What goes wrong when cells go wrong?

The *Origins* of

BREAST CANCER!

Robert D. Cardiff, M.D., Ph.D

University of California, Davis

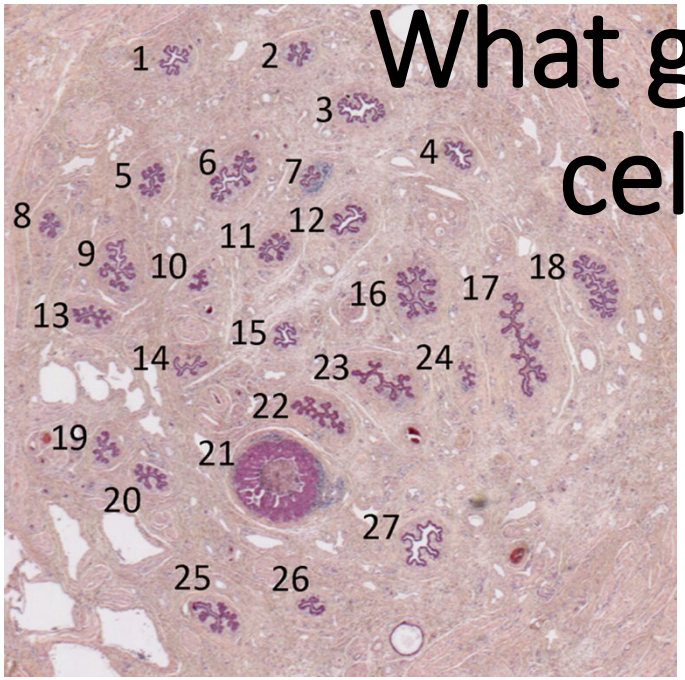
Welcome Trust

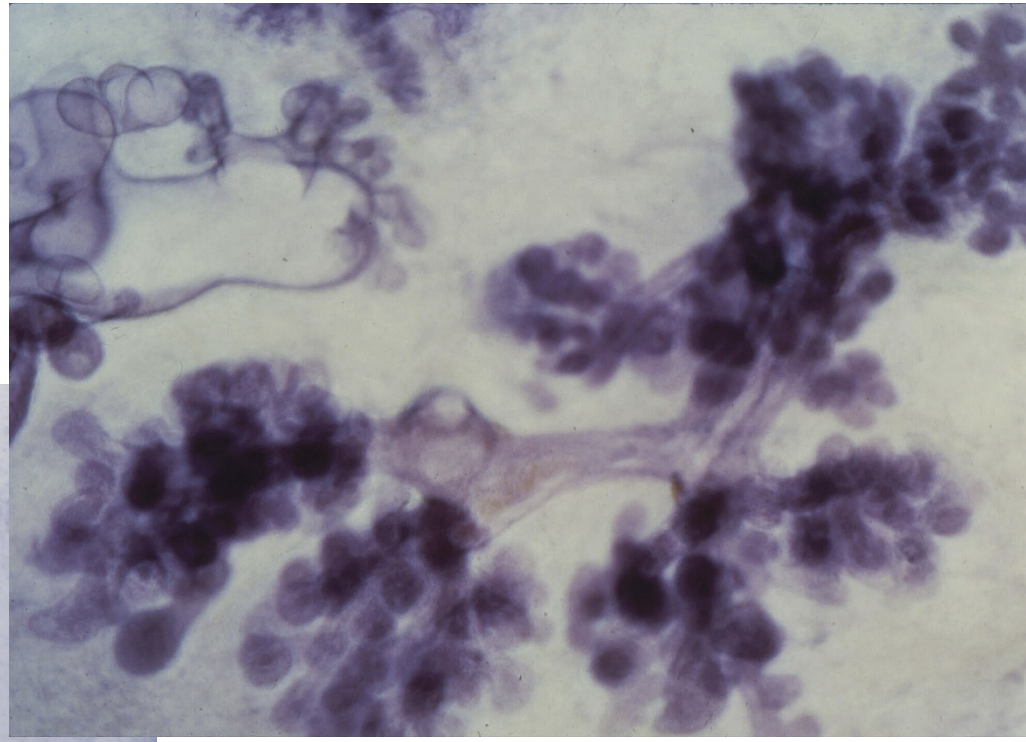
Delta Trust

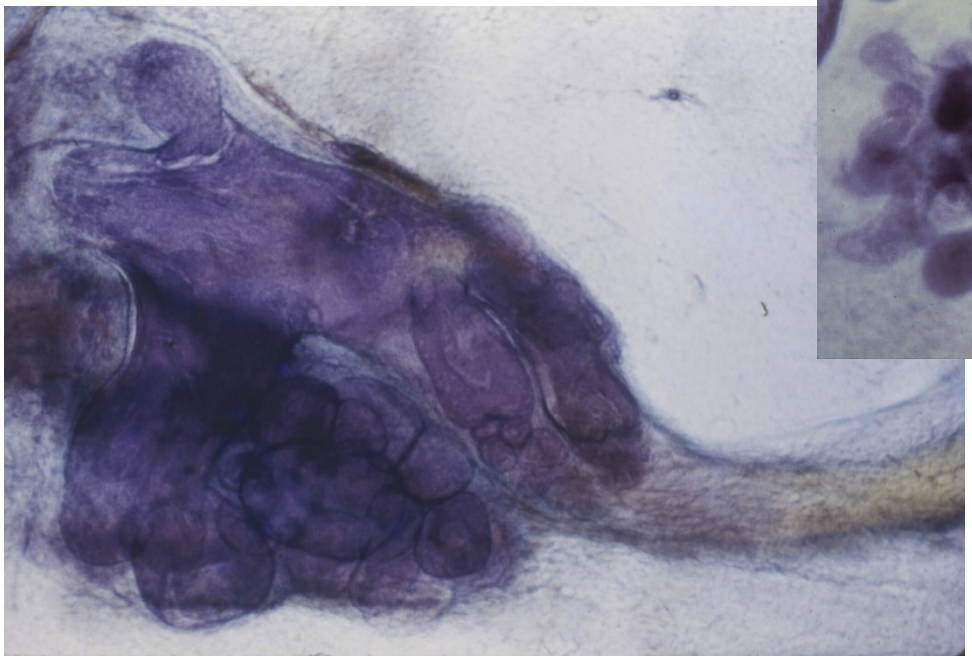
Session3

December 15, 2021

What goes wrong when cells go wrong?







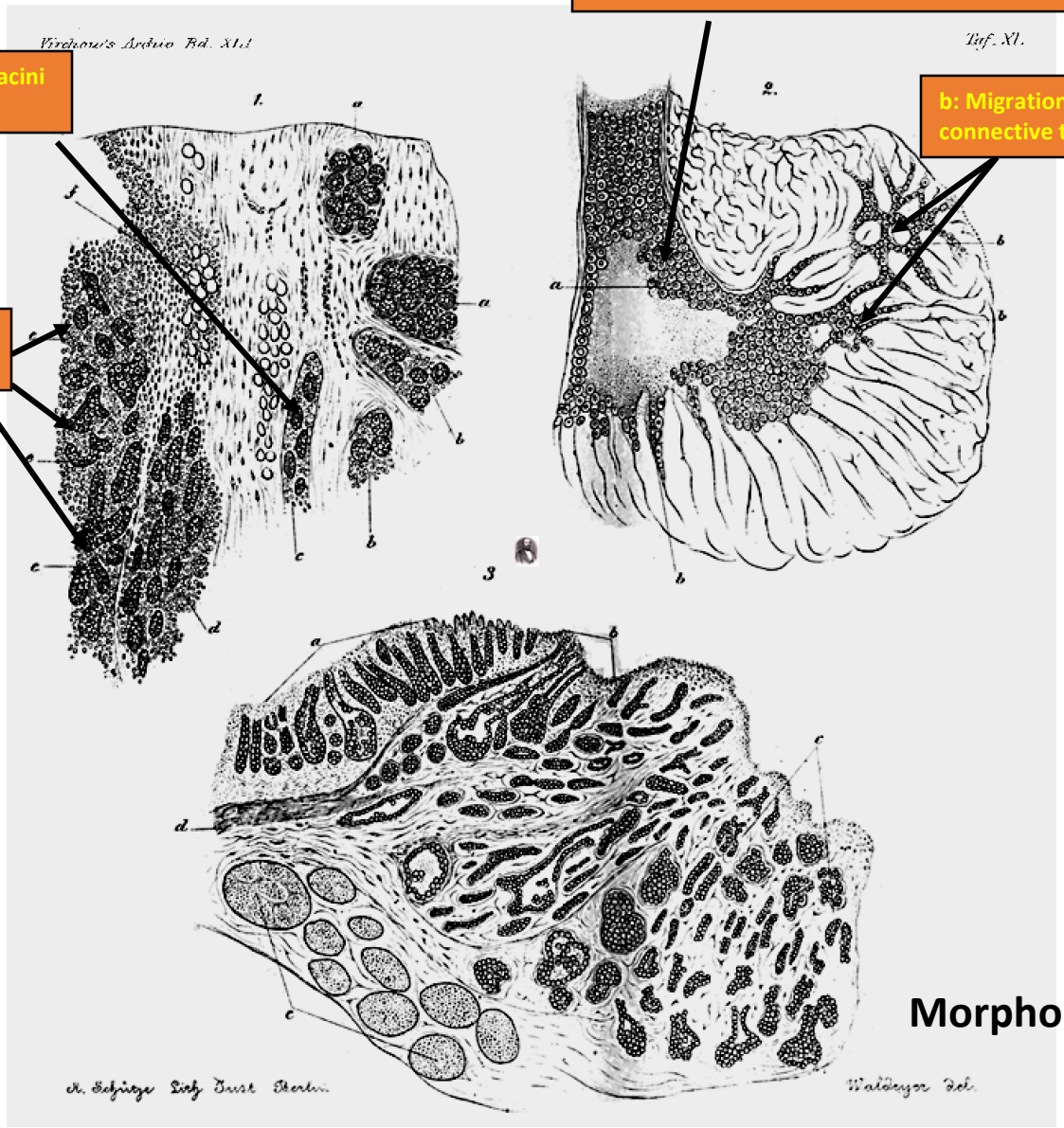
CANCER ORIGIN AND PROGRESSION *circa* 1867

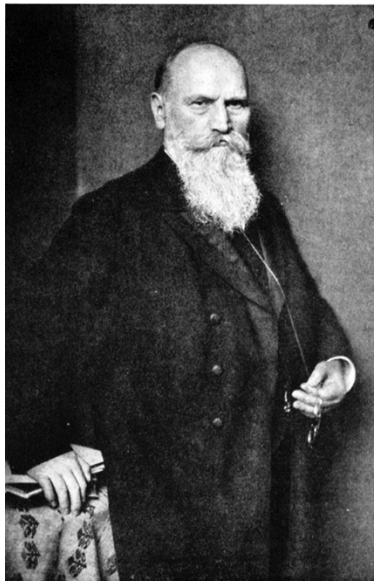
a: Epithelial growth starting from the milk duct.

c: Glands with altered acini and periacinar growth.

b: Migration from epithelial cells into connective tissue fissures.

d: True cancerous section of the mamma.





