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January 13, 1993

Stephen Dapson, Ph.D.
Toxicology Branch II - Herbicide, Fungicide, and Antimicrobial Support
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Dear Steve:

Enclosed please find the evaluation of the Cyromazine rat mammary gland data which you requested. As you will see, I backed away a bit from merely considering the three tumor types as a whole. I did this after reviewing some recent publications and after talking to two pathologists (Drs. Hailey and Eustis) at NTP responsible for reviewing these types of data.

I have enclosed a copy of a very good paper on mammary gland proliferative lesions in rats. It is the final proposed document for the Society of Toxicological Pathologists. Hope you find it useful.

If you have any questions, please don't hesitate to call.

Sincerely,

Lucas H. Brennecke, D.V.M.

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January 13, 1993

SUBJECT: Mammary Tumors in Cyromazine Rats

FROM: Lucas H. Brennecke, D.V.M.
Expert Pathology Consultant
Health Effects Division

TO: Stephen Dapson, Ph.D.
Toxicology Branch II - Herbicide, Fungicide, and Antimicrobial Support
Health Effects Division (H7509C)

Registrant: CIBA-GEIGY Corporation

Action Requested: Evaluate Mammary Gland Tumor Data in CGA-72662 Technical Two-Year Chronic Oral Toxicity and Oncogenicity Study

Conclusion:

(1) The adenomas, adenocarcinomas, and fibroadenomas should be considered separately as well as together when evaluating carcinogenic response.

(2) Statistical evaluations were not provided to this reviewer, but the incidence of each type of mammary neoplasm was well within the range of historical controls for that tumor type.

Discussion:

While the relative make-up of each of the three tumor types may vary considerably, the fact that each of the neoplasms contains the same cell types (glandular and ductal epithelium and supporting stroma) indicates that the tumors may have a common origin. In addition, it is not uncommon for purely glandular/epithelial tumors (adenomas and adenocarcinomas) to arise within a fibroadenoma. If an adenocarcinoma does arise within a fibroadenoma, then the entire tumor is classified as an adenocarcinoma. Occasionally, the malignant component will completely efface the benign component. On the other hand, a fibroadenoma within which is a focus or nodule having a purely (or primarily) epithelial component would probably be classified as a fibroadenoma.

The National Toxicology Program evaluates mammary tumors in rats in three ways: (1) Separately (adenoma, adenocarcinoma, and fibroadenoma); (2) Partially mixed (adenoma with adenocarcinoma, and fibroadenoma); and (3) Together as a group (all three).

In the NTP testing program (using the F344 rat), there have been 12 chemicals (13 counting 2,4- and 2,6-Toluene diisocyanate as two separate chemicals) which have been shown to cause mammary gland neoplasms in female rats in carcinogenicity studies. Of these, eight induced only fibroadenomas (Dichloromethane, 2,4-Dinitrotoluene, Cytembena, Nithiazide, Nitrofurazone, *o*-Toluidine-HCl, and 2,4- and 2,6-Toluene diisocyanate), two induced only adenomas (3,3'-Dimethoxybenzidine-2HCl and 5-Nitroacenaphthene), and two induced both (2,4-Diaminotoluene and Glycidol). All but two of the chemicals were positive in the *Salmonella typhimurium* assay for mutagenesis. It must be emphasized, however, that the Fischer 344 rat has a much lower incidence of spontaneous mammary gland neoplasia than the Sprague-Dawley rat.

Finally, the body weight data should be checked closely. There is good historical evidence which shows that a reduction in body weight decreases the incidence of some tumors such as benign mammary gland tumors and anterior pituitary tumors in the female rat. (Rao, G,N, et. al., "Influence of body weight on the incidence of spontaneous tumors in rats and mice of long-term studies", Am. J. Clin. Nutr., 1987; 45: 252-60)

Final Proposal
May 31, 1992

PROLIFERATIVE LESIONS OF THE MAMMARY GLAND IN RATS

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INTRODUCTION

The rat mammary gland has been utilized extensively as a model for mammary carcinogenesis. The several strains of albino rat commonly used in chronic toxicology studies exhibit varying susceptibility to chemical or radiation induced neoplasia; the Fischer (F344) strain being less susceptible than the Sprague Dawley (SD) or Wistar derived strains (van Zwieten, 1984). In the Fischer rat the mammary gland is one of the more common sites at which carcinogenic effects are seen after exposure to chemicals. The National Toxicology Program has exposed Fischer rats to over 250 different chemicals; mammary gland tumors were induced in females by 13 of these chemicals (Boorman, 1990). In Sprague Dawley rats, the incidence of spontaneous tumors often approaches 50% in control animals in lifetime studies; these rats are also extremely sensitive to radiation-induced mammary tumors (van Zwieten, 1984)

Several factors greatly influence the susceptibility, magnitude and type of neoplastic response, and growth rate of mammary neoplasms in the rat. In addition to genetic factors, these include degree of differentiation of the mammary gland at the time of chemical exposure, physiological and hormonal status, and diet (Boorman, 1990). The rat mammary gland becomes less susceptible to chemical carcinogenesis with increasing age; pregnancy and lactation also reduce susceptibility (Russo, 1987). With decreased sensitivity there is not only a reduction in the total number of induced neoplasms, but also an increase in the number of benign tumors (fibroadenomas and adenomas) compared to malignant lesions (adenocarcinomas). Studies with chemical carcinogens such as 7,12-dimethylbenz[a]anthracene (DMBA) (Russo, 1987) or

Studies with chemical carcinogens such as 7,12-dimethylbenz[*a*]anthracene (DMBA) (Russo, 1987) or irradiation (van Zwieten, 1984) suggest that a common pathogenic pathway for mammary carcinogenesis exists for different etiologic agents.

The developing rat mammary gland consists of a branching parenchyma in which the terminal ductal structures end in a terminal end bud (TEB) in the young virgin rat. Over time, these TEBs progressively differentiate into alveolar buds and alveolar lobules. The number of proliferating cells is greatest (and the cell cycle shortest) in the least differentiated structure, the TEB, while the alveolar buds have the fewest proliferating cells and the longest cell cycle. The number of TEBs in the mammary gland is not equal throughout the animal; thoracic glands contain more TEBs than do abdominal glands. The highest number of tumors are observed when DMBA is administered between 40-46 days of age - the period during which TEBs are most actively differentiating into alveolar buds. After 55 days, the number of TEBs drops significantly, as does the incidence of induced tumors. Thus it is the presence of the terminal end bud that makes the mammary gland a target for DMBA chemical carcinogenesis (Russo, 1989), while benign lesions such as adenomas, cysts, and fibroadenomas appear to arise from the more differentiated alveolar buds (Russo, 1987).

