This dissertation has been microfilmed exactly as received 67-16,318

MURAD, Tariq Mohammed, 1936-
AN ULTRASTRUCTURAL STUDY OF FIBROCYSTIC DISEASE AND FIBROADENOMA OF THE BREAST.

The Ohio State University, Ph.D., 1967
Health Sciences, pathology

University Microfilms, Inc., Ann Arbor, Michigan
AN ULTRASTRUCTURAL STUDY
OF FIBROCYSTIC DISEASE
AND FIBROADENOMA
OF THE BREAST

DISSERTATION

Presented in Partial Fulfillment of the Requirements of
the Degree of Doctor of Philosophy
in the Graduate School of
The Ohio State University

Approved by

Emmerich von Haam, M.D.,
Adviser
Department of Pathology
ACKNOWLEDGMENTS

The author wishes to express his great appreciation to Professor Emmerich von Haam, his adviser and Chairman of the Department of Pathology. Only through his close supervision and consistent advice, criticism and encouragement was the author able to achieve the quality and results of this work.

The generous support of the Department of Pathology of The Ohio State University is gratefully acknowledged.

The author is greatly indebted to Professor Dante G. Scarpelli and Dr. Marie Greider for their invaluable advice in electron microscopy. The opinion of Dr. Francis E. Cuppage is greatly appreciated in editing this dissertation.

The author also wishes to express his gratitude to Miss Marian Snavely who helped in correcting the manuscript into the proper form and to Miss Arlene Horvath, who typed the first draft of the dissertation. For the preparation of the many light micrographs the author is pleased to acknowledge Mr. Gilford Millard. The technical help of Miss Trecia Alderson deserves special expression of thanks.

Finally the author wishes to thank his parents, Dr. and Mrs. Mohammed Murad for providing him with his earliest education and for their patience while the author was a student.
VITA

July 28, 1936 . . Born Karbala, Iraq

July, 1959 . . M.B. Ch. B., University of Baghdad, School of Medicine, Baghdad, Iraq

July-October, 1959 . . . . . . Resident in Surgery, Alshaal Hospital, Baghdad, Iraq

October, 1959- February, 1961 . . Almansoor Military Hospital, Iraq

February, 1961- May, 1962 . . Demonstrator in Pathology, University of Baghdad School of Medicine

July, 1962 - June, 1963 . . Fellow and Resident in Pathology, Washington University School of Medicine, St. Louis, Missouri

June, 1963 - June, 1965 . . Resident in Pathology, The Ohio State University, Columbus, Ohio

June, 1965 . . M. Sc., The Ohio State University, Columbus, Ohio

July, 1965 . . Instructor, Department of Pathology, The Ohio State University, Columbus, Ohio

*    *    *

PUBLICATIONS


MAJOR FIELD OF STUDY

Major field: Pathology
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>ii</td>
</tr>
<tr>
<td>VITA</td>
<td>iii</td>
</tr>
<tr>
<td>PUBLICATIONS</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF ILLUSTRATIONS</td>
<td>vi</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Review of the literature</td>
<td>2</td>
</tr>
<tr>
<td>1. Normal breast</td>
<td>2</td>
</tr>
<tr>
<td>2. Fibrocystic disease</td>
<td>4</td>
</tr>
<tr>
<td>3. Fibroadenoma</td>
<td>8</td>
</tr>
<tr>
<td>MATERIALS AND METHODS</td>
<td>10</td>
</tr>
<tr>
<td>RESULTS</td>
<td></td>
</tr>
<tr>
<td>Normal mammary ducts</td>
<td>12</td>
</tr>
<tr>
<td>Epithelial cells</td>
<td>12</td>
</tr>
<tr>
<td>Myoepithelial cells</td>
<td>14</td>
</tr>
<tr>
<td>Periductal stroma</td>
<td>16</td>
</tr>
<tr>
<td>Fibrocystic disease</td>
<td>18</td>
</tr>
<tr>
<td>1. Blunt duct adenosis</td>
<td>18</td>
</tr>
<tr>
<td>2. Epithelial hyperplasia</td>
<td>22</td>
</tr>
<tr>
<td>a. Proliferation of ductular epithelium</td>
<td>22</td>
</tr>
<tr>
<td>b. Sclerosing adenosis</td>
<td>24</td>
</tr>
<tr>
<td>3. Cysts</td>
<td>26</td>
</tr>
<tr>
<td>Proliferation of apocrine epithelium</td>
<td>28</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>29</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>35</td>
</tr>
<tr>
<td>Normal mammary gland</td>
<td>35</td>
</tr>
<tr>
<td>Fibrocystic disease</td>
<td>47</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>58</td>
</tr>
<tr>
<td>SUMMARY AND CONCLUSION</td>
<td>66</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>70</td>
</tr>
<tr>
<td>ILLUSTRATIONS</td>
<td>87</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Normal mammary duct</td>
</tr>
<tr>
<td>2</td>
<td>Normal mammary duct</td>
</tr>
<tr>
<td>3</td>
<td>Normal mammary duct</td>
</tr>
<tr>
<td>4</td>
<td>Normal mammary duct</td>
</tr>
<tr>
<td>5</td>
<td>Normal mammary duct</td>
</tr>
<tr>
<td>6</td>
<td>Normal mammary duct</td>
</tr>
<tr>
<td>7</td>
<td>Normal epithelial cell</td>
</tr>
<tr>
<td>8</td>
<td>Normal mammary duct</td>
</tr>
<tr>
<td>9</td>
<td>Normal mammary ducts</td>
</tr>
<tr>
<td>10</td>
<td>Normal myoepithelial cell</td>
</tr>
<tr>
<td>11</td>
<td>Normal myoepithelial cell</td>
</tr>
<tr>
<td>12</td>
<td>Normal myoepithelial cells</td>
</tr>
<tr>
<td>13</td>
<td>Normal myoepithelial cells</td>
</tr>
<tr>
<td>14</td>
<td>Normal mammary duct surrounded by dark and light myoepithelial cells</td>
</tr>
<tr>
<td>15</td>
<td>Normal mammary ducts</td>
</tr>
<tr>
<td>16</td>
<td>Stromal tissue of normal mammary gland</td>
</tr>
<tr>
<td>17</td>
<td>Stromal tissue of normal mammary gland</td>
</tr>
<tr>
<td>18</td>
<td>Capillary blood vessel</td>
</tr>
<tr>
<td>19</td>
<td>Capillary blood vessel</td>
</tr>
<tr>
<td>Figure</td>
<td>Illustration Description</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------------</td>
</tr>
<tr>
<td>20</td>
<td>Capillary blood vessel</td>
</tr>
<tr>
<td>21</td>
<td>Capillary blood vessels surrounded by a pericyte</td>
</tr>
<tr>
<td>22</td>
<td>Capillary blood vessels with a pericyte</td>
</tr>
<tr>
<td>23</td>
<td>Capillary blood vessels surrounded by a pericyte</td>
</tr>
<tr>
<td>24</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>25</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>26</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>27</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>28</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>29</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>30</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>31</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>32</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>33</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>34</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>35</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>36</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>37</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>38</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>39</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>40</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>41</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>42</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>43</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>44</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>45</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>46</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>47</td>
<td>Blunt duct adenosis</td>
</tr>
<tr>
<td>48</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>49</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>50</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>51</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>52</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>53</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>54</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>55</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>56</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>57</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>58</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>Figure</td>
<td>Illustration Description</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>59</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>60</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>61</td>
<td>Epithelial cell hyperplasia</td>
</tr>
<tr>
<td>62</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>63</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>64</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>65</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>66</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>67</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>68</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>69</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>70</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>71</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>72</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>73</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>74</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>75</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>76</td>
<td>Cyst</td>
</tr>
<tr>
<td>77</td>
<td>Cyst</td>
</tr>
<tr>
<td>78</td>
<td>Cyst</td>
</tr>
<tr>
<td>Figure</td>
<td>Illustration</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>79</td>
<td>Cyst</td>
</tr>
<tr>
<td>80</td>
<td>Cyst</td>
</tr>
<tr>
<td>81</td>
<td>Cyst</td>
</tr>
<tr>
<td>82</td>
<td>Cyst</td>
</tr>
<tr>
<td>83</td>
<td>Cyst</td>
</tr>
<tr>
<td>84</td>
<td>Cyst</td>
</tr>
<tr>
<td>85</td>
<td>Cyst</td>
</tr>
<tr>
<td>86</td>
<td>Cyst</td>
</tr>
<tr>
<td>87</td>
<td>Cyst</td>
</tr>
<tr>
<td>88</td>
<td>Apocrine epithelium</td>
</tr>
<tr>
<td>89</td>
<td>Apocrine cell</td>
</tr>
<tr>
<td>90</td>
<td>Apocrine cell</td>
</tr>
<tr>
<td>91</td>
<td>Apocrine cell</td>
</tr>
<tr>
<td>92</td>
<td>Apocrine cell</td>
</tr>
<tr>
<td>93</td>
<td>Apocrine cell</td>
</tr>
<tr>
<td>94</td>
<td>Apocrine cell</td>
</tr>
<tr>
<td>95</td>
<td>Apocrine cell</td>
</tr>
<tr>
<td>96</td>
<td>Apocrine cell</td>
</tr>
<tr>
<td>97</td>
<td>Intracanalicular fibroadenoma</td>
</tr>
<tr>
<td>98</td>
<td>Intracanalicular fibroadenoma</td>
</tr>
</tbody>
</table>
## LIST OF ILLUSTRATIONS -- Continued

<table>
<thead>
<tr>
<th>Figure</th>
<th>Image Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>Intracanalicular fibroadenoma</td>
<td>190</td>
</tr>
<tr>
<td>100</td>
<td>Intracanalicular fibroadenoma</td>
<td>190</td>
</tr>
<tr>
<td>101</td>
<td>Intracanalicular fibroadenoma</td>
<td>192</td>
</tr>
<tr>
<td>102</td>
<td>Intracanalicular fibroadenoma</td>
<td>192</td>
</tr>
<tr>
<td>103</td>
<td>Intracanalicular fibroadenoma</td>
<td>194</td>
</tr>
<tr>
<td>104</td>
<td>Intracanalicular fibroadenoma</td>
<td>194</td>
</tr>
<tr>
<td>105</td>
<td>Intracanalicular fibroadenoma</td>
<td>196</td>
</tr>
<tr>
<td>106</td>
<td>Intracanalicular fibroadenoma</td>
<td>196</td>
</tr>
<tr>
<td>107</td>
<td>Intracanalicular fibroadenoma</td>
<td>198</td>
</tr>
<tr>
<td>108</td>
<td>Fibroblasts</td>
<td>198</td>
</tr>
<tr>
<td>109</td>
<td>Pericanalicular fibroadenoma</td>
<td>200</td>
</tr>
<tr>
<td>110</td>
<td>Duct in fibroadenoma</td>
<td>200</td>
</tr>
<tr>
<td>111</td>
<td>Duct in fibroadenoma</td>
<td>202</td>
</tr>
<tr>
<td>112</td>
<td>Duct in fibroadenoma</td>
<td>202</td>
</tr>
<tr>
<td>113</td>
<td>Duct in fibroadenoma</td>
<td>204</td>
</tr>
<tr>
<td>114</td>
<td>Duct in fibroadenoma</td>
<td>204</td>
</tr>
<tr>
<td>115</td>
<td>Duct in fibroadenoma</td>
<td>206</td>
</tr>
<tr>
<td>116</td>
<td>Duct in fibroadenoma</td>
<td>206</td>
</tr>
<tr>
<td>117</td>
<td>Duct in fibroadenoma</td>
<td>208</td>
</tr>
<tr>
<td>118</td>
<td>Duct in fibroadenoma</td>
<td>208</td>
</tr>
<tr>
<td>Figure</td>
<td>Page</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>119</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>121</td>
<td>212</td>
<td></td>
</tr>
<tr>
<td>122</td>
<td>212</td>
<td></td>
</tr>
<tr>
<td>123</td>
<td>214</td>
<td></td>
</tr>
<tr>
<td>124</td>
<td>214</td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>126</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>127</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>128</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>129</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>131</td>
<td>222</td>
<td></td>
</tr>
<tr>
<td>132</td>
<td>222</td>
<td></td>
</tr>
<tr>
<td>133</td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>134</td>
<td>224</td>
<td></td>
</tr>
</tbody>
</table>
INTRODUCTION

Our recent study of the common types of human breast carcinoma (Murad, 1965) uncovered certain differences between the scirrhous and the medullary types of mammary carcinoma that had been previously identified by light microscopic studies. Furthermore, the study suggested that the medullary carcinoma arises from the ductular epithelial cells while the scirrhous type originates from the myoepithelial cell (Murad and Scarpelli, 1967). Because of these results it seemed worthwhile to extend our studies to include the two most common benign lesions of the human female breast, fibrocystic disease and fibroadenoma. Fibrocystic disease is important because of a higher incidence of mammary carcinoma in patients with this lesion than in the same age group of the general population. Both fibrocystic disease and fibroadenoma have some relationship to the function of ovarian hormones and develop mainly during active sex life (Ochsner, 1963 and Rodman, 1935). Fibroadenoma has both a fibrous and a glandular tissue component, but the cell responsible for this lesion has not yet been identified. Recent advances in the application of light and electron microscopic techniques to the study of biological material should permit a more accurate identification of the cytological components of fibrocystic disease and fibroadenoma. The purpose of this investigation was therefore to study by these techniques the cytological characteristics of these lesions in the
hope that such a study might provide needed information concerning the formation and progression of these entities. An ultrastructural study of the normal human mammary glands will serve as a control or a baseline from which to ascertain the changes producing these two diseases.

REVIEW OF THE LITERATURE

1. Normal breast.

The breast is, developmentally, a modified sweat gland (Loeb, 1932). In the human embryo the milk lines appear at about the sixth week of gestation. These lines then atrophy but during the ninth week the site of the permanent mammae can be recognized by the persistence of the epithelial thickening (primitive nipple bud). In the fifth month of fetal life the breasts start to develop as an invagination from the surface epithelium, from the basal layer of the primitive nipple, into the subjacent connective tissue in the form of epithelial cords. These cords then become canalized and develop into ducts (Dawson, 1934). The transformation of the solid cords into ducts begins with the appearance of a few independent lacunae which are usually localized near the center of developing ducts (Myer, 1917). At birth the breasts of the two sexes are similar. This primitive type of breast persists until near the time of sexual maturity when the ovarian hormones, mainly estrogen, exert their effect on the female breast.
The normal histologic structure of the mammary gland consists of a system of branched ducts, the ramifications of which vary greatly in response to endocrine stimulation (Dempsy, 1947). In the resting gland the ducts are lined by a double layer of cells. The inner layer is composed of epithelial cells, and the outer layer of myoepithelial cells. As observed with the electron microscope, the myoepithelial cells form a discontinuous layer around the duct (Wough, 1962). A basement membrane separates the duct from the connective tissue stroma. The ducts are separated from each other by the periductal connective tissue. The periductal connective tissue differs from the dense interlobular connective tissue in that it possesses an elastic network and is more richly supplied with capillaries (Bonser, 1961). The normal human breast consists of 12-20 lobules, each of which opens into the nipple through a duct. The normal mammary lobules consist of a group of small tubules, branches of a small duct lying within a zone of relatively loose and cellular connective tissue. The size of the lobules and their number vary greatly with the individual (Taylor, 1940). Dawson (1935) found only ducts in the lobules, while acini developed during pregnancy.