Heinrich Wilhelm Waldeyer

Morphological Continuum

Waldeyer, W. (1867). Die Entwicklung der Carcinome. *Arch. Path. Anat. Phys. Klin. Med.* 41, 470-523.

BLASTEMA
(A STEM CELL)

Julius Connheim

Rudolf Virchow

CLINICAL VS EXPERIMENTAL REASONING

- Guilt-by-Association: Medical logic is inferential. Based on the evidence, the diagnosis is inferred.

- Test-by-Experimentation: Scientific logic requires experiments. In mice, the experimental proof requires transplantation.

CLINICAL VS EXPERIMENTAL BIOLOGY

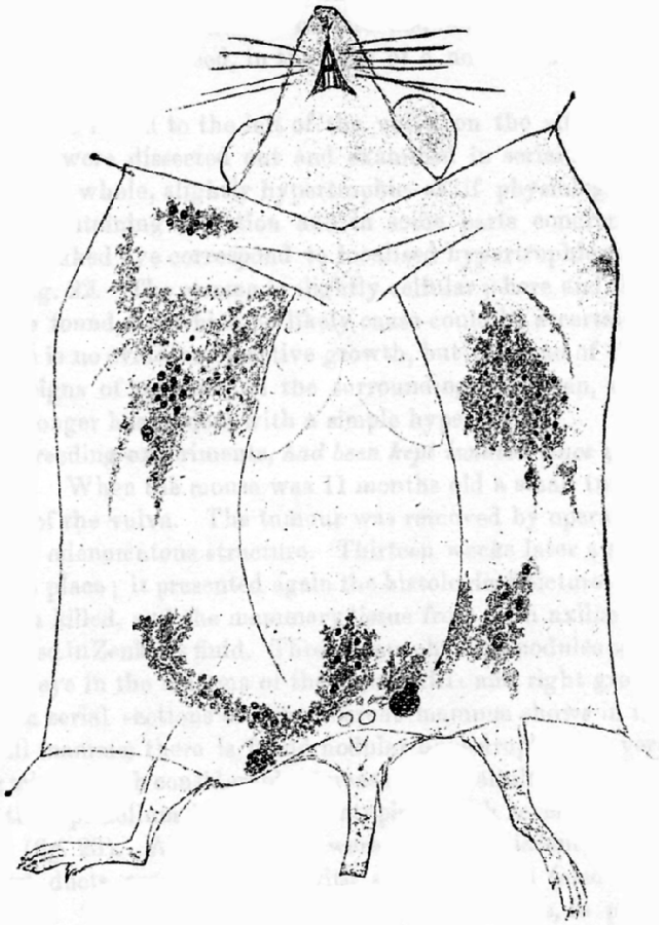
- **Human**: observations, demographics, epidemiology and *statistical analysis* of *heterogeneous* populations ***(guilt-by-association)***.
  - Experimental: tissue culture and xenografts.

- **Mouse**: observation, demographics, genetic engineering, and statistical analysis of *homogeneous* populations.
  - Experimental: Test by transplantation into syngeneic host and orthotopic sites. (***Test-by-transplantation***).

OF MICE AND MEN

Apolant
DeOme
Wellings
Page

The Hyperplastic Alveolar Nodules (HAN)
PRECANCER?

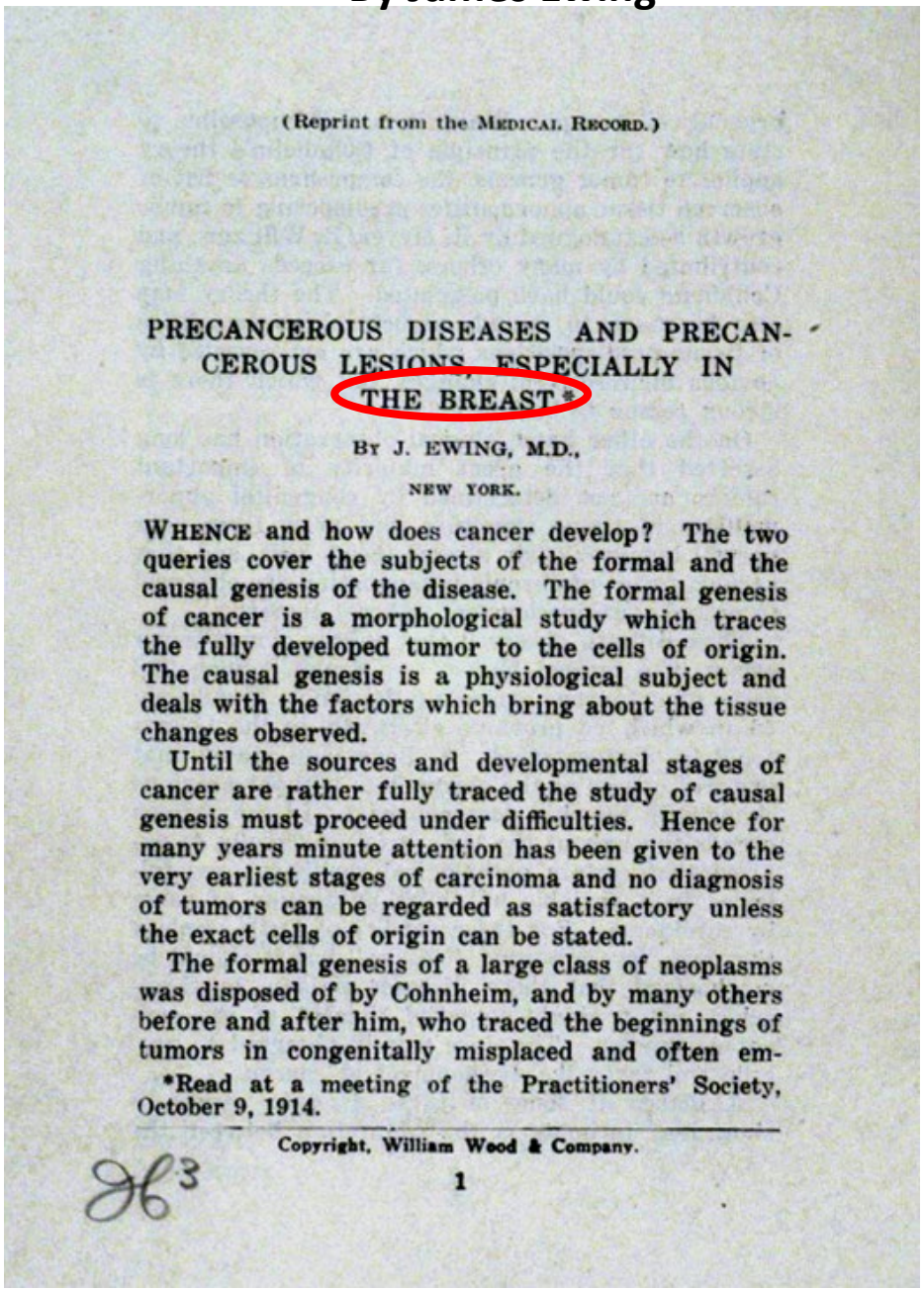


J. R. Ford del.

FIG. 21.—Mouse 490. Multiple minute hypertrophic nodules in the mammæ, reflected with the skin. The structure of one of the nodules in the right axillary mamma is shown in fig. 22. The figure also illustrates the zone free from mammary gland (*cf.* Third Sci. Report, fig. 24, p. 84), employed for autologous inoculation (*cfr.* p. 56).

Haaland 1911

WORD "PRECANCER": FIRST USED AND DESCRIBED IN 1914
By James Ewing



(Reprint from the MEDICAL RECORD.)

PRECANCEROUS DISEASES AND PRECANCEROUS LESIONS, ESPECIALLY IN THE BREAST*

BY J. EWING, M.D.,

NEW YORK.

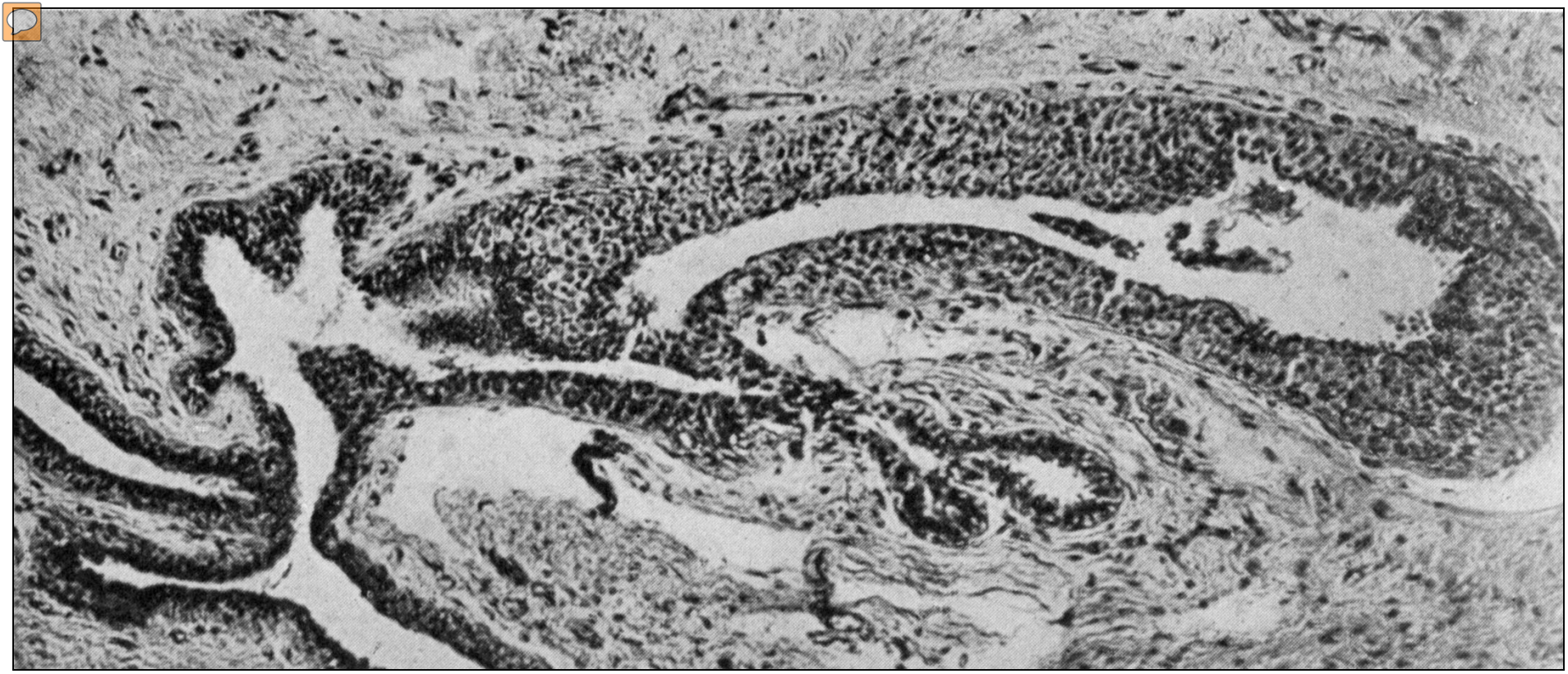
WHENCE and how does cancer develop? The two queries cover the subjects of the formal and the causal genesis of the disease. The formal genesis of cancer is a morphological study which traces the fully developed tumor to the cells of origin. The causal genesis is a physiological subject and deals with the factors which bring about the tissue changes observed.