Histologically, the mammary glands are classified as compound tubuloalveolar glands. They consist of an arborescent system of ducts, with the secretory portions located at the ends of the branches. The terminal secretory portions of the gland form irregular branching tubules with many evaginations from their walls and from their blind ends. This terminal secretory portion is referred to as a **ductule** or **alveolus**, the latter term being used when the terminal epithelial unit is dilated and filled with secretion. The ductules (or alveoli) form a compact cluster around the small intralobular duct; this entire structure is a **lobule**. Intralobular ducts run between individual lobules. The interlobular ducts from many lobules form larger ducts which unite to form the main lactiferous duct. In the rat, a single main lactiferous duct, or galactophore, passes through the nipple by way of the nipple sinus to open onto the surface in the nipple canal.

MORPHOLOGY OF PROLIFERATIVE LESIONS OF MAMMARY GLAND

NONNEOPLASTIC PROLIFERATIVE LESIONS

LOBULAR HYPERPLASIA

This lesion consists of enlarged lobules of relatively normal appearing alveoli; both the number and size of the alveoli are increased. The alveoli may be filled with a proteinaceous secretion which may contain lipid droplets. Alveolar cysts are often present within the hyperplastic lobules. The alveolar epithelial cells are one layer thick, well-differentiated and cuboidal. The individual alveoli within a hyperplastic lobule are separated by a thin connective tissue stroma. This lack of a prominent collagenous stroma aids in differentiating lobular hyperplasia from fibroadenomas, which also form discrete nodules. Occassionally, larger ducts may be surrounded by a thicker collagenous band. Because of the wide variation in size of normal lobules in young rats, it may be difficult to diagnose minimal or mild degrees of lobular hyperplasia.

FOCAL HYPERPLASIA WITH ATYPIA

This change consists of irregular proliferation of epithelium within ducts or alveoli and is distinguished primarily by cellular atypia. Epithelial hyperplasia may present as papillary infolding, arches, solid nests or plaques which extend into the lumen from the epithelial layer. Small alveoli may become solidly filled with cells while larger dilated alveoli may exhibit stratification of the epithelium with one or more layers. Features of cellular atypia may include enlarged cells with vesicular or hyperchromatic nuclei and cytoplasm which be intensely eosinophilic or basophilic. Eosinophilic cells resemble secretory cells and contain clear lipid droplets, while basophilic cells resemble duct epithelium and usually are devoid of vacuoles.

CYSTS

Cystic changes are the most common non-neoplastic change in the mammary gland of the rat. These thin-walled epithelial-lined spaces which are often round, may arise from either ductal or lobular

elements. Ductal cysts may be from 10 to 100 times normal ductal diameter and are lined by a single layer of flat, cuboidal epithelial cells. Myoepithelial cells are present and are compressed against the basement membrane. The distended lumen is filled with a granular, eosinophilic proteinaceous material. Cholesterol crystals and laminated partially-mineralized concretions may be present. Alveolar cysts are lined by a low cuboidal epithelium with round or oval nuclei which are compressed against the basement membrane. Some of the epithelial cells may contain large vacuoles or exhibit decapitation of the apical cytoplasm. Some alveolar cysts have an irregular contour due to multiple papillary ingrowths of hyperplastic epithelium.

BENIGN NEOPLASMS

FIBROADENOMA

Fibroadenomas are the most common benign neoplasms occurring in the rat mammary gland. They are composed of both connective tissue and mammary epithelial cells. The proportion of these two cell types varies considerably, from tumors which are mainly epithelial to those which are composed almost entirely of connective tissue. This variability has led to a number of subclassifications of fibroadenoma. Since many or all of the subclassifications may be encountered in a single tumor, there seems to be little value in subclassifying these lesions.

One common type of fibroadenoma has a lobular pattern, and consists of ductules lined by a single layer of epithelium evenly distributed throughout the tumor and separated from one another by numerous concentric layers of mature collagenous connective tissue. The single layer of epithelium has small nuclei and a single nucleolus; lipid vacuoles may be present in the cytoplasm. The alveolar lumens may be dilated and contain secretory material.

At the other end of the spectrum is a fibroadenoma which consists of multiple concentric layers of

dense connective tissue with a small number of widely dispersed ductules. The ductular epithelium is often attenuated or atrophic. Numerous mast cells may be present in the dense connective tissue. Some fibroadenomas may contain large cysts. Rarely, mature adipose cells may be a prominent stromal component of the fibroadenoma.

Some fibroadenomas contain focal areas of epithelium exhibiting unusual growth patterns, cellular pleomorphism and atypia. The epithelial changes may include small papillary projections, bridging septae, papillary infoldings or solid nests of epithelial cells. The epithelial cells are basophilic and have a high nuclear/cytoplasmic ratio. Increased numbers of mitoses are often present as well.

FIBROMA

Fibromas are tumors composed entirely of collagenous connective tissue without any epithelial component and which arise in the subcutaneous regions normally occupied by the mammary glands. This diagnosis should be made with great care because of the extensive variation of the epithelial component in fibroadenomas as mentioned above. The criteria for fibroma in the mammary gland are no different than for those in other parts of the body.

ADENOMA

Adenomas are discrete, non-encapsulated circumscribed masses composed almost entirely of glandular epithelial structures with a scant connective tissue stroma. The alveolar lumens may range from empty to wide distention by proteinaceous secretion. The epithelium is usually uniform, cuboidal to columnar, and is often vacuolated, especially in those tumors with distended alveoli. Nuclei are small; a single nucleolus may be present. The lumenal surface is generally round and may be either smooth or serrated. Focal areas with an altered growth pattern with pleomorphism and/or cellular atypia may be present as well as a slight increase in mitotic figures. The more commonly seen patterns include tubular, secretory, papillary and cystic papillary.

Adenomas with a tubular pattern consist of small tightly packed, regularly arranged round alveoli or ductules. The alveolar lumens are generally empty or contain minimal secretion. The characteristic change of secretory pattern adenomas is the wide distention of the ductules or alveoli by proteinaceous secretory material. Adenomas with a papillary pattern are characterized by papillary projections of epithelium which protrude into dilated ductal lumens. The papillae consist of a fibrous connective tissue core lined by a single layer of cuboidal or low columnar epithelium which may be vacuolated or appear pseudostratified. The cystic papillary pattern consists of numerous simple or multiloculated cystic spaces with many papillary projections protruding into the luminal space which is often filled with abundant secretion.