Endocrine secretions, mainly the ovarian and pituitary hormones, have a definite influence on the survival and development of the breast tissue. Nandi (1958) has shown that in the mouse early ductular proliferation is the result of estrogen and somatotropic hormone secretion,
while progesterone plays an important role in alveolar development. The mechanism by which estrogen produces its effect on the epithelial cells of the breast is still unknown. Bonser (1961) suggested that this may be accomplished by a dual action: indirectly by stimulating the pituitary to secrete mammotrophic hormone, and directly by acting upon the mammary epithelium and connective tissue. Ovarian hormones alone have no effect upon mammary growth in the absence of the pituitary gland. The combination of somatotrophic hormone and estrogen cause breast hypertrophy, while each hormone alone has no effect. Therefore the hormonal effect on the breast may be summarized as follows:

1) Ductular growth in the breast is induced and maintained by estrogen and somatotrophic hormone or mammotrophic hormone acting on the mammary rudiment.

2) Mammotrophic hormone, possibly combined with somatotrophic hormone, together with progesterone acts on the developed duct system to give acinar proliferation.

3) All four hormones, i.e., somatotrophic hormone, mammotrophic hormone, estrogen and progesterone, are necessary for maintaining the fully developed mammary duct and acinar system thus produced.

2. Fibrocystic disease:

Fibrocystic disease is a benign alteration of the female breast that is characterized by various pathological changes including both
proliferative and nonproliferative. Brodie, in 1846, was first to recognize that the cysts were due to dilatation of the lactiferous tubules and that the disease was restricted to the period of active sex life. Lewis (1934) found that the majority of cases occurred in unmarried women or in married women with no children. Bloodgood (1929) noted that this condition is always bilateral and may involve a quadrant, a hemisphere, or the entire breast. After an analysis of 153 cases, Lewison (1953) found the highest incidence in women 41-45 years of age.

The etiology of fibrocystic disease of the breast is not known. Lewis (1934) stated that the changes are due to alteration in the action of ovarian hormones. Nathanson (1944) found the data to support this opinion still far from conclusive. Ingleby (1942) postulated that in cystic disease the cyclic changes of the breast are altered, and whereas normally only part of the duct wall grows at a given moment during the menstrual cycle, in cystic disease the entire duct will grow. In this case the size of the cyst depends on the site of the affected branches. Taylor (1940) thought that the earliest lesion in cystic disease is loss of the normal architectural relation of the lobules resulting from three principal processes: (1) fibrosis of specific connective tissue of the lobules, (2) extensions of the glands beyond the confines of the lobules, and (3) cystic changes of the glands within the lobules.
The importance of chronic cystic disease lies in the reported higher incidence of carcinoma of the breast in patients with this entity. Various incidences have been reported. MacCarty and Mensing (1915) reported the coincidental occurrence of cancer of the breast and chronic cystic mastitis in all of 967 cases of mammary carcinoma. Their criteria for the diagnosis of chronic cystic disease included the presence of one or more of the following lesions: fibrosis with or without hyalinization; lymphocytic infiltration; distortion with partial or complete destruction of the acini; obliteration or dilatation of acinar lumina; atrophy, hypertrophy or hyperplasia of the parenchyma. From this it is apparent that the authors' criteria were too all-inclusive and that this is the explanation for the higher coincidence in their study. Bloodgood (1922), Campbell (1934), Lewis (1938) and Davis (1960) considered fibrocystic disease a benign lesion with no malignant potential. However, most investigators believe that fibrocystic disease is precancerous (Warrens, 1940, 1946; Foot and Stewart, 1945; Lewison, 1953; Swerdlow, 1963).

Fibrocystic disease presents a variety of histological pictures several or all of which may be present in the same breast. Bloodgood (1921) classified the microscopic changes seen in fibrocystic disease under ten main divisions, whereas most investigators limit their histological classification to four or five types. The classification used in the present study is a modification developed mainly from Foot and
Steward (1945), Cole and Rossiter (1944) and Karpas (1965), and in­
cludes the following histological variations:

(1) Blunt duct adenosis: proliferation of the ductular elements. The ductules are lined by the usual two to three layers of cells. The lumina contain no identifiable material. Thick basement membrane and hyalinized stroma may separate one ductule from another. The ductules may have an irregular outline and varying sizes and shapes. Focal epithelial degeneration is rarely encountered.

(2) Epithelial hyperplasia: proliferation of the duct epithelium, which appears to be several layers thick and may form papillary pro­
jec­tions. It usually involves the larger ducts. One or more ducts may be involved. The epithelial hyperplasia is usually focal along the in­
volved ducts. This process may be exaggerated to the point of papillary formation. When the myoepithelial cells proliferate to form an island of epithelial-like cells, the process is referred to as sclerosing adenosis. This latter process is usually limited to one mammary lobule.

(3) Cyst formation. The epithelium is usually shrunken and atrophic. The lumen is usually dilated.

(4) Proliferation of apocrine epithelium. It appears to be glandu­
lar or cystic in structure. The lining epithelium is columnar and contains eosinophilic cytoplasm and small basal nuclei. The apical cytoplasmic margins have a knobby appearance.
3. **Fibroadenoma:**

Fibroadenoma is the most common benign tumor of the human breast in females 20 to 25 years of age (Stewart, 1950; MacFarland, 1924). The tumors are usually small, well-encapsulated fibroepithelial lesions in which either the pericanalicular or the intracanalicular type of connective tissue predominates (Moran, 1935). The lesion is located most frequently in the upper and outer quadrant and occurs with about equal frequency in the two breasts. The cell responsible for this proliferation has not been identified. Oliver (1934), after an analysis of 400 cases, stated that of the various components of the connective tissue of the mammary gland no one predominates in all cases of fibroadenoma. This author regarded fibroadenoma not as a true neoplasm but as a localized mass of hypertrophied and hyperplastic breast tissue with or without involution. Greenough and Simmons (1911) found an abundance of periductal fibrous tissue about the gland ducts in the 44 cases they reported. This periductal tissue may vary in cellularity from that of normal fibrous tissue to that observed in sarcomatous type.

The etiology of fibroadenomas has not been proven, but many investigators have associated this type of lesion with ovarian hormones. Ingleby (1932) found that in cyclic changes the connective tissue of the breast proliferates and degenerates in an inverse ratio to the ductular epithelium. This author regarded fibroadenoma as the result of a
local aberration of the menstrual cycle. Bioassay of the tissue of fibroadenoma revealed a high concentration of estrogen. Geshickter (1934) explained this finding as the result of having a genetically hypersusceptible tissue capable of concentrating the hormone at the site of the lesion.

Thus while the incidences of fibrocystic disease and fibroadenoma of the breast remain high, little is known concerning the cellular origin and development of these entities. These entities are both significant diseases of the breast with definite associations with malignant neo-plasms of this gland. With these facts in mind, the present investigation has been undertaken to characterize these alterations.
MATERIALS AND METHODS

Biopsies were obtained from 4 normal breasts (2 adult premenopausal and 2 postmenopausal), 17 cases of fibrocystic disease, 26 cases of fibroadenomas of the breast, and one case of pericytoma of the neck. The tissues collected were hemisected and one half was placed in 5 percent cold glutaraldehyde at 4°C in phosphate buffer at pH 7.3 for one hour (Sabatini et al., 1963). After the frozen section diagnosis was established by study of the sections of the other half of the biopsy, the glutaraldehyde-fixed tissue was washed with phosphate buffer, cut into 1 mm³ blocks and fixed for 2 hours in ice cold one percent osmium tetroxide in phosphate buffer, pH 7.3, containing 5.4 percent glucose (Millonig, 1961).

Eight cases of fibroadenomas were studied histochemically. These tissues were fixed in buffered formal calcium according to the method described by Scarpelli and Kanczak (1965). Frozen sections 40 micra and 10 micra thick were cut from these cases and then incubated at room temperature for 20 minutes in the media for localization of the enzyme ATPase according to Engel and Tice (1964), and for 35 minutes in the media for localization of the enzyme IDPase according to Novikoff and Goldfischer (1961) and Novikoff et al. (1962). After incubation, the 10 micra thick sections were stained with ammonium sulfide and
studied with the light microscope. The 40 micra thick sections were trimmed into 1.0 or 0.5 mm squares, fixed in one percent osmium tetroxide, and processed for electron microscopic studies.

The tissues were embedded in Maraglas (Freeman and Spurlock, 1962) as modified by Spurlock (1963), or in DER (Lockwood, 1964). Sections one micron thick were cut from 11 blocks of each case on a Porter-Blum microtome. The sections were mounted on slides and then placed on a hot plate at 100-150°C for 15-20 minutes. The sections were stained with toluidine blue (Trump et al., 1961) and examined with the light microscope. After the proper areas were selected, the blocks were trimmed accordingly, and thin sections (600 Å) which exhibited a gray to silver interference color were cut.

After the thin sections were mounted on uncoated copper grids, they were double-stained with uranyl acetate (Watson, 1958) and lead citrate (Reynolds, 1963). The sections for localization of the enzymes were stained with uranyl acetate only. The sections were then examined and photographed on an RCA EMU-3F electron microscope.
RESULTS

Normal Mammary Ducts

The normal human mammary gland consists of several lobules. Each lobule is composed of ducts which are surrounded by the periductal connective tissue. In the light microscope (Fig. 1) the ducts appear to consist of two layers of cells—an inner layer of cuboidal epithelial cells and an outer layer of spindle cells (arrow). The ducts appear either singly or connected to each other by a narrow neck of epithelial cells, giving the ducts an irregular outline (D). The periductal connective tissue separates one duct from another, and it is characteristically rich in capillaries, fibroblasts, plasma cells, lymphocytes and other mesenchymal cells.

On the ultrastructural level the division of the ducts into two layers of cells is obvious (Fig. 2)—an outer layer of myoepithelial cells (My) and an inner layer of epithelial cells (Ep). The basal parts of the myoepithelial cells rest on a basement membrane (BM) of various thicknesses which separates them from the stroma. The lumens (Lu) of the normal ducts are filled with homogeneous osmiophilic material.

Epithelial cells:

The epithelial cells are columnar or cuboidal with centrally located nuclei (Fig. 3). The nucleus (N) is oval or elongated and frequently has indentations of its nuclear membrane (Fig. 3). The nuclear chromatin
is randomly distributed within the nucleus and is composed of a network of fine granules and filaments. The size and density of the granules vary. The chromatin has minor condensations near the nuclear envelope. The nucleus contains one or two nucleolar complexes which are centrally or paracentrally located (Figs. 2, 4). The nucleolus (No) is composed of ribbon-shaped interweaving elements of osmiophilic material and is surrounded by the chromatin network of the nucleus (Fig. 4). The epithelial cells are attached to each other either by a few desmosomes (Fig. 5, De) or by the infolding of the plasma membrane of adjacent cells (Fig. 4). Near the lumen of the duct the epithelial cells are attached to each other by terminal bars. The apical part of the plasma membrane is thrown into many folds to form minute projections, or microvilli, which abut directly into the lumen (Fig. 6). The cytoplasm contains well developed rough-surfaced endoplasmic reticulum (Fig. 7, ER). The endoplasmic membranes and sacs are dispersed irregularly; however, parallel orientation of the endoplasmic reticulum is not uncommon (Fig. 8, 14). The endoplasmic sacs are filled with homogeneous material. Ribosomes and polysomes form a major part of the cytoplasmic constituents (Fig. 7, 14). Secretory granules of irregular sizes and densities may be seen in the apical portion of the cytoplasm (Fig. 6, arrow). Various numbers of electron-dense bodies which might be lipid vacuoles, lysosomes or microbodies can be seen scattered in different areas of the cytoplasm.
(Figs. 3, 8). The mitochondria (M) are moderate in number and are found in various areas of the cytoplasm. They are usually round, oval or elongated and may show different degrees of indentation of their membrane (Fig. 7). They are lined by an outer smooth membrane and an inner infolding membrane which forms the cristae. The mitochondrial cristae are usually short and run perpendicular to the long axis of the mitochondria. They are separated by homogeneous material (Fig. 7). Various numbers of small, dense granules are visible in the mitochondria (Fig. 5).

The Golgi apparatus (G) is usually small and occupies a paranuclear position (Fig. 7). It is composed of many layers of smooth parallel membranes and various numbers of small granules. No focal cytoplasmic degradation and no glycogen particles were identified in the epithelial cells of the normal mammary ducts.

Myoepithelial cells

The myoepithelial cells (My) lie on the epithelial side of the basement membrane. They are spindle or ellipsoidal in shape and either completely or incompletely surround the ducts (Fig. 9). Both dark- and light-staining cells can be recognized with the electron microscope. The basal plasma membrane of the myoepithelial cell is thrown into many folds toward the stroma, carrying the basement membrane with it. This gives the basal part of the cell a serrated appearance (Fig. 10).
The nucleus (N) of the myoepithelial cell (My) is oval or irregular in outline and is located eccentrically (Fig. 11). The apical plasma membranes of the myoepithelial cells have relatively smooth contours and show no substantial infolding with the neighboring epithelial cells. The nuclear chromatin appears to be homogeneous in distribution with focal densities throughout the nucleoplasm (Fig. 11).

The cytoplasmic organelles are usually limited to the para- or perinuclear cytoplasm. The rest of the cytoplasm is filled with very fine filaments (Fig. 10, 11, F). The granular portion of the cytoplasm contains a well developed rough-surfaced endoplasmic reticulum with irregularly distributed endoplasmic membranes and sacs. The endoplasmic cisternae are filled with a homogeneous material. Ribosomes and rarely polysomes are found on the membranous part of the endoplasmic reticulum but seldom in the filamentous part of the cytoplasm. The mitochondria (M) are small, few in number, and have a few irregular cristae (Fig. 11, insert). An occasional mitochondrion is found in the filamentous part of the cytoplasm. The cytoplasmic filaments are very fine, measuring 50-70 Å in diameter, and frequently show focal condensation parallel to their long axes. The filaments (F) traverse the cytoplasm in a direction parallel to the long axis of the nucleus (Fig. 11, 12). On occasion another stream of filaments is oriented in a direction other than the usual one. The cytoplasmic filaments appear to be related to the
hemidesmosomes (Fig. 10, insert). The plasma membrane abutting the basement membrane exhibits focal condensations (Fig. 10). Pinocytotic vesicles (Pv) are present mainly on the plasma membrane abutting the basement membrane (Fig. 11) but are also seen on the plasma membrane between adjacent myoepithelial cells (Fig. 12). Pinocytotic vesicles are absent from the epithelial side of the plasma membrane. A few desmosomes are present between adjacent myoepithelial cells and epithelial cells (Fig. 13).

Dark myoepithelial cells are frequently found surrounding the ductular epithelium. The dark appearance is not limited to one type of cell organelle but is shared by all cytoplasmic organelles and by the nucleus (Fig. 13). As a rule, it is present whenever a continuous layer of myoepithelial cells surround the ducts. However, dark and light myoepithelial cells may alternate and some of them appear to surround the epithelial cells (Fig. 14).