Until the sources and developmental stages of cancer are rather fully traced the study of causal genesis must proceed under difficulties. Hence for many years minute attention has been given to the very earliest stages of carcinoma and no diagnosis of tumors can be regarded as satisfactory unless the exact cells of origin can be stated.

The formal genesis of a large class of neoplasms was disposed of by Cohnheim, and by many others before and after him, who traced the beginnings of tumors in congenitally misplaced and often em-

*Read at a meeting of the Practitioners' Society, October 9, 1914.

96 3

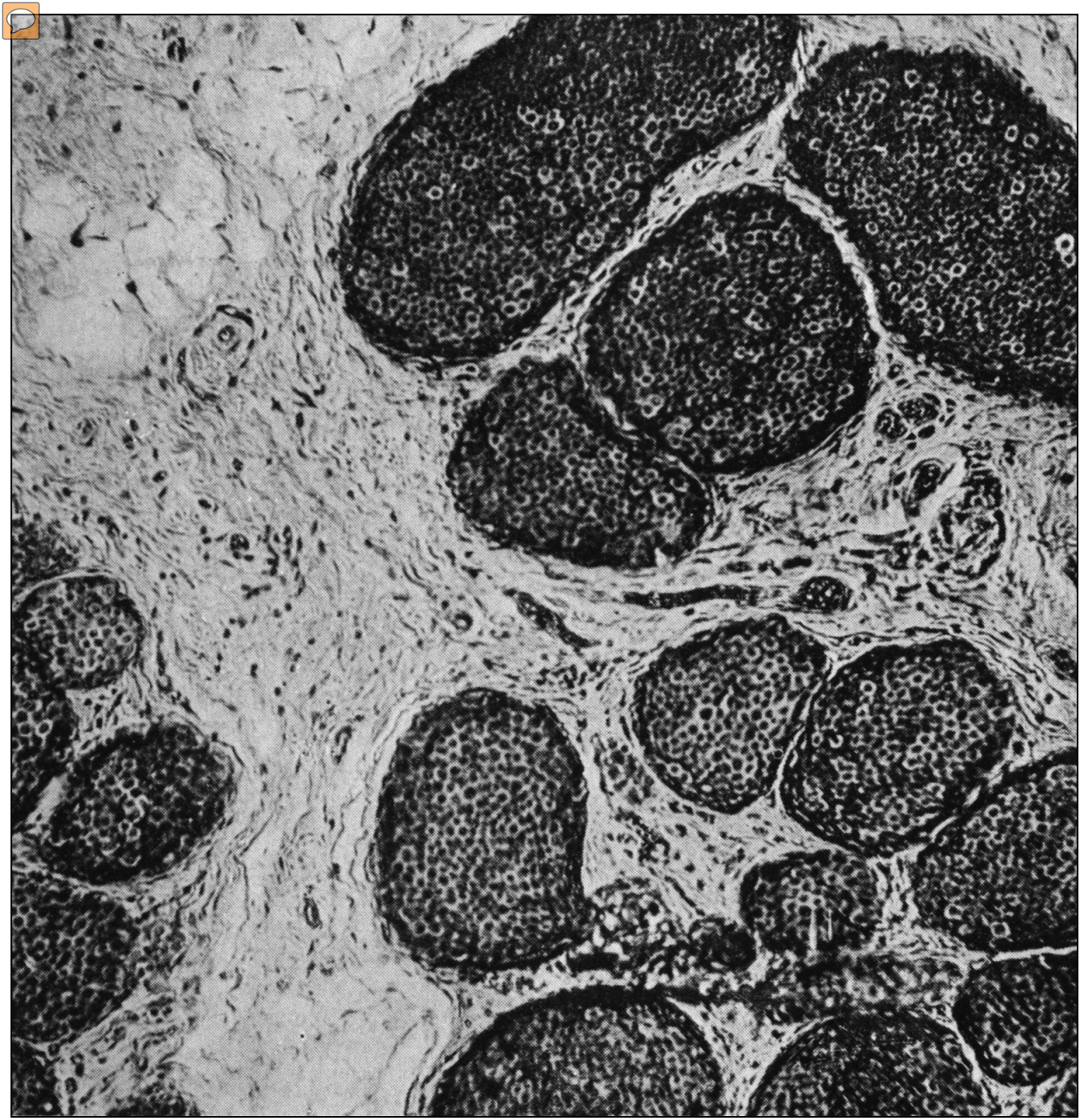


Ewing. 1919. Fig. 185. Precancerous changes in the breast. Atypical proliferation in a segment of a duct.

1985 and 1988 = Ductal involvement by cells of atypical lobular hyperplasia

Courtesy of Dr. David Page

Ewing, J. 1919. *Neoplastic Diseases: A Textbook on Tumors.* W.B. Saunders, Philadelphia, PA



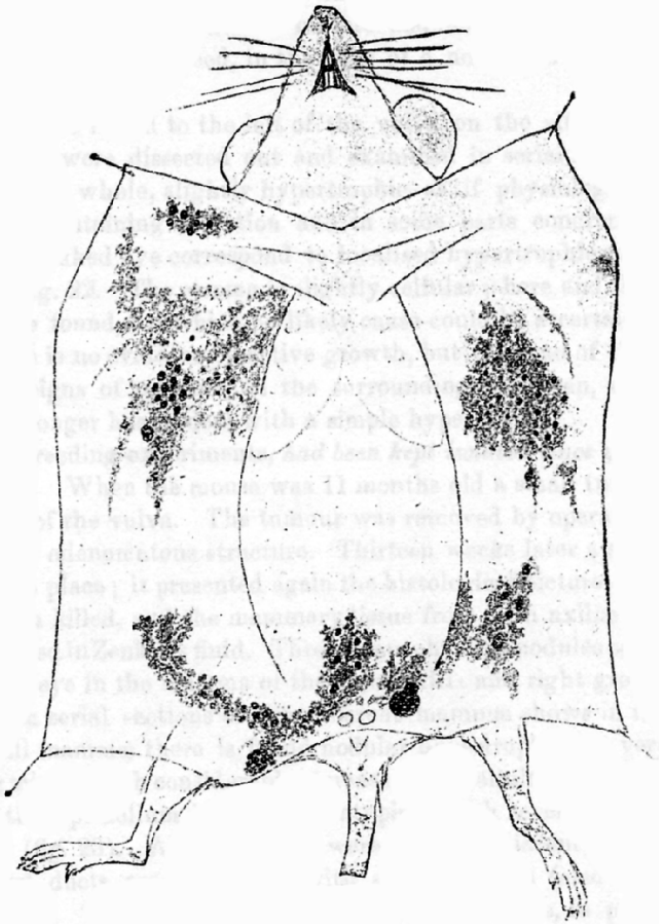
Ewing, 1919
Fig. 184
“Precancerous changes in breast.
Filling of small ducts and acini with atypical cells. No infiltration.”

Courtesy of Dr. David Page

LUMPS AND BUMPS
OF
POLYCYSTIC BREAST DESEASE:

COOPER’S DISEASE
SCHIMILLBUSH’S DISEASE
BLOODGOOD’S DISEASE
AND
OTHERS.

Apolant 1907
Haaland 1911

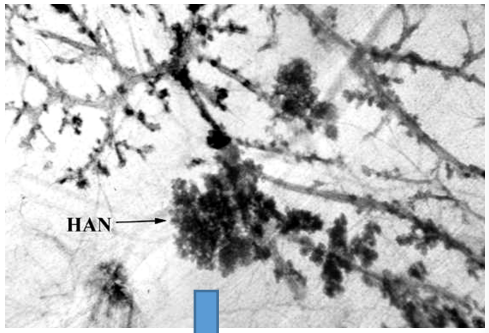


J. R. Ford del.

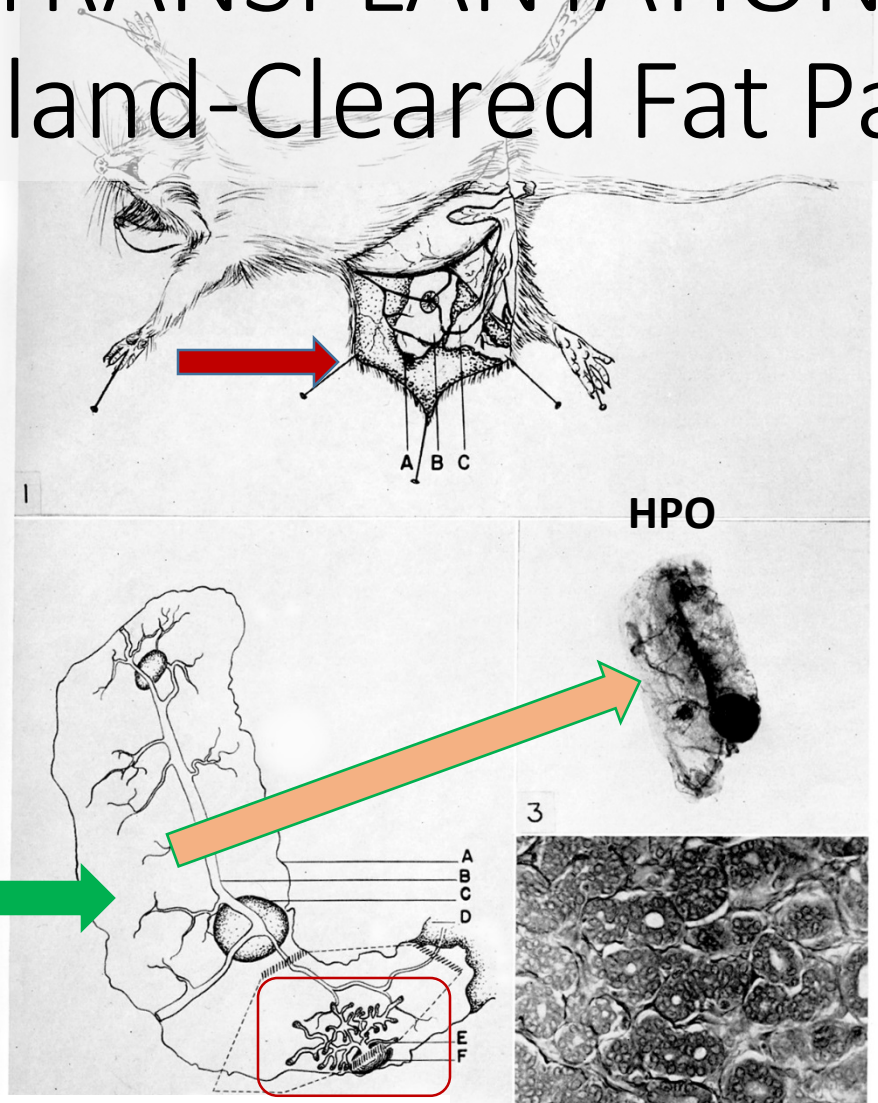
FIG. 21.—Mouse 490. Multiple minute hypertrophic nodules in the mammæ, reflected with the skin. The structure of one of the nodules in the right axillary mamma is shown in fig. 22. The figure also illustrates the zone free from mammary gland (*cf.* Third Sci. Report, fig. 24, p. 84), employed for autologous inoculation (*cfr.* p. 56).