MALIGNANT NEOPLASMS

Although distant metastases have long been considered the *sine qua non* of malignancy, rat mammary tumors seldom metastasize. Similarly, the incidence of local invasion by mammary tumors is quite low. Transplantability has also been suggested as evidence of malignancy; however mammary fibroadenomas have been shown to be transplantable under appropriate experimental conditions (Russo, 1989).

In the case of mammary tumors of the rat, other widely accepted histologic and cytologic features are therefore generally used as criteria of malignancy. These include altered and variable growth patterns, cellular atypia characterized by increased nuclear/cytoplasmic ratio, altered chromatin content and prominent nucleoli, increased numbers of mitoses and the presence of abnormal mitotic figures, along with cellular and nuclear pleomorphism. Mammary carcinomas induced by chemical carcinogens often have a prominent stromal mononucelar cell infiltrate.

ADENOCARCINOMA

This neoplasm may exhibit a broad range of histologic patterns. The more commonly seen patterns include papillary, tubular, and cribriform-comedo. The neoplastic epithelial cells are generally from one

to four or more cell layers thick, uniform with basophilic to eosinophilic cytoplasm and round to oval nuclei which are located either centrally or near the base of the cell. The chromatin tends to be clumped and a single small nucleolus is often present. Mitotic figures sometimes exceed 10-15/hpf. The degree of atypia varies from focal to extensive. The papillary pattern consists of multiple branching papillae covered by one or more layers of cuboidal to columnar epithelial cells oriented perpendicular to the fibrovascular core. The tubular pattern is characterized by a monotonous expanse of closely packed tubular structures which vary from round to elongated. The tubules are lined by from one to four or more layers of epithelial cells. In general the tubular lumens are small and empty. The cribriform (or sieve-like) pattern is due to numerous secondary lumina which are small round spaces, filled with proteinaceous secretion, dispersed throughout the solid tumor mass. The comedo pattern is characterized by distended ductules filled with sheets of neoplastic cells which have become centrally necrotic. The central cavity contains cellular debris and occasional calcifying concretions.

Squamous metaplasia is occasionally present in carcinomas with the cribriform or comedo pattern; however, mammary carcinomas with a predominantly squamous pattern are not reported in the rat. Cartilaginous or sebaceous metaplasia have also been reported to occur in mammary carcinomas of the rat.

CARCINOSARCOMA

This uncommon tumor consists of both malignant epithelium and stroma in varying proportions. The epithelial portion consists of irregular tubular structures which are surrounded by poorly defined stromal cells with numerous mitoses and anaplasia. In some areas there appears to be a transition between the epithelial and stromal cells, leading some authors (Boorman, 1990) to suggest that the stromal cells are actually anaplastic epithelial cells rather than stromal cells and that the tumor would be better called an anaplastic carcinoma.

CRITERIA FOR PROLIFERATIVE LESIONS OF THE MAMMARY GLAND

NON-NEOPLASTIC PROLIFERATIVE LESIONS

LOBULAR HYPERPLASIA

1. Lobule enlarged by increased number of apparently normal alveoli
2. Alveoli separated by a delicate connective tissue stroma
3. Single layer of well-differentiated alveolar epithelium without atypia
4. Epithelium may contain lipid vacuoles; alveoli may be filled with proteinaceous secretion
5. Alveolar cysts often present within hyperplastic lobule
6. Larger ducts may be surrounded by dense collagen collars

FOCAL HYPERPLASIA WITH ATYPIA

1. Focal irregular proliferation of epithelium within ducts or alveoli
2. Proliferation forms papillae, arches, nests extending into lumen
3. Cellular atypia/pleomorphism present

CYSTS

1. From 10-100 times normal lumenal diameter
2. Lumen filled with eosinophilic granular material composed of lipids and proteinaceous material
3. May be lined by flat, cuboidal epithelium with myoepithelial cells compressed against the basement membrane (ductal cyst)
4. May be grapelike or become confluent, forming one large cyst, lined by low cuboidal or flattened epithelium (alveolar cyst)

BENIGN NEOPLASMS

FIBROADENOMA

1. Composed of glandular epithelium and fibrous connective tissue
2. Epithelium is generally single layered and uniform
3. Connective tissue distributed within and between lobules ranges from well-differentiated to dense hyalinized collagen with few interspersed fibrocytes.
4. Smaller tumors often have ductules lined by single layer of epithelium which may contain lipid vacuoles
5. Focal areas of atypia and/or cellular pleomorphism may be present
6. Mast cells may be frequent

FIBROMA

1. Consists entirely of collagenous connective tissue
2. A subcutaneous tumor in an area normally occupied by mammary tissue

ADENOMA

1. Discrete nonencapsulated mass consists of proliferating alveolar structures in clusters separated by scanty connective tissue septa
2. Alveoli have a single layer of low cuboidal to columnar epithelium with small nuclei and a single nucleolus; epithelium often vacuolated
3. Alveolar lumens may be empty or filled with minimal secretion (tubular pattern) or may be widely distended by proteinaceous secretion (secretory pattern)
4. Luminal surface generally round, may be smooth or serrated
5. Focal areas of atypia and/or pleomorphism may be present
6. Papillary projections of epithelium may occur, either protruding into dilated ductal lumens (papillary pattern) or into cystic spaces which may be simple or multiloculated (cystic papillary pattern)

MALIGNANT NEOPLASMS

ADENOCARCINOMA

1. May be noninvasive or invasive
2. Seldom exhibit distant metastases
3. Histologic criteria important for establishing malignancy
4. Neoplastic epithelial cells from 1-4 or more layers thick
5. Uniform epithelial cells basophilic to eosinophilic with round to oval centrally located nuclei Chromatin clumped, single small nucleolus. Numerous mitotic figures
6. Multiple branching papillae covered by cuboidal to columnar epithelium (papillary pattern)
7. Closely packed, generally empty, tubular structures which may be round or elongated (tubular pattern)
8. Neoplastic epithelial proliferation in a solid sheet with the formation of secondary lumina (cribriform pattern)
9. Distended ductules lined by a multilayered epithelium surrounding a central core of necrotic tumor cells (comedo pattern)

CARCINOSARCOMA

1. Malignant epithelium and malignant stroma both present in varying proportions
2. Irregular tubular epithelial component surrounded by sheets of poorly defined or slightly fusiform stromal cells
3. Numerous mitoses and anaplasia present in sarcomatous area
4. May see areas of transition from epithelial to mesenchymal component

