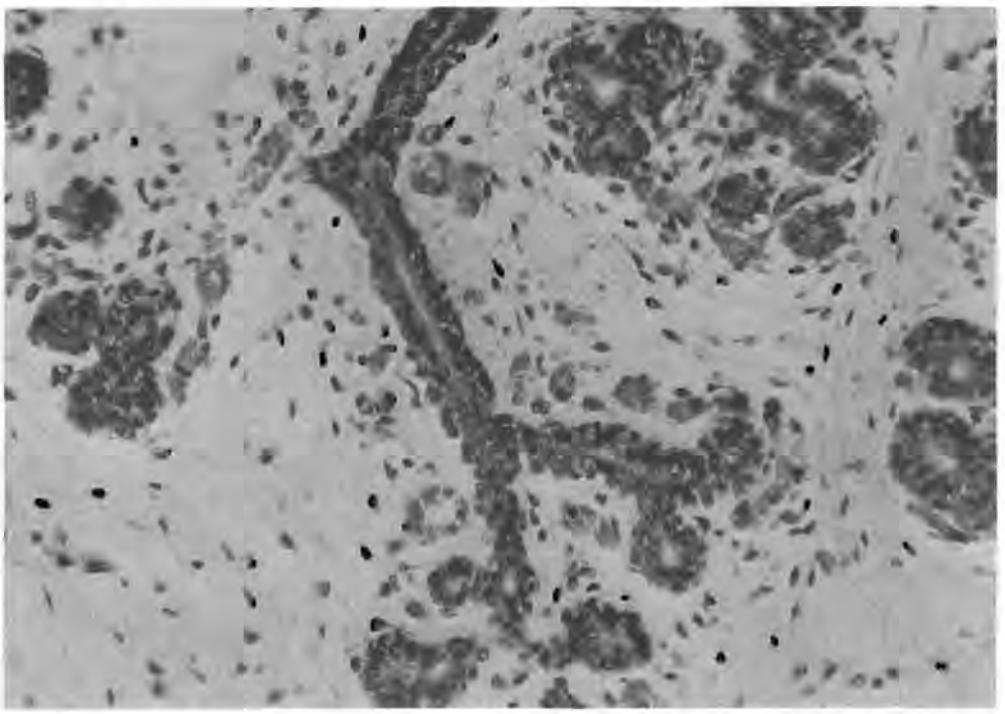


FIGURE 1. A 22-week-old fetal parotid. Formation of terminal tubules. (Hematoxylin-eosin; magnification × 200.)

In the distal cell mass, an elegant process of microfilament contraction narrows the basal portion of discrete groups of cells so that they appear to sink inwards forming clefts.[5,6] Several well-formed epithelial branches extend into the mesenchyme and each terminates in one or more cellular bulbs. Lumen formation gives rise to terminal tubules (Figure 1) lined by progenitor cells which eventually differentiate into intercalated duct cells and other specialized cells of the secretory unit.[7] Myoepithelial and secretory epithelial differentiation, which takes place mainly during postnatal life,[8] appears to be synchronized.[9] Most workers believe that both of these cell types lose their mitotic capacity when fully differentiated.[7,10,11]

In mature human salivary glands, the pluripotential intercalated duct cell or IDC (also referred to as the intercalated duct reserve cell) gives rise to other IDCs, acinar cells, striated duct cells, and myoepithelial cells.[1,7,10,12] The excretory duct reserve cell (or EDRC) acts as stem cell compartment for the remainder of the ductular system (Figure 2). Clear cells which are present in the secretory unit of the submandibular gland transform directly into myoepithelium[13] and should be regarded as an intermediate stage in their development.

Interaction between epithelial cells of the developing salivary gland and mesenchymal elements, basement membrane proteins, and nerve axons appears to be of fundamental importance during the process of morphogenesis and cytodifferentiation; epithelial mesenchymal contacts through the basement membrane of the developing rat submandibular gland have been identified[14] and it has also been proven that collagen is involved in initiating new branching points and stabilizes epithelium participating in this process.[15,16] Furthermore, branching morphogenesis is dependent on the presence of extracellular basement membrane proteoglycan[17] (an acid mucopolisaccaride) and epithelial nerve contacts have been postulated to play a role in salivary gland epithelial differentiation.[7]

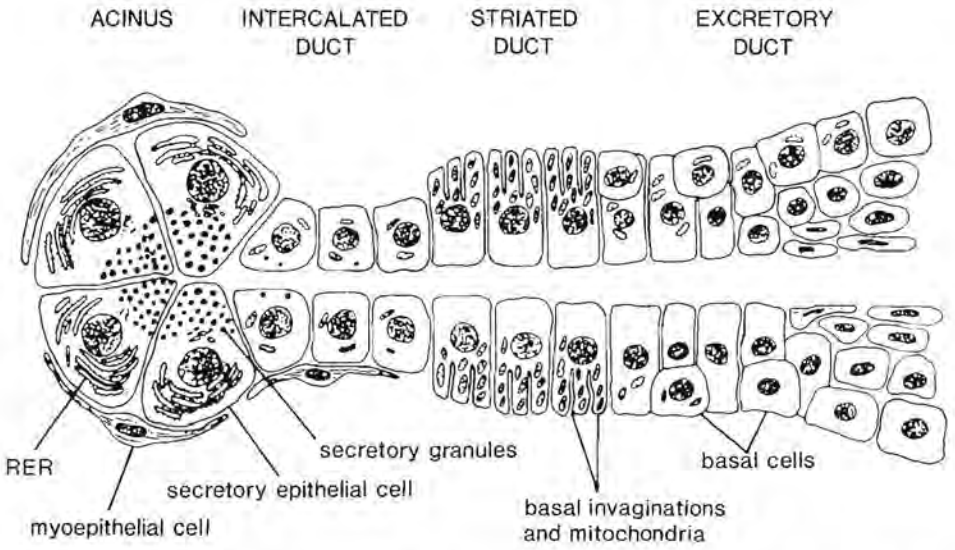


FIGURE 2. Schematic representation of the components of a human salivary gland unit. (Redrawn from Batsakis, J. G., *Tumors of the Head and Neck, Clinical and Pathological Considerations*, Williams & Wilkins, Baltimore, 1979, chap. 1. With permission.)

2. Functions

Evidence from structural and functional studies supports the belief that salivary gland myoepithelium has a contractile function.[18-21] Although species differences do exist, these cells have a dual innervation by parasympathetic as well as sympathetic nerves and impulses from both types cause contraction.[22-24] Synchronization of contraction is made possible by gap junctions and overlaps between myoepithelial cell processes.[25,26]

Contraction of the stellate-shaped acinar myoepithelial cells facilitates expulsion of secrete by rupturing "ripe" mucus cells,[21] reducing lumenal volume[22] and preventing distention of acini.[25,27] The acini of the rat,[28-30] rabbit,[31] and African elephant *(Loxodonta africana)*[237] parotid glands which excrete a watery product are devoid of myoepithelial cells. This phenomenon is the most likely explanation for the lower intraductal pressure developed by the rat parotid in comparison with that of the submandibular gland during autonomic stimulation.[32] The sublingual gland of the monotreme echnida, *Tachyglossus aculeatus*, which secretes an extremely viscous saliva, shows well-developed acinar myoepithelial cells, almost forming a complete muscular coat around the endpieces.[11] A similar arrangement has been demonstrated in the submandibular salivary gland of the African elephant (Figure 3). The saliva produced by this gland is, however, of a watery (serous) nature and factors other than the viscosity of the secrete also appear to have a bearing on the prominence of acinar myoepithelial cells.

Acinar myoepithelial contraction may modify the concentration of saliva by decreasing the surface area of the secretory apparatus exposed to interstitial fluid.[21] Such an effect would diminish loss of fluid into the tissues and is probably important when viscid saliva has to be forced through narrow ductules in a gland.[22] Myoepithelial cilia, projecting into invaginations in adjacent secretory cells,[11,21,22] may act as chemoreceptors in this regard as they have been postulated a sensory function.[21]

Contraction of elongated myoepithelial cells surrounding the intercalated ducts shortens and widens these structures,[28,33,34] thereby overcoming peripheral resistance. Extension of their processes onto the proximal regions of allied acini facilitates rigidity and patency in glands which may become distorted by masticatory movements.[28]

FIGURE 3. Scanning electron micrograph of acinar myoepithelium in the submandibular salivary gland of the African elephant after removal of the basement membrane. Note the interdigitating myoepithelial cell processes.

The role of the myoepithelial cell in transportation of metabolites to and from secretory cells is a controversial issue.[22,35] Basal infoldings of human submandibular salivary gland myoepithelium[36] and finger-like extensions on the surface of rat lacrimal myoepithelium[37] could serve to increase the surface area[36] and pinocytotic vesicles;[21,38] positive staining for the iron binding protein ferritin[39] and high levels of alkaline phosphatase and magnesium-dependent adenosine triphosphatase (ATPase) activity[40,41] are all features supporting active myoepithelial involvement in the transportation of metabolites involved in the secretory process. It has been pointed out, however, that ATPase and adenylate cyclase activity in myoepithelial cells of the palatine glands of rats are rather implicated in cell contraction and that the vesicle-like structures are in fact invaginations of the plasma membrane and continuous with the extracellular space.[42]

Finally, myoepithelial cells are important in the formation and maintenance of the basement membrane. Fibronectin, laminin, and elastin are major components of basement membranes and are found to be produced by myoepithelial cells.[39,43] Any epithelial cell in a basal location, however, could be expected to synthesize basement membrane components.[44]

B. Mammary Gland Myoepithelium

1. Embryology

A thickening of the ectoderm, the ectodermal ridge (or milk line), appears on the anterior body wall during the sixth week of intrauterine development. Normally the thickening regresses except in the pectoral region, where, during the 5th month of intrauterine life, a group of 15 to 20 solid chords grow deeper into the subcutaneous

(s.c.) tissue.[46] After a process of branching and lumen formation which extends throughout juvenile life, the distal portions (or terminal buds) differentiate into two cell types. Radioactive thymidine studies[46] have indicated that these cells represent two distinct lineages; the outer layer ultimately develops into myoepithelium and the inner lumenal epithelium. The early stage of differentiation of myoepithelial cells is characterized mainly by slight condensation of chromatin, numerous polyribosomes, and sparse myofilaments.[47] These cells are probably identical to type I promyoepithelial cells described on immunohistochemical grounds.[48] In a later stage of development, myoepithelial precursors are characterized by rather well-developed ergastoplasmic cisternae and Golgi apparatus, association of myofilaments to form bundles, and the appearance of dense bodies and small attachment areas. These cells are closely associated with basement membrane deposits[47] and correspond to the type II promyoepithelial cell.[48] Although a simple stem cell origin for myoepithelial and lumenal epithelial cell types is not supported by all workers,[49] in vitro tissue culture[50] and ultrastructural studies[47,51] favor this concept. A recent immunohistochemical investigation[48] failed to identify cells with markers for both lineages, an indication that the long-held view of transition between myoepithelial and lumenal epithelial cell types is incorrect.