TRANSPLANTATION: Gland-Cleared Fat Pad

HAN



Gland-Cleared Fat Pad



Dr. K.B. DeOme
CRGL, UCBerkeley

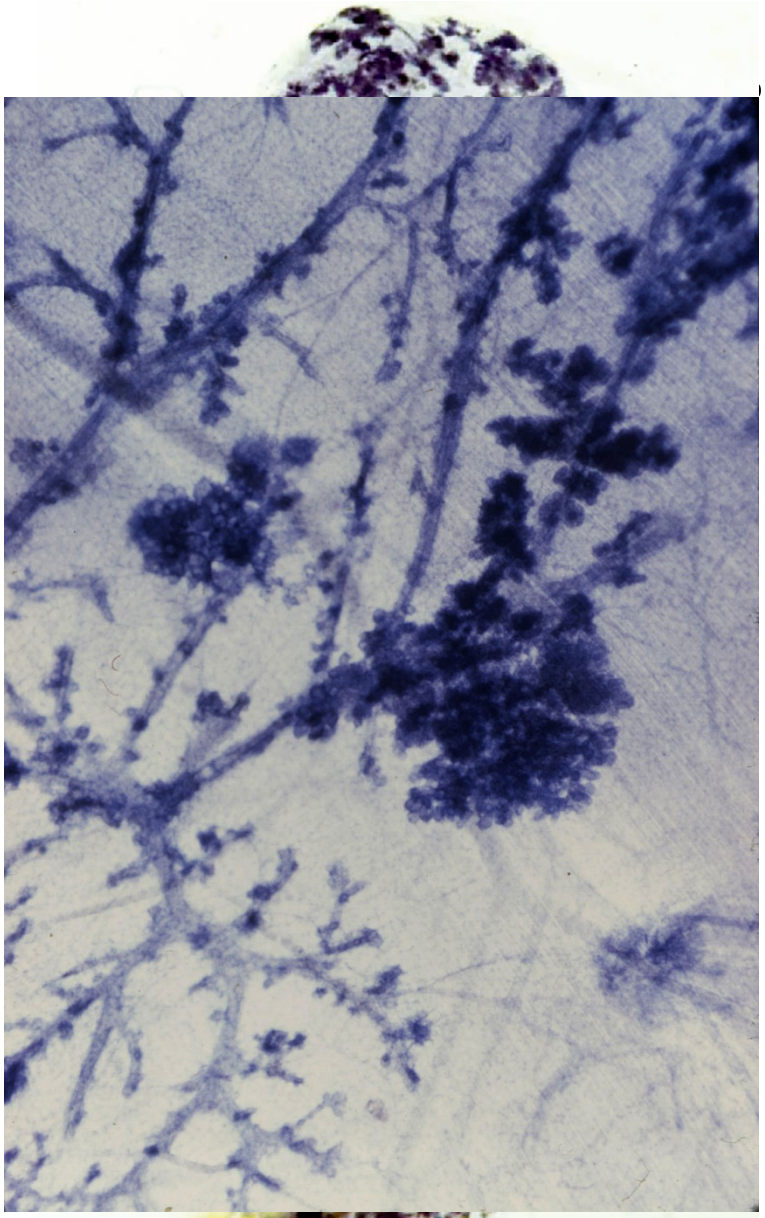
Cancer Res. 1959 Jun;19(5):515-20.

Development of mammary tumors from hyperplastic alveolar nodules transplanted into gland-free mammary fat pads of female C3H mice.

DEOME KB, FAULKIN LJ Jr, BERN HA, BLAIR PB.

PMID: 13663040 [PubMed - indexed for MEDLINE]

WELLINGS



An Atlas of Subgross Pathology of the Human Breast With Special Reference to Possible Precancerous Lesions [1, 2]

S. R. Wellings,[3] H. M. Jensen,[3] *and* R. G. Marcum [4]

SUMMARY—One hundred ninety-six whole human breasts were examined by a subgross sampling technique with histologic confirmation. The method permitted the enumeration and identification of essentially all the focal dysplastic, metaplastic, hyperplastic, anaplastic, and neoplastic lesions. Of the 196, 119 were suitable for complete quantitative morphologic analysis of the focal lesions by type. They consisted of 67 breasts obtained by autopsy, 29 cancerous breasts obtained by mastectomy, and 23 contralateral to those with cancer. All lesions, photographed subgrossly, were subsequently confirmed and correlated histologically. Morphologic evidence supported the hypothesis that most lesions traditionally grouped as mammary dysplasia or fibrocystic disease, including apocrine cysts, sclerosing adenosis, fibroadenomas, various forms of lobules (sclerotic, dilated, hypersecretory, hyperplastic, atypical, or anaplastic), ductal carcinoma in situ (DCIS), and lobular carcinoma in situ (LCIS), arose in terminal ductal-lobular units (TDLU) or in the lobules themselves. A probable exception was papilloma of ducts larger than terminal ones. Isolated foci of DCIS within the TDLU were seen in 40% of cancerous breasts, which indicated that the disease often was multifocal. Of the contralateral breasts, the 60% with clinical cancer contained such lesions, and data were in accord with the clinically

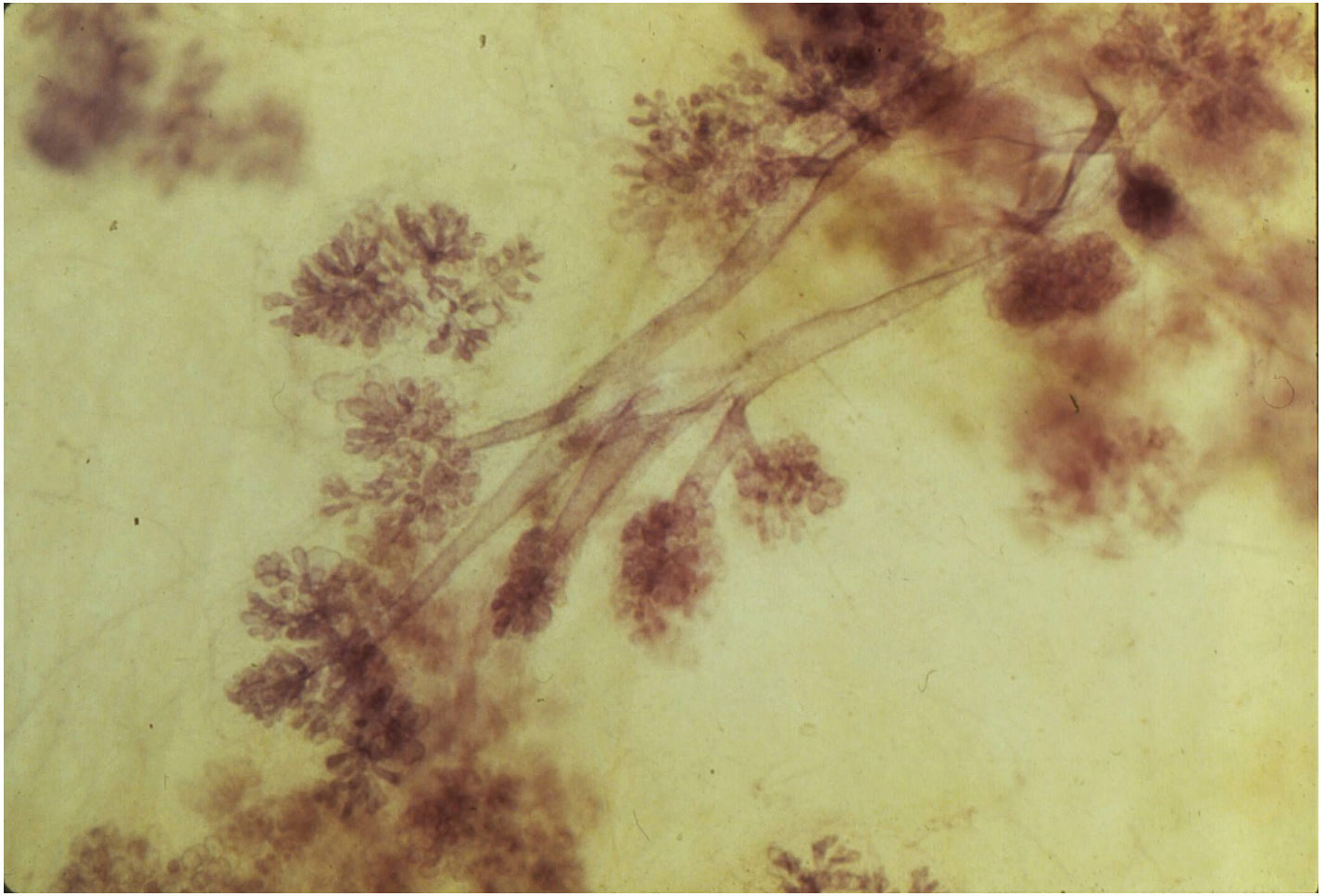
This study originated 7 years ago as a search for precancerous lesions in the human breast. From the outset, the rationale was based on our prior experience with rodent models. In these systems, the study of wholemounts permits the recognition and quantification of focal lesions that stand out from the background appearance of the mammary gland. The most famous rodent lesion is the hyperplastic alveolar nodule(s) (HAN) first described by Apolant in 1906 (*1*) and again by Haaland in 1911 (*2*). The HAN was proved to be preneoplastic by direct experimental means; its presence is partly the result of activity of the mammary tumor virus (MTV), and it is probably a site of MTV synthesis (*3–5*). In the mouse, HAN have at least six additional properties relevant to the human problem (*6–14*): 1) HAN are much more common in strains that have a high incidence of mammary cancer than in those with low incidence, 2) they increase in number with age, 3) they show variable degrees of independence from the hormones that support and maintain normal mammary gland growth and development, 4) they are lobulo-alveolar, 5) they are large enough to be visible at low powers (2–4×) of the dissecting microscope and at times with the unaided eye,

J Natl Cancer Inst. 1975 Aug;55(2):231-73.