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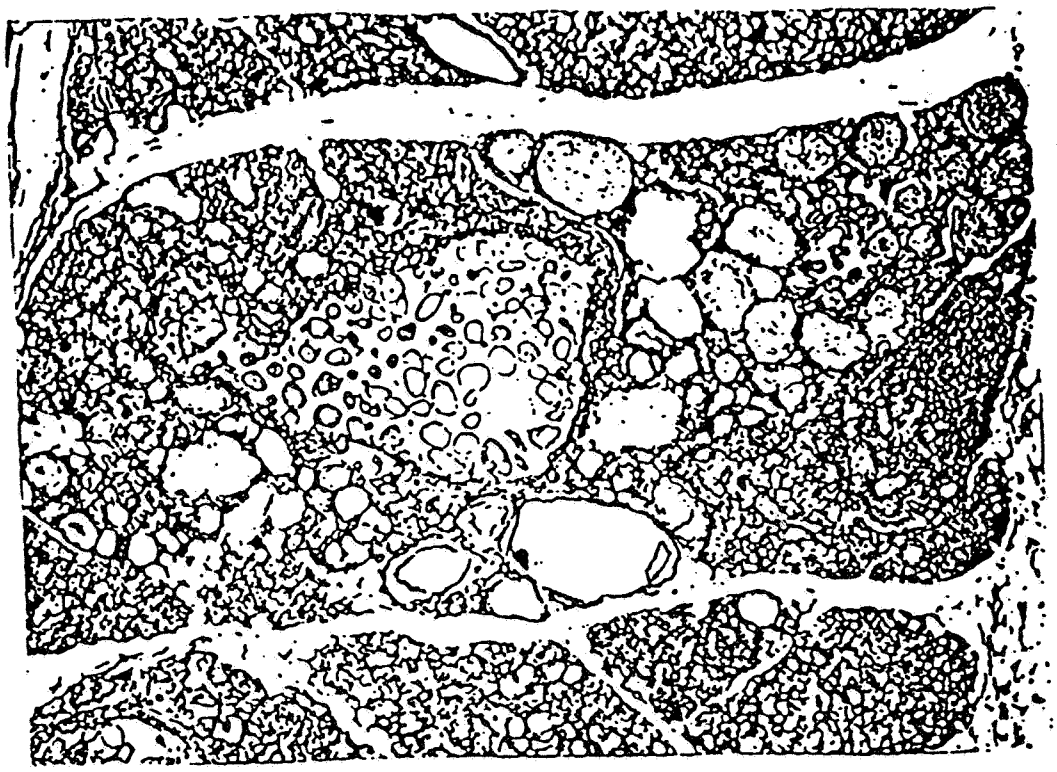
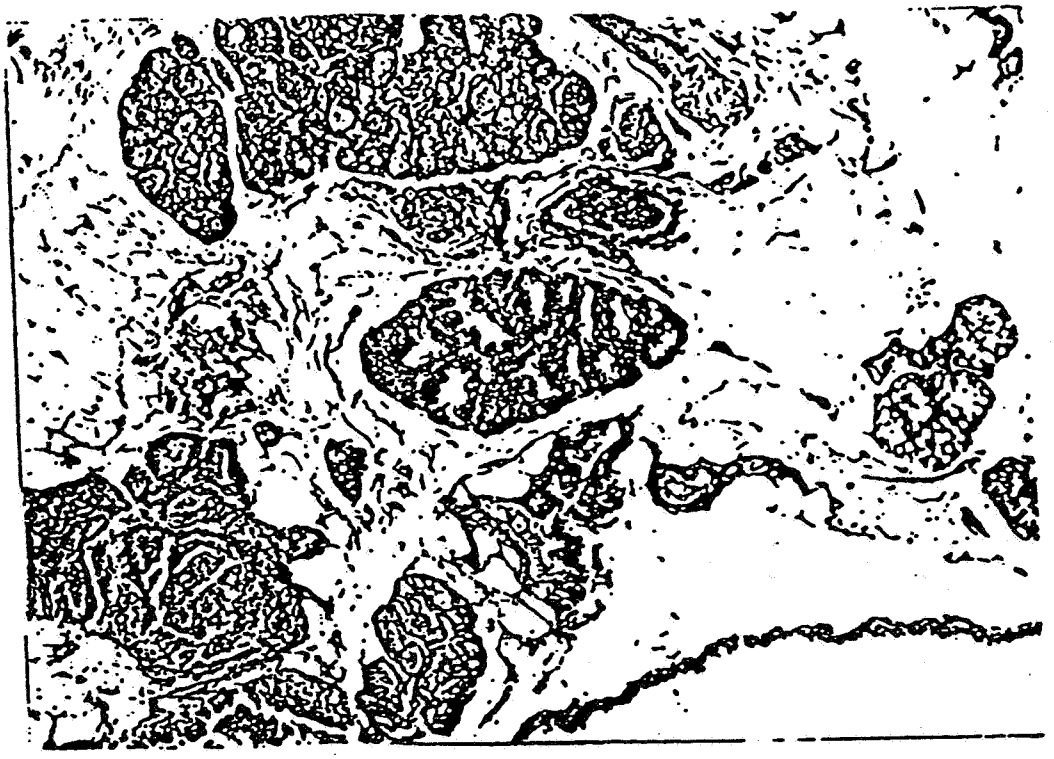
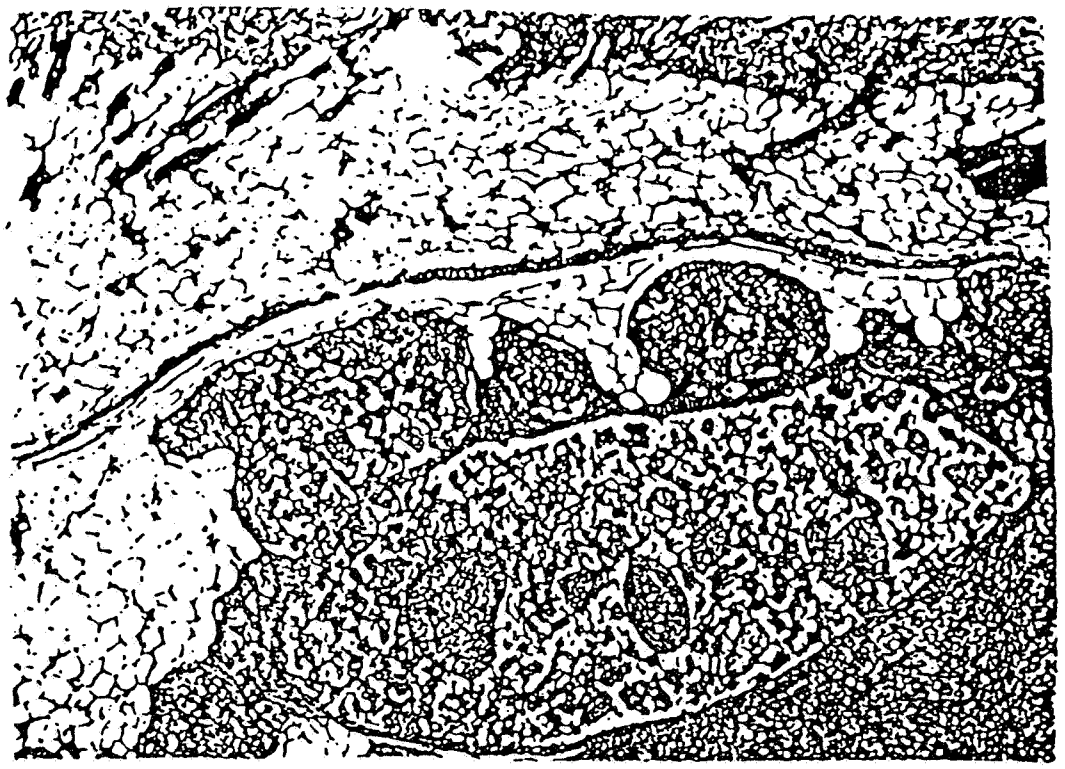