Multiplication of stem cells, two cell-type differentiation, and cellular maturation in the terminal buds are controlled by both hormones and environmental factors. Estrogen, progesterone, insulin, relaxin, and pituitary polypeptide growth hormones stimulate mitotic activity and facilitate extension of the ductular system.[47,52-54] In males, testosterone, that begins to be secreted in midgestation, inhibits growth and development of the ductules.[55] Hormonal factors may also play a role in selecting morphologic cell types during stem cell differentiation.[56] Attachment of breast epithelial cells to type IV (basement membrane) collagen is a specific environmental requirement for multiplication and differentiation.[57-59] This process is enhanced by the presence of laminin, a glycoprotein found in the lamina lucida of basement membranes, which binds to type IV collagen forming a laminin-type IV collagen complex.[56,58,60] Breast epithelial cells do not grow on type I collagen[57] and collagenase-digested epithelial explants proliferate less markedly than nonenzyme-treated duct explants.[61]

Hormones released during pregnancy result in slight hyperplasia of myoepithelial cells,[62,63] followed by epithelial cell proliferation and formation of the first true lobuloalveolar structures.[49] Before parturition lumenal cells of the acinus enlarge due to their accumulation of secrete and myoepithelial cell processes are stretched and become thin and tenuous.[62] Portions of the secretory epithelial cells bulge outwards and appear to embed myoepithelial cell processes (Figure 4). The number of myoepithelial cells and primary cytoplasmic processes per cell remains unchanged, but that of secondary and tertiary processes increases moderately.[64,65] Myoepithelial hypertrophy ceases by the end of pregnancy.[66]

Electron microscopic investigation of the normal female breast identified, in addition to myoepithelial cells, basally located clear cells.[67] These cells were initially regarded as variants of myoepithelium.[68] A more recent ultrastructural study,[69] however, has proved the clear cells to be unrelated to epithelium and to have phagocytic capacity with an important role in the uptake of cellular debris after lactation. This phenomenon has led Hamperl[70] to incorrectly hypothesize a phagocytic function for myoepithelium.

2. Functions

Myoepithelial contraction in the lactating female breast facilitates ejection of milk and is triggered by oxytocin, a pituitary hormone released after mechanical stimulation of the nipple. Specific oxytocin binding sites are present in the cytoplasmic membranes

FIGURE 4. Scanning electron micrograph of acinar myoepithelial cells in the lactating mammary gland of the African elephant after removal of the basement membrane. Note acinar enlargement, stretching of myoepithelial processes, and outward bulging of portions of secretory cells.

of isolated myoepithelial cells,[71] and due to close intercellular contact, stimulation leads to contraction of a functional syncitium of cells.[72] Oxytocin receptor affinity and availability appear to be modified by the presence of certain metal ions.[71] Myoepithelial sensitivity increases with pregnancy and is the greatest post partum. This is the result of an increase in the number of receptor sites on hypertrophied and elongated myoepithelial cells of the lactating breast. Elevation of myoepithelial oxytocin receptor concentration appears to persist after postlactation involution, a phenomenon which facilitates removal of dead secretory epithelial cells by myoepithelial contraction.[71] Furthermore, during postlactation involution, myoepithelial cells are more resistant to degeneration than secretory epithelium and apparently play an important role in maintaining structural integrity of the acinus.[73] The terminal ductules, around which myoepithelial cells are arranged longitudinally, have been shown to widen and shorten in response to oxytocin at a state of involution when degenerating alveoli no longer secrete milk.[33] This dilatation reduces the chance of ductular obstruction during passage of cellular debris.

The myoepithelial cell membrane forms part of the hypothetic epithelial stromal junction (ESJ) of the mammary gland which consists of the plasma membranes of epithelial and myoepithelial cells, intercellular substance, basement membrane, adjacent fibrillar connective tissue, and a layer of delimiting fibroblasts.[74] Transport of metabolites to and from secretory cells is mediated by the ESJ. The concentration of alkaline phosphatase, an enzyme implicated in the transport of substances over cell membranes, was demonstrated to be ten times greater in myoepithelial cells than in purified lumenal epithelium.[71] In addition, the presence of transferrin[75] and frequent pinocytotic vesicles[69] appears to be more than adequate for myoepithelial cell metabolism especially if their relatively low anabolic requirement (proven by the scanty cyto-

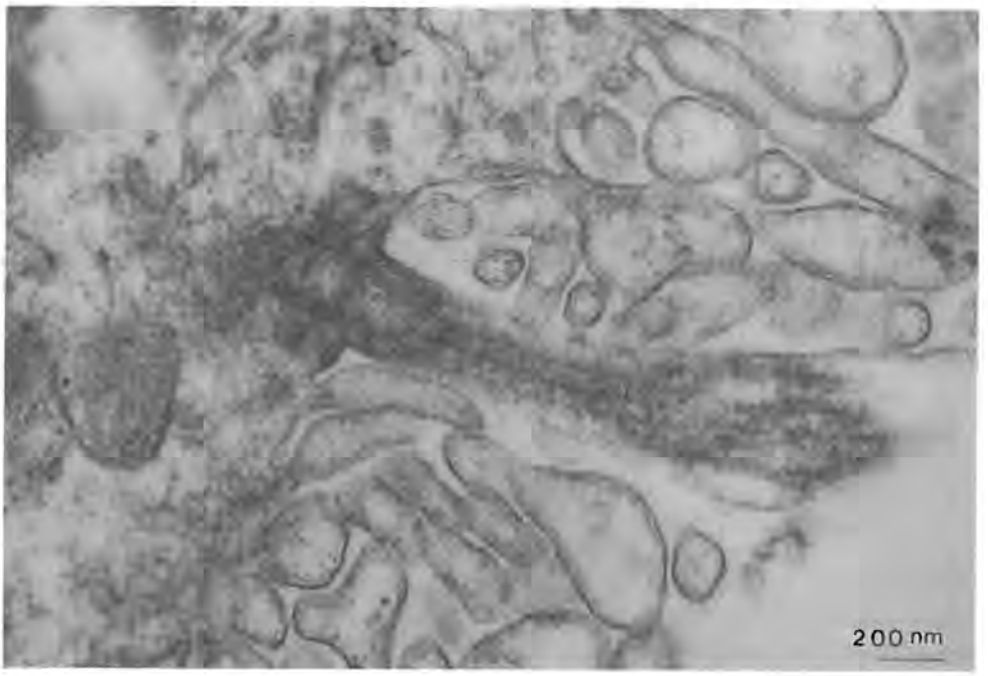


FIGURE 5. Transmission electron micrograph of a cultured rat mammary myoepithelial cell cilium.

plasmic organelles) is taken into account. Morphologic evidence therefore indicates that myoepithelial cells may in fact participate in the transportation of metabolites to and from secretory cells. Plasmalemmal interdigitations and microvilli on surfaces in contact with adjacent secretory cells[69] may serve to enlarge the cell-to-cell contact area, a feature which could increase the effectiveness of a proposed transport mechanism.

Myoepithelial cells synthesize fibronectin, laminin, and collagen type IV[59,76] and are probably responsible for the production of most of the epithelial basement membrane of the breast.[59,76-79] As indicated earlier, basement membrane components are necessary not only for growth and differentiation, but also mammary cell survival.[80] Accumulation of basement membrane deposits seen in the lactating mammary gland is evidence of increased myoepithelial metabolic activity. On the other hand, degeneration of the basement membrane in the involuting gland is a sign of decreased myoepithelial anabolism[77] and leads to a loss of secretory epithelial cell viability.[59]

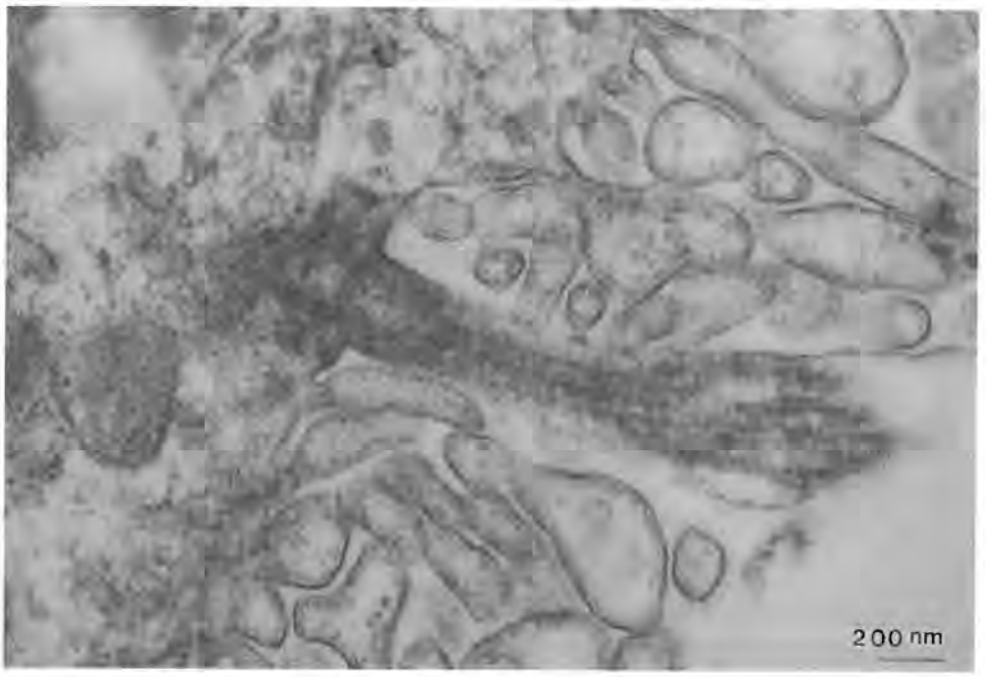
The function of myoepithelial cilia (Figure 5), which are in close contact with secretory epithelial cells, is speculative. They may act as mechano- or even chemoreceptors and initiate contraction upon stimulation.[81]

C. Sweat Gland Myoepithelium

1. Embryology

The stratum germinativum of the embryonal skin differentiates into three distinct progenitor cell populations. The basal cells give rise to the keratinizing epidermis, primary epithelial germs to hair follicles, sebaceous glands and apocrine glands and eccrine gland germs to eccrine glands.[82] Of all these structures, only the secretory portions of apocrine[4,83] and eccrine glands[84] contain myoepithelial cells.

Both primary epithelial and eccrine gland germs initially consist of crowding of deeply basophylic cells in the basal layer of the epidermis. Proliferation of these cells gives rise to solid epithelial buds which protrude into the dermis.[82]



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At 16 weeks of gestation, the distal tip of the solid eccrine gland anlagen begins to form a coil in the dermis and lumen formation takes place by separation of desmosomal attachments.[85] The primitive tubular structure is lined at this stage by an inner (lumenal) and outer (basal) cell layer. The outer cells of the distal coiled portion give rise to secretory epithelium and small pyramidal-shaped cells wedged in between the basal portions of secretory epithelial cells.[86] These cells develop myoepithelial characteristics at 22 weeks of embryonal age.[85] At birth, most eccrine glands seem to have completed development and resemble that of the adult.[82] Regenerative capacity of eccrine secretory and myoepithelial cells resides in scattered germinal cells in the secretory segment of the gland.[87]

In apocrine glands, which only become fully developed at puberty, myoepithelial cells appear to originate from basal cells of the terminal portion of the intradermal duct. Myoepithelial cell numbers increase gradually towards the secretory portion of the gland where all mitotic activity ceases.[83]

2. Functions

Myoepithelial cells are exclusive to the secretory portion of eccrine and apocrine glands and it therefore does not seem unreasonable to postulate their participation in the formation or propulsion of sweat. Furthermore, the smooth muscle-like features of myoepithelium and firm attachment to secretory epithelium[84] support a contractile function. Myoepithelial contraction appears to be responsible for the pulsatile nature of low-grade sweating[88] and peristaltic contractile waves have been identified in apocrine myoepithelial cells after mechanical, neural, and hormonal stimulation.[89] Myoepithelial contraction also influences the composition of the secrete by altering the pore size of the membranes of secretory cells.[88] Moreover, myoepithelial cell processes decrease in diameter during contraction, a phenomenon which may open wide gaps allowing interstitial fluid to come in direct contact with secretory cells.[3] Alkaline phosphatase in apocrine myoepithelium[83] and eccrine myoepithelium[3,87,90] and ATPase[3,90] and micropinocytotic vesicles[90] in eccrine myoepithelium are probably associated with active transport of metabolites to secretory cells (these enzymes are also present in capillary endothelium[87] which are known to have a transport function). Complex foldings of the plasma membrane of myoepithelial cells[83] increase their surface area and could play a role in improving the efficiency of a hypothetic transport mechanism. Most electron microscopic studies failed to identify secretory activity in cells with myoepithelial features,[3,83,85] invalidating a previously held concept of transition between myoepithelial and secretory epithelial cell types.[84]

III. MYOEPITHELIAL IDENTIFICATION

Although myoepithelial cells are recognized with difficulty in routine paraffin sections, their location in the terminal portion of most exocrine glands (Figure 6) makes reliable identification possible. The value of reports postulating myoepithelial differentiation in pathologic conditions where all landmarks are lost depends to a great extent on the criteria applied during their characterization. Publications dealing with myoepithelial differentiation in pathologic conditions require careful scrutiny in this respect.