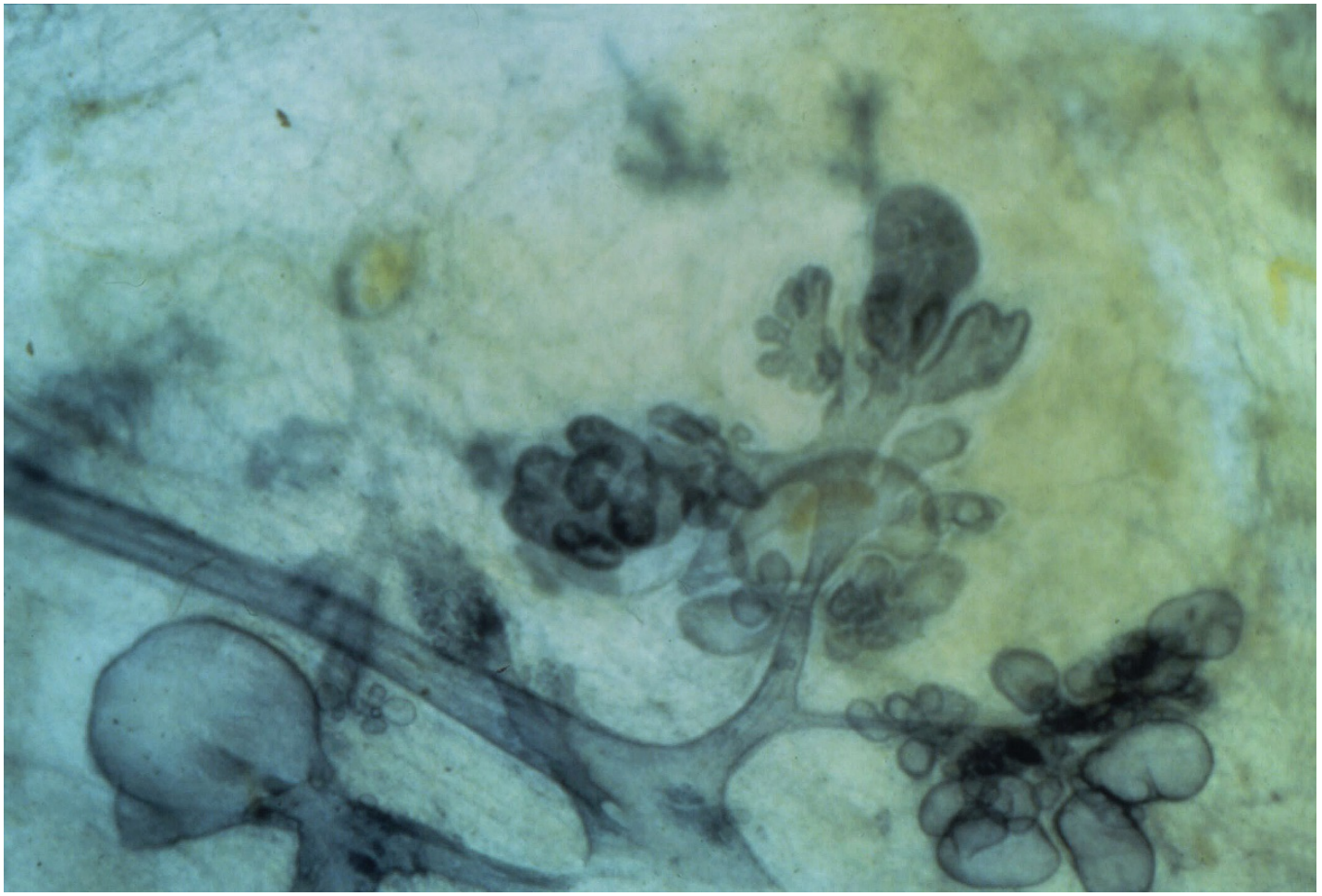
An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions.

Wellings SR, Jensen HM, Marcum RG.

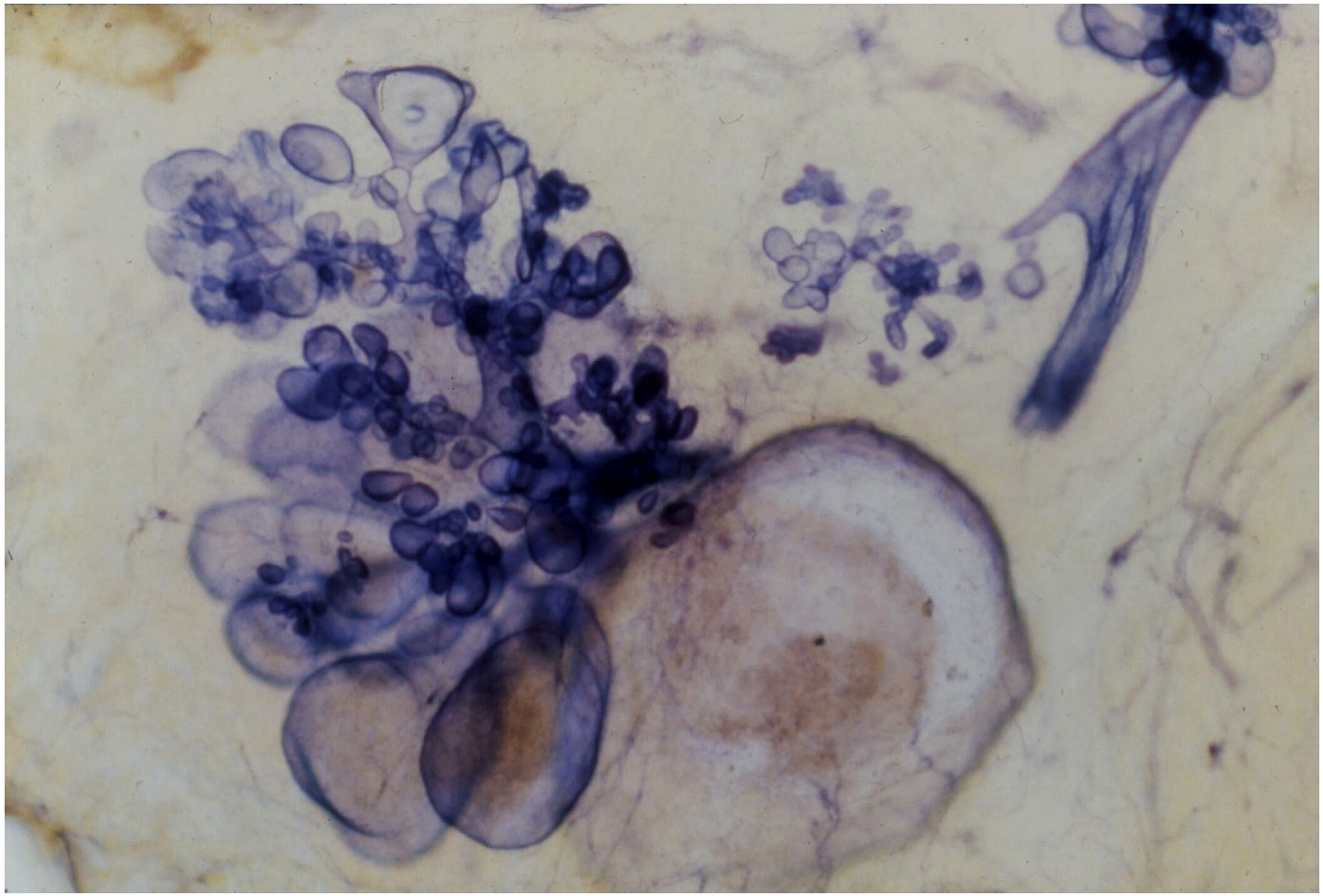
Mature Adult TLDUs



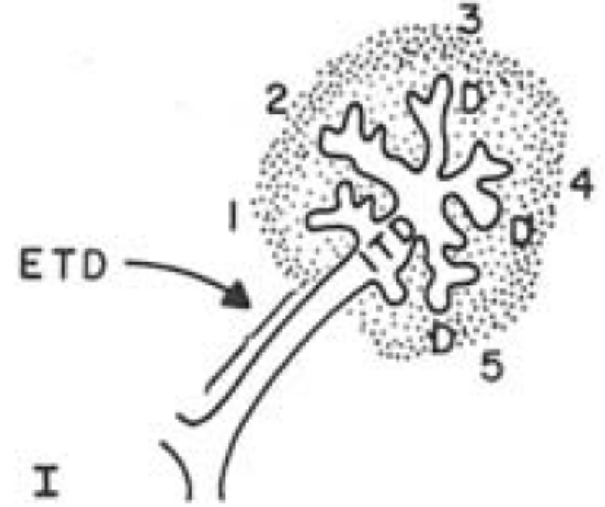
CYSTIC TDLUs

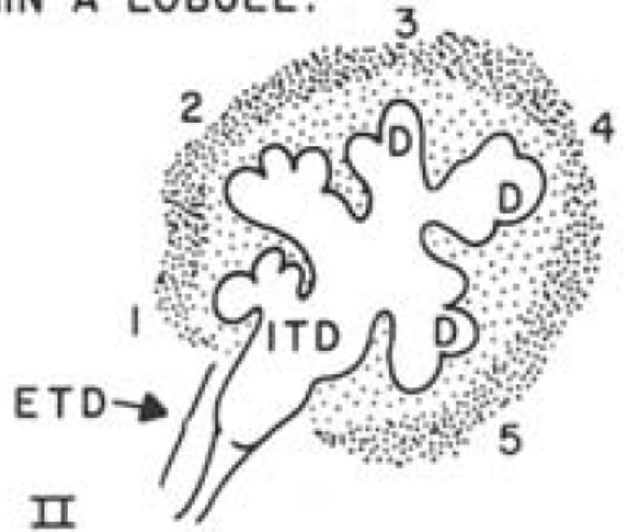


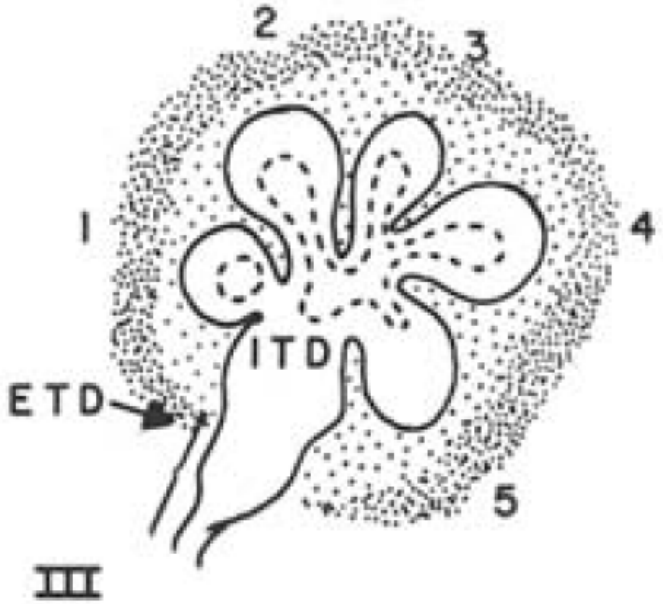
D-03-*Dilated lobule cysts*-SG

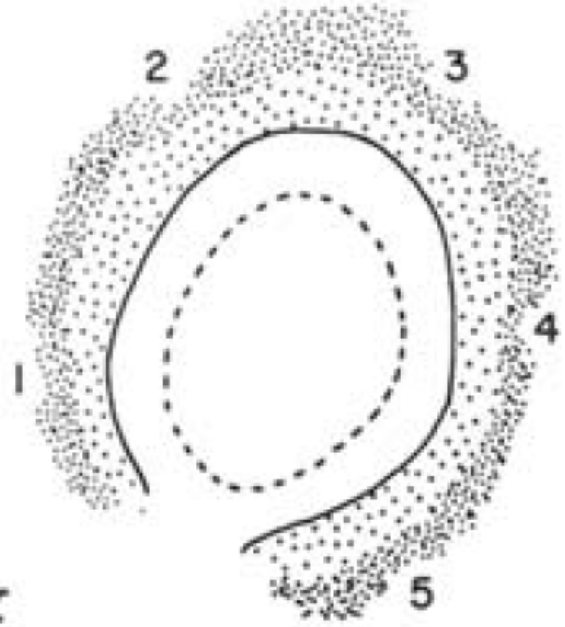


DIAGRAMMATIC ILLUSTRATION OF PROGRESSION OF CARCINOMA IN SITU OF DUCTAL TYPE WITHIN A LOBULE.