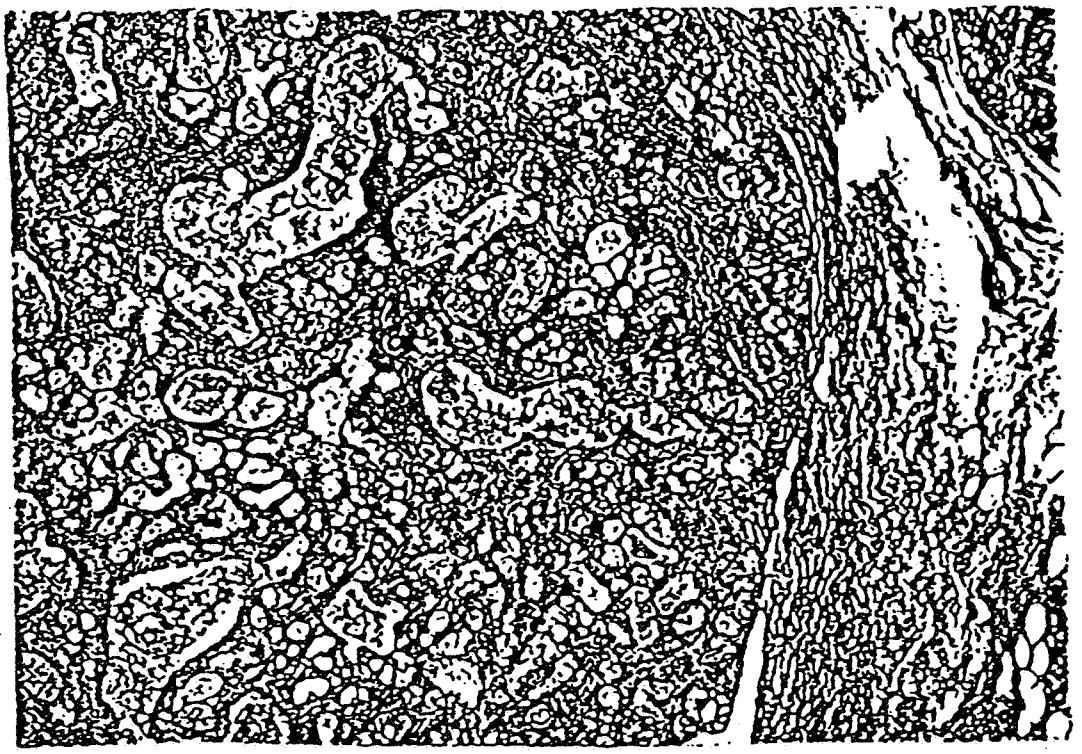
Lobular Hyperplasia. Increased numbers of alveoli, many with vacuolated epithelium. Alveolar cyst present within lobule. 4x



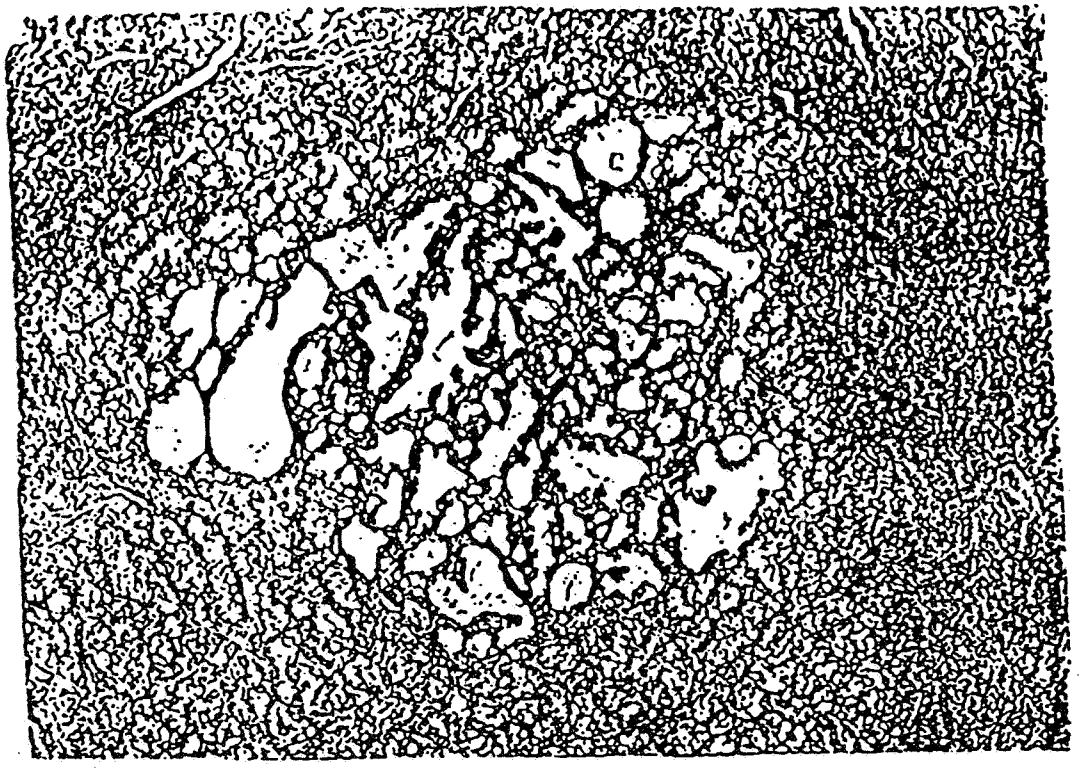
Focal hyperplasia with atypia. Basophilic epithelial cells with papillary projections into alveolar lumen. 10x