The three principle light microscopic presentations of myoepithelial cells in pathologic conditions of salivary glands are reported to be hyaline or plasmacytoid (Figure 7), fibroblastic or myoid (Figure 8), and epithelial-like.[91] The latter often appears as mucin-negative glycogen-rich clear cells (Figure 9). It should be noted that clear cells unrelated to myoepithelium are often found in a number of definable salivary gland

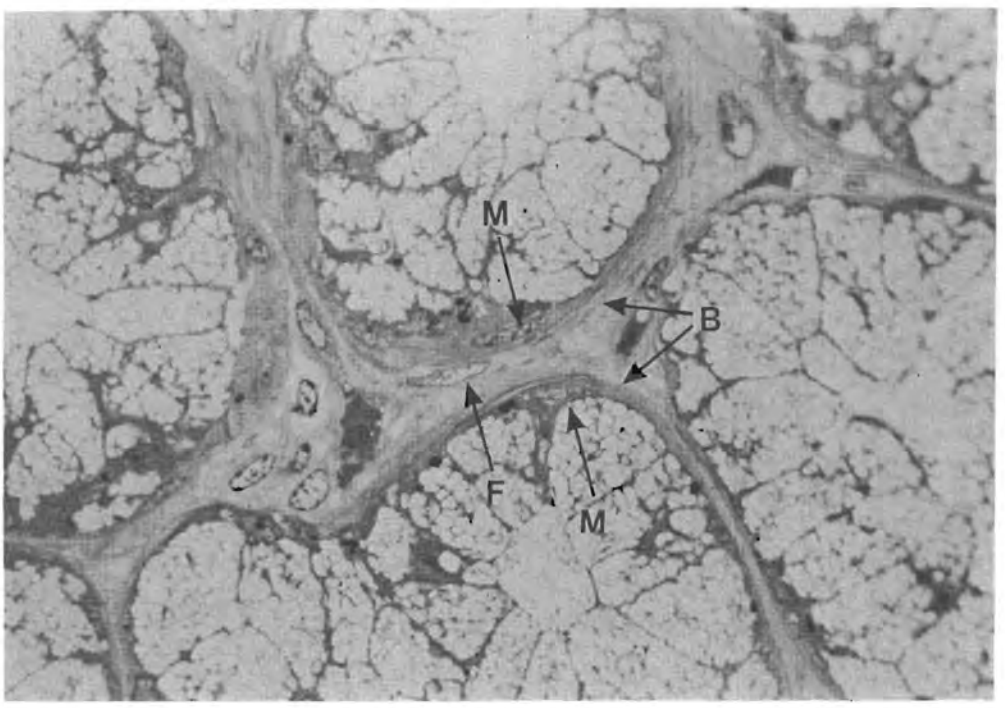

FIGURE 6. Myoepithelial cell (M) located beneath the epithelial basement membrane (B) of the parotid gland of the African buffalo *(Syncerus caffir)*. Note the fibroblast (F) located on the mesenchymal aspect of the basement membrane. (Hematoxylin-eosin; magnification × 1250.)

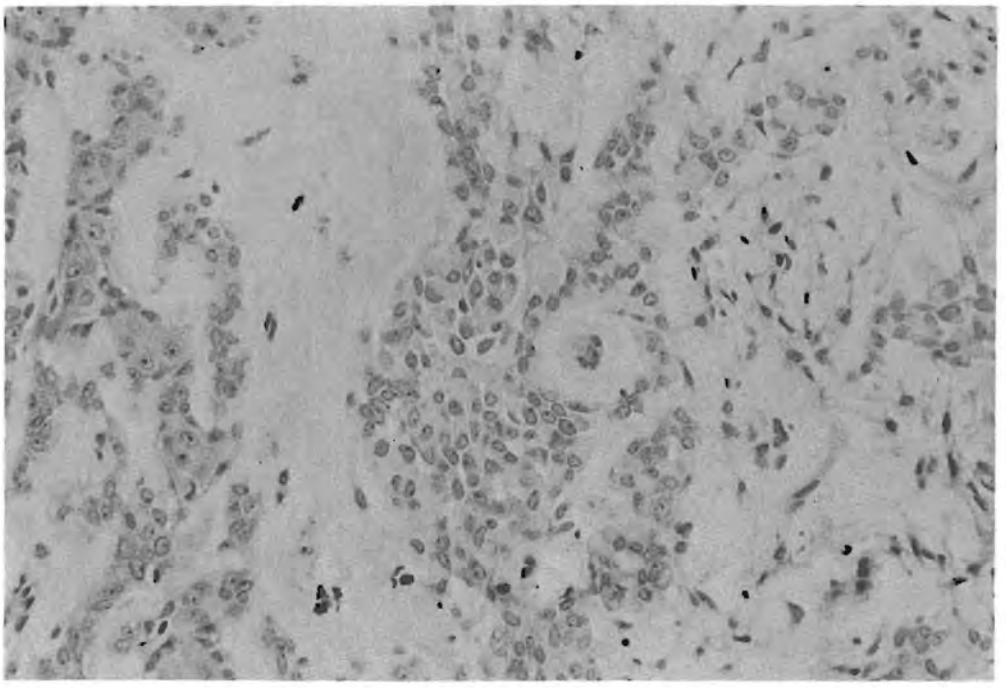

FIGURE 7. Plasmacytoid-type myoepithelial differentation, pleomorphic adenoma of the palate. (Hematoxylin-eosin; magnification × 300.)

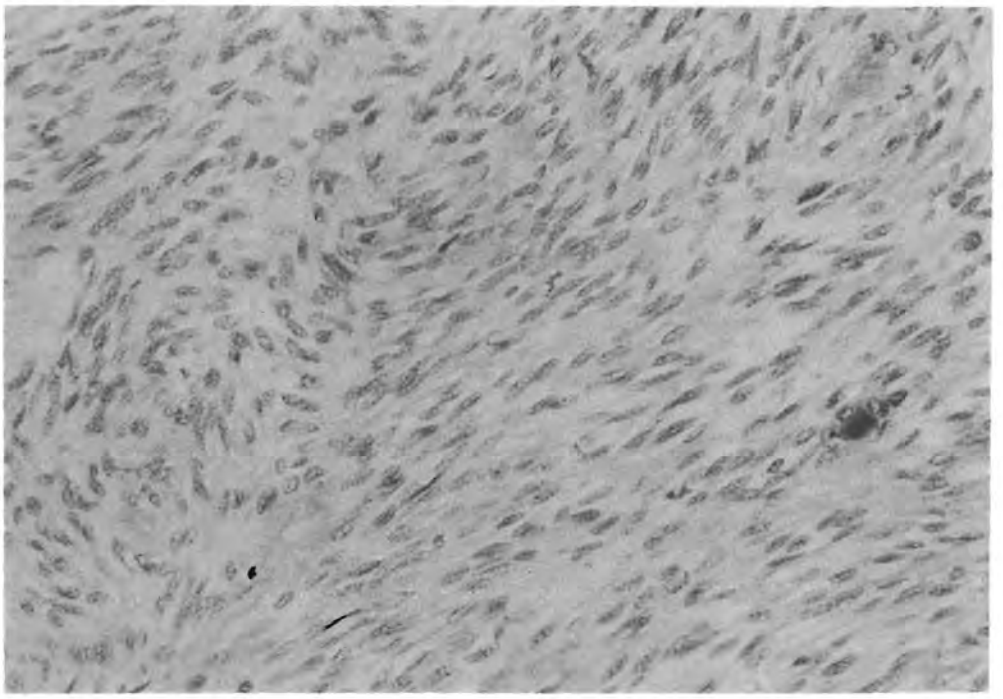

FIGURE 8. Fibroblastic (myoid)-type myoepithelial differentiation, pleomorphic adenoma of the parotid. Note ductular differentiation. (Hematoxylin-eosin; magnification × 300.)

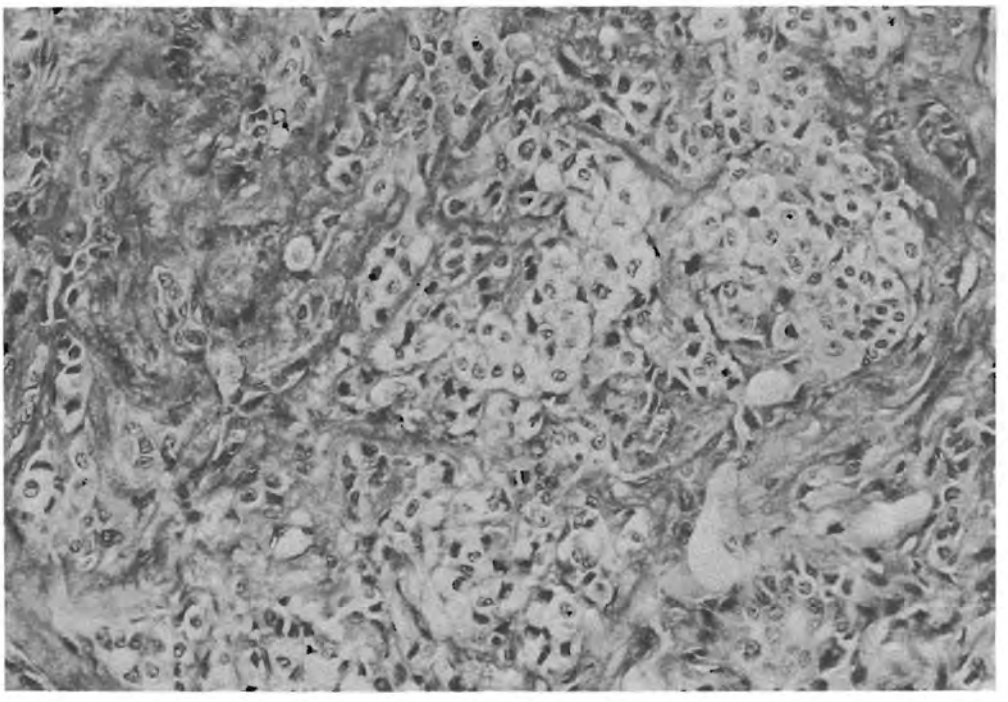

FIGURE 9. Epithelial-like or clear cell-type myoepithelial differentiation, pleomorphic adenoma of the parotid. (Hematoxylin-eosin; magnification × 300.)

tumors of which mucous clear cells in mucoepidermoid tumors and sebaceous clear cells in sebaceous lymphadenomas are only two examples.[92] Furthermore, plasmacytoid (or hyaline cell) differentiation is not uncommon in tumors unrelated to myoepithelium[93] and various mesenchymal proliferations may give rise to cells with fibroblastic or myoid features.