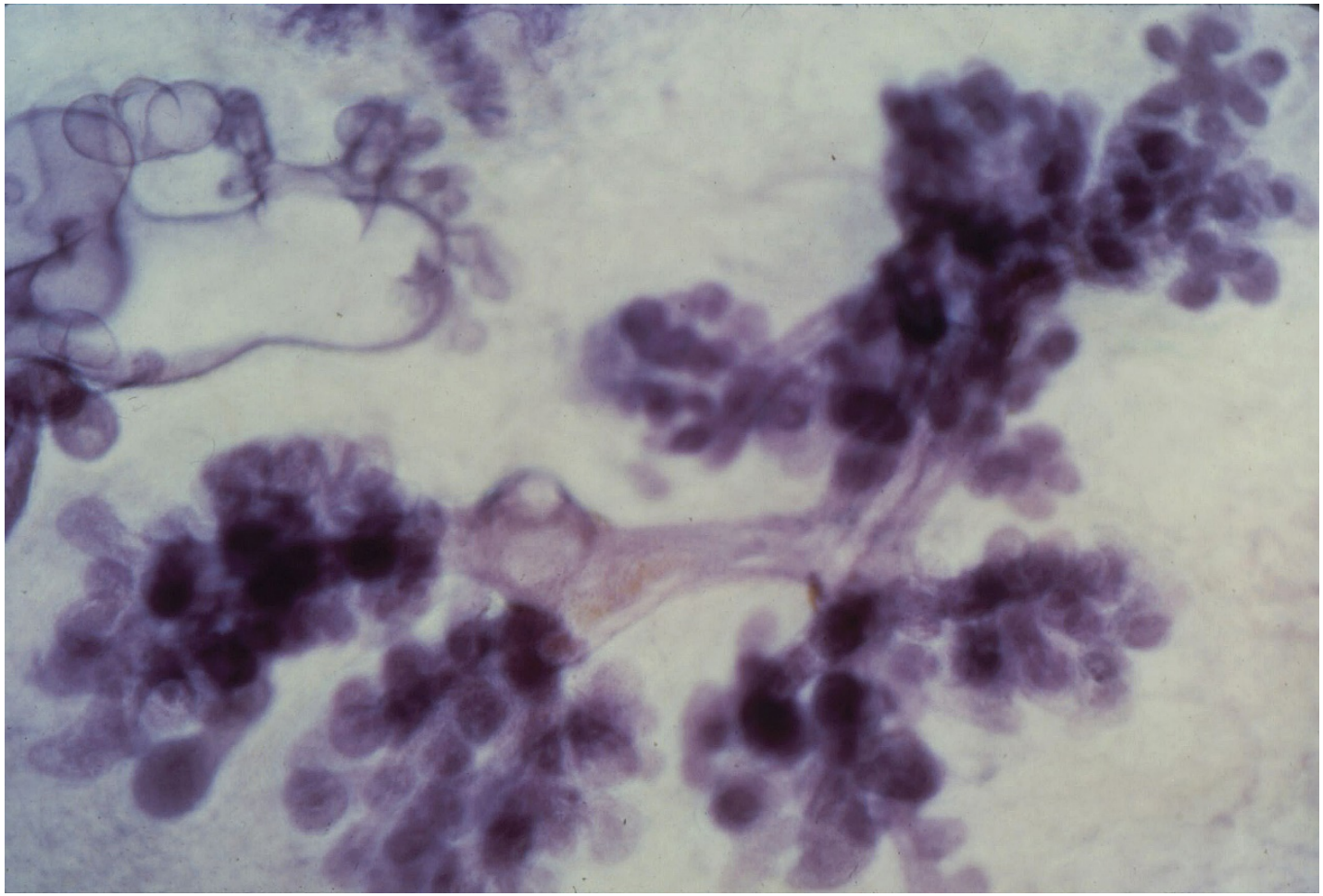




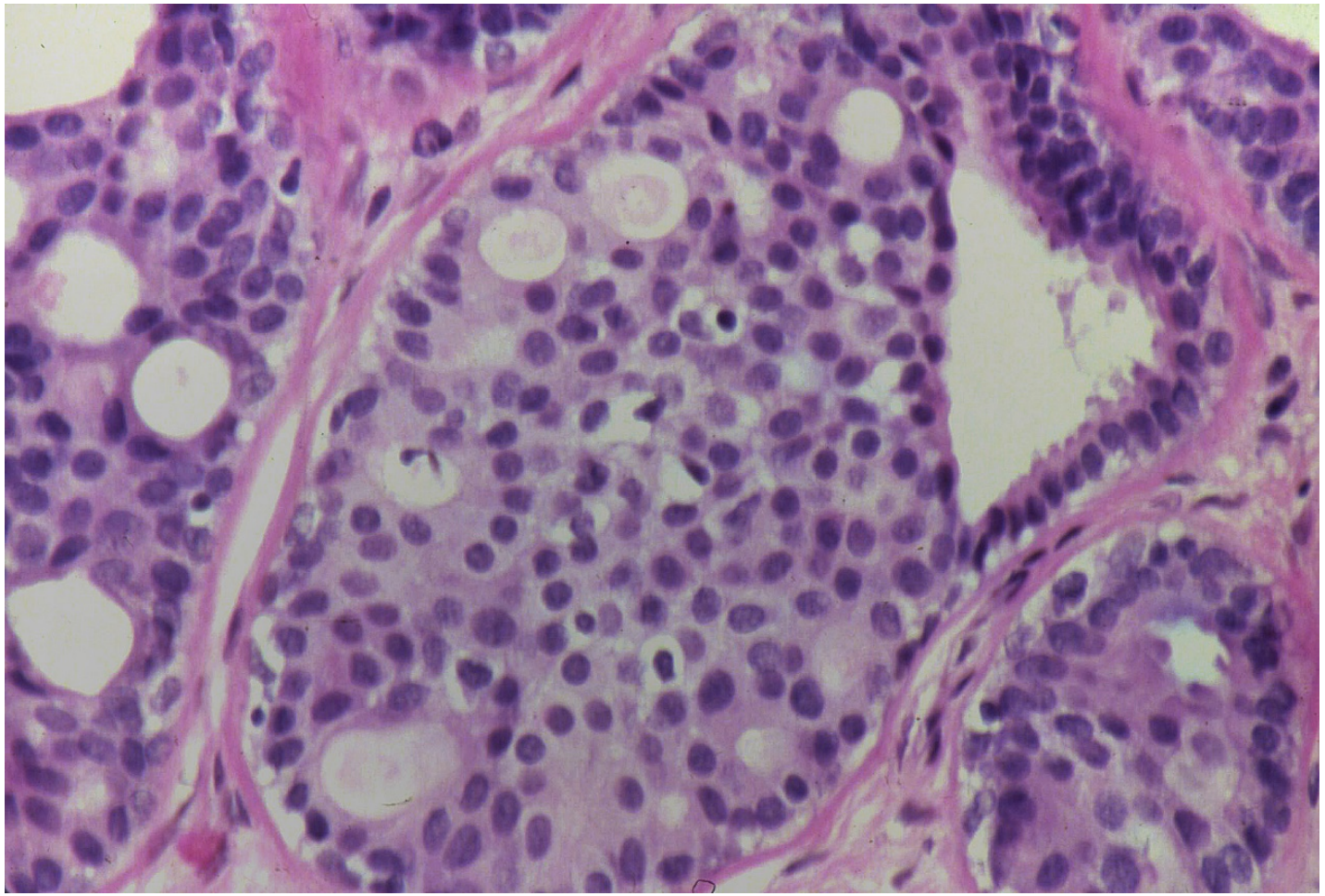




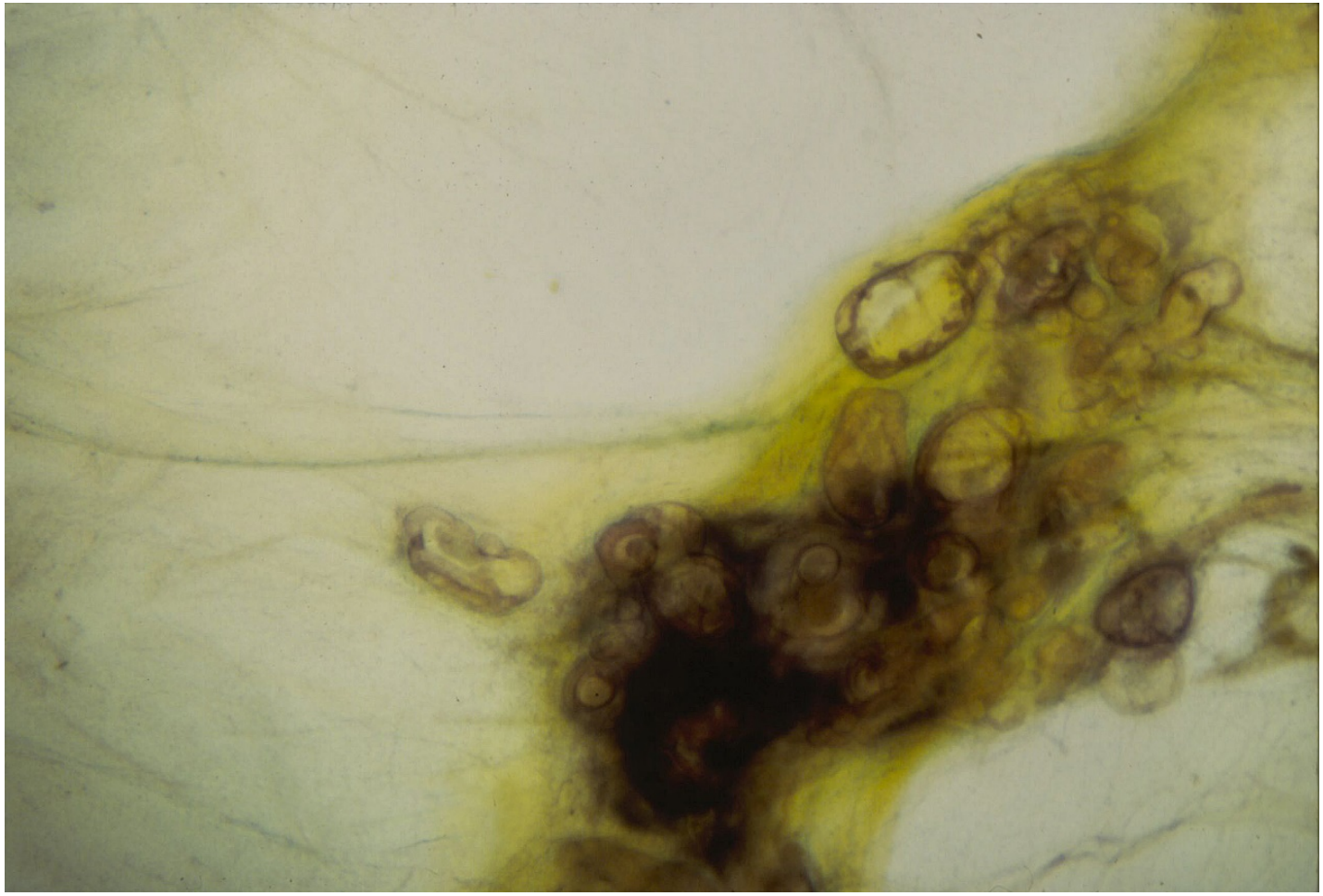
D-16-ALA3-ALB4-LCIS-SG
Lobular Carcinoma In Situ