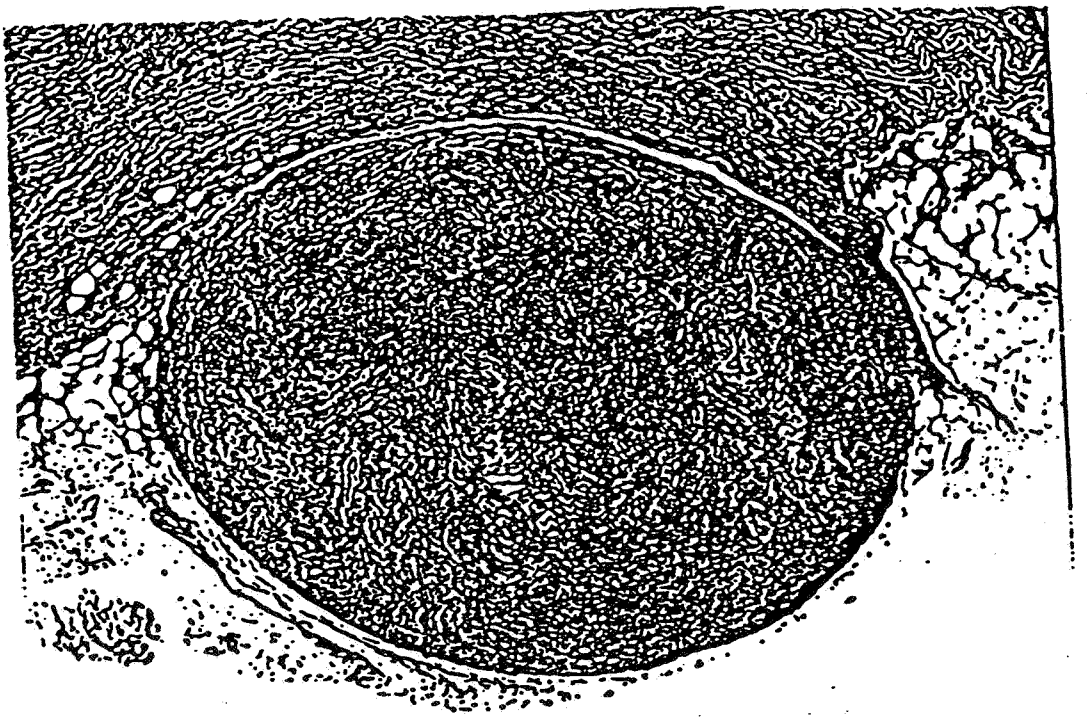
Cyst. Dilated duct filled with proteinaceous material and laminated concretions. 10x



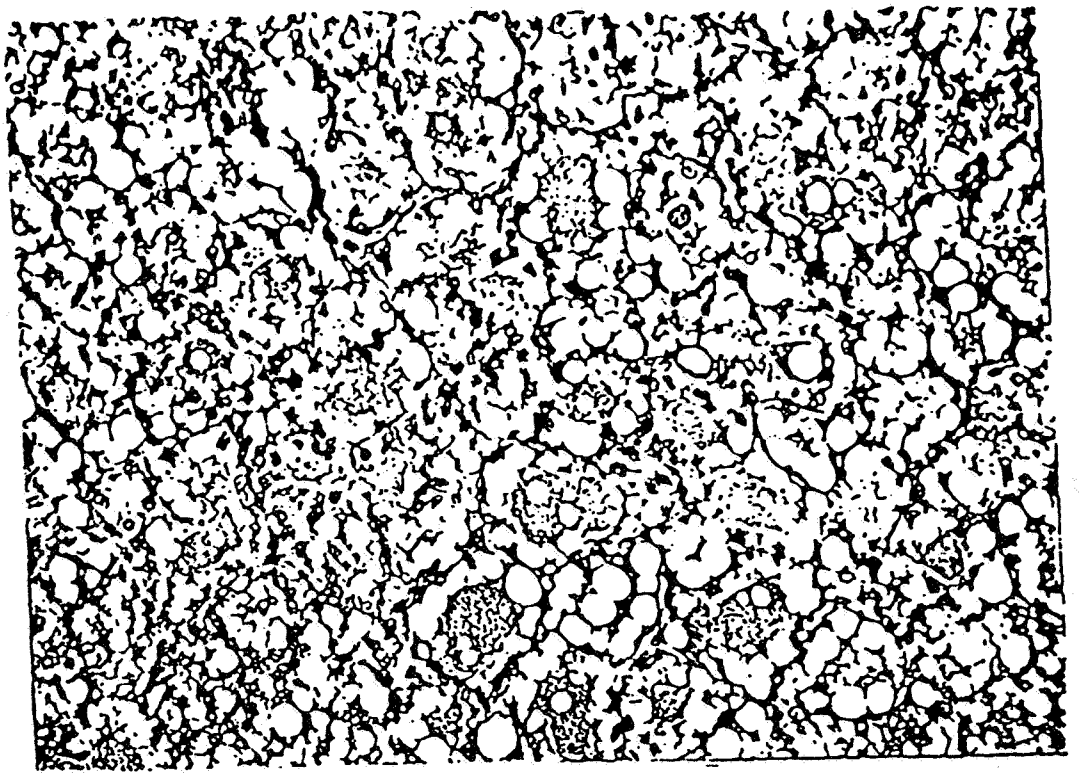
Fibroadenoma. Mature connective tissue interposed between alveolar structures, many of which are distended with secretion. 5x