Ultrastructurally, cytoplasmic myofilaments are present in myoepithelial cells, smooth muscle cells, and myofibroblasts. Frequent participation of the latter cell type in pathologic conditions of the breast[94] has led to erroneous reports postulating myoepithelial involvement. In contrast to myoepithelium, myofibroblasts stain positive for collagen type III[95] and vimentin, a marker protein for cells of mesenchymal origin.[96] All eukaryotic cells contain contractile proteins[97] and neoplastic change is usually associated with a sharp increase in their concentration.[98] Furthermore, myofilaments in myoepithelial cells have been reported to exhibit features similar to tonofilaments in epithelial cells,[51,99] an additional source of confusion on the ultrastructural level.[2]

Positive enzyme histochemical reactions for alkaline phosphatase, acid phosphatase, and ATPase were regarded by many as characteristic of myoepithelium. Their presence is of limited value and should not be accepted as exclusive to myoepithelial cells. Alkaline phosphatase activity is also localized in the plasma membranes of endothelium engaged in active transport,[100,101] acid phosphatase has been demonstrated in myoepithelial cells, secretory epithelium of involuting rat mammary glands, and capillary endothelium,[102] and magnesium-dependent ATPase activity is found in both secretory epithelial and myoepithelial cells of rat mammary glands. A second type of ATPase activity, which is not magnesium but sodium and potassium dependent, appears to be an exclusive feature of rat mammary myoepithelial cells.[103] Species differences in the distribution of enzymes in salivary gland myoepithelium appear to make animal studies meaningless; the alkaline phosphatase reaction is useful in salivary gland myoepithelial identification in the cat and rat, but not in man, dog, or opossum, while the ATPase reaction is useful in man, but not in the cat or dog.[24,28,104]

Immunochemical typing of cytoplasmic filaments has aided myoepithelial identification. Archer and Kao,[105] Archer et al.,[45] and others[44,106] demonstrated the presence of myosin and actomyosin related proteins in myoepithelial cells of human salivary, sweat, and mammary glands. The use of antiactin antibodies in salivary myoepithelial identification has been questioned as it appears that although the antibody stains myoepithelial cells, it is not sufficient to differentiate clearly between myoepithelial and duct epithelial cells of normal salivary glands.[44] Identification of myosin appears to be more specific. The presence of this microfilament, however, is by no means exclusive to salivary myoepithelium, as it is found in a wide range of cells, including nonmuscle cells of epithelial origin and their tumors.[107,108] In the human female breast, myoepithelial cells are distinguished from mature lumenal epithelium by staining positive with antibodies to myosin and actin[77,105,109,110] and by staining negative with antimilk protein antibodies.[48] Intermediate-sized cytoplasmic filaments of the cytokeratin type in salivary[111,112] and mammary[77,109,110] myoepithelia and the demonstration of basement membrane proteins, the production of which has already been referred to, are useful immunocytochemical aids in improving the reliability of myoepithelial identification. In addition, S100 protein has been reported to be a marker for myoepithelial cells in normal and neoplastic salivary glands[113] (Figure 10), sweat glands, and mammary glands.[114] Immunoelectron microscopy[113] showed that S100b protein is distributed on the membrane of the endoplasmic reticulum and the outer nuclear membrane of salivary gland myoepithelial cells. This seems to indicate that the protein is produced by myoepithelial cells themselves.

The foregoing discussion emphasizes that myoepithelial cells share features in com-

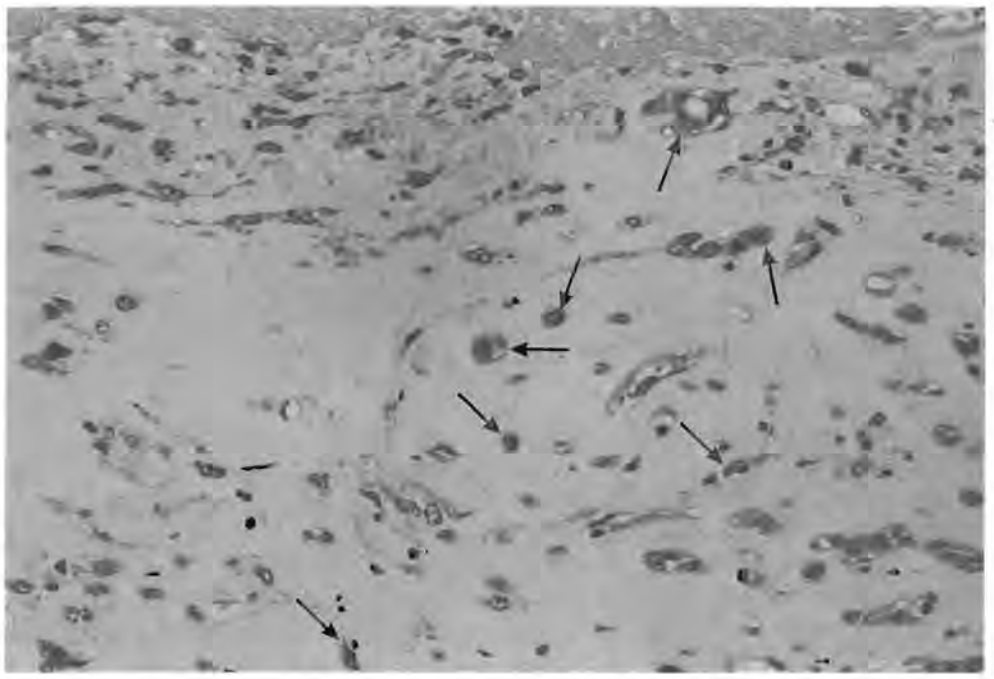

FIGURE 10. S100b positive cells (arrows) embedded in cartilagenous deposits in a pleomorphic adenoma. (Peroxidase antiperoxidase technique; magnification × 400.)

mon with other cell types. Reliable proof of their presence in pathologic conditions is therefore best achieved by a combination of structural, histochemical, and immunocytochemical techniques.

IV. MYOEPITHELIAL PROLIFERATIONS

A. Salivary Glands

1. Nonneoplastic Conditions

The bulk of research on salivary gland myoepithelial proliferations is focused on neoplasms and very little is subsequently known of myoepithelial participation in nonneoplastic conditions.

Emmelin et al.[115] found architectural changes affecting myoepithelial cells of the parotid and submandibular glands of cats after ductal ligation. Processes of myoepithelial cells protruded into the interstitial spaces, giving rise to bizarre appearances. In addition, folds of basal lamina tended to be aggregated, especially around protruberant parts of myoepithelial cells thereby increasing the space between their cell membranes and nerve endings. This probably reduces neuroeffector efficiency and together with the mechanical disadvantage of the altered arrangement of myoepithelial cells helps to explain the modified intraductal pressure responses that occurred after stimulation. Ensuing increase in the intraductal pressure when inducing secretion often caused ballooning disruption of the first parts of the striated ducts which lack support by myoepithelial cells.[22] It is not yet known whether a similar mechanism has any bearing on human sialectasis. Alkaline phosphatase, when present, tends to be lost from myoepithelial cells by the time that extensive parenchymal atrophy has occurred after ductal obstruction.

The diagnostic terms, lymphoepithelial lesion, chronic recurrent (punctate) sialad-

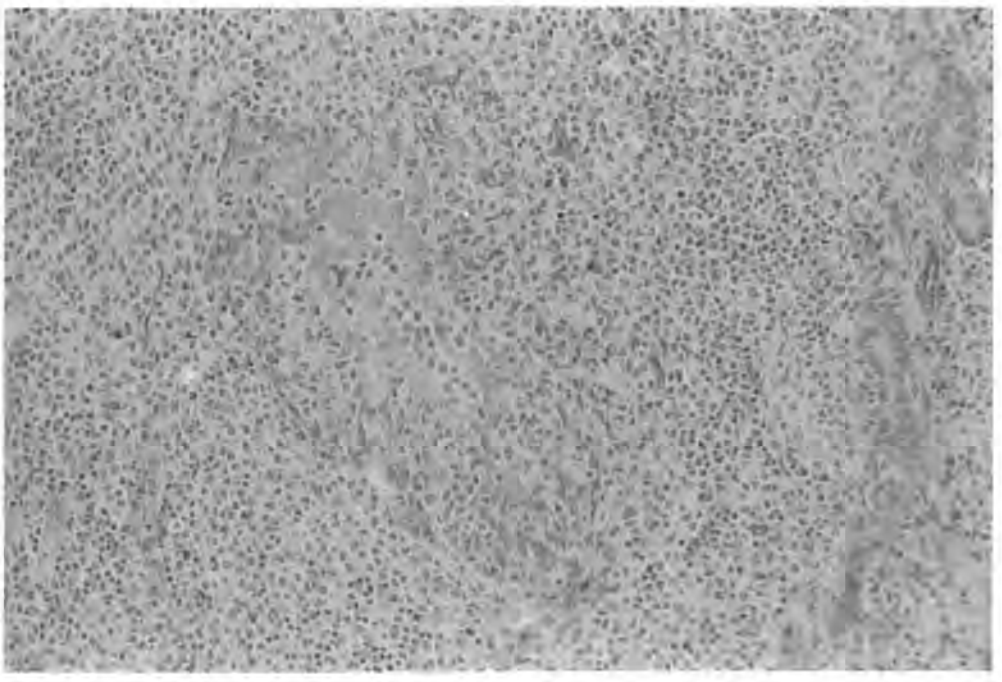

FIGURE 11. Epimyoepithelial island in a benign lymphoepithelial lesion of the parotid. (Hematoxylin-eosin; magnification × 200.)

enitis, sicca syndrome, and Sjogren's syndrome, share nearly common histopathologic changes characterized by a lymphoreticular cell proliferation associated with atrophy of the parenchyma and ductal changes ending in so-called "epimyoepithelial islands" (Figure 11). These islands are formed by metaplastic proliferation of ductal epithelium accompanied by myoepithelial cells. Controversy exists on the prominence of the latter cell type. Some workers believe myoepithelial cells to be few in number and located around the periphery of the islands.[117] The majority, however, agrees that myoepithelial cells are prominent and form an integral part of the epimyoepithelial islands.[118,119] This controversy emphasizes the difficulty in identifying myoepithelial cells in a state other than normal.

2. Neoplastic Conditions

It is generally accepted that the basal cells of the excretory duct (or EDRC) and the intercalated duct cells (or IDC) act as stem cell compartments for the more differentiated portions of salivary-type glands both during the later stages of development and in the mature gland. The EDRC gives rise to columnar and squamous cells of the excretory duct and the IDC gives rise to acinar cells, other intercalated duct cells, striated duct cells, and myoepithelial cells.[1,120,121] It is important to note that of the two stem cells, only the IDC has the potential to differentiate into myoepithelial and acinar cells (Figure 12).