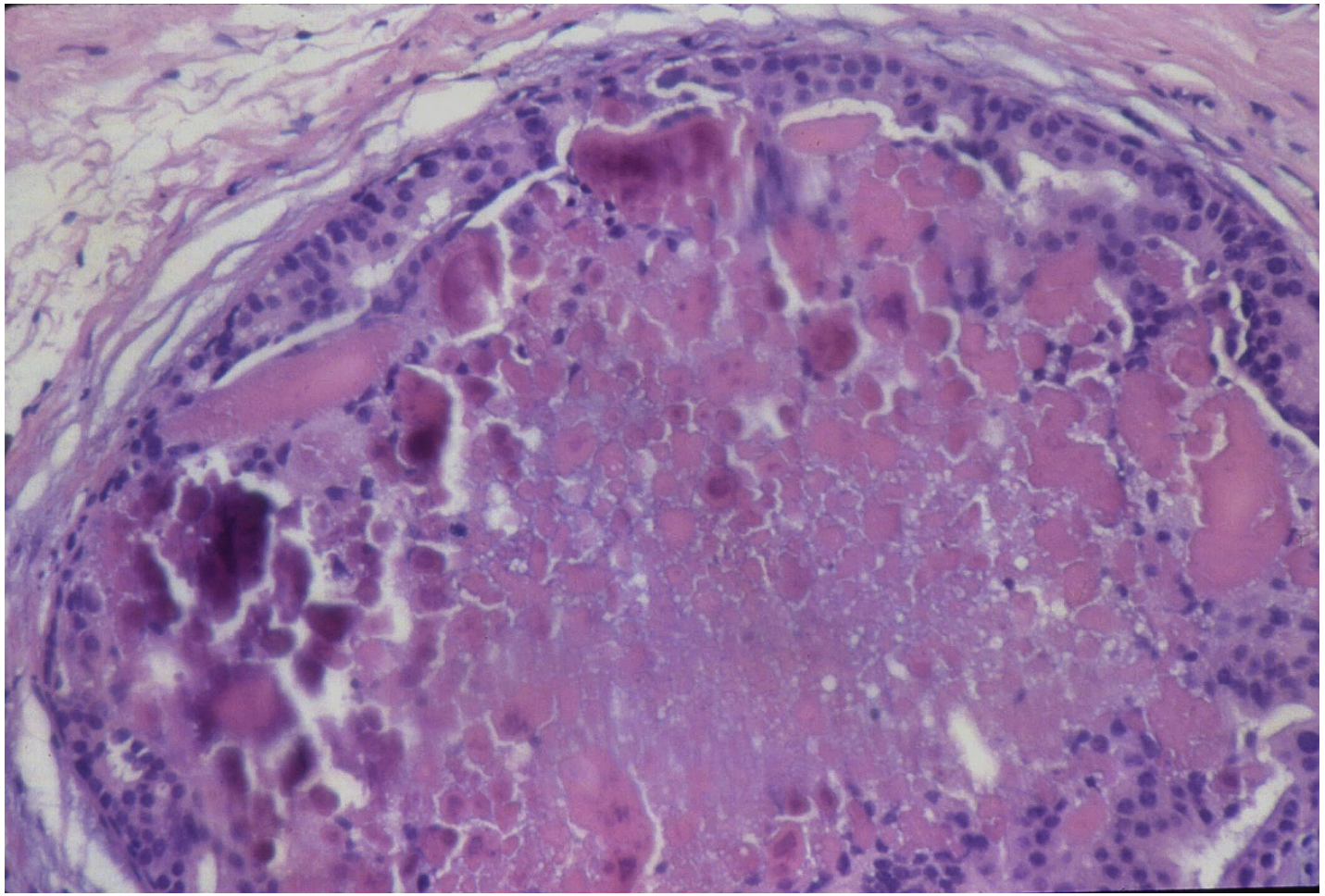
D-15-ALA Atypical-Histo



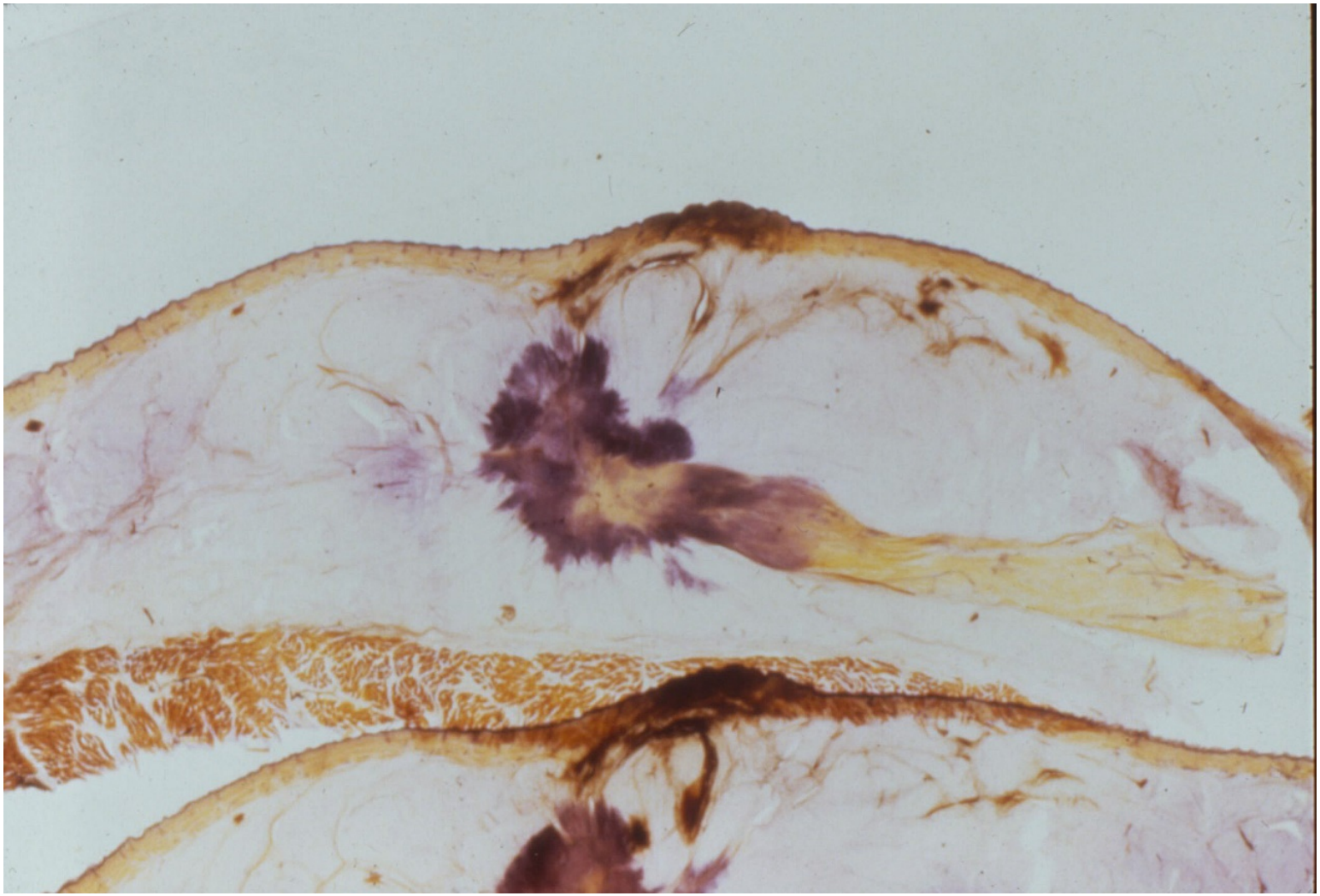
D-24-DCIS-SG



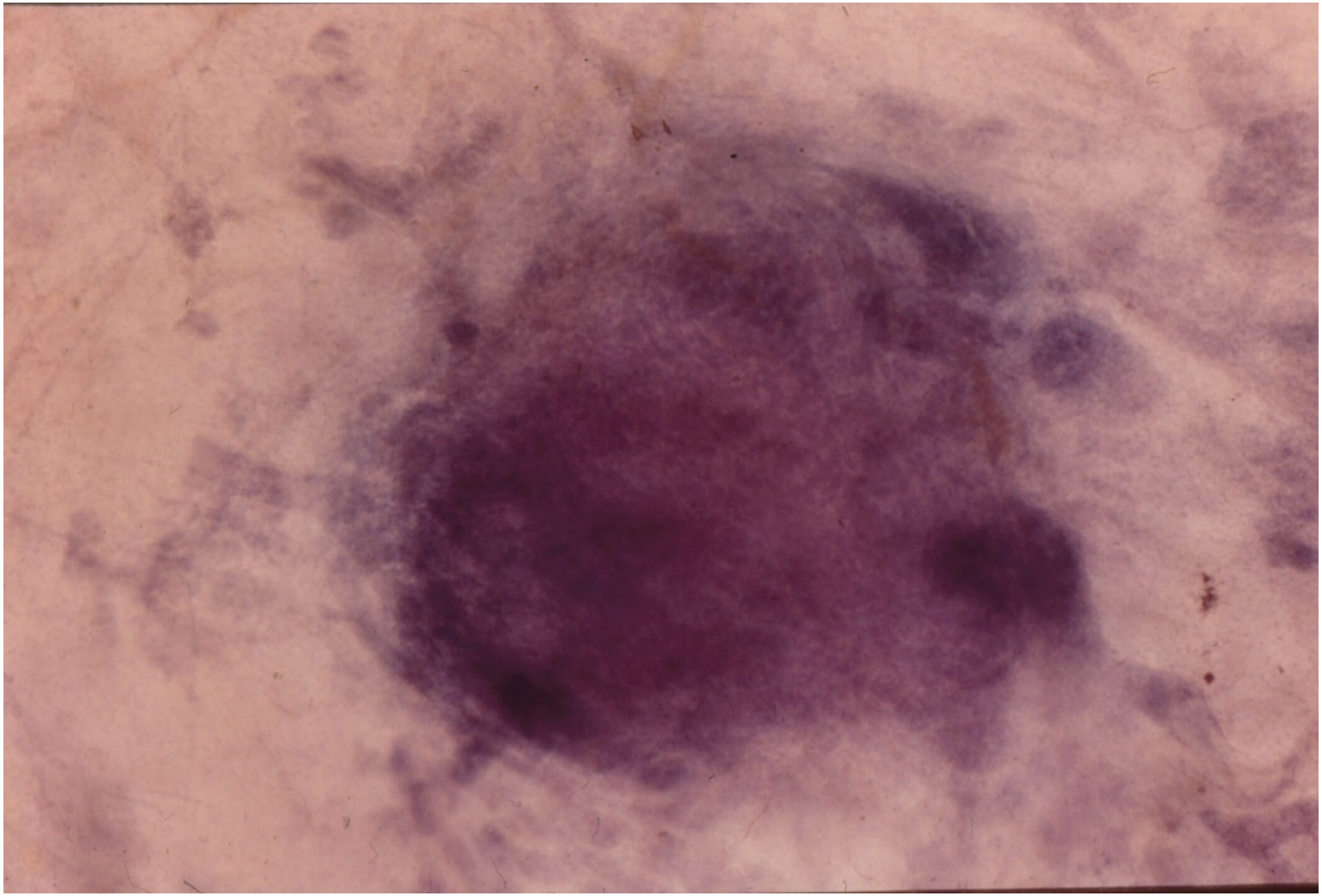
D-25-DCIS-Histo
ComedoCarcinoma



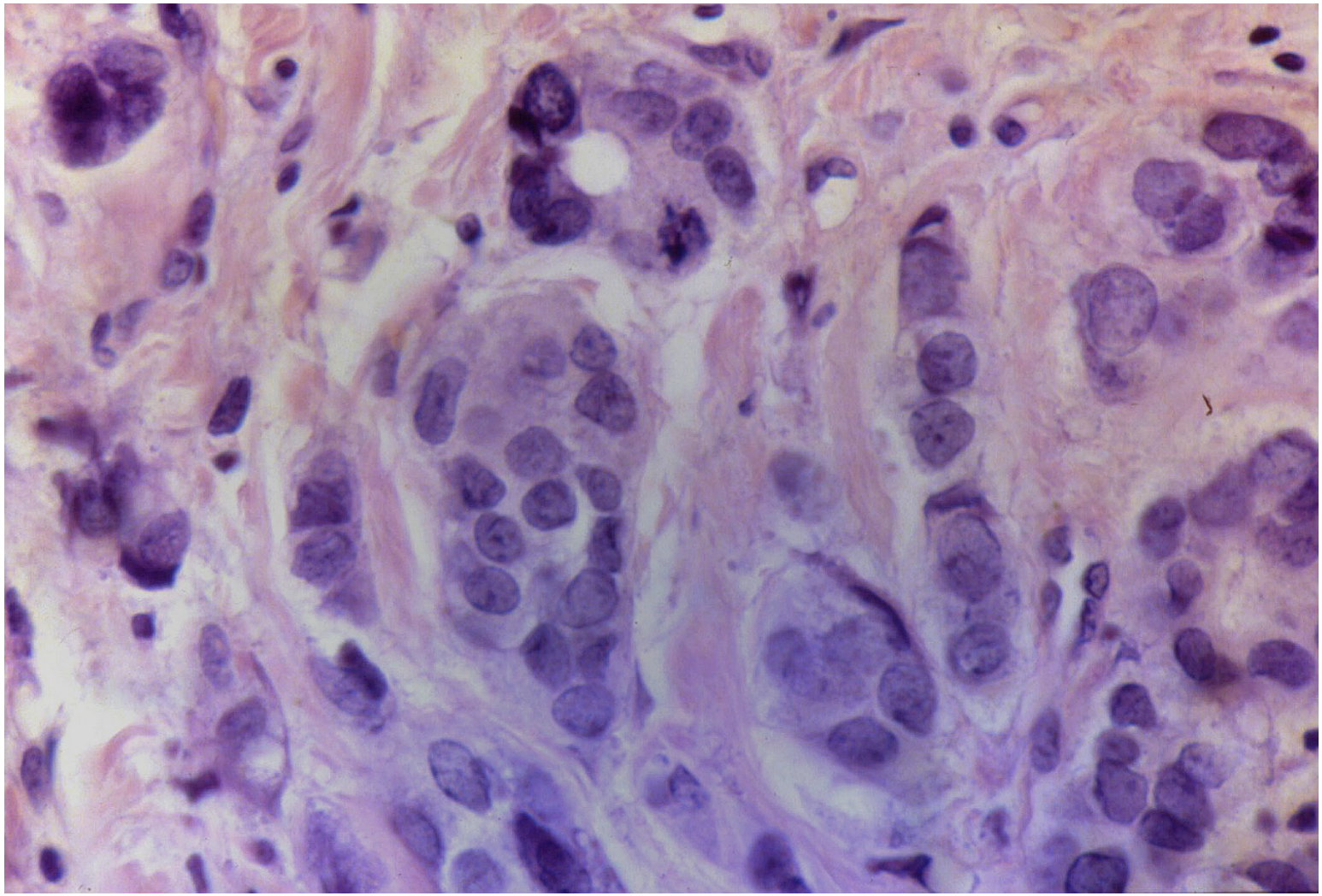
G-17-Infiltrating *duct* carcinoma-SG



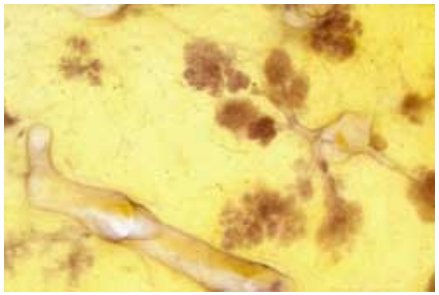