**Periductal stroma:**

The ductules are separated from each other by the stromal connective tissue (Fig. 15). This tissue is rich in capillary blood vessels (CP) and fibroblasts (f), and occasional plasma cells and lymphocytes may be present (Fig. 16). The fibroblasts are spindle-shaped cells with oval nuclei. The nuclear chromatin appears in scattered patches, mainly near the nuclear membrane and in the center of the nucleus.
The cytoplasm completely surrounds the nucleus with bipolar extensions giving the fibroblast its spindle shape. The cytoplasm has well developed rough-surfaced endoplasmic reticulum, the cisternae (C) of which are dilated and filled with light osmiophilic material (Fig. 17). The mitochondria are oval or elongated and their cristae are perpendicular to the long axis.

The capillaries (CP) are composed of endothelial cells which are attached to each other by the attachment belt (Fig. 18). The outer plasma membrane of the endothelial cells is separated from the stroma by a basement membrane. The inner plasma membrane of these cells is thrown into many folds. The nuclei of the endothelial cells are elongated with their long axes oriented parallel to the basement membrane (Fig. 18). The nuclear membrane is frequently indented and thrown into many folds. The nuclear chromatin is homogeneously distributed with a narrow rim of peripheral condensations. Fine filaments (F) are present in the cytoplasm of the endothelial cells (Fig. 19). Pinocytotic vesicles are present on both the inner and outer plasma membranes (Fig. 20).

The pericytes, the cells which surround the capillaries, are separated from the endothelial cells by the basement membrane of the endothelial cells and from the stroma by their own basement membrane (Fig. 19). The cytoplasm is characterized by its long cytoplasmic processes which invest part of the capillary (Fig. 18, 19). The outer plasma
membrane exhibits focal condensation or hemidesmosomes (Fig. 18, 20, HD). Pinocytotic vesicles (PV) may be present on both the outer and inner plasma membranes but are more commonly found on the outer plasma membrane (Fig. 20). Mitochondria are large and few in number. A few fine cytoplasmic filaments (F) are present in the pericytes. They run in various directions and may assume focal thickening (Fig. 21). Microtubules are occasionally seen in the cytoplasm. The nuclei of the pericytes assume a variety of forms and may be round, oval, or elongated (Fig. 19, 22). The nuclear membrane is frequently indented and on occasion the infolding of the nuclear envelope becomes very prominent. In this case the nucleus appears to be segmented with each segment attached to the stem nucleus by a narrow ribbon of chromatin (Fig. 22, 23).

**Fibrocystic Disease**

This condition, as stated previously, has been divided according to histological changes into four major classifications, which will be described separately.

1. **Blunt duct adenosis.**

In the area of blunt duct adenosis the ducts appear similar to those of the normal breast. The ducts consist of the usual two layers of cells—myoepithelial and epithelial cells (Fig. 24). However, the ducts are irregular in size and shape. Occasionally one may encounter small areas of the ducts in which the myoepithelial cells seem to undergo
proliferation; however, no mitotic figures can be identified in these areas (Fig. 25). Tall columnar cells line some of the ducts. The stroma between these ducts is rich in fibrous connective tissue and in a few instances it appears to be hyalinized (Fig. 26).

On the ultrastructural level two or more layers of cells are present. The epithelial cells are irregular in distribution (Fig. 27) and many of them are flat. The cytoplasm contains well developed rough-surfaced endoplasmic reticulum with many ribosomes and polysomes (Fig. 29). The Golgi apparatus (G) is moderate in size and is scattered in the lateral and apical parts of the cytoplasm (Fig. 27, 28). The mitochondria are moderate in number, are oval or elongated in shape, and contain normal appearing cristae (Fig. 29). The nucleus is large, elongated, and occupies a large portion of the cytoplasm (Fig. 30). It is centrally located and its long axis is parallel with the long axis of the cell. The nuclear chromatin is homogeneous in distribution with focal areas of condensations in the nucleoplasm and near the nuclear envelope. The apical parts of the epithelial cells are lined by short microvilli and the lumen of the duct is usually empty.

In other areas the duct may also be lined by an inner layer of epithelial cells and an outer layer of myoepithelial cells in which the chromatin is less dense, more homogeneous, and without the focal condensations (Fig. 31). The cytoplasm is rich in ribosomes and
polysomes. Varied numbers of electron-dense granules appear in the cytoplasm of some epithelial cells (Fig. 32). They are usually located near the plasma membrane. These granules (arrow) are membrane-limiting, have varying sizes and shapes, measure between 80 and 250 millimicra, and are composed of homogeneous osmiophilic material (Fig. 33). The cytoplasm of these epithelial cells is filled with very fine filaments (F) which in certain areas appear to be related to the desmosomes. The mitochondria (M) are usually swollen.

Many layers of epithelial cells may be found lining some ducts (Fig. 34). This may represent a tangential section of the duct since there are no identifiable cytological changes from those described in Figure 27.

The myoepithelial cells occupy similar positions to that in the normal breast (Fig. 27). The cytoplasm of the myoepithelial cell is composed of filamentous and granular parts (Fig. 35). The filaments have no specific orientation but appear to traverse the cytoplasm in different directions. The myoepithelial cells rest on a thick basement membrane (BM), from which they are separated by a narrow space (Fig. 35). The myoepithelial cells (My) may become somewhat ovoid with irregular nuclei. In some sections dark and light myoepithelial cells surround a duct (Fig. 36). The granular cytoplasm of the light myoepithelial cell contains lipid droplets. On higher magnification (Fig. 37) the mitochondria of the light cell appear to be worm shaped. They have a few cristae,
which are irregular in shape and location. The intercrystal matrix is filled with a dense osmiophilic substance. No normal-appearing mitochondria can be identified in these cells. In certain ducts the myoepithelial cells appear locally increased in number (Fig. 25), displacing the epithelial cells toward the lumen.

On the ultrastructural level, the nuclei of these myoepithelial cells are irregular in outline (Fig. 38). The epithelial cells, however, retain their normal appearance (Fig. 39). The nuclear chromatin is very dense and occurs in patches which fill most of the nucleoplasm. In other areas, which may represent a later stage, the nuclear chromatin is separated into irregular, deeply staining patches which are separated by light-staining chromatin threads and granules (Fig. 40). In a few areas the nuclear envelope seems to have disappeared (arrow) and the light chromatin material is continuous with the endoplasmic reticulum (Fig. 41). Blebs of nuclear material are frequently seen (Fig. 41, arrow). The cytoplasmic filaments appear to be decreased in number. The nucleolus (No) is visible in some cells. In a later stage the nuclear chromatin deposits (arrow) appear as threadlike structures which are irregularly dispersed in the cytoplasm surrounding some of the cytoplasmic organelles (Fig. 42). An occasional desmosome (De) may be seen incorporated within the chromatin mass (Fig. 43).
Glycogen is not uncommon in some ductular cells. It is usually distributed in patches (Fig. 44, arrow) throughout the cytoplasm but appears to be concentrated mainly in the basal part of the epithelial cells. On the ultrastructural level the glycogen is found principally in the epithelial cells and less commonly in the myoepithelial cells and fibroblasts (Fig. 45). On higher magnification the glycogen is composed of granules measuring 150-350 Å that are roughly isodiametric, are disposed in monoparticulate and rosette-like aggregates, and are designated as alpha and beta particles (Fig. 46). Glycogen particles are also present in the myoepithelial cells where they are confined to the granular portion of the cytoplasm (Fig. 47). The mitochondria and other cytoplasmic organelles seem to occupy their normal locations and are not disturbed by the presence of glycogen in these cells.

2. Epithelial hyperplasia.

(a) Proliferation of ductular epithelium. This may involve the entire duct but more commonly involves only focal areas (Fig. 48, 49). The epithelial cells are tall columnar or cuboidal cells which frequently exhibit focal hyperplasia. In certain ducts the apical parts of the epithelial cells assume a knobby appearance (Fig. 48). The myoepithelial cells are flat spindle cells with many stromal projections. Many fibroblasts are scattered throughout the stroma. On the ultrastructural level the duct is lined by two or three layers of epithelial cells, while the
myoepithelial cells become less prominent and more difficult to identify (Fig. 50). The apical portion of the cytoplasm of the inner layer of the epithelial cells is thrown into many folds, giving it the knobby appearance (Fig. 51). The length of the inner projections of the apical cytoplasm varies from cell to cell. There seems to be an inverse relation between the size and length of the knob, or inner projection, and the number and length of the microvilli which line the apical plasma membrane. The longer the projections, the smaller the number and size of the microvilli (Fig. 52). Keratin-like fibrils become prominent in the cytoplasm of the epithelial cells (Fig. 53, K). Moderate numbers of electron-dense granules are seen scattered in the cytoplasm of the epithelial cells (Fig. 53, 55). The cytoplasm contains well developed rough-surfaced endoplasmic reticulum with many ribosomes (Fig. 54). The mitochondria, as in blunt duct adenosis, are elongated, with numerous thin cristae (Fig. 55). Occasionally focal degeneration is present in the mitochondrial cristae (Fig. 54). The Golgi apparatus is moderately developed and occupies the usual juxtanuclear position.

In certain areas the proliferating epithelial cells form papillary projections (Fig. 56). The cells are similar to those described in early hyperplasia, and the apical plasma membranes of the inner layer of epithelial cells are also thrown into many folds, forming knobs (Kn). In another area a different picture of epithelial cell hyperplasia is exhibited.
The nuclei are irregular in size and shape, and the nuclear envelopes are frequently indented (Fig. 57). The nuclear chromatin is less dense and the nuclei contain one or two nucleoli. Lipid and electron-dense bodies are present in the cytoplasm (Fig. 58). The apical plasma membranes show numerous microvilli but do not appear knobby (Fig. 59). The cytoplasm contains well developed rough-surfaced endoplasmic reticulum with narrow cisternae (Fig. 60). Polysomes are numerous in certain parts of the cytoplasm (Fig. 59). The most prominent change appears mainly in the mitochondria and consists of alteration of their density (Fig. 60, 61). This varies from a decreased density of the mitochondrial ground substance to local swelling and lamillar infoldings of their inner membrane, giving the appearance of myelin figures (Fig. 60, 61). Many bundles of keratin-like fibrils (K) are found scattered in the cytoplasm (Fig. 59, 61).

(b) Sclerosing adenosis. In light microscopy this appears as irregular islands of epithelial cells which invade the stroma and are separated by fibrogenic connective tissue (Fig. 62). The lumens are difficult to identify in these islands of cells. Frequently these nodules of cells grow in diverse directions, giving the ducts an irregular outline (Fig. 63). Many layers of epithelial-like cells may be found forming a large duct with no lumen (Fig. 62). On the ultrastructural level, the islands of cells appear to be composed mainly of myoepithelial cells
(Fig. 64). The nodule is irregular in outline and the stroma is filled with collagen fibers (Fig. 65, CF). The cells forming these nodules are irregular in outline and frequently contain narrow projections extending in various directions toward the stroma (Fig. 66). The filaments (f) are usually well developed and run in bundles that have focal condensations along their lengths. The direction of the filaments is usually toward the pointed ends of the nodules (Fig. 66, 67). The nodules are interconnected by narrow stalks of cytoplasmic projections (Fig. 68, arrow), and on higher magnification the filaments seem to run from one nodule to another through these cytoplasmic projections (Fig. 69). The filaments have many points of bifurcation along their length (arrow).

In some myoepithelial cells a few granules are found which appear to be surrounded by membranes and are filled with dense osmiophilic material (Fig. 70). Occasional microtubules (t) are seen in the cytoplasm. No obvious alterations in the form or orientation of the filaments in sclerosing adenosis can be observed to serve as criteria for distinguishing them from the filaments found in normal myoepithelial cells. An occasional keratin-like structure can be identified in the cytoplasm of some myoepithelial cells (Fig. 70). The filaments are confined mainly to the peripheral part of the cytoplasm (Fig. 69, 71). Although the stromal cells in the area of sclerosing adenosis bear some similarity to the fibroblast, they usually contain fine filaments which have focal
condensations along their lengths similar to those found in the filaments of myoepithelial cells (Fig. 72, 73). These proliferating cells in sclerosing adenosis are therefore identified as myoepithelial cells. The filaments of the single myoepithelial cells have focal condensations along their lengths and also exhibit peripheral locations. The nuclei of the stromal myoepithelial cells are rod-shaped or oval with many indentations of their nuclear envelopes. These cells appear to produce collagen fibers (Fig. 73), arrow). No basement membrane is observed around single stromal myoepithelial cells. Collagen fibers appear also to be produced by nodules of myoepithelial cells (Fig. 74). Some stromal cells become extremely large and have very long cytoplasmic processes (Fig. 75). Their filaments are similar to those of normal myoepithelial cells, and the direction of the filaments is parallel to the cytoplasmic extensions.

3. Cysts.

The epithelium lining the cyst is usually shrunken, atrophic, and generally oriented with its long axis parallel to the wall of the cyst (Fig. 76). The lumen contains no identifiable material. A few large, elongated spindle cells are found in the stroma adjacent to the cyst. On the ultrastructural level the wall of the cyst appears thin and its lining cells differ in their electron densities (Fig. 77). The dark cells are found mainly in the basal part and inner wall of the cyst and surround the light cells (Fig. 78). The nuclei of the dark cells are elongated
and may be segmented (Fig. 79). A few lipid bodies (lp) are present in the cytoplasm. Short microvilli line the apical cytoplasm of the inner-lining cells of the cyst. The epithelial cells contain well developed rough-surfaced endoplasmic reticulum with narrow cisternae and are less osmiophilic than the myoepithelial cells (Fig. 78). The nuclei of the light cells show a homogeneous network of chromatin material with peripheral condensations (Fig. 80). A thick basement membrane is present below the basal plasma membrane of the dark cells. On higher magnification fine filaments in the cytoplasm of the dark cells suggest that they are myoepithelial cells (Fig. 81). As in the normal myoepithelial cells, these filaments exhibit focal condensations (Fig. 81). The granular part of these cells contains keratin-like bundles of fine fibrils (Fig. 81). A single large nucleolus (No) is present. Many layers of flat cells are found in some parts of the cyst (Fig. 82, 83). This hyperplasia is due mainly to an increase in the number of the dark cells (myoepithelial cells). In these cases the epithelial cells appear shrunken and are obviously decreased in number (Fig. 82, 83). There is always continuity between the basal myoepithelial cells and those abutting the lumens (Fig. 81). Many small dark bodies are present in the cytoplasm of the dark cells. Terminal bars and desmosomes are the main source of attachment of these cells (Fig. 84). The Golgi apparatus is small and is limited to a juxtanuclear position (Fig. 85). In rare instances the epithelial cells
remain lining the inner wall of the cyst (Fig. 86). In this case the apical plasma membrane has a knobby appearance. The stroma around the cyst contains large myoepithelial cells with long cytoplasmic processes (Fig. 87). The nuclei of the stromal myoepithelial cells are large and elongated, with indentation of the nuclear envelope (Fig. 87).

4. Proliferation of Apocrine Epithelium.

The ducts with apocrine changes of the epithelial cells are usually dilated, forming cystic spaces. The ducts are lined by flat spindle-shaped myoepithelial cells (arrow), which are more osmiophilic than the epithelial cells and are separated by the basal part of the apocrine cells (Fig. 88). The apocrine cells are tall columnar cells with round nuclei and prominent nucleoli (Fig. 88). The nucleus is usually located in the basal part of the cell (Fig. 89). The apical plasma membranes abutting the lumens are lined by short microvilli. Small intercellular ductular spaces (Dt) are also seen between adjacent apocrine cells (Fig. 89). The basal part of the apocrine cell projects downward between the myoepithelial cells to rest directly on the basement membrane (Fig. 90).