The bicellular theory on the histogenesis of salivary gland neoplasms, initially proposed by Eversole[122] and recently modified by Regezi and Batsakis[120] and Batsakis,[121] divides these lesions into two groups, based on the stem cell population of origin. Depending on where on the curve of differentiation an oncogenic stimulus acts, the IDC population is the epithelial source for adenoid cystic carcinomas, acinous cell carcinomas, monomorphic adenomas, mixed tumors, and some of the ductal carcino-

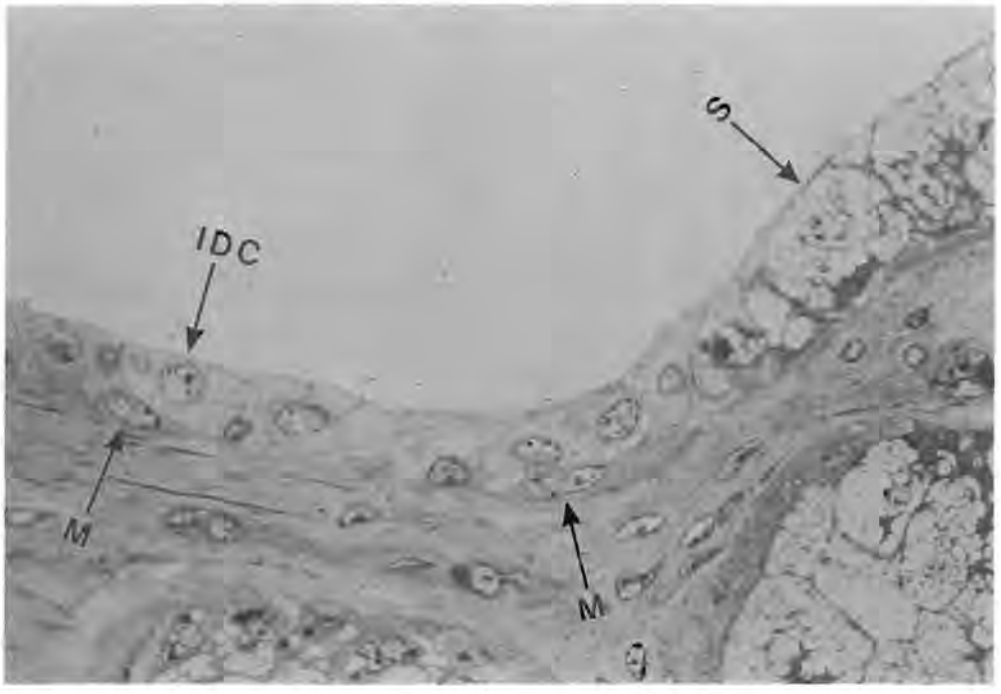

FIGURE 12. Epithelium of the intercalated duct (IDC) indicating its relationship to myoepithelial cells (M) and secretory epithelial cells (S) in the parotid gland of the African buffalo. (Toluidine blue stain; magnification × 1000.)

mas.[121,123-125] Theoretically, most of these tumors and even some monomorphic adenomas may, to a greater or lesser extent, contain myoepithelial cells.[126] The possibility of myoepithelial differentiation on the other hand should, according to this theory, not be considered in tumors that arise from the EDRC (mucoepidermoid carcinomas, papillary mucinous adenocarcinomas, and primary salivary squamous carcinomas).[91]

If the reserve epithelial cell populations of salivary glands are accepted as the progenitor for salivary gland neoplasms, what is the significance of myoepithelial differentiation? Although this question remains greatly unanswered, it should be noted that in the sister exocrine gland, the pancreas, which lacks myoepithelial cells, the variety and diversity of salivary gland neoplasms are absent.[123] Implication, however, is not proof and the deficient evidence on myoepithelial differentiation in neoplasms is in part the result of the difficulty in recognizing myoepithelial cells with certainty.

a. Mixed Tumor

In the past, a variety of cellular differentiation pathways have been proposed to account for the derivation of mixed tumors. Throughout recent years, the mixed epithelial mesenchymal theory of origin[127] has lost ground and differentiation of neoplastic myoepithelial cells in these tumors has been proven beyond doubt.[128,129] Although duct cells are the major component of mixed tumors,[44,130,131] a variety of epithelial cell types participate, ranging from secretory epithelial cells at one end of the spectrum to myoepithelium at the other with less-differentiated cells in between.[39,41,132] This spectrum corresponds to the differentiation potential of the IDC.[1,120,121] In addition, a histogenetic link has been proposed between the IDC and epithelial component of pleomorphic adenomas after detecting lysozyme and lactoferrin in both cell types.[133] Mixed tumors therefore probably represent neoplastic transformation of the IDC[120,134] and

form a central and major component of a class of epithelial neoplasms with monomorphic adenomas (constituted entirely of ductal or excretory cells) at one pole of the spectrum and myoepitheliomas (constituted entirely of myoepithelial cells) at the other.[120,135]

The phenotypic expression of myoepithelial differentiation in mixed tumors may be hyaline (or plasmacytoid)[136] (Figure 7), fibroblastic (or myoid)[91] (Figure 8), or that of mucin-negative glycogen-rich clear cells[92] (Figure 9). Some cellular mixed tumors, sparse in myoepithelial cells, resemble monomorphic adenomas in appearance. In other examples, the bulk of the lesion is largely composed of myoepithelial cells and stroma, i.e., a mixed tumor with myoepithelial dominance. These lesions are often misinterpreted as mesenchymal neoplasms.[137]

Much of the debate on the histogenesis of mixed tumors has centered around the identity of characteristic myxoid, chondroid, osteoid, elastic, and fibrous interstitial deposits. It has been investigated chemically, histochemically, and ultrastructurally and in tissue cultures. The mesenchymal nature of these deposits has been proven beyond doubt[138,139] and evidence on myoepithelial participation in their production has accumulated.[39,43,120,128,138-141] Some of the spindle-shaped cells, often associated with stromal deposits, were found to react positively with immunochemical stains for S100 protein[113,129,142] (Figure 10), microfilaments of the myosin and actin type[129,143] and intermediate-sized filaments of the prekeratin type,[112,144] characteristics not short from proving myoepithelial differentiation. In addition, these cells display a positive vimentin stain[39,132,144,145] which can be regarded as immunochemical evidence of mesenchymal conversation, a phenomenon proved in other epithelial-derived cell lines.[146] This finding introduces new concepts with regard to the mixed nature of these tumors, among which an origin from cells which is characterized by prekeratin filaments, but which after neoplastic transformation acquires the ability to produce vimentin filaments, were suggested,[144] a proposal not far separated from an earlier theory postulating mesenchymal metaplasia of neoplastic myoepithelium.[70,120,141] Since myoepithelial cells already exhibit features of smooth muscle, neoplastic change may expose other mesenchymal characteristics.[120]

Myoepithelial participation in malignant mixed tumors has not yet been determined. Metastatic deposits of these rare lesions contain tissues of epithelial and mesenchymal nature (either as a homologue of a benign appearing mixed tumor or a carcinosarcoma). This could lead one to hypothesize that although the neoplastic cells undergo malignant transformation (i.e., develop metastatic potential), a relatively high level of cytodifferentiation is responsible for the "mixed" features of the malignancy. Metastatic deposits should therefore contain epithelial and myoepithelial cells and mesenchymal interstitial deposits related to the latter cell type. However, whether a direct parallel could be drawn between benign and malignant mixed tumors remains to be proven.

b. Myoepithelioma

Myoepitheliomas are histogenetically related to mixed tumors as both lesions originate from IDCs.[120,147] It is extremely rare for these tumors to occur in a pure (monomorphic) form[148] and a diagnosis of myoepithelioma should only be made in the absence of chondroid interstitial deposits and/or conspicuous epithelial differentiation usually in the form of ducts. Pure myoepitheliomas are composed primarily of spindle-shaped cells, plasmacytoid (hyaline) cells (Figure 13), or a combination of the two cell types; stellate and clear cell variants are less common.[147] The neoplastic cells in these tumors have been shown to possess synthetic and secretory activity[149] and are capable of producing connective tissue mucins.[150] A total of 39 of the 41 myoepitheliomas of the head and neck reported in the English literature are benign with a behavior and postoperative recurrence rate similar to that of mixed tumors.[147]

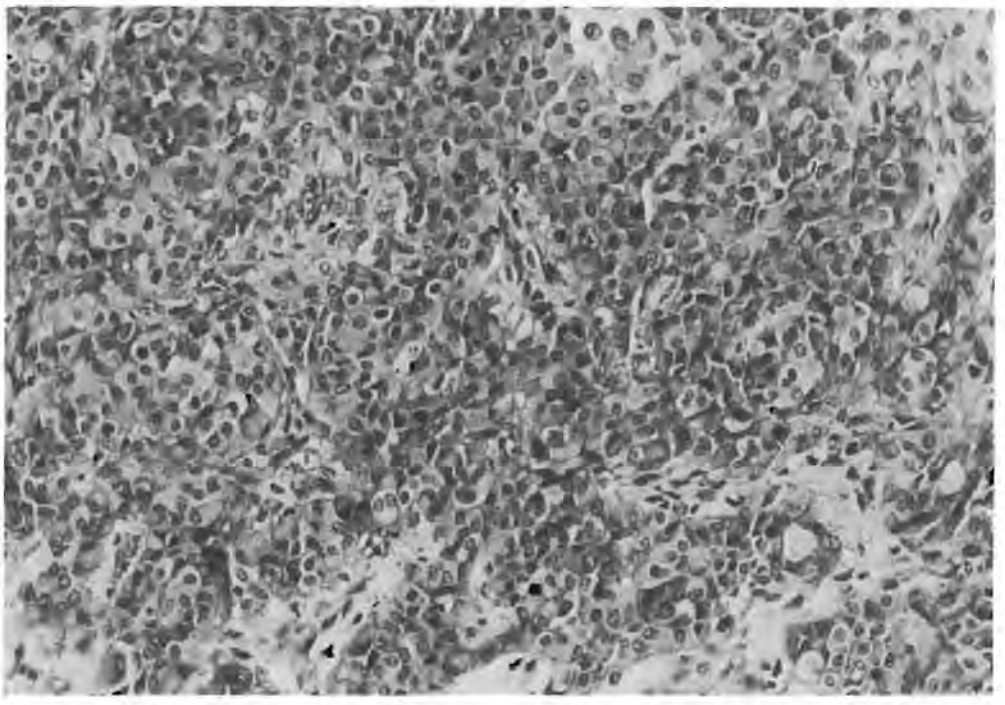

FIGURE 13. Plasmacytoid myoepithelioma of the palate. Note the extensive plasmacytoid differentiation of neoplastic myoepithelial cells. (Hematoxylin-eosin; magnification × 200.)

c. Adenoid Cystic Carcinoma

Although adenoid cystic carcinomas occur more commonly in salivary glands, tumors with this growth pattern have been recognized in other organs including the tracheobronchial tree, nasal cavity, paranasal sinuses and larynx, breast, uterine, cervix, Bartholins gland, lacrimal gland, skin, and prostate. Participation of myoepithelial cells in adenoid cystic carcinomas was initially emphasized by Bauer and Fox,[151] who introduced the term "adenomyoepithelioma". Although this concept was initially supported,[152] a few ultrastructural reports failed to identify myoepithelial differentiation in these tumors.[153,154] This failure could be related to embedding artifacts or poorly differentiated features of the tumors studied as recent ultrastructural,[155-157] histochemical,[155,157] and immunofluorescent[158] investigations support myoepithelial differentiation in adenoid cystic carcinoma. Hoshino and Yamamoto[155] go further and consider the myoepithelial cell to be responsible for the high recurrence rate after radiation. The characteristic pseudocysts (Figure 14) are extracellular spaces containing connective tissue mucins, multilayered basement membrane material,[138,156,159] and elastic tissue.[160] These spaces are lined by cells exhibiting cytoplasmic filaments of the actin and keratin types and produce basement membrane collagen type IV,[158] features sufficient for positive myoepithelial identification. Similar deposits surround nests of tumor cells and account for the so-called cylindromatous appearance of one of the forms of adenoid cystic carcinoma.[161] The second cell type in adenoid cystic carcinoma forms true acinar structures and is of a secretory epithelial nature.[155,156,158] Myoepithelial and secretory epithelial differentiation producing epithelial and connective tissue mucins, respectively,[159] are hallmarks of these tumors. These cells correspond to the differentiation potential of the IDC, from which the origin of salivary gland adenoid cystic carcinomas has been postulated.[155]