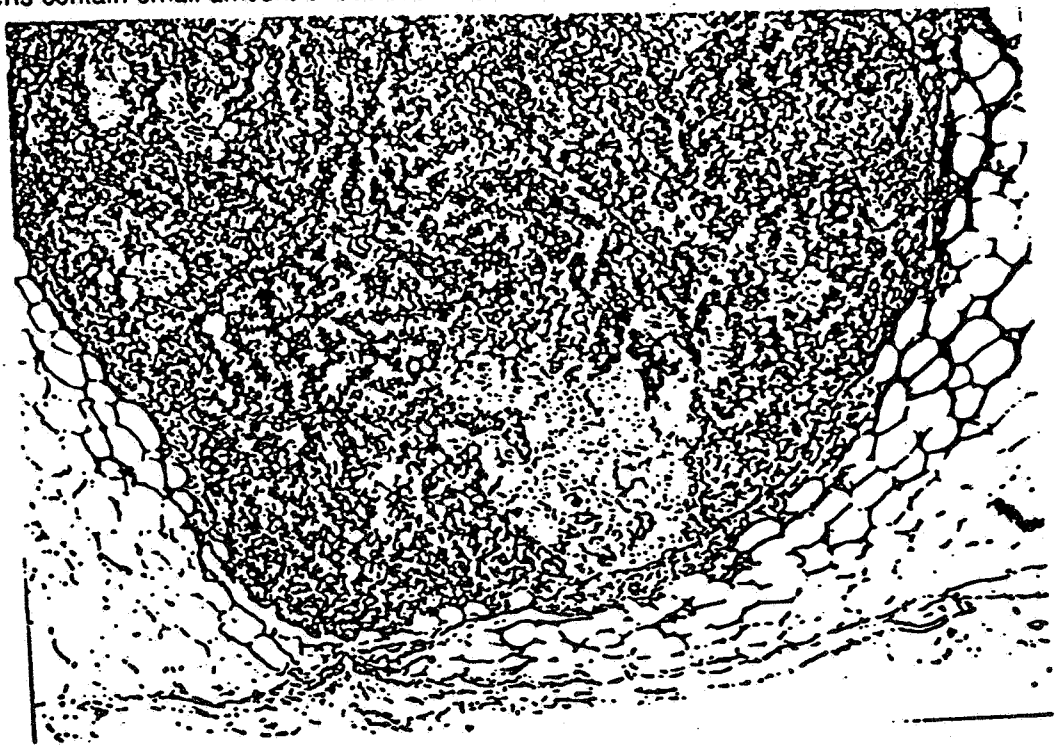
Fibroadenoma. Focal area of basophilic alveolar epithelium with papillary infoldings in a background of mature connective tissue. 13.2x



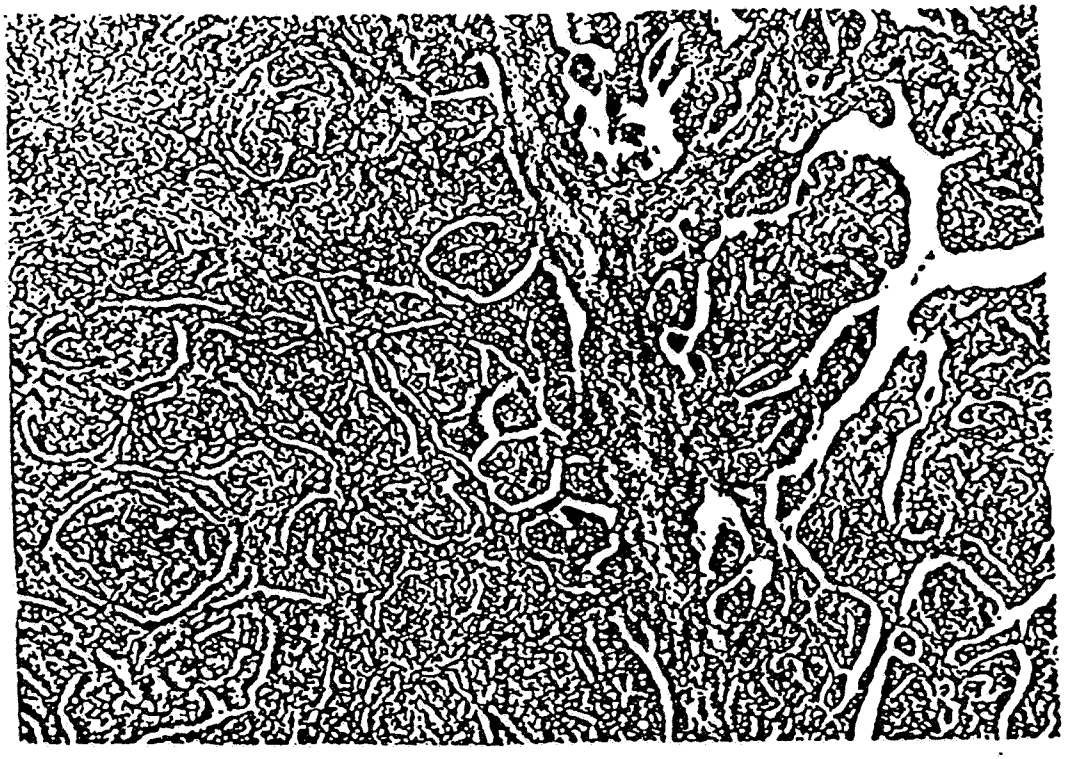
Fibroma. Mass consists entirely of connective tissue. 10x



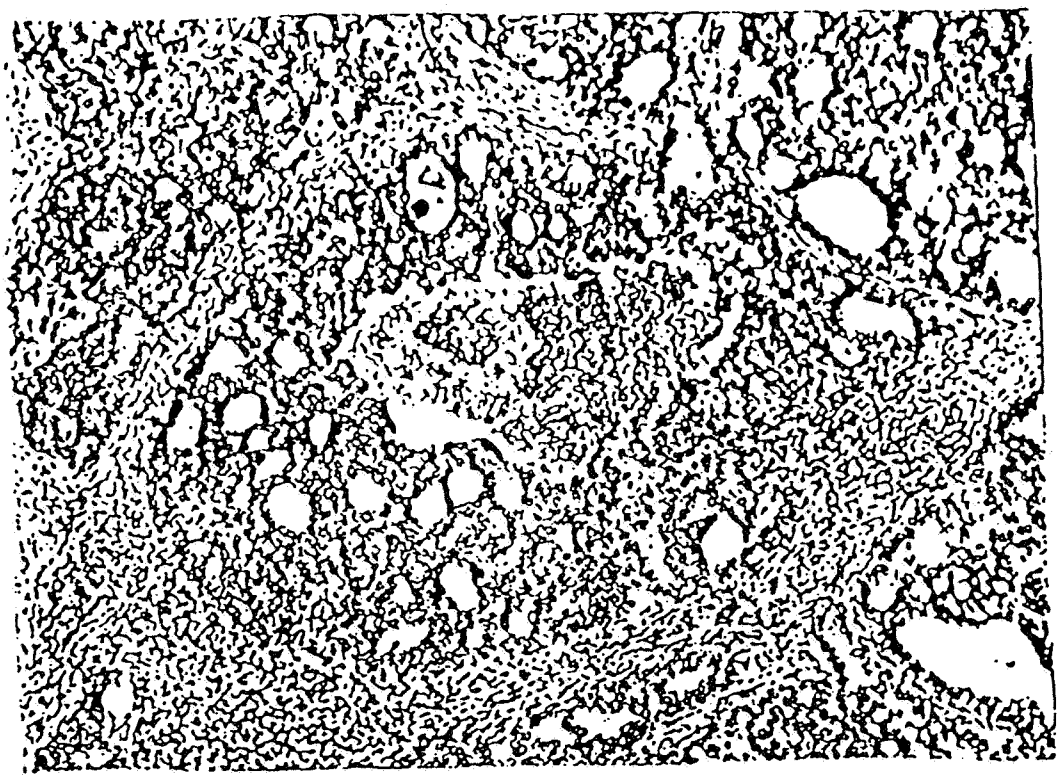
Adenoma (tubular pattern). Proliferating structures lined by single layer of vacuolated epithelial cells. Lumens contain small amount of secretion. 20x