The apocrine cells are loaded with cytoplasmic organelles. The mitochondria are characteristic for this cell type. They are concentrated mainly near the basal part of the cell (Fig. 89), whereas the apical portion of the cytoplasm contains a large number of electron-dense granules (Fig. 89). In addition to the obvious increase in number of the
mitochondria, they show extreme variations in size and shape (Fig. 91). They may be round, oval, pear-shaped, elongated, or plump with irregular outlines (Fig. 91,92). The cristae are long and thin and the intercristal matrix is filled with dense homogeneous osmiophilic material (Fig. 92). The Golgi apparatus is hard to find but when present, is usually large and occupies a juxtanuclear position (Fig. 93). The cytoplasm contains well developed rough-surfaced endoplasmic reticulum which is filled with a light electron-dense material (Fig. 94). The apical plasma membrane is thrown into many folds, giving it a knobby appearance (Fig. 95). The apical cytoplasm contains numerous electron-dense bodies. On higher magnification numerous lipid droplets are present in this portion of the cytoplasm (Fig. 96). A few keratin-like fibrils are present in the cytoplasm of the majority of the apocrine cells (Fig. 92).

**Fibroadenoma**

Fibroadenoma is composed of both epithelial and fibrous tissue overgrowth, the relative amounts of which may vary from neoplasm to neoplasm and in different areas of the same neoplasm. In the area of connective tissue overgrowth the stromal tissue appears to grow toward the ductular epithelium, causing distortion of the latter (Fig. 97). In these areas the ducts appear elongated with many side branches. The epithelium lining the distorted duct in Figure 97 has many areas of focal degeneration (arrow, d). In the area of maximum stromal tissue overgrowth,
the epithelium lining the duct disappears completely and in that area the duct is represented by the remaining intact basement membrane (Fig. 97, arrow, BM). The stromal cells are large, elongated, and are separated from each other by fluffy material similar to the basement membrane. The stromal tissue in the intracanalicular type of tumor stains for acid mucopolysaccharides by the alcian blue, periodic acid-Schiff method, whereas the stromal tissue in the pericanalicular type of tumor takes the satin for neutral mucopolysaccharides. When the intracanalicular type is examined on the ultrastructural level, it appears that the cells of the stromal tissue are responsible for this type of proliferation. They are usually large, elongated, and have very large nuclei. The nucleus is multisegmented, and each segment is attached to the main nucleus by a narrow stalk of chromatin (Fig. 98). The nuclear chromatin is homogeneously distributed with minimal peripheral condensations (Fig. 99). The intercellular stroma is filled with light electron-dense material (Fig. 100). Occasional electron-dense bodies are present in the cytoplasm of some cells (Fig. 101). A large Golgi apparatus and centriole (C) are present in the juxta-nuclear region (Fig. 102). Glycogen particles and a few lipid bodies are not uncommon in these cells (Fig. 102). A cilium is rarely present (Fig. 103). They are usually short with characteristic basal bodies.

Long cytoplasmic processes are one of the characteristic features of the intracanalicular stromal cells (Fig. 104). The cytoplasm contains
well developed rough-surfaced endoplasmic reticulum and many poly­somes (Fig. 105). The cisternae are usually moderately filled with relatively electron transparent material simulating the material found outside these cells (Fig. 103, 105). Bundles of fine filaments are seen in the cytoplasm of these cells. The filaments (F) are similar to those found in pericytes. Occasionally microtubules (t) are present (Fig. 105). Basement membrane-like material (BM) surrounds some cells. In rare in­stances pinocytotic vesicles (pv) and focal condensations of the peripheral plasma membrane (hemidesmosomes) are seen (Fig. 106). The mitochon­dria (M) are large, few in number, and have irregularly distributed cris­tae (Fig. 107. A few fibroblasts and collagen fibers are scattered between the stromal cells (Fig. 108).

In the areas of epithelial cell proliferation, the ducts appear irreg­ular in shape and distribution (Fig. 109). On the ultrastructural level the ducts, as in the normal breast, are lined by epithelial and myoepi­thelial cells (Fig. 110). More than two layers of cells may line the ducts (Fig. 111). In tangential sections of the ducts, myoepithelial cells appear to incompletely surround the epithelial cells (Fig. 112). No hemi­desmosomes are present between the basal part of the epithelial cells and the basement membrane. The apical parts of the epithelial cells are lined by microvilli (Fig. 113). Moderate numbers of electron-dense granules are present in the cytoplasm of the epithelial cells. The Golgi
apparatus (G) is well developed and lies in the apical part of the cytoplasm (Fig. 114). Large numbers of secretory granules are seen, mainly near the apical plasma membrane (Fig. 115, 116). The mitochondria of the epithelial cells are oval or rod-shaped and their cristae are perpendicular to their long axes (Fig. 116). On rare occasions focal swelling and myelin figures are seen in some mitochondria (Fig. 115). The cytoplasm contains well developed rough-surfaced endoplasmic reticulum with many ribosomes and polysomes. Bundles of fine filaments are seen in the cytoplasm of a few epithelial cells (Fig. 115). The cell to cell attachment may occur by interdigitation of the plasma membrane (Fig. 117) or by the presence of many desmosomes (Fig. 118). The myoepithelial cells are similar to those of the normal ducts. Occasionally their nuclei exhibit irregularity and segmentation (Fig. 119). The myoepithelial cells may completely or incompletely surround the duct. In a few instances the cytoplasm of the myoepithelial cells bridges two neighboring ducts (Fig. 120). Rarely, dark myoepithelial cells are seen proliferating around mammary ducts. The plasma membranes of these cells show large numbers of pinocytotic vesicles (Fig. 121). The lining cells of this duct simulate the light type of myoepithelial cells. A few desmosomes constitute the main connection between epithelial and myoepithelial cells (Fig. 122). Focal aggregations of glycogen appear in the cytoplasm of some myoepithelial cells (Fig. 123). In the area of maximum stromal
tissue growth, the ductular lining cells show degenerative changes which appear to affect the epithelial cells first, followed by changes in the myoepithelial cells. The changes vary in severity from focal cytoplasmic dissolution (Fig. 124) to complete degeneration and exfoliation of the epithelial cells, leaving only the myoepithelial cells intact (Fig. 125). Later on, the myoepithelial cells degenerate and are represented only by their long cytoplasmic extensions (Fig. 126). In some instances the epithelial as well as the myoepithelial cells are seen to undergo degeneration and exfoliation while the stromal cells (st) remain intact (Fig. 127). In all cases the basement membrane remains intact.

ATPase activity is localized in the plasma membranes of adjacent myoepithelial cells and also in the plasma membranes between the myoepithelial and epithelial cells. The plasma membranes between adjacent epithelial cells do not show this enzyme activity (Fig. 128). The cytoplasmic organelles, the filaments, and the nucleus do not show this enzyme activity (Fig. 129). IDPase is similarly localized (Fig. 130). However, on rare occasions the plasma membrane between adjacent epithelial cells gives a positive reaction for this enzyme (Fig. 131). The stromal cells, the capillary endothelial cells, and the pericytes show no ATPase or IDPase activities (Fig. 132).

The tumor cells of the one case of pericytoma studied were similar to the elongated stromal cells of fibroadenoma (Fig. 133). Cells of both
tumors exhibited segmentation of their nuclei, and each segment was attached to the main nucleus by a narrow ribbon of chromatin material. In both types of tumors the intercellular spaces were filled with similar electron-dense materials that simulate basement membrane. As in the cells of fibroadenoma and in normal pericytes, cytoplasmic fibrils were seen in the cells of pericytoma (Fig. 134).
DISCUSSION

Our ultrastructural study of fibrocystic disease and fibroadenoma has shown distinct cytological differences between these two conditions and the normal mammary gland. It has also shown that the cytological features of the proliferating cells are sufficiently characteristic as to suggest their cellular origin. Since the low resolution of the light microscope does not permit such identification, many earlier studies have contributed little to a clear understanding of these two disease of the mammary gland. Before the ultrastructural changes in fibrocystic disease and fibroadenoma are discussed, a brief discussion of the normal mammary gland appears to be in order.

The mammary gland consists of a system of branching ducts with terminal vesicular enlargements of smaller ductules into acini. The two layers of epithelium of which the ducts are composed consist of an elongated form abutting upon the stroma and a cuboidal epithelium lining the lumen (Loeb, 1932). The former cells are thought to be modified epithelial cells (Dempsy, 1947; Leeson, 1956; Shear, 1956; Scott, 1959) with contractile properties (Richardson, 1949) and are termed myoepithelial cells. The cuboidal layer is considered to be true epithelium capable of secretory activity. The free surface of the epithelial cells lining a duct is characterized by the formation of microvilli which greatly amplify the available surface area and presumably have as their major
function the discharge of secretory granules into the lumen. Microvilli are most highly developed in such cells as those lining the small intestine, in which absorption is a prime function.

A basement membrane of varying thickness is found not only around the mammary ducts but also around the capillary endothelial cells and the pericytes. Pierce and his associates (1962, 1963, 1964), Hay and Revel (1963 and Hay (1964) have firmly established that the basement membrane is largely elaborated by epithelial cells. Murad and Scarpelli (1967) proposed that in multilayered epithelium only the basal layer of cells is capable of synthesizing basement membrane. This would explain the presence of basement membrane around the basal plasma membrane of the mammary duct but does not explain the presence of basement membrane around the capillary endothelium and pericytes, which are of mesenchymal origin. That basement membrane may be produced by less differentiated cells is suggested by the basement membrane production of parietal yolk sac carcinoma, which is produced in such quantity as to permit its pure isolation and chemical analysis (Mukerjee et al., 1965). Moscona (1962) suggested that basement membrane plays an important role as cell binding in aggregates of embryonic cells.

The mammary gland, with the dynamic changes produced by its hormone-dependent cellular proliferation, is an excellent organ in which to study the problem of differentiation in vivo (Lyons, 1958; Nandi, 1958;
Reece, 1958; Cowie and Folley, 1961; and Jacobson, 1961) and in vitro (Daniel and DeOme, 1965; Ichinose and Nandi, 1965; and Jergens et al., 1965). During pregnancy and lactation the epithelial cells play an important role in the secretory activity of the mammary gland and during this period these cells have a relatively uniform appearance. This uniformity has been noted in the glands of more than one animal species. Both lipid and proteins are found in the epithelial cells during the secretory period. The fat droplets are invariably found to be related to the endoplasmic reticulum (ER), from which they are transported to the apical plasma membrane and then are released into the lumen (Bargmann, 1961). The protein is secreted as small droplets which are related to the Golgi apparatus. Hollmann (1965) has shown that in the lactating rabbit the protein granules undergo fusions and rearrangements in the cytoplasm of the epithelial cells before they are secreted.

The ductular epithelial cell has a well developed nucleus, rough-surfaced endoplasmic reticulum, and a moderate number of mitochondria. It is the membranous envelope surrounding the nucleus that is probably mainly responsible for regarding the nucleus as a structural and functional unit. Moses (1964) has suggested that the nuclear size is determined by its content of chromatin and deoxyribonucleic acid (DNA). The nucleus itself possesses a dual capacity: (1) a source of genetic information and (2) a metabolic "transcriber" for instructing and directing the
synthetic activities of the cell. The nucleus contains the genetic material DNA that determines the specificity of cellular behavior and controls its metabolic activities.

It is well established that three types of RNA (ribosomal, transfer, and messenger) are found in most cells, each performing an essential role in protein synthesis. Recent studies indicate that the sequential arrangement of nucleotides in each species of RNA is reflected by a complementary sequence of nucleotides located in some portion of the chromosomal DNA. This and other biochemical evidence strongly suggest that some, if not all, of the RNA is made on a DNA template (Giacomoni and Spiegelman, 1962). Autoradiographic studies of higher organisms further indicate that most of the RNA of the cytoplasm is nuclear in origin. Some RNA appears to be synthesized in the bulk of the chromatin and some in the nucleolus (Wood, 1959; Amono and LeBlond, 1960; Feinendegen et al., 1960; Prescott, 1960; Perry, 1960; Zalokar, 1960). Of the three types of RNA, the transfer RNA has been shown to be produced in both the nuclear chromatin and the cytoplasm but not in the nucleolus (Wood and Zubay, 1965). Messenger RNA, first described by Jacob and Monod (1961), is formed on the DNA template within the nucleus and is then transported from its site of synthesis to the cytoplasm. This nuclear cytoplasmic movement of messenger RNA has been shown by biochemical study.
(Perry, 1962; Scherrer et al., 1963), autoradiographic studies (Goldstein and Plaut, 1955; Prescott, 1960; and Zolokar, 1961) and was suggested by electron microscopic studies (Stevens and Swift, 1966).

On the basis of electron microscopic and radioautographic studies, it has been assumed that ribosomal RNA is finally assembled, if not entirely synthesized, within the nucleolus (Swift, 1959; Edstrom, 1960; Marinoxzi, 1962; Perry, 1962). By utilizing gradient centrifugation Birnstiel et al., (1963) have established that subribosomal particles can be found in the nucleolus. Recent work suggests that the final step in ribosome formation occurs in the cytoplasm (Gerard et al., 1964). The function of ribosomes in protein synthesis includes several integral reactions, none of which is well understood (Hulten, 1964). In cell synthesizing protein for secretions, as in the epithelial cells of the mammary gland, the majority of ribosomes are attached to the membranes of the endoplasmic reticulum (Palade, 1956; Porter, 1961). Upon cell fractionation, this organelle is fragmented into vesicles which are isolated as the microsomal fraction (Palade and Siekevitz, 1956). The association ribosomes and membranes of endoplasmic reticulum, which is preserved in the microsomes, has special functional significance. Porter (1961) suggested that the membranes are not essential to the synthetic activity of the ribosomes. However, microsomes constitute in vivo a more efficient protein synthesizing system than free ribosomes (Siekevita and Palade, 1960).
The newly synthesized protein is transferred from its site of synthesis on the ribosomes to the cisternae of the endoplasmic reticulum (Redman et al., 1966). This would be the first step in protein secretion which involves several cell organelles. The presence of well developed rough-surfaced endoplasmic reticulum in the epithelial cells of the mammary gland suggests that these cells play important roles in protein synthesis. The endoplasmic reticulum and the Golgi apparatus are highly specialized structures, and the various morphological aspects of the endoplasmic reticulum connected with its functional state and capacity (Oberling, 1959).