G-23-Scirrhous carcinoma-SG

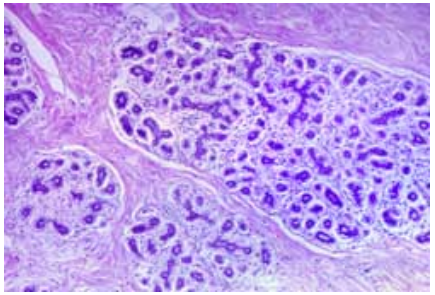


G-20-Carcinoma-Histo

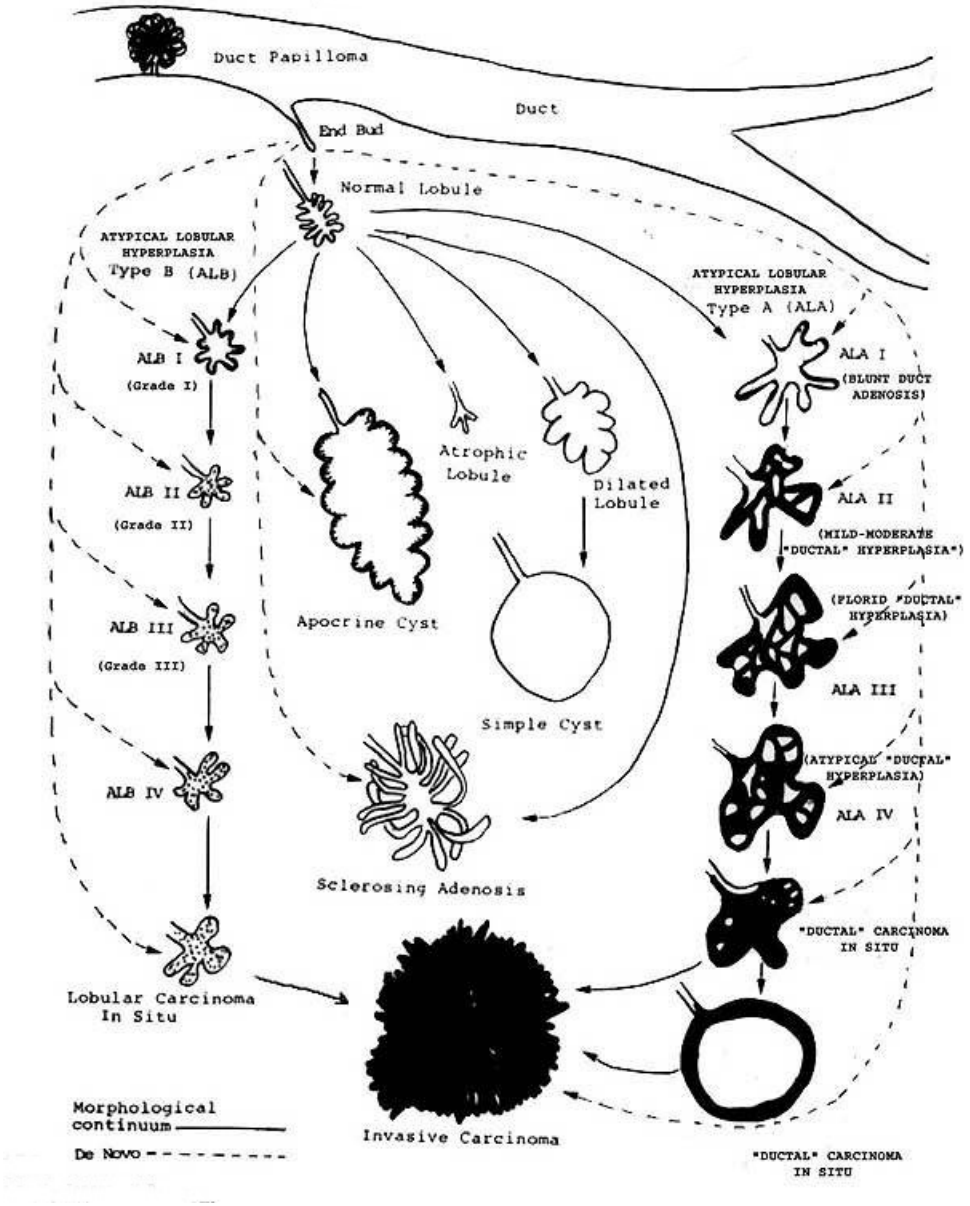


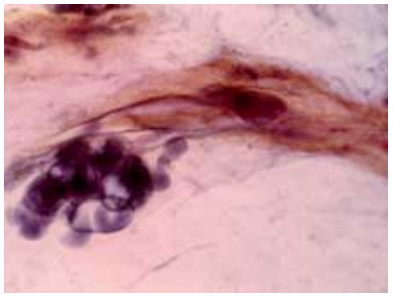
PROGRESSION OF THE NORMAL TDLU TO CARCINOMA AS DEPICTED IN 1973

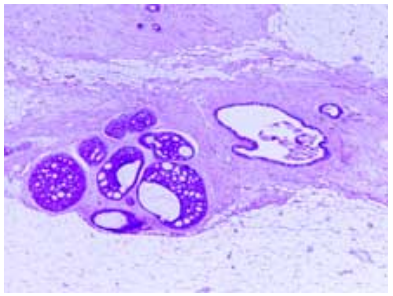




NORMAL TDLU