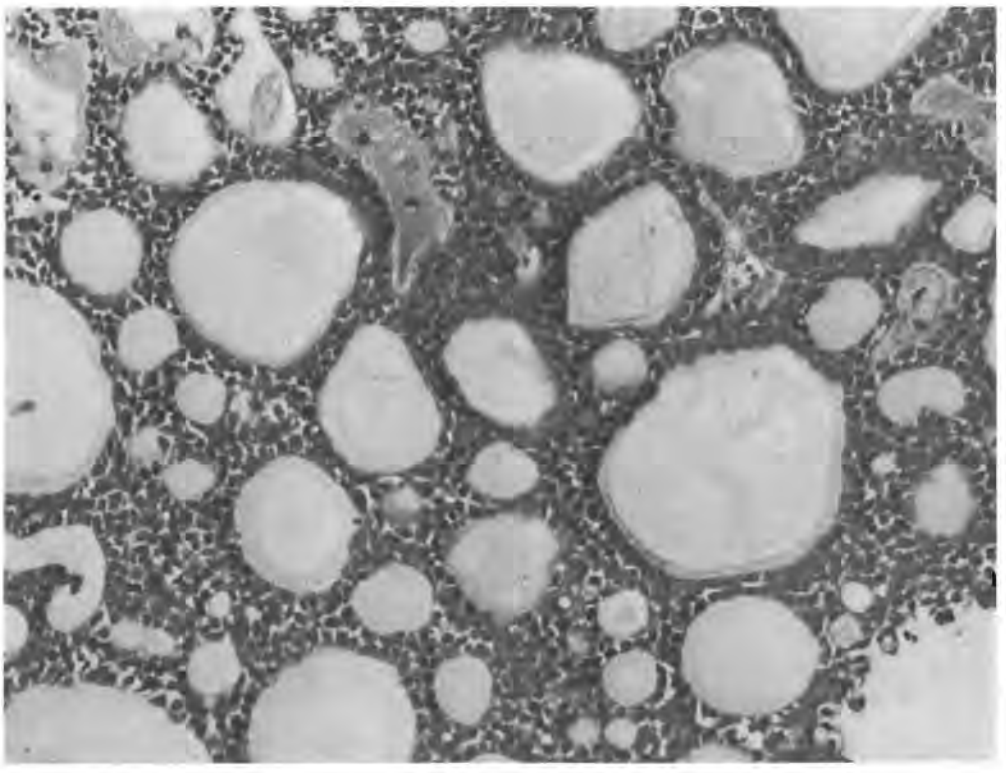

FIGURE 14. Pseudocysts containing basement membrane-like material. (Adenoid cystic carcinoma, PAS stain; magnification × 200.)

d. Epithelial-Myoepithelial Carcinoma

Primary malignant tumors of IDC origin not only include adenoid cystic carcinomas and malignant mixed tumors, but also a recently described entity, epithelial-myoepithelial[162] or tubular[92] carcinoma. These lesions have a bicellular histologic composition, with variable proportions of the two cell types evident from case to case as well as within the same lesion.[92,163] Characteristically, dark cells with few cytoplasmic organelles (resembling IDCs) from the inner layer of ductular structures and clear cells rich in glycogen (myoepithelial differentiation) form the outer layer[92,162] (Figure 15). A distinctive interepithelial hyaline-like ground substance separates the double-layered ducts.[92] The appearance of a dual population of cells is expressive of a dichotomatous differentiation pattern of a common precursor, the IDC.[163] The complex growth pattern and stromal complexity of the mixed tumor, however, are not seen in the epithelial-myoepithelial carcinoma.[163] Analogous cases have been described in the literature under a variety of names, including tubular solid adenoma,[164] cystic adenoma,[165] adenomyoepithelioma,[70,166] clear cell adenoma,[167] and glycogen-rich adenoma.[168] Recent publications[162,169,170] clearly point to the strong probability that the majority, if not all of the nonmucinous clear cell tumors of the major and minor salivary glands, are at least low-grade carcinomas. Although epithelial-myoepithelial carcinoma exhibits a high degree of cellular differentiation, it is considered to be malignant because of its infiltrative and destructive growth pattern, multifocal growth tendency, perineural involvement with remote metastasis, frequent recurrences, and foci of necrosis.[92,162]

e. Lobular Carcinoma of Minor Salivary Glands

Although this tumor has been referred to in the past as "polymorphous low-grade

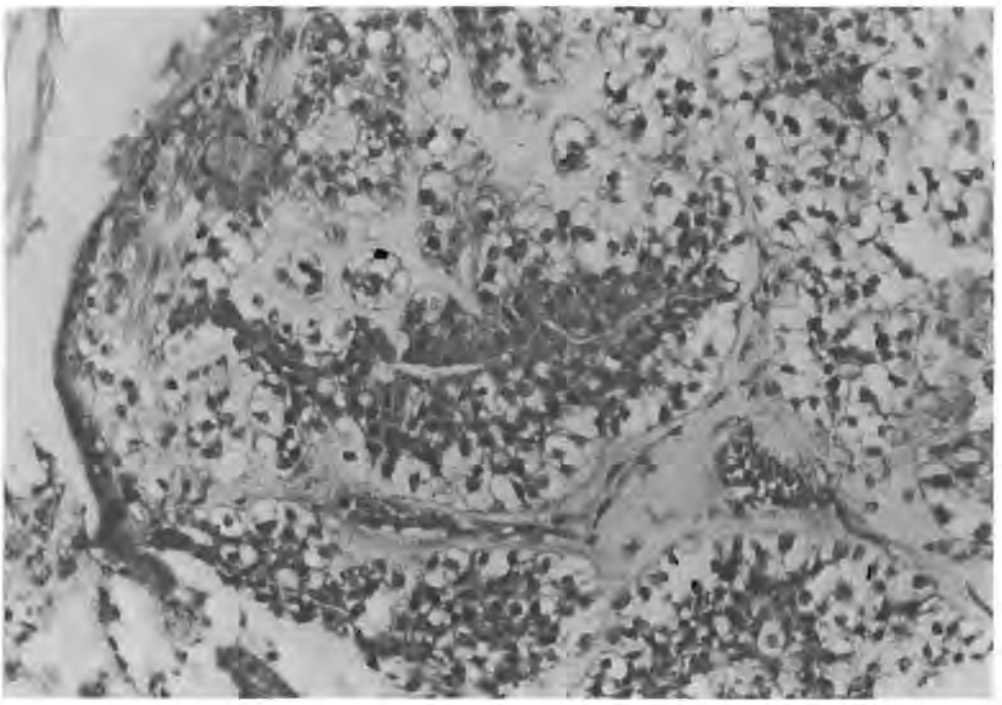

FIGURE 15. Epithelial-myoepithelial carcinoma, parotid. Tubular structures exhibiting two cell-type differentiation. Note the hyaline-like basement membrane interfacing with the clear cell component of the tumor. (Hematoxylin-eosin; magnification × 250.)

adenocarcinoma of minor salivary gland origin"[171] or "terminal duct carcinoma",[125] lobular carcinoma[172,173] appears to be the most appropriate designation as the microscopic appearance of the lesion calls to mind that of mammary lobular carcinoma. Salivary gland lobular carcinomas occur most frequently on the palate[173] and are likely related to the clear cell class of salivary gland neoplasia,[92] specifically the epithelial-myoepithelial carcinoma of intercalated duct cell origin.[125] The peripheral clear cell, often glycogen-rich, mantle distinguishes the latter neoplasm from lobular carcinoma which consists of duct-like structures often surrounded by spindle-shaped cells arranged in a characteristic lobular configuration. Only a small number of these neoplasms have been reported[173] and their clinical course appears to be akin to that of adenoid cystic carcinomas, with neural invasion as a prominent feature.[125] Whether they represent histopathologic variants of adenoid cystic carcinomas, however, cannot be confirmed yet. Although a mucohyaline stromal element, faintly reminiscent of the myxoid change in pleomorphic adenomas, is seen in many lobular carcinomas, myoepithelial differentiation has not yet been proven beyond doubt. The elongated appearance of some cells appears to be the result of stromal compression of a single cell type rather than an expression of biphasic cellularity.[173]

B. Mammary Glands

1. Nonneoplastic Conditions

Proliferation of myoepithelial cells has been identified in breast tissue of elderly females, especially in cases of senile involution where glandular atrophy and hyalinization of the fibrous stroma is evident.[174] Groups or "rosettes" of myoepithelial cells with a clear vacuolated cytoplasm are initially seen on the periphery of the ductules.[175]

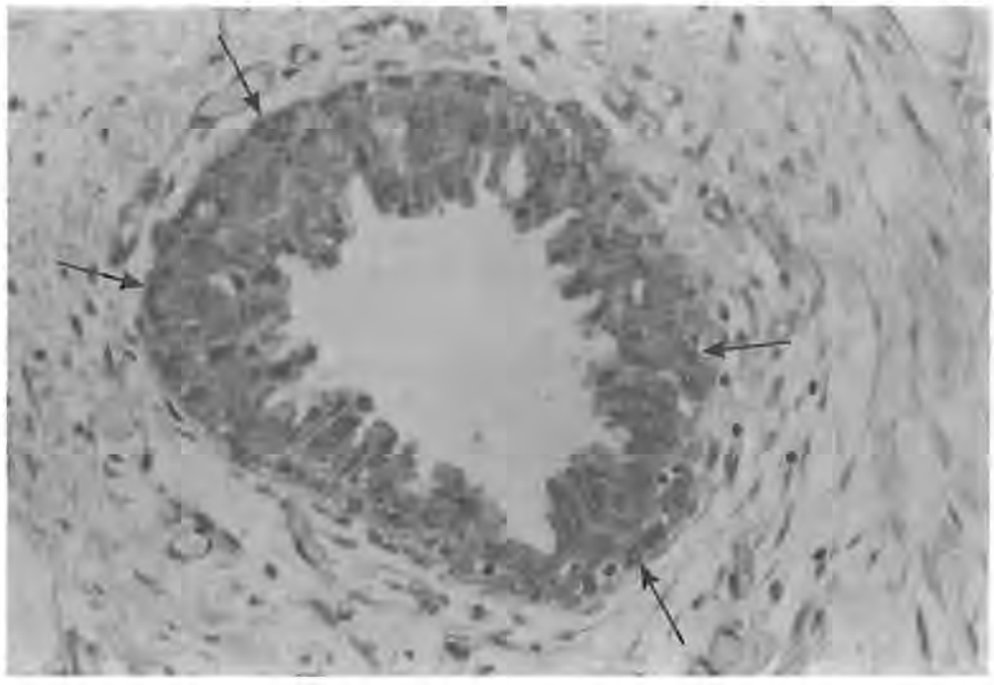

FIGURE 16. Ductular hyperplasia in the early stage of gynecomastia. Note the prominent peripheral flattened myoepithelial cell layer, the cytoplasm of which stains granular with antimyosin serum (arrows). (Indirect immunofluorescence; magnification × 400.)