Two types of endoplasmic reticulum have been described. The smooth-surfaced endoplasmic reticulum is composed of tubular or disc-like membranes 50-100 Å in thickness which are arranged in varying degrees of compactness. The smooth-surfaced endoplasmic reticulum differs from the rough-surfaced endoplasmic reticulum in that it lacks ribosome granules. Rough-surfaced endoplasmic reticulum is associated with small attached particles on the outer surface of the membranous sacs. This type of endoplasmic reticulum frequently has a regional distribution, is predominantly elongated, and shows a parallel orientation (Fawcett, 1955; Palade, 1956). The smooth-surfaced form of endoplasmic reticulum is present in many cell types, especially those engaged in the synthesis of lipid and glycogen. Christensen and Fawcett (1960, 1961) reported
the presence of a large amount of smooth-surfaced endoplasmic reticulum in the interstitial cells of the opossum testis, in comparison to the presence of rough-surfaced endoplasmic reticulum of these cells. Enzymes carrying out important steps in the synthesis of androgens have been localized in the microsomes fraction of the testis, thus it was suggested that the agranular reticulum of these cells is involved in the biosynthesis of androgenic steroids from cholesterol as a precursor. A similar type of endoplasmic reticulum is also present in other steroid-producing glands.

The mammary duct epithelium has well developed rough-surfaced endoplasmic reticulum, but smooth-surfaced endoplasmic reticulum is lacking. A few lipid bodies are found, but glycogen is not visualized in the normal epithelial cells. In the epithelial cells of the mammary ducts during pregnancy and lactation, lipid is found in association with the endoplasmic reticulum (Jeffers, 1935; Hollmann, 1959). Glycogen is found in mammary duct carcinoma, mainly in the medullary type (Murad and Scarpelli, 1967), and also in some epithelial cells in fibrocystic disease. This may suggest an alteration of the rough-surfaced endoplasmic reticulum probably due to hormonal stimulation or genetic alteration. Since both rough- and smooth-surfaced endoplasmic reticulum are found connected to each other, Palade (1956) has postulated that this may represent local differentiation within a common system rather than two different unrelated cytoplasmic structures.
The Golgi complex is considered to be an important cell organelle in all cell types, where it is visualized by light microscopy as a network of argentophilic and osmiophilic threads or plates, frequently associated with argentophilic and osmiophilic components (Dalton and Felix, 1953). It closely resembles the endoplasmic reticulum but is devoid of particles (Haguenau, 1958), and in some cells the membranes of the Golgi complex have been observed in direct continuation with the endoplasmic reticulum (Palay and Palade, 1955). It is now well established that the Golgi apparatus plays important roles in the secretory process (Godman, 1960; Becker et al., 1961; Freeman, 1962; Sheldon and Kimball, 1962; Jamieson and Palade, 1966). In the mammary gland the Golgi complex is associated only with the secretion of small protein particles (Hollmann, 1965). Mollenhauer and Whaley (1963) have suggested that the Golgi complex, if it is to function in the secretory process, must also involve a mechanism for membrane formation to allow for segregation of the secretory material. The presence of a moderately well developed Golgi apparatus in the mammary gland epithelium correlates with the important role these cells play in the secretion of milk during lactation.

De Duve and Berthet (1954) discovered a family of particles smaller than mitochondria which contain acid phosphatase, cathepsin, $\beta$-glucuronidase, ribonuclease, DNAase, and cholinesterase. These particles were termed lysosomes and were thought to represent cytoplasmic
bodies whose sole function was that of intracellular digestion. The lysosomes, first identified in rat liver cells, have since been found in many if not all animal cells. The membrane of the lysosome, according to de Duve (1959, 1960), permits retention of enzymes which, if liberated, can digest the entire contents of the cells. Lysosomes and microbodies are present in human mammary ducts but in small number. It has been suggested that numerous physiological and pathological agents augment the permeability of the membrane of the lysosomes and provoke them to liberate their contents (Gajdos, 1966a, b). The liberated lysosomal enzymes play an important role in normal as well as in pathologic states, as in cellular autolysis and in the determination of certain inflammatory and immunologic phenomena (Gajdos, 1966a, b). The release of lysosomal enzymes may distinctly affect living cells, depending on whether the enzymes are released into the cytoplasm, into a phagocytic vacuole, or outside the cell (Gordis, 1966).

Although the number and size of the mitochondria vary from one epithelial cell to another, in general they are moderate in size and are evenly distributed throughout the cytoplasm of the mammary duct epithelium. Green and Fleischer (1963) described mitochondria as structural subcellular units that have two major functions: (1) the conversion of energy released by oxidation to the bound energy of ATP and; (2) the conversion of the energy released by oxidation to the accumulation of ions against
a concentration gradient. The structural elements of mitochondria consist of an external envelope and internal cristae. Within the phospholipid membranes of these components are macromolecular complexes of enzymes termed elementary particles that are capable of oxidation of appropriate substrates. The elementary particles are associated with the internal cristae and contain the complete electron transport chains for the oxidation of succinate or nicotinamide adenine dinucleotide-H by molecular oxygen. About 60 percent of the mitochondrial protein is structural protein; the remainder is soluble matrix protein (Cornwell and Harrocks, 1964). Blair et al., (1963) have suggested that lipid constitutes 30 percent of the dry weight of mitochondria and 45 percent of the isolated electron transport particles. The number and size of the cristae of the mitochondria appear to be related to the metabolic activities of the organ from which the mitochondria are derived (Boune and Tewari, 1964). The presence of a moderate number of normal appearing mitochondria in the epithelial cells of the mammary ducts suggests that these cells carry on only a moderate metabolic activity.

The myoepithelial cells, the other cell type composing the mammary duct, are found in many glands of ectodermal origin. Richardson (1949) suggested that these cells are contractile and that their filaments are related to smooth muscle filaments. Myoepithelial cells have been studied in sweat glands (Leeson, 1960), in the prostate (Rowlatt and Franks, 1964),
in the Harderian gland (Chiquoine, 1958), in apocrine glands (Hibbs, 1962; Hurley and Shelley, 1954), in exocrine sweat glands (Hibbs, 1958; Munger, 1961a, b), in the mammary gland (Dempsy, 1947, Richardson, 1949; Silver, 1954; Hollmann, 1959), and in the esophageal wall of the Ascaris (Reger, 1965). In the Ascaris esophagus the myoepithelial cells differ from the rest of the myoepithelial cells in possessing two types of filaments: a thin bundle (35-75 Å) and a thick myofilament (140-175 Å). In an electron microscopic study of the normal mammary duct, Wough (1962) observed that myoepithelial cells surround the duct incompletely. All investigators have agreed that the filaments of the myoepithelial cells are similar to the filaments in smooth muscle cells. In some glands the contractile function of the myoepithelial cells has been clearly demonstrated (Hurley et al., 1954; Linzell, 1955). Hollmann (1959) suggested that the myoepithelial cells are in no way related with the secretory function of the mammary gland. Myoepithelial cells are known to play an important role in the formation of salivary gland tumors (Mylius, 1960), mixed mammary carcinoma in dogs (Moulton, 1961) and human mammary scirrhous carcinoma (Murad and Scarpelli, 1967). In the malignant changes of the myoepithelial cells of humans, definite alterations occur in the form, thickness, orientation, and direction of their filaments.
The finding of dark and light myoepithelial cells may suggest that two types of myoepithelial cells surround a mammary duct. It is possible that the light myoepithelial cells transform into secretory epithelial cells, while the dark cells play a major part as supportive cells. Hibbs (1958) found in sweat glands a transitional form between myoepithelial and secretory cells. On the other hand, Ellis (1965) failed to find such a relationship. Although myoepithelial cells are similar to smooth muscle cells, ultrastructural differences between the two cell types have been described (Ellis, 1965). Generally, the orientation of filaments in the myoepithelial cells is parallel to the long axis of the particular part of the cell in which they lie. It was shown that although individual filaments within a closely packed group may cross over one another or diverge and become part of a neighboring group, in general the streams of filaments do not intersect (Tamarin, 1966). Our study confirms these observations.

Pinocytotic vesicles were mainly found in the plasma membrane of myoepithelial cells abutting the basement membrane. These structures, first described in tissue culture by Lewis (1931), were thought to represent a means of cell drinking. Palay and Karlin (1959) demonstrated, in the epithelial cells lining the small intestine, that fat was transported across the cells by a process of pinocytosis. This process also plays an important role in the transport of digested substances across the intestinal epithelial cells. In fat cells, Barnett and Ball (1960) showed a significant
increase in pinocytosis in the presence of insulin and correlated it with an increased glucose uptake. Brandt (1962) postulated that insulin plays an important role in the binding step of glucose to plasma membrane which is followed by the formation of pinocytotic vesicles. Large numbers of these vesicles were demonstrated in the capillary endothelium by Moor and Ruska (1957). The presence of many pinocytotic vesicles in myoepithelial cells strongly suggests that these cells play an important role in selective absorption of certain metabolites across their membrane.

**Fibrocystic Disease**

Fibrocystic disease is the most frequently encountered abnormality of the human breast and has been linked to endocrine imbalance (Ochsner, 1963). Frantz et al., (1951) found gross cystic disease in 19 percent of 225 autopsy cases. When the presence of apocrine epithelium and simple cysts was considered, the incidence rose to 53 percent. Microscopic involvement of the opposite breast was always present. Endocrine etiology was suggested principally because of the high incidence of fibrocystic disease in the age groups of 20-50 years (Bartlett, 1924; Cheatle, 1928), with a peak in the climacteric period (Lindgren, 1936; Frantz, 1951). Keynes (1923-24 suggested that in the non-lactating breast the secretion is not discharged through the nipple and is normally balanced by reabsorption. During involution of the breast, this mechanism is altered and may lead to fibrocystic disease. McFarland (1922)
has postulated that fibrocystic disease is the result of a perversion of involution resulting in the accumulation of cellular and amorphous debris that obstructs the outlets of the ducts. This in turn will lead to retention of secretion and exudation of fluid with cyst formation. Burrow (1936) has shown that estrogen compounds are important in the development of the mammary duct system with little development of acini. In our study, focal accumulation and proliferation of the ductular cells were frequently found. This proliferation may involve the myoepithelial cells only. The focal proliferation of both epithelial and myoepithelial cells may result in complete obstruction of the duct followed by accumulation of the secretory product of the epithelial cells and later cyst formation. Rodman (1935) suggested that fibrocystic disease is probably an exaggeration of the normal physiological changes that occur in the breast tissue between puberty and menopause. In the same study, a coexistence of fibrocystic disease and some benign neoplasms of the breast was found, including adenofibroma and papillary cystadenoma. The author believed that all these conditions were due to ovarian dysfunction. According to Syms (1916), fibrocystic disease is primarily an inflammation and the varied pathological pictures represent different stages of the same disease. In our study, inflammatory cells were frequently found, most of which were of the lymphocytic and plasma cell series. The presence of these cells in fibrocystic disease is thought to represent a reaction of the tissue
to the discharge of cyst contents into the stroma. It was Cheatle's (1928) opinion that the pathological changes in fibrocystic disease of the mammary gland simulate those found in the skin after tar application. He therefore concluded that fibrocystic disease is the result of irritation.

In our study the different types of lesions have been grouped into four major histopathological patterns. This classification has helped to explain some aspects of the disease, since as visualized by the electron microscope, the proliferating cells differed greatly from each other and from those of the normal mammary duct. Because of the reported higher incidence of carcinoma of the breast in fibrocystic disease (Greenough and Simmons, 1914; Logie, 1942; McGlannon, 1943; Davis and Simmons, 1955), we paid special attention to the cellular changes in this condition and compared these changes with those observed in our previous study of carcinoma of the breast.

In areas of blunt duct adenosis, the picture closely resembled that of the normal mammary duct and differed from it mainly in the size and chromatin content of the nuclei. This may suggest some changes in the protein synthesis since the majority of the ducts did not contain the secretory material found in the normal mammary duct. The presence of some swollen mitochondria in the epithelial cells could be due to changes in ion transport across the mitochondrial membrane. Utzumi (1965) produced mitochondrial swelling by the administration of parathyroid hormones.
He postulated that the mitochondrial swelling is a consequence of osmotic pressure caused by ion accumulation. He also found that in the presence of magnesium, ion accumulation does occur, but mitochondrial swelling is minimal under this condition. Mitochondrial swelling is usually associated with simultaneous oxidation of pyridine nucleotide, which suggests that both the mitochondrial swelling and respiratory response are the result of primary action of the hormone. Mitochondrial swelling has been observed in vitro in the presence of oxytocin and vasopressin (Lehninger, 1961; Greenbaum, 1963a, b) and were thought to be related to the disulfide group linkage of these hormones. The large numbers of electron-dense granules found in the cytoplasm of these cells may suggest the ability of the epithelial cells to carry on a normal secretory function. The accumulation of secretory bodies along the plasma membranes of adjacent cells may result from an aberration of the mechanism which controls the secretory process and which would normally direct the secretory products toward the lumen of the cells.

We cannot explain the presence of glycogen particles in the ducts of some cases of fibrocystic disease. Drochmans (1962), Revel (1964), and Revel et al., (1960) designated the glycogen particles found in many cells as alpha and beta particles with focal aggregates of the monoparticulate form. Biava (1963) observed that in normal tissues the rosette form was found only in the cytoplasm of liver cells, while the
monoparticulate glycogen was common in other cell types including the glomerular and tubular cells of the kidneys and the Kupffer cells of the liver. It was suggested that glycogen precursors or enzymes necessary for glycogen synthesis accumulate within the Golgi vacuoles and that such substances are subsequently discharged from the vacuoles into the surrounding cytoplasm. The endoplasmic reticulum in this case would serve as a vehicle supplying either the glycogen precursors or the enzymes necessary for glycogen synthesis (Karrer and Cox, 1960). The presence of glycogen aggregates in some cases of fibrocystic disease and their absence from normal mammary duct suggest one of the following possibilities:

1. It is the result of new synthetic function associated with the disease condition as a result of new enzyme formation.

2. It is the result of some defect in enzymes which normally degradate the glycogen into glucose.

3. It is a normal phenomenon which infrequently occurs in the mammary gland and its absence in our study is purely a matter of chance because of the limited materials studied.

The finding of dark and light myoepithelial cells suggests the presence of two types of these cells which may serve different functions. The close similarity between the light myoepithelial cells and the secretory epithelial cells suggests that the former can transform into epithelial
cells while the dark myoepithelial cells would play an important role as a supportive cell. The focal areas of myoepithelial cell proliferation found in some ducts suggest that these cells may be important in the etiology of fibrocystic disease. The proliferation of these cells could very well lead to ductular obstruction and result in cyst formation. The patches of chromatin condensation spread in irregular strings in the cytoplasm of these cells suggest an abnormal prophase of the mitotic cycle. This is supported by the absence of spindle formation in these cells. The large nucleolus frequently found could be due to the formation of new ribosomal RNA, since this organelle is known to play an important role in ribosomal formation as previously described.

In epithelial hyperplasia the epithelial cells form many layers, even to the extent of papillary formation. The principal findings in these cells were keratin-like bundles of fine filaments in the cytoplasm and increased numbers of swollen mitochondria with condensations of their internal cristae. Both of these may represent a response to an overstimulation of the ductular epithelial cells by some hormones. Farbman (1966) showed that plasma membrane thickening occurred during keratinization. We did not observe this in our study, probably because little keratinization was present in these cells, nor did we identify keratin granules in these cells as described by Matoltsy and Parakkal (1965).
Marcus (1962) stated that there is an association between epithelial hyperplasia and the tendency toward continued progress of the disease which was not related to the age of the patient.