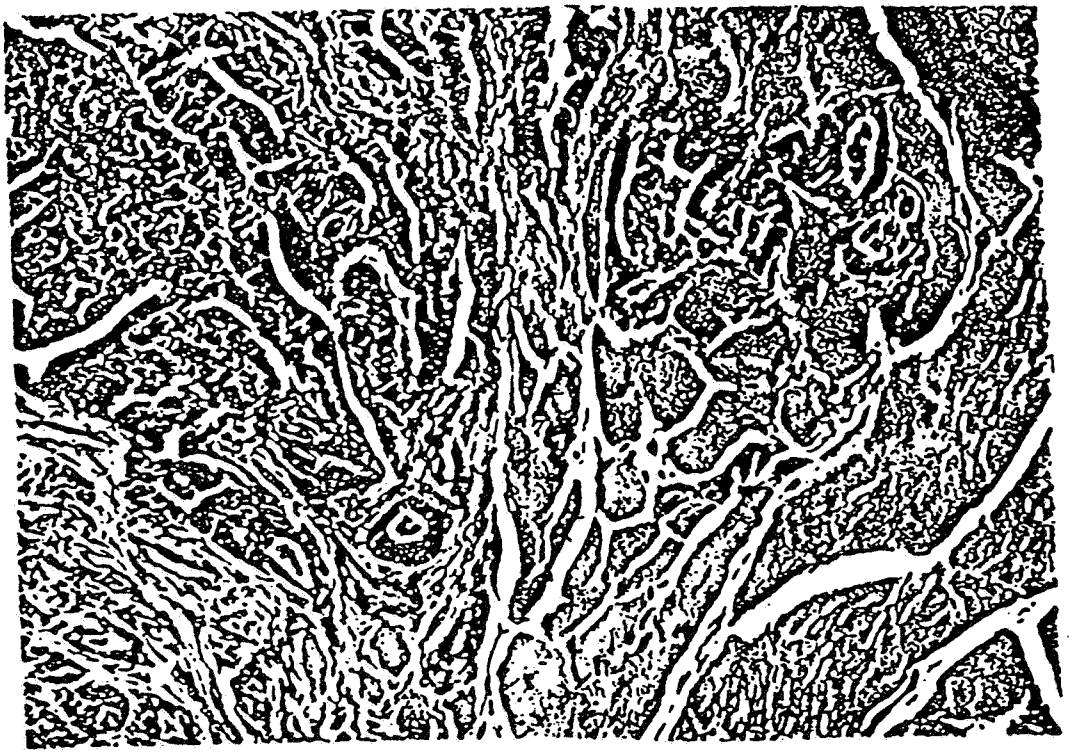
Adenoma (cystic papillary pattern). Papillary projections lined by single layer of epithelial cells protrude into multiloculated lumenal spaces filled with abundant secretion. 4x



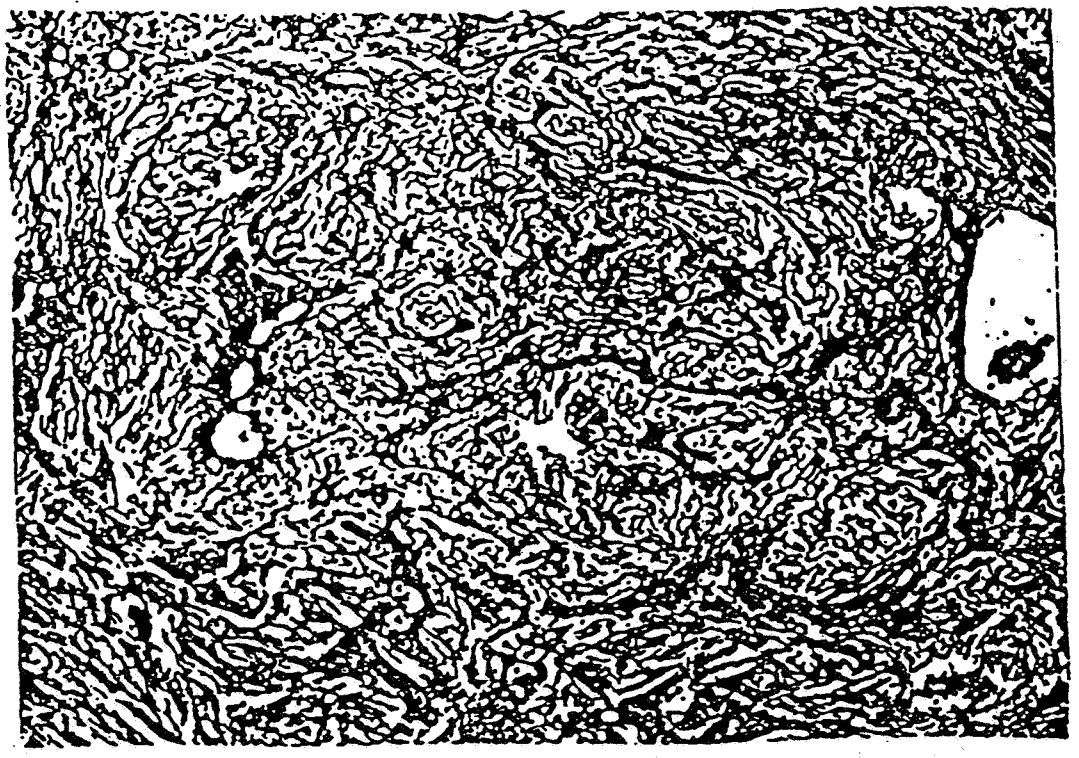
Carcinoma (papillary pattern). Neoplastic cells form branching papillae several cells thick with fibrovascular cores. Papilae extend into and distend alveolar spaces. 16x



Carcinoma. Solid sheet of neoplastic cells with a high mitotic rate. Numerous secondary lumens present (Cribriform pattern). Central core of necrotic tumor cells within distended ductule (Comedo pattern). 10x



Carcinoma. Malignant epithelial cells invading adjacent skeletal muscle. 50x



Carcinosarcoma. Malignant epithelial cells surrounded by fusiform malignant stromal cells. 40x