It has been reported that in some cases glandular structures disappear, resulting in the formation of nests of hyperchromatic densely packed spindle cells, interpreted as myoepithelium, in a dense fibrous stroma.[174] Experimentally, changes similar to senile involution have been induced by blocking basement membrane collagen (type IV) formation by myoepithelial cells.[80] In the quiescent stage of gynecomastia, when ductular atrophy and fibrosis occurs, myoepithelial cells appear to persist longer than lumenal epithelium,[176] supporting the concept of pure myoepithelial islands in breast conditions characterized by fibrosis and atrophy. In the early (florid) stage of gynecomastia, hyperesterinism probably induces ductular hyperplasia (Figure 16).[177] Myoepithelial cells may either proliferate alone, forming projections into the periductule connective tissue, or together, with lumenal epithelium leading to intraductal epithelial growth.[176]

Focal hyperplasia of myoepithelial cells has been demonstrated in cystic disease of the breast[174,175] and it has been postulated that these cells play an important role in initiating the condition.[178] Ultrastructural examination and alkaline and acid phosphatase stains identified stretched myoepithelial cells mainly in the walls of small and medium-sized cysts.[179,180] In areas of apocrine (oncocytic) metaplasia, basally located myoepithelial cells were reported to be quite conspicuous, with well-developed myofilaments[2] and increased numbers of mitochondria,[181] the significance of which appears to be speculative.

Various morphologic types of periductal myoepithelial proliferations have been reviewed by Hamperl.[70] Circumscribed hyperplasia of myoepithelial cells in the lining of a duct may either protrude outwards (centrifugal) or inwards (cetripetal) and both forms occur in gynecomastia. Diffuse hyperplasia of myoepithelial cells is occasionally associated with partial or circumferential basement membrane deposits, the latter leading to so-called "cylindromatous transformation". The occurrence of diffuse myoe-

pithelial proliferations in chronic mastopathies is an indication that the extent of hyperplasia is not an indication of the type, but rather the stage of a proliferative breast disease.

2. Neoplastic Conditions

Although a myoepithelial histogenesis has been suggested for certain fibrosarcomas, osteosarcomas, and carcinosarcomas of the breast,[70] all cases studied lack convincing evidence of myoepithelial participation. Only neoplasms in which myoepithelial differentiation has been proved beyond doubt will subsequently be discussed.

a. Intraductal Epithelial Proliferations

Epitheliosis (benign intraductal epithelial proliferation) is often difficult to distinguish microscopically from ductal carcinoma *in situ*. This indecision is reflected by the designation "atypical hyperplasia". Ahmed[179] found that ductal epitheliosis is comprised principally of myoepithelial cells and regarded it as an important distinguishing feature from carcinoma. It should be pointed out that the positive enzyme histochemical reactions which he utilized as confirmatory evidence of the principal myoepithelial nature of epitheliosis lack specificity. Only an occasional myoepithelial cell could be demonstrated ultrastructurally in typical epitheliosis by Fischer,[2] substantiating the inaccuracy in Ahmed's description. A recent study, utilizing immunological markers, identified an intact basement membrane and normal peripherally located myoepithelial cells in epitheliosis.[109] In addition, the intralumenal proliferation was found to consist of a major epithelial and minor myoepithelial component. Distinction between epitheliosis and intraduct carcinoma on the myoepithelial cell component appears to be more pragmatic than real and pathologists should rather utilize other cardinal criteria which have proved to be diagnostic.[182] However, loss of definition of the basement membrane, discontinuities in the myoepithelial cell layer, and an epithelial rather than myoepithelial cell type seem to favor a diagnosis of carcinoma *in situ*.[78,99,109,183,184]

Another pitfall in diagnostic histopathology is the interpretation of papillary lesions of the breast. Two cell-type differentiation is for practical purposes a feature of papillomas[110] and statements by various authors that myoepithelial differentiation is present in papillary carcinomas should be rejected as these studies utilized nonspecific techniques and applied doubtful criteria during myoepithelial identification. Immunocytochemical methods for epithelial and myoepithelial cell markers employed on fixed and paraffin-embedded tissue[109] offer the best potential in distinguishing benign from malignant papillary lesions of the breast.[110]

b. Ductal Carcinoma

Cellular differentiation in infiltrating ductal carcinomas is predominantly towards cells with epithelial as opposed to myoepithelial characteristics.[109,185] Analogies can perhaps be drawn with rat mammary tumors where neoplastic cells with a common ancestry are capable of differentiating into more than one morphologic cell type.[56] The selection of differentiating patterns appears to be related to clonal, environmental, and/or hormonal factors influencing variation in gene expression.[56,109] Myoepithelial cell differentiation in some infiltrating breast carcinomas is supported by immunohistochemical identification of scattered laminin positive cells[186] and cells staining with antimyosin antibodies.[187] Experimental studies have indicated that laminin may promote the attachment of neoplastic cells to subendothelial basement membrane proteins during the process of metastatic spread[188] and identification of lymph nodal micrometastasis is facilited by staining for laminin.[186] The degree of myoepithelial differentiation and presence of extracellular basement membrane deposits appear to be related to

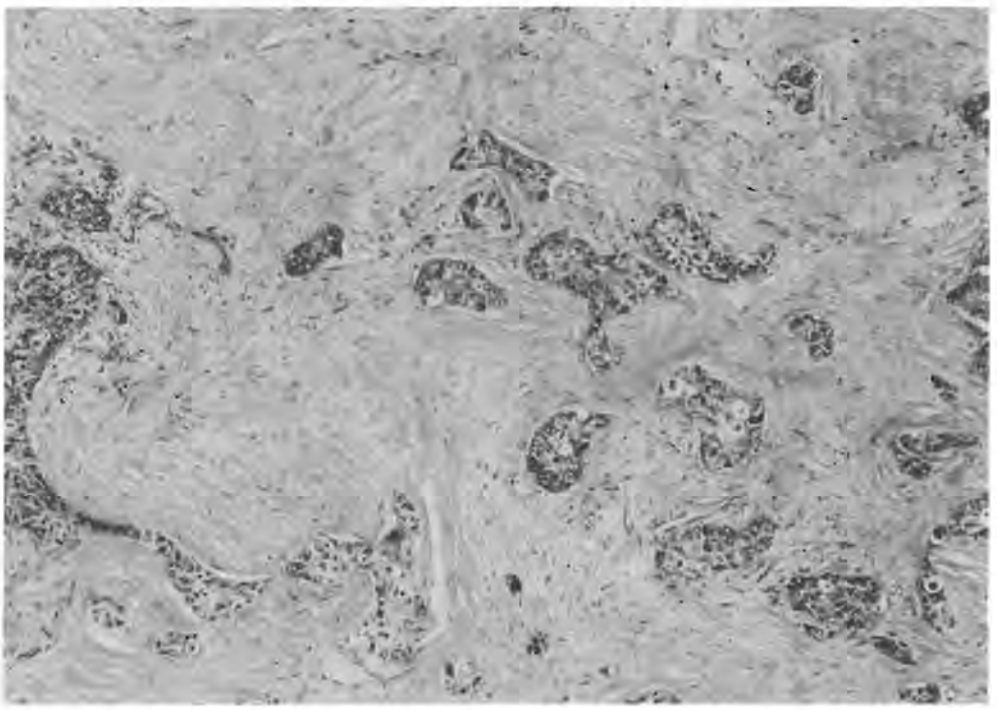

FIGURE 17. Scirrhous carcinoma, female breast. (Hematoxylin-eosin; magnification × 150.)

the differentiation of the neoplasm: in better differentiated lesions, positive staining for basement membrane proteins is present[186] and the number of cells with myoepithelial features appears increased.[189,190] Loss of basement membrane in poorly differentiated tumors could be related to the production of plasminogen activators resulting in proteolytic degradation.[191] As already pointed out, care should be taken not to interpret stromal myofibroblasts, a prominent component in scirrhous carcinomas (Figure 17), as myoepithelial in origin.

c. Lobular Carcinoma

In an immunochemical and ultrastructural study of five cases of lobular carcinoma *in situ,*[192] the orientation of myoepithelial cells appeared to identify three distinct phases of the disease: in an early stage, myoepithelial cells exhibited the classic peripheral arrangement. In other cases, they appeared perpendicular to the basement membrane and showed several cytoplasmic projections extending between the neoplastic cells. One advanced case, associated with infiltrative carcinoma, exhibited myoepithelial cells diffusely dispersed among neoplastic cells that filled the ductules. This change in myoepithelial orientation and distribution indicates a process of myoepithelial hyperplasia and migration (tumoral colonization) analogous to that of nonneoplastic melanocytes colonizing infiltrative breast carcinoma[193] or basal cell carcinomas of the skin[194] and could identify a preinvasive stage of lobular carcinoma *in situ.*[192] Furthermore, in light of the supportive nutritional function of myoepithelial cells, hyperplasia may be related to the increased nutritional requirement of the fast-proliferating neoplastic epithelial cells.[99,195] Secretory epithelial differentiation was proven both ultrastructurally[99,196] and immunochemically[196,197] in infiltrating lobular carcinoma, invalidating the long-held view that this neoplasm was primarily of myoepithelial origin.

d. Fibroadenoma, Sclerosing Adenosis, and Phylloides Tumor

In fibroadenoma, sclerosing adenosis, and phylloides tumor, myoepithelial cells are generally arranged in a single layer, though multilayering is not infrequent.[78,178,198] The basal portion of myoepithelial cells often appears markedly undulated with long finger-like projections referred to as "budding". In sclerosing adenosis, the number of acini initially increases and then develops through a series of phases in which myoepithelial cells play an ever increasing role, until the epithelial elements become compressed and myoepithelial cells take on a spindle morphology.[109] Apparent bridging of myoepithelial cells from one ductule to the other may also be observed.[78]

Multiple layering of myoepithelial cells appears rather characteristic of well-differentiated proliferative disease processes.[183] It is not surprising to find reduplication of the basement membrane in such areas, as myoepithelial cells are, as already pointed out, responsible for production of basement membrane proteins. Peripherally located myoepithelial cells resting on a delimiting basement membrane are, however, not a feature of all benign epithelial breast lesions. Microglandular adenosis, a tumor often misinterpreted as tubular carcinoma, can be distinguished from other forms of adenosis by the absence of myoepithelial cells and basement membrane deposits.[199]

e. Mixed Tumor

Mixed adenomas (salivary type) of the human female breast are very rare and only a few undisputed cases have been reported. The histogenesis is apparently similar to that of its rival in salivary glands.[200,201] In animals, especially dogs, these tumors are more common and electron microscopic,[202,203] histochemical,[204] and immunohistochemical[203] studies support the myoepithelial nature of stromal cells. Demonstration of desosomes between undifferentiated cells, however, is not enough evidence for myoepithelial derivation as they may also be present between a variety of mesenchymal cell types.

f. Adenoid Cystic Carcinoma

Adenoid cystic carcinomas of the female breast originate from stem cells in the terminal ducts which have the capacity to produce all the epithelial elements of the gland and so recapitulate the ductal acinar unit.[205] Immunofluorescent,[206] light, and electron microscopic studies[78,207,208] identified myoepithelial cells at the periphery of the ductal epithelial islands in adenoid cystic carcinomas. The biphasic histologic growth pattern[206] and the production of basement membrane proteins by the myoepithelial component[78,207] are well differentiated histologic features compatible with an excellent prognosis.