Sclerosing adenosis was described by Urban (1949) as a benign breast lesion, which he divided into florid and fibrous sclerotic types. In our electron microscopic study the proliferating cells in this type of lesion were identified as myoepithelial cells. These myoepithelial cells retain their normal filaments with focal condensation along their lengths. Kuzma (1943) described proliferation of myoepithelial cells in fibroadenoma, fibrocystic disease, and in senile involution and fibrosis of the breast. He further stated that the proliferation is usually benign when they retain the characteristics of their epithelial ancestry but may become malignant when forming derivatives of mesodermal elements. This author finally concluded that suspicious breast lesions with myoepithelial cell proliferation are benign. From our studies we concluded that myoepithelial cells play an important role in many benign and malignant conditions of the breast. They are probably the principal proliferating cells in scirrhoues carcinoma.

In fibrocystic disease, depending on the histopathological picture, myoepithelial cells may proliferate either focally or diffusely with infiltration of the stroma. From our study, we believe that infiltration of the stroma is not related to malignancy as long as these cells retain
normal nuclei and filaments. However, if changes in the filaments, with or without nuclear changes, become apparent, then a malignant transformation should be considered. The changes in the filaments include decrease in number, changes in their diameter or orientation, and focal aggregation. Some myoepithelial cells may be seen infiltrating the stroma as individual isolated cells. These cells are usually not surrounded by a basement membrane and frequently seem to deposit collagen. Collagen appears also to be deposited by myoepithelial cells of the nodules, in sclerosing adenosis. This finding helps to explain the fibrogenic and hyalinized stroma found in sclerosing adenosis and also in scirrhou8 carcinoma. It is interesting that collagen is not necessarily deposited by the fibroblast but may be synthesized by cells of nonfibroblastic origin, as shown by Green and Goldberg (1965) in the KB cells derived from epidermoid carcinoma of naropharynx and FL cells derived from human amnion and in Hela cells in tissue culture. The finding of proliferating myoepithelial cells without epithelial cells in nodules of sclerosing adenosis may suggest that in proliferative conditions of the breast myoepithelial cells represent the early proliferating cells. These cells then either transform into epithelial cells or form the skeleton along which the epithelial cells proliferate. The presence of keratin-like filaments and a few secretory granules in the granular part of their cytoplasm strongly suggests an epithelial origin of these cells.
In cysts with atrophic epithelium the proliferation occurs mainly in the myoepithelial cells while the epithelial cells undergo degeneration and atrophy. The probable explanation for this is that myoepithelial cells can better resist an unfavorable environment than epithelial cells.

In cysts lined by apocrine epithelium the myoepithelial cells appear atrophic while the epithelial cells are responsible for the apocrine changes. It is of interest that apocrine glands of the skin are considered to represent a group of glands having a single type of seromucous secretory cells (Munger, 1964). In man, "apocrine" is usually used to characterize a cell whose secretion consists of decapitation of the apical cytoplasm into the gland lumen. In serial sections of human apocrine sweat glands, Shelley and Levy (1955) were unable to substantiate the existence of apocrine secretion. Bargmann et al. (1961) and Hollmann (1959) failed to demonstrate any evidence of apocrine secretions in the mammary gland. In the cat and monkey, an apocrine mode of secretion could not be demonstrated and it was assumed that these cells utilize a merocrine manner for liberating their secretory product (Munger, 1965a). In the human, the secretory cells of apocrine sweat glands are characterized by the presence of large numbers of mitochondria that have scant cristae and an electron-opaque matrix. Electron-opaque granules, described as keratin, are present in their apical cytoplasm (Munger, 1965b).
Many spherical mitochondria with extensive internal membrane are found in the brown adipose tissue of the interscapular region of the bat (Fawcett, 1966a). These mitochondria with their abundant cristae were thought to be related to the high energy required for synthesis of fat from carbohydrates and for the degradation of fat to yield the heat necessary to raise the body temperature during arousal of the bat from hibernation. Many mitochondria are also present in the oncocyes that are found in some salivary gland tumors (Tandler and Shipkey, 1964; Balogh and Roth, 1965), and in normal salivary gland (Tandler, 1966). Although the mitochondria in these cells are increased in number, they usually retain their normal appearance. In the apocrine cells of the mammary gland the mitochondria are numerous and show marked alterations in size, shape, and electron density. Their matrices become so opaque that the mitochondria are differentiated with difficulty from other electron-opaque bodies in the cytoplasm of apocrine cells. Most of the mitochondria are in the basal portion of the cell while the secretory granules predominate in the apical portion. In the sweat gland a similar distribution of cell organelles was observed and was explained as due to the supply of oxidative enzymes necessary for early synthesis of the secretion (Biempica and Montes, 1965). The finding of large numbers of secretory granules in the apical part of the apocrine cells in our study suggests that these are secretory cells. However, the lumens of the ducts lined
by apocrine epithelium are usually empty and it is therefore doubtful whether these cells are actually secretory cells. Furthermore, the finding of distorted mitochondria with few cristae suggests that these organelles are in a state of enzymatic deficiency. We have no proof for this hypothesis since no enzymatic analyses of these organelles were performed.

The formation of apocrine cells in the epithelium lining a duct cannot be explained. It is now established that mitochondria carry within them a genetic DNA (Nass et al., 1965). A mutation in the mitochondrial genome or in the chromosome may explain the presence of a few apocrine cells scattered among the epithelial lining cells but does not account for the presence of apocrine cells lining an entire duct. In the skin, the apocrine glands develop after the hair follicles have formed from the uppermost hump of the developing hair in the fifth month of fetal life (Montagna, 1959). Since the breast ducts are formed directly from the basal part of the epidermis, then apocrine epithelium is misplaced. Waddington (1966) suggested that differentiation of the cells depends on the presence of a particular set of genes which have been pulled during the period of competence. The determination of the functioning genes is strongly influenced by the environment of these cells. It is possible that during the cyclic changes of the breast the early proliferative ductular cells are in the competence or determined period. Therefore
if we assume that in fibrocystic disease a different environment exists for the developing cells than is present in the proliferating normal duct, this will explain some of the findings in this condition, including the formation of apocrine epithelium.

Fibroadenoma

Previous studies of fibroadenoma have been limited to examination with the light microscope. The present investigation clearly shows that the tissue responsible for the formation of this type of neoplasm is the stromal element, while the ductular proliferation is probably secondary to the connective tissue overgrowth. The fact that the stromal cells of fibroadenoma are completely different from those of the normal breast, whereas the ducts in the two conditions are similar, is strong support for this assertion. Our study further shows that the cells responsible for this neoplasm in no way resemble fibroblasts or other stromal cells present in the normal breast. These cells are very similar to the pericytes which surround the capillary blood vessels and small venules. Pericytes have been observed in almost all tissues of the body except the spleen (Murray and Stout, 1942). In tissue culture, these cells are characterized by their long cytoplasmic processes. The ultrastructural morphology of pericytes has been studied in many tissues (Hogan and Feeney, 1963; Fernando and Movat, 1964a, b; Movat and Fernando, 1963, 1964; Epling, 1966). Our own study concurs with the previous
description of pericytes with the additional finding that the nuclei of these cells have a tendency for segmentation. Although segmented nuclei are more prominent in the cells of fibroadenoma than in normal pericytes, this finding probably represents an exaggeration of the normal irregularity of the pericyte nuclei as a result of stimulation.

Movat and Fernando (1964) found that on stimulation pericytes become activated, increase in number, detach from the blood vessels, and assume an amoeboid form. Under these conditions the pericytes are no longer surrounded by a basement membrane. Basement membranes are rarely encountered in the neoplastic cells of fibroadenoma, but the intercellular spaces are filled with a substance somewhat similar to the fibrillar material constituting the basement membrane. The basement membrane is composed of a continuous layer of mucopolysaccharide (Fawcett, 1966b). In the intracanalicular form of fibroadenoma the intercellular material stains for acid mucopolysaccharide, while in the pericanalicular form the stromal tissue gives a positive stain for neutral mucopolysaccharide. The term acid mucopolysaccharide has been widely used to denote a group of chemical compounds which appear to be high molecular weight polymers composed of hexosamine, glucosamine or galactoseamine, and glucuronic acid acetate (Dorfman, 1955). Acid mucopolysaccharides are important in the problems concerned with the
exchange of electrolytes between circulation and extracellular fluid and between extracellular fluid and cells. They are present in the ground substance of connective tissue. Because of their negative charge, they affect the transport of ions (mainly the cation) and water (Dorfman, 1958). Since insulin plays an important role in the biosynthesis of these compounds, the metabolism of acid mucopolysaccharide is impaired in diabetic animals. As far as we know, no mention has been made in the literature concerning the effect of diabetes on patients with fibroadenoma. It will be interesting to determine whether any correlation exists. Such study was not made in our material.

A relationship between pinocytotic vesicles and basement membrane is apparent for whenever pinocytotic vesicles are present a basement membrane can be identified. The reason for this phenomenon is unknown, but it may be the result of filtration and concentration of the soluble material before it is pinocytosed.

Fine cytoplasmic fibrils are not uncommon in the neoplastic cells of fibroadenoma. In common with the fibrils of normal pericytes, these fibrils have no special orientation and thus probably have no contractile properties. Fine filaments are a common component of the cytoplasm of many cells but are much more abundant in some types of cells than in others. They are most obvious in stratified squamous epithelium, where they are associated with interlacing bundles that terminate on the
cell surface. Because of the apparent involvement of these cells in the process of keratinization, it has commonly been assumed, without adequate evidence, that these filaments are composed of the fibrous protein keratin. Similar filaments are also found in the endothelial cells, neuroglia, neuron, podocytes of the renal glomeruli and many others (Fawcett, 1966c). Chemical determination failed to find keratin in these filaments.

Long cytoplasmic processes are a characteristic of these neoplastic cells. They resemble the cytoplasmic processes of normal pericytes. The cytoplasmic processes may be concerned with the direction of movement of these cells. They are known to play an important role in the movement of amoebae and leukocytes. Endothelial cells are similar to pericytes and to the stromal cells of fibroadenoma, but endothelial cells do not exhibit long cytoplasmic processes. Stout and Murray (1942) suggested that this characteristic makes it possible to differentiate endothelial cells from pericytes in tissue culture. Herdson (1967) reported a similarity in the morphological appearance of pericytes and endothelial cells and found that the pericytes exhibited less pinocytotic activity. In our study, the similarity between pericytes and endothelial cells was so great that differentiation of the two was impossible. However, pericytes are always characterized by their long cytoplasmic processes, a feature which endothelial cells do not possess. However,
this point of differentiation could be relative since pericytes are usually studied as a single cell having no contact with another pericyte. On the other hand, endothelial cells are always found in close proximity to another endothelial cell. It is therefore quite possible that endothelial cells, when they lose their relationship to each other, will exhibit long cytoplasmic processes. A similar feature with respect to myoepithelial cells was found in our study of fibrocystic disease. Ordinarily myoepithelial cells surround the duct and do not exhibit long cytoplasmic processes, but when they lose their relationship and invade the stroma, long cytoplasmic processes are always present.

Pinocytotic vesicles were present in both pericytes and endothelial cells, and their number could not be used as a criterion for differentiating these two cell types. The presence or absence of pinocytotic vesicles was thought to be related to the functional state of these cells. Hemidesmosomes are found only in the plasma membrane of pericytes and are lacking in endothelial cells. They are more prominent in the plasma membrane of myoepithelial cells. Hemidesmosomes are occasionally found in the stromal cells of fibroadenoma. It is possible that when pericytes leave their locations near the capillaries they also lose the hemidesmosomes. It is probable that for the formation of desmosomes or hemidesmosomes another membrane is required. For the formation of the former, the plasma membrane of the neighboring cell will serve as the required
membrane and each cell will form its half desmosome to compose the complete desmosome. In plasma membrane abutting basement membrane, due to lack of the other cell, only a hemidesmosome is formed. One may also assume that the ability to form hemidesmosomes is limited to certain cell types.

The origin of pericytes is not clear. Most investigators believe that these cells are related to smooth muscle cells (Zimmerman, 1923; Enterline and Roberts, 1955; and Fisher, 1960). We believe that pericytes are multipotential cells that can differentiate into other mesenchymal cells. This theory seems supported by the wide variation in their ultrastructural appearance. It is possible that the pericyte is a cell which is intermediate in its differentiation between myoepithelial and endothelial cells.

The occasional finding of a cilium in some stromal cells of fibroadenoma cannot be explained. Cilia are known to originate from the centrioles and have been found in animals of all major groups except the Nematoda. They have functions connected with locomotion, feeding, digestion, respiration, excretion, reproduction, sensory reception, and the cleansing of surfaces (Sleigh, 1966).

The localization of ATPase and IDPase between the myoepithelial cells and in the plasma membrane between adjacent myoepithelial cells suggests that the plasma membrane of the myoepithelial cells plays an
important role in selective transport of material (Novikoff et al., 1962). The lack of these enzyme reactions in the cells of the capillaries and in the stromal cells of fibroadenoma would exclude the myoepithelial cell as the cell of origin in this neoplasm. Furthermore, the finding of degenerated myoepithelial cells as well as epithelial cells in the presence of healthy stromal tissue suggests that the stromal cells interfere with the nutrition of the ductular cells. They may either compete for the same nutritional substances or may deposit extracellular material which interferes with the accessibility of nutrient to the ductular cells. The latter is the more likely possibility since it is known that acid mucopolysaccharide, the substance found in the intracanalicular form, plays an important role in cation transport across the cell membrane (Dorfman, 1958). The finding of myoepithelial cell proliferation may be due to the same etiological factors that result in the proliferation of these cells in fibrocystic disease.

The connections of one duct to another by the cytoplasmic extensions of some myoepithelial cells strongly suggest that these cells play an important role in the formation of the supportive skeleton of the proliferating ducts. It would also suggest that the myoepithelial cells are the earlier cells to proliferate, followed by the epithelial cell proliferation.

The close similarity between the ultrastructural morphology of
the neoplastic cells of our one case of pericytoma and the stromal cells
of fibroadenoma strongly suggests that these two types of neoplasm are
related. In both neoplasms segmentation of the nuclei, long cytoplasmic
processes, and deposition of fluffy extracellular material were observed.
SUMMARY AND CONCLUSION

In this investigation breast tissues from 4 normal breasts, 17 cases of fibrocystic disease, 26 cases of fibroadenoma, and one case of pericytoma of the neck were examined by light and electron microscopy. Ultrastructural histochemistry for the enzymes ATPase and IDPase was performed on 8 cases of fibroadenoma.

The studies showed that in the normal mammary gland the ducts are lined by two layers of cells—an outer interlacing layer of myoepithelial cells and an inner layer of epithelial cells. The epithelial cells are cuboidal to columnar in shape with centrally located nuclei. Their apical plasma membranes are lined by short microvilli projecting toward the lumen. The cytoplasm contains well developed endoplasmic reticulum, moderate numbers of mitochondria, varying numbers of secretory granules, and small Golgi apparatus.

The myoepithelial cells are elongated and lie on the epithelial side of the basement membrane. The finding of dark and light myoepithelial cells suggests the presence of two, functionally different types of cells. The cytoplasm of the myoepithelial cells is divided into a filamentous and a granular component. The cell organelles are located in the granular part. The ductules are separated from each other by the stromal connective tissue. This tissue is rich in capillary blood vessels.
and fibroblasts and contains occasional plasma cells and lymphocytes. The capillary blood vessels are surrounded by pericytes, which have characteristically long cytoplasmic processes, well developed Golgi apparatus, a few large mitochondria, and large irregular nuclei that may exhibit partial segmentations.

In fibrocystic disease, the lesions involve mainly the ductular epithelial and myoepithelial cells. The lesions are divided histologically into four group.

In blunt duct adenosis, the lesions are thought to represent the atrophic changes that occur in normal mammary ducts. These ducts differ from the normal by the infrequent finding of proliferating myoepithelial cells. The focal proliferation of myoepithelial cells is thought to play an important role in ductular obstruction with later cyst formation. The presence of glycogen particles in some ducts and not in others is thought to represent either new formation or lack of degradation because of certain enzyme defects that may be associated with this lesion.

The lesion of epithelial cell hyperplasia was divided into two types according to the proliferative cell. When the ductular epithelium proliferates, the hyperplasia is frequently focal. The apical plasma membrane is thrown into many folds, giving it a knobby appearance. Bundles of filaments, swelling of the mitochondria with myelin figures of their inner membranes, and hypertrophy of other cell organelles are encountered.
In myoepithelial cell hyperplasia, referred to as sclerosing adenosis, the myoepithelial cells invade the stroma either as a group or as a single cell. Many single cells lose their basement membranes and appear to form collagen fibers. The filaments of the myoepithelial cells traverse the cytoplasm along the direction of infiltration. The possibility of malignancy of these cells was excluded because of the maintenance of their normal cytological appearance. In cysts, the myoepithelial cells form the major part of the lining epithelium while the epithelium is atrophic.

In cysts with apocrine changes, the apocrine cells originate from the epithelial cells. These cells are characterized by large numbers of mitochondria which are irregular in size and shape and are located mainly in the basal part of the cells. The cells also contain secretory granules near the apical part of the cytoplasm and a few bundles of filaments.

In fibroadenoma, certain stromal cells appear to be the cells responsible for this type of neoplasm. They are structurally similar to normal pericytes. They vary in shape, have large segmented nuclei, long cytoplasmic processes, areas of granular endoplasmic reticulum, and well developed Golgi apparatus. Occasional basement membrane-like material surrounds these cells. The ductular components of fibroadenomas are similar to the ductules of the normal breast.
The neoplastic cells of pericytoma are similar to the stromal cells of fibroadenoma. ATPase and IDPase activities are localized on the plasma membranes of adjacent myoepithelial cells and between myoepithelial and epithelial cells.

These studies suggest that the stromal cells of fibroadenoma are the neoplastic cells and that these stromal cells originate from the pericytes. The cytochemical studies suggest that membrane transport is also a function of myoepithelial cells. The latter studies also helped to exclude the myoepithelial cells as the cell of origin of this tumor.

Balogh, K., Jr., and Roth, S.I. Histochemical and electron microscopic studies of eosinophilic granular cells (oncocyes) in tumors of parotid gland. Lab. Invest. 1965, 14, 310.

Bargmann, W., Fleischhauer, K. und Knoop, A. Über die morphologie der milchsekretion. II. Zugleich fine kritik am schema der sekretions morphologie. Z. Zellforsch. 1961, 53, 545.


Biava, C. Identification and structural forms of human particulate glycogen. Lab. Invest. 1963, 12, 1179.


Bloodgood, J.C. Benign lesions of female breast for which operation is not indicated. J.A.M.A. 1922, 78, 859.


Ingleby, H. Relation of fibro-adenoma and chronic mastitis to sexual cycle changes in the breast. Arch. Path. 1932, 14, 21.


Perry, R.P. On the nucleolar and nuclear dependence of cytoplasmic RNA synthesis in Hela cells. 

Perry, R.P. The cellular sites of synthesis of ribosomal and 4s RNA. 

*Amer. J. Path.* 1962, 41, 549.


*Amer. J. Path.* 1964, 45, 929.


Silver, I.A. Myoepithelial cells in the mammary and parotid glands. *J. Physiol.* 1954, **125**, 8P.


Stewart, F.W. Tumors of the breast. Armed Forces Institute of Pathology, Washington D.C., 1950, Sec. IX, Fas. 34, 105.


Tice, L.W., and Engel, A.G. Histochemical studies of a cation-sensitive adenosine triphosphatase of the sarcoplasmic reticulum. *J. Cell Biol.* 1964, **23**, 97A.


Normal mammary gland: Ducts are lined by two layers of cells, an inner layer of cuboidal epithelial cells, and an outer layer of spindle-shaped myoepithelial cells (Arrow). Some ducts are connected to each other by a narrow neck of epithelial cells, giving the ducts an irregular outline (D). X 600

Normal mammary duct: An inner layer of epithelial cells (Ep) and an outer continuous layer of myoepithelial cells (My). Basement membrane (BM), is seen surrounding the basal part of the myoepithelial cells. The lumen (Lu) is filled with homogeneous dense osmiophilic material. X 5,000
Figure 3  Normal mammary duct with tall columnar epithelial cells and centrally located nucleus. The nucleus (N) shows indentation of its nuclear envelope. The nuclear chromatin is homogeneously distributed. X 8,500

Figure 4  Normal epithelial cell (Ep): The nucleus contains large nucleolus. The nucleolus (No), is composed of ribbon-shaped osmiophilic material that is coiled into a round complex. Small granules are present in the nucleolar complex that are similar to the ribosomal granules in the cytoplasm. Note the infolding of the plasma membrane of adjacent cells. X 31,000
Figure 5  Many desmosomes (De) are seen along the plasma membranes of adjacent epithelial cells. The mitochondria show small electron-dense granules. X 31,000

Figure 6  Normal mammary duct: The apical plasma membrane of the epithelial cells is thrown into many folds to form microvilli that project directly into the lumen. Many secretory granules (Arrow) are present in the apical cytoplasm. X 17,000
Figure 7  Normal epithelial cells showing small Golgi apparatus (G), well developed endoplasmic reticulum (ER), and a moderate number of round to oval mitochondria (M). X 31,000

Figure 8  Normal mammary duct: Various numbers of electron-dense granules are prominent in the cytoplasm of the epithelial cells (Arrow). X 7,000
Figure 9  Two normal mammary ducts are seen separated by the stromal tissues. The myoepithelial cells (My) are seen on the epithelial side of the basement membrane. They are spindle shaped with eccentrically-located nuclei.

X 5,000
Figure 10  Normal myoepithelial cells. The basal plasma membrane has a serrated appearance. Focal condensations (Hemi-desmosomes) are present along this membrane. X 23,800

Insert:  Continuations of the cytoplasmic filaments with the hemidesmosomes are demonstrated. X 49,200
Figure 11  Higher magnification of the myoepithelial cells showing its oval nucleus. The nuclear chromatin is homogeneous with focal densities throughout the nucleoplasm. The cytoplasm is divided into a filamentous part (F) and a granular part. The granular part contains well developed endoplasmic reticulum and small numbers of small mitochondria. X 17,000

Insert:  Round and oval mitochondria with few irregular cristae are present. X 26,000

Figure 12  Normal myoepithelial cells show bundles of fine filaments (F) traversing the cytoplasm. Focal condensation is seen along the length of these filaments. Many pinocytotic vesicles (Pv) are seen in the plasma membrane of adjacent myoepithelial cells and in the plasma membrane abutting the basement membrane. X 17,000
Figure 13  A continuous layer of dark myoepithelial cells (My) is seen surrounding the duct. Few desmosomes (De) are present between myoepithelial cells and epithelial cells. X 7,000

Figure 14  Normal mammary duct: Dark and light myoepithelial cells (My) are seen surrounding the duct in alternating fashion. The endoplasmic reticulum (ER) of the epithelial cells shows parallel orientation. X 8,500
Figure 15  Low magnification showing the stromal connective tissue that separates one ductule from another. X 5,000

Figure 16  Normal duct is seen in the upper right. The stromal tissue contains fibroblasts (Fb), plasma cells (P) and capillary blood vessels (Cp). X 4,500
Figure 17  Stromal tissue of normal mammary gland showing part of the cytoplasms of two fibroblasts (Fb) and a capillary blood vessel. X 11,200

Figure 18  Capillary blood vessels lined by many endothelial cells (En) that are separated from the stroma by a basement membrane. Part of the cytoplasmic process of pericytes are seen (P). Hemidesmosomes are present on the outer plasma membrane of the pericytes. X 8,500
Figure 19  Capillary blood vessels showing fine filaments (F) in the cytoplasm of endothelial cells. The cytoplasm of a pericyte (P) is seen investing part of the capillary. X 8,500

Figure 20  Capillary with RBC in the lumen. Part of the cytoplasmic process of a pericyte. Large mitochondria and few microtubules are present in the cytoplasm. The outer plasma membrane shows many hemidesmosomes (HD). X 20,500
Figure 21  Capillary blood vessels surrounded by a pericyte (P). The cytoplasm of the pericyte contains large numbers of fine filaments (F) that run in different directions and exhibit focal condensation. X 20,500

Figure 22  Capillary blood vessels surrounded by a pericyte. The nucleus of the pericyte is irregular in outline. X 8,500
Figure 23  Capillary blood vessels surrounded by a pericyte. The pericyte nucleus shows partial segmentation. These segments are attached to each other by a narrow stalk of chromatin. X 15,000

Figure 24  Blunt duct adenosis showing many ducts that are irregular in size and shape. The myoepithelial cells (Arrow) are more osmiophilic than the epithelial cells. Some ducts have lumens while others do not. X 6,000
Figure 25  Blunt duct adenosis showing focal proliferation of myoepithelial cells (My) which appear more osmiophilic than the epithelial cells. X 800

Figure 26  Blunt duct adenosis showing few distorted ducts with empty lumens. The stromal tissue separating these ducts is hyalinized. X 600
Figure 27  Blunt duct adenosis. The duct is lined by epithelial cells (Ep) and myoepithelial cells (My). The epithelial cells are irregular in outline. X 11,200

Figure 28  Blunt duct adenosis. The epithelial cell shows Golgi apparatus (G) of moderate size and a well developed rough-surfaced endoplasmic reticulum. X 20,500
Figure 29  Epithelial cells in blunt duct adenosis showing a moderate number of mitochondria. The mitochondria are oval to elongated with normal-appearing cristae. Many ribosomes and polysomes are present in the cytoplasm. X 20,500

Figure 30  Blunt duct adenosis. The nuclei are large, elongated and their long axes are parallel to the long axes of the cells. The apical plasma membrane is lined by microvilli. The lumen contains no secretory material. X 7,000
Figure 31  Blunt duct adenosis. The nuclear chromatin is homogeneous with no focal areas of condensation. Few mitochondria show focal condensation of their cristae. X 7,000

Figure 32  Blunt duct adenosis. Various numbers of electron-dense granules are present near the plasma membrane of adjacent cells (Arrow). The mitochondria are swollen and the matrices are empty. X 11,200
Figure 33 High magnification. The granules are membrane-limiting and are filled with homogeneous dense osmophilic material (Arrow). The cytoplasms of these cells are filled with fine filaments (F1). These filaments appear to be related to the desmosomes. X 20,500

Figure 34 Blunt duct adenosis. Many layers of epithelial cells are seen lining some ducts. X 4,500
Figure 35  Blunt duct adenosis. The myoepithelial cell (My) lies on the epithelial side of the basement membrane (Bm). The filaments of the myoepithelial cell have no specific orientation. Thick basement membrane (Bm) is seen abutting the basal plasma membrane. X 20,500

Figure 36  Blunt duct adenosis. Dark and light myoepithelial cells are seen surrounding the duct. The cytoplasm of the light myoepithelial cells contains lipid bodies. X 8,500
Figure 37  Higher magnification of the previous picture shows a worm-like mitochondria (M) present in the cytoplasm of the light myoepithelial cell. X 20,500

Figure 38  Blunt duct adenosis. Focal area of myoepithelial cell proliferation. The nuclei are irregular in outline. The nuclear chromatin is very dense. X 7,000
Figure 39  Blunt duct adenosis. Myoepithelial cells are seen surrounding some epithelial cells. The nuclei of the myoepithelial cells show partial segmentation. Patches of dense chromatin material are seen in the nuclei of myoepithelial cells. The epithelial cell nuclei (Ep) appear normal. X 4,500

Figure 40  Blunt duct adenosis. The chromatin segregation is obvious. The nuclear envelope disappears in certain areas (Arrow) and the light chromatin material is continuous with the cytoplasm. A large nucleolus (No) is obvious in the nucleus. Few irregular patches of fine filaments (F) can be identified in the cytoplasm. X 15,000

Insert: High magnification of the previous picture showing an area of disappearance of the nuclear envelope. X 36,000
Figure 41  Blunt duct adenosis. The nuclear chromatin is segregated into about equal halves. Mitochondria and ribosomes are seen in the middle of the chromatin. The nuclear envelope disappears in certain areas (square). Blebs of nuclear material are seen projecting from the nuclear area (Arrow). X 20,500

Insert:  Higher magnification of the area between the square showing disappearance of the nuclear envelope. X 49,200

Figure 42  Blunt duct adenosis. An area of myoepithelial cell proliferation. The nuclear chromatin (Arrow) appears as a thread-like structure which is irregularly dispersed in the cytoplasm surrounding few cytoplasmic organelles. A connection between the nuclear chromatin and the cytoplasm is seen (square). X 20,500

Insert:  Higher magnification of the nucleo-cytoplasmic connection. X 49,200
Figure 43  An area similar to the previous figure showing a desmosome (De) in the middle of the chromatin mass. X 20,500

Figure 44  Blunt duct adenosis: Large patches of glycogen appear in the basal parts of the epithelial cells (Arrow). It is more osmiophilic than the rest of the cells. The stroma contains a large number of fibroblasts. X 600
Blunt duct adenosis: Glycogen (Gl) is found mainly in the epithelial cells. It appears as large patches in the paranuclear portion and less commonly as small patches throughout the cytoplasm. The myoepithelial cells appear flat and more osmiophilic than the epithelial cells. X 4,500

Glycogen aggregate composed mainly of the monoparticulate form or the beta particles and few rosette-like alpha particles. X 15,000
Figure 47  Blunt duct adenosis: Patches of glycogen particles (Gi) are found in the myoepithelial cell cytoplasm. The mitochondria (M) are swollen. X 11,200

Figure 48  Proliferation of ductular epithelium. Irregular areas of epithelial cell hyperplasia are found. In other areas the duct is lined by tall columnar epithelial cells. The apical plasma membrane assumes a knobby appearance. X 600
Figure 47

Figure 48
Figure 49  Focal epithelial cell hyperplasia is seen. The myoepithelial cells are seen to send many cytoplasmic projections toward the stroma. The stroma contains many young fibroblasts. X 600

Figure 50  Epithelial cell hyperplasia showing two to three layers of epithelial cells (Ep). The myoepithelial cells are difficult to identify. X 4,500
Figure 51 Epithelial cell hyperplasia: The apical cytoplasm is thrown into many folds giving it a knobby appearance. X 4,500

Figure 52 Higher magnification showing that the apical folds are lined by microvilli. Note that the larger the fold the smaller the microvilli. X 8,500
Figure 51

Figure 52
Figure 53  Epithelial cells hyperplasia: Large number of keratin-like bundles of fine filaments are present in the cytoplasm. Various numbers of electron dense bodies are seen. Note also swollen mitochondria with condensation of the inner membrane. X 11,200

Figure 54  Epithelial cell hyperplasia: Well developed rough-surfaced endoplasmic reticulum is seen. Most of the mitochondria appear normal except for a few which show myelin figure of their inner membrane. Few bundles of fine filaments are present (K). X 20,500
Figure 55  Epithelial cell hyperplasia: The mitochondria (M) have numerous thin cristae. The cytoplasm contains well developed rough-surfaced endoplasmic reticulum. A Golgi apparatus is seen in the upper part of the picture. Moderate numbers of electron dense bodies are seen scattered in the cytoplasm. X 20,500
Figure 56  Epithelial cell hyperplasia forming papillary projections.