g. Myoepithelioma

Although hyperplasia of myoepithelial cells is encountered in many benign neoplasms of the breast, it is rarely the main component of a tumor. A few undisputed myoepitheliomas of the human female breast have recently been reported.[209-212] These cases probably represent one pole of a spectrum of tumors ranging from uniform spindle-cell proliferations such as the mammary myoepithelioma reported by Erlandson and Rosen[211] and the leiomyoma-like myoepithelioma reported by Toth[210] to proliferations of basiloid ductal cells without a myoepithelial component such as seen in tubular carcinomas.[78,208] In cases where both myoepithelial and epithelial components are active participants in the neoplastic process, the lesions are referred to as adenomyoepitheliomas.[209,212] These observations support a hypothetic stem cell origin with multidirectional differentiating potential.[211] Furthermore, neoplastic transformation of mature myoepithelial cells is not possible as they are highly differentiated and not

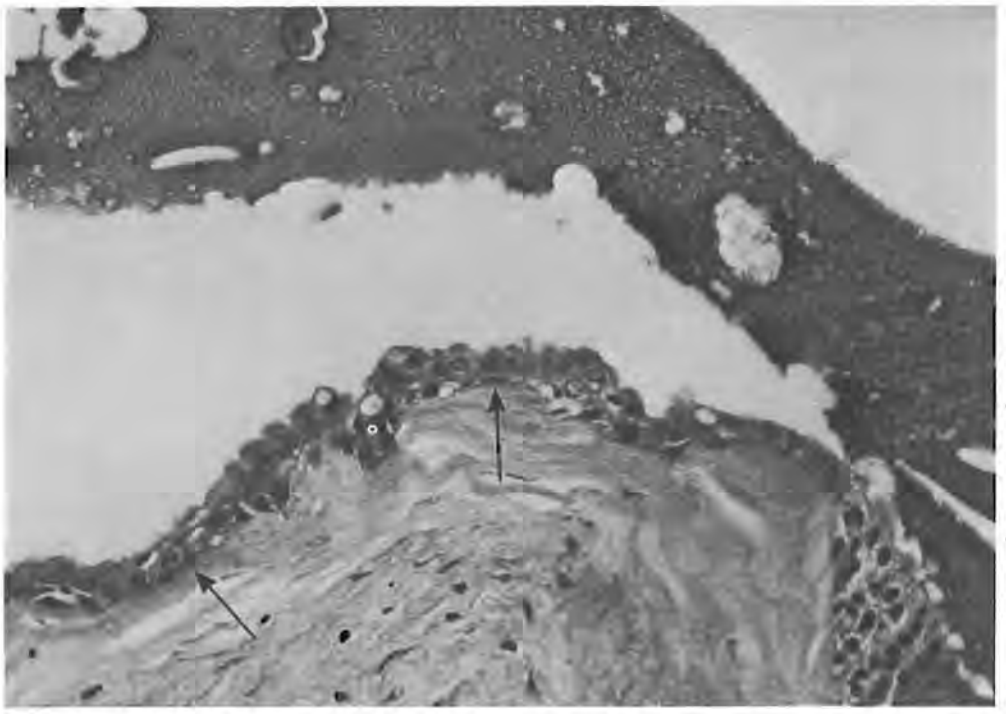

FIGURE 18. Apocrine hydrocystoma. Note myoepithelial differentiation (arrows). (Hematoxylin-eosin; magnification × 400.)

capable of proliferation.[210] Although Schlotke[213] produced a well-documented report of metastasizing malignant myoepitheliomas found in bitch mammary glands, the clinical behavior of a lesion of this nature in humans is unknown and, until larger series are available, therapy should be directed to complete excision of the tumor. The one case reported in the literature as a low-grade malignant myoepithelioma[212] does not warrant this diagnoses as a recurrent growth is not necessarily an indication of malignancy. Furthermore, suggestions that some spindle-cell carcinomas of the breast[214] and even leiomyosarcomas[215] originate from myoepithelial cells should not be accepted without immunocytochemical evidence.

C. Sweat Glands

Neoplastic conditions of skin appendages do not arise from mature cells or dormant embryonal epithelial rests as believed earlier, but from pluripotential precursor cells that form continuously during life.[216] Only tumors originating from the precursor cells of secretory coils of eccrine and apocrine glands have the capacity to differentiate towards myoepithelium.[217]

Apocrine and eccrine nevi, which represent hyperplastic proliferations of apocrine and eccrine glands, respectively, resemble their mature counterparts[216] and contain a normal myoepithelial component.

Apocrine hydrocystoma, a tumor characterized by large cystic spaces lined by cells showing "decapitation secretion",[216] contains a peripheral layer of elongated myoepithelial cells[218] (Figure 18). This feature is in contrast with eccrine hydrocystomas, where a fully differentiated myoepithelial cell layer is reported to be absent.[216] An outer layer of cuboidal cells, staining positive with alkaline phosphatase and containing numerous myofilaments ultrastructurally,[219,220] represents myoepithelial differentiation in hidradenoma papilliferum.

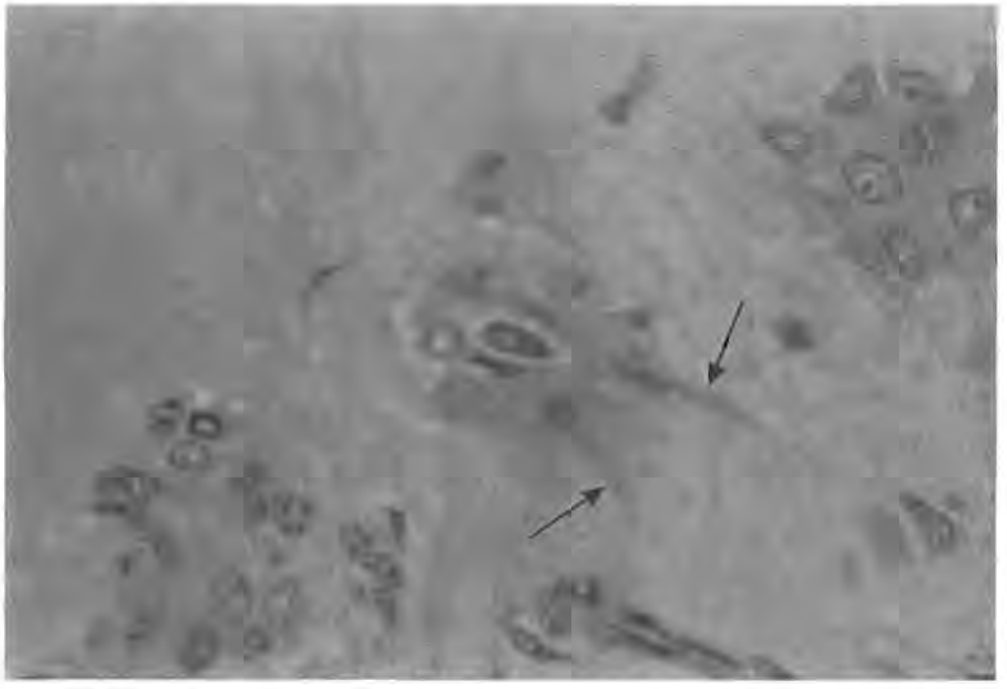

FIGURE 19. Chondroid syringoma. Myoepithelial cells (arrows) proliferating from a ductal structure into the interstitial tissue. (Hematoxylin-eosin; magnification × 1250.)

A few myoepithelial cells have been identified around the periphery of the tubular structures in eccrine spiradenoma.[221,222] Clear cell hidradenoma, referred to in the past as clear cell myoepithelioma,[223,224] shows differentiation towards intraepidermal as well as intradermal eccrine structures, ranging from poral epithelium to cells of the secretory segment.[225] A multipotential reserve cell theory of origin[226] serves as an explanation for the diverse cellular differentiation seen in this tumor. Although myoepithelial differentiation appears to be a hypothetical possibility, the clear cells, which were originally accepted as representing myoepithelial cells,[86,223,224] do not contain alkaline phosphatase or myofilaments and should rather be regarded as immature poral epithelial cells[216] or cells of the outer sheath of hair follicles.[227]

Chondroid syringomas (mixed tumors of the skin) originate from a multipotential stem cell differentiating towards eccrine ductal epithelial and myoepithelial cells[216,228] and are histologically identical to mixed tumors of salivary glands.[229] Myoepithelial cells proliferate into the stroma (Figure 19) and produce the characteristic chondroid deposits.[216,228] This is supported by positive staining of cells incorporated in the chondroid deposits for S100 protein.[114] The cartilage-forming myoepithelial cells differ from chondrocytes by being enveloped in a basement membrane and contain large numbers of intracytoplasmic fibrils and no glycogen.[228] The stroma is, although produced by myoepithelial cells, histochemically similar to normal cartilage.[230]

Tumors dominated by myoepithelial cells are relatively rare in the skin. Efskind and Eker[224] studied 21 tumors which allegedly consisted mainly of myoepithelial cells in two forms: a polygonal cell with a clear glycogen-rich cytoplasm and a spindle-shaped cell arranged in chords and strands. Most examples contained variable numbers of glands lined by epithelium with apocrine features. Their study is unfortunately based on conventional light microscopic techniques only.

Cylindromas (occasionally referred to as turban tumors) are innocuous lesions con-

stituted of tubular structures and epithelial nests, comprised of cells with small dark-staining nuclei arranged in a palissade at the periphery and cells with large light-staining nuclei in the center.[216] Analogous and nearly homologous relationship has been found between dermal cylindromas and certain monomorphic adenomas of salivary gland origin.[231] Although the absence of myoepithelial differentiation in cylindromas has been reported in ultrastructural studies,[232] these tumors warrant further immunohistochemical investigation as their morphology appears to be consistent with variable cytodifferentiation of a basic stem cell of apocrine ductal origin.[216,232]

Primary adenoid cystic carcinoma of the skin has been a very rarely reported neoplasm and due to the absence of ultrastructural and immunohistochemical investigations, it is not possible to delineate myoepithelial participation. Light microscopic evidence appears to indicate that these lesions have a histogenesis and biologic behavior similar to that of adenoid cystic carcinomas of salivary gland origin.[233]

Basal cell epitheliomas are derived not from basal cells, but rather primary epithelial[234] and eccrine gland germs and they represent the least differentiated of the appendage tumors.[216] All studies so far have failed to identify significant myoepithelial differentiation.

D. Other

Myoepithelial cells have not been described in the human uterine cervix. Their differentiation in cervical adenoid cystic carcinomas probably takes place after neoplastic transformation of the subcolumnar reserve cells which are thought to be the progenitors of most other cervical carcinomas.[156,158] A similar histogenesis can be propogated for prostatic adenoid cystic carcinomas as ultrastructural[235] and recent immunofluorescent[45] studies have failed to identify contractile cells in the basal region of human prostatic glands.

The absence of myoepithelial cells in the pancreas should not rule out the possibility of their occurrence in pancreatic tumors. The concept of dedifferentiation, metaplastic neoplasia, or regression could explain their occurrence in a pancreatic microcystic adenoma reported recently.[236] Myoepithelial differentiation in pancreatic tumors should, until further evidence becomes available, be regarded as exceptional.

ACKNOWLEDGMENTS

The author wishes to thank Dr. V. de Vos (Research Division, Kruger National Park) for making the material reflected in Figures 3, 4, 6, and 12 available and Dr. J. P. van Niekerk (Electron Microscope Unit, Medunsa) for performing all ultrastructural examinations. Valuable assistance was given by D. P. du Plessis and P. Mokonoto of the Research Division of Anatomical Pathology and I am indebted to Mrs. C. S. Begemann for secretarial assistance.

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