The apical plasma membranes are thrown into many folds or knobs (Kn). X 9,000
Figure 57  Epithelial cell hyperplasia: The nuclei of the epithelial cells have different sizes and shapes and the nuclear envelopes are frequently indented. The nuclear chromatin is less dense and many nucleoli are seen. X 7,000

Figure 58  Epithelial cell hyperplasia: Many lipid (Lp) and electron dense bodies (Eb) are present in the cytoplasm of these cells. X 8,500
Figure 59 Epithelial cell hyperplasia: The apical plasma membrane form many microvilli. Many ribosomes and polysomes are present in the cytoplasm (ER). Many mitochondria show focal swelling and their matrices are less dense. X 11,200

Figure 60 Epithelial cell hyperplasia: Well developed endoplasmic reticulum with collapsed cisternae (ER) is present. Many mitochondria are swollen and some appear to open into the cytoplasm. (Arrow). X 15,000
Figure 61  Epithelial cell hyperplasia: Many keratin-like bundles of fine filaments (K) are present in the cytoplasm. Myelin figures are found in many mitochondria (M). Well developed endoplasmic reticulum and few electron-dense granules are seen. X 20,500

Figure 62  Sclerosing adenosis: Irregular islands of cells infiltrating the stroma. No lumens can be identified in these cells. Large numbers of epithelial cells are seen forming a large duct with no lumen. X 600
Sclerosing adenosis: Many islands of cells infiltrating the stroma. Some ducts (Dt) are seen to have irregular outlines and their cells are seen to grow in different directions. X 600

Sclerosing adenosis: Islands of myoepithelial cells are recognized in the electron microscope infiltrating the stroma in an irregular fashion. X 4,500
Figure 65  Sclerosing adenosis: The nodule infiltrates the stroma in different directions. Note that the bundles of filaments follow the directions of infiltration. Large numbers of collagen fibers (Cf) are seen in the stroma. X 4,500

Figure 66  Sclerosing adenosis: The nodules are composed of myoepithelial cells. The myoepithelial cells are irregular in shape with large irregular nuclei. The filaments are concentrated mainly at the peripheral part of the cells. X 7,000
Figure 67  Sclerosing adenosis: Nodules of myoepithelial cell (My).
Note that the filaments (F) retain their normal appearance
with focal thickening along their length. Note also that
the direction of the filaments is toward the pointed end
of the nodule. X 4,500

Figure 68  Sclerosing adenosis: Many nodules are seen connected
with each other by the cytoplasmic projections of myo-
epithelial cells (Arrow). X 4,500
Figure 69  Sclerosing adenosis: Connection between one nodule and another through the cytoplasmic extension of myoepithelial cells. Note that the cytoplasmic filaments (F) traverse the connecting cytoplasm. Many points of bifurcation of these filaments can be demonstrated (Arrow). X 7,000

Figure 70  Sclerosing adenosis: The cytoplasm contains a moderate number of electron-dense granules. The granules are membrane-limited and are filled with homogeneous electron-dense material (Arrow). Microtubules (t) and keratin-like bundles of fine filaments (K) are also present in the cytoplasm. X 26,000
Figure 71  Sclerosing adenosis: The filaments are confined mainly to the peripheral part of the cytoplasm close to the plasma membrane. X 20,500

Figure 72  Sclerosing adenosis: Single myoepithelial cell is seen infiltrating the stroma. The nucleus is rod shaped. X 7,000
Figure 73  Sclerosing adenosis: Single myoepithelial cell is seen infiltrating the stroma. Many collagen fibers (Cf) are seen to be laid out by these cells. (Arrow) X 7,000

Figure 74  Nodule of myoepithelial cells. Many collagen fibers (Cf) appear to be produced by the myoepithelial cell cytoplasm. No basement membrane can be identified in these areas. X 15,000
Figure 75  Sclerosing adenosis: Part of myoepithelial cells with long cytoplasmic processes. Note that the direction of the filaments is the same as the direction of the cytoplasmic processes. X 7,000

Figure 76  Cyst: The epithelium lining the cyst is flat. The long axis of the epithelial cells is in the same direction as that of the cyst wall. X 600
Figure 77  Cyst: The wall of the cyst is lined by two types of cells, dark and light cells. X 7,000

Figure 78  Cyst: Dark cells surround the light cells. The light cells (the epithelial cells (EP) ) contain well developed endoplasmic reticulum. X 7,000
Figure 79  Cyst: The myoepithelial cells are more osmiophilic than the epithelial cells. Segmented nucleus is present in the apical myoepithelial cell. Few lipid bodies (Lp) are seen. The apical plasma membrane of the inner myoepithelial cell is lined by microvilli. X 7,000

Figure 80  Cyst: The nucleus (N) of the epithelial cell (Ep) contains a homogeneous network of chromatin. A thick basement membrane separates the stroma from the cyst wall. The stroma contains many collagen fibers. (Cf). X 15,000
Figure 81  Cyst: Two dark myoepithelial cells are separated by part of the epithelial cell cytoplasm. Note the connection between the two cells (Arrow). Note also the microvilli lining the apical plasma membrane and the bundles of filaments with focal condensations along their length (F). Also notice the keratin-like bundles of filaments (K) in the granular part of the cytoplasm. X 20,500

Figure 82  Cyst: Many layers of cells are seen lining the cyst. The dark cells are the myoepithelial cells and the light ones are the epithelial cells. X 7,000
Figure 83  Cyst: Many layers of cells are seen lining the cyst. The epithelial cells (Ep) are shrunken and show an obvious decrease in number. X 4,500

Figure 84  Cyst: The myoepithelial cell (My) contains few lipid bodies. Desmosomes and terminal bars form the main cellular attachments. X 7,000
Figure 85  Cyst: The Golgi apparatus (G) appears in a paranuclear portion as a small lamellar structure. X 20,500

Figure 86  Cyst: The wall is lined by an outer myoepithelial cell and an inner layer of epithelial-like cells. Few pino-cytotic vesicles are seen lining the apical plasma membrane of the epithelial cell (Arrow). X 11,200
Figure 87  Cyst: The wall is lined by epithelial (Ep) and myoepithelial cells (My). The stroma contains large myoepithelial cells with long cytoplasmic processes. X 7,000

Figure 88  Apocrine epithelium: The myoepithelial cells (Arrow) appear as flat, small, spindle-shaped cells and are found in the outer layers of the cyst. They are more osmiophilic than the apocrine cells. The apocrine cells are tall and columnar with round nuclei and prominent nucleoli. The nuclei are frequently found in the basal part of the cell. The apical plasma membrane has a knobby appearance. X 600
Figure 89  Apocrine cell: The cells are tall and columnar with basal nuclei (N). Intercellular duct (Dt) is present near the basal part of the cell. Many lipid bodies (Lp) are seen in the upper half of the cell. X 7,000

Figure 90  Apocrine cells: A large number of mitochondria is present, mainly in the basal part of the cell. The basal part of the apocrine cell (Ap) projects downward between myoepithelial cells (My) to rest directly on the basement membrane. X 7,000
Figure 91  Apocrine cell: A large number of mitochondria is seen. These mitochondria vary in size and shape. X 20,500

Figure 92  Apocrine cell: The mitochondria assume different sizes and shapes. Their cristae are thin, long and are unevenly distributed. The intercristae matrix is more osmiophilic than the rest of the cell organelles. Keratin-like bundles of fine filaments are present (K). X 15,000
Figure 93  Apocrine cell: Large Golgi apparatus is present in the cytoplasm of the apocrine cells. X 20,500

Figure 94  Apocrine cells show well developed rough-surfaced endoplasmic reticulum and few narrow cisternae. (Arrow). These cisternae, with many ribosome granules on their membranous side, appear to be related to the mitochondria. X 20,500
Figure 95  Apocrine cells: The apical plasma membrane is thrown into irregular folds giving it a knobby appearance. Short microvilli line the apical plasma membrane. X 4,500

Figure 96  Apocrine cells: Many electron-dense granules are seen in the apical cytoplasm. Terminal bars form the cellular attachments near the lumen. X 15,000
Figure 97  Intracanalicular form of fibroadenoma featuring outgrowth of the stromal tissue toward the ducts causing the latter to be distorted. The duct epithelium is degenerated in many areas (Arrow, d) and in one area only the basement membrane remains intact (BM, arrow). The stromal cells are elongated and are separated by fluffy material simulating the basement membrane. X 600

Figure 98  Large stromal cell of fibroadenoma featuring segmentation of its nucleus (N). Each segment is attached to the main nucleus by a narrow stalk of chromatin. X 8,500
Figure 99  Stromal cell of intracanalicular form: Notice the large nucleus. The nuclear chromatin is homogeneously distributed with minimum peripheral condensations. X 11,200

Figure 100  Two stromal cells of the intracanalicular form of fibroadenoma. The intercellular spaces are filled with light electron dense material. X 11,200
Figure 101  Stromal cell of fibroadenoma showing few electron-dense bodies in its cytoplasm. X 15,000

Figure 102  Stromal cell of fibroadenoma with large Golgi apparatus (G), a centriole, few lipid bodies (Lp) and few glycogen particles (Gl). The nucleus contains few perichromatin granules (Arrow). X 20,500
Figure 103 Stromal cell of fibroadenoma. A short cilium with its characteristic basal body is present (Arrow). X 11,200

Figure 104 Stromal cell of fibroadenoma with long cytoplasmic processes (Arrow). A large Golgi apparatus is also present (G). X 8,500
Figure 105  Stromal cell of fibroadenoma: The cytoplasm contains well developed rough-surfaced endoplasmic reticulum (ER) with narrow cisternae. The cisternae are filled with electron-dense material similar to the one found outside the cell. Bundles of fine filaments (F) and few microtubules (t) are seen. X 15,000

Figure 106  Stromal cell of fibroadenoma: The cell is surrounded by a basement membrane (BM). Few pinocytotic vessels (Pv) are present along its plasma membrane. Notice also the focal condensation of the plasma membrane. X 20,500
Figure 107 Stromal cell of fibroadenoma: Few large mitochondria (M) are present. The cristae are thin, few in number and are irregularly distributed. X 20,500

Figure 108 Two fibroblasts and a large number of collagen fibers: Note the rod-shaped nuclei with their smooth nuclear envelopes. X 15,000
Figure 109  Pericanalicular form of fibroadenoma: Large numbers of mammary ducts are present. These are irregular in shape. The stroma contain large numbers of capillary blood vessels. X 600

Figure 110  Duct lined by an inner layer of epithelial cells (Ep) and an outer layer of myoepithelial cells. X 4,500
Figure 111  Many layers of cells are seen lining the duct. Short microvilli line the apical plasma membrane. The lumen is empty. X 4,500

Figure 112  Tangential section of the duct showing that the myoepithelial cells (My) incompletely surround the epithelial cell (Ep). X 4,500
Figure 113  Duct in fibroadenoma: The apical plasma membrane is lined by numerous microvilli. A moderate number of osmiophilic granules is scattered mainly in the apical cytoplasm of the epithelial cells. X 5,600

Figure 114  A well developed Golgi apparatus (G) is present in the apical cytoplasm in a juxtanuclear position. X 5,600
Figure 115 Epithelial cells in pericanalicular form. A large number of secretory granules is present in the apical cytoplasm. Few swollen mitochondria (M) with myelin figure of their inner membrane are present. Fine filaments are seen in the cytoplasm (F). X 11,200

Figure 116 Epithelial cells in pericanalicular form. The lumen is empty. A large number of secretory granules is present near the apical plasma membrane. A moderate number of mitochondria are present. They are oval or rod-shaped and their cristae are perpendicular to their long axes. X 8,500
Figure 117  Epithelial cells in the pericanalicular form. Interdigitation of the plasma membrane is one form of cell attachment found in these cells. X 26,000

Figure 118  Many desmosomes (De) are seen to form another type of cell attachment found in these cells. X 15,000
Figure 119  Myoepithelial cells with segmented nuclei are seen. The outer plasma membrane of the myoepithelial cells has a serrated appearance. X 7,000

Figure 120  Two ducts are seen connected by the cytoplasmic process of myoepithelial cell (Arrow). X 7,000
Figure 121  Duct: Many layers of dark myoepithelial cells are seen around the duct. These cells are surrounded totally by a basement membrane. Large number of pinocytotic vesicles are present along their plasma membrane. The lighter cells are also surrounded by a basement membrane and contain cytoplasmic filaments with focal condensation (Arrow). X 7,000

Figure 122  Duct: Few desmosomes (De) form the main cellular attachment between the epithelial and myoepithelial cells. X 11,200
Figure 123  Duct: The myoepithelial cell shows patches of glycogen particles (G1). These are composed of aggregate of the beta particles. X 20,500

Figure 124  This duct shows focal areas of cytoplasmic dissolution of the epithelial cell. X 8,500
Figure 125 Duct: The epithelial cell disappeared. The myoepithelial cell is degenerated. Note the large dense body and the partial loss of the cytoplasm. The filaments (F) are still present. Note the intact basal plasma membrane. X 15,000

Figure 126 Duct: Most of the myoepithelial cells (My) are degenerated. Long cytoplasmic processes are seen projecting into the stroma. The basement membrane is still intact. Note also that the extra ductular material consists of fluffy, extremely fine filaments resembling basement membrane. X 15,000
Figure 127 Duct: Both the epithelial as well as the myoepithelial cells are exfoliated into the lumen. The basement membrane remains intact. The stromal cells (St) maintain their normal appearance. X 4,500

Figure 128 Duct: ATPase activity is localized in the plasma membrane of adjacent myoepithelial cells (My) and between the epithelial cells (EP). The plasma membrane between two epithelial cells do not show this enzymatic activity. X 8,500
Figure 129  Duct: ATPase activity is lacking from all the cytoplasmic organelles of myoepithelial cells. X 11,200

Figure 130  IDPase activity is localized between adjacent myoepithelial and epithelial cells. The plasma membrane between adjacent epithelial cells does not show this enzyme activity. X 11,200
Figure 131 Duct: IDPase assumes similar activity as in the above picture except that in this case the plasma membrane between the two epithelial cells is also positive. X 11,200

Figure 132 IDPase activity is limited to the plasma membrane of the ductular cell. Note that the stromal cell (st), the pericytes (P), and the endothelial cell (En) all do not show this enzyme activity. X 7,000
Figure 133 Tumor cells of pericytoma: Notice the segmentation of their nuclei and the presence of intercellular fluffy material. X 11,200

Figure 134 Pericytoma: Longitudinal section of capillary blood vessel is seen (CP). Note the cytoplasmic projection of an endothelial cell (En). Outside the blood vessel is a tumor cell with bundles of fine filaments (F) in its cytoplasm. X 11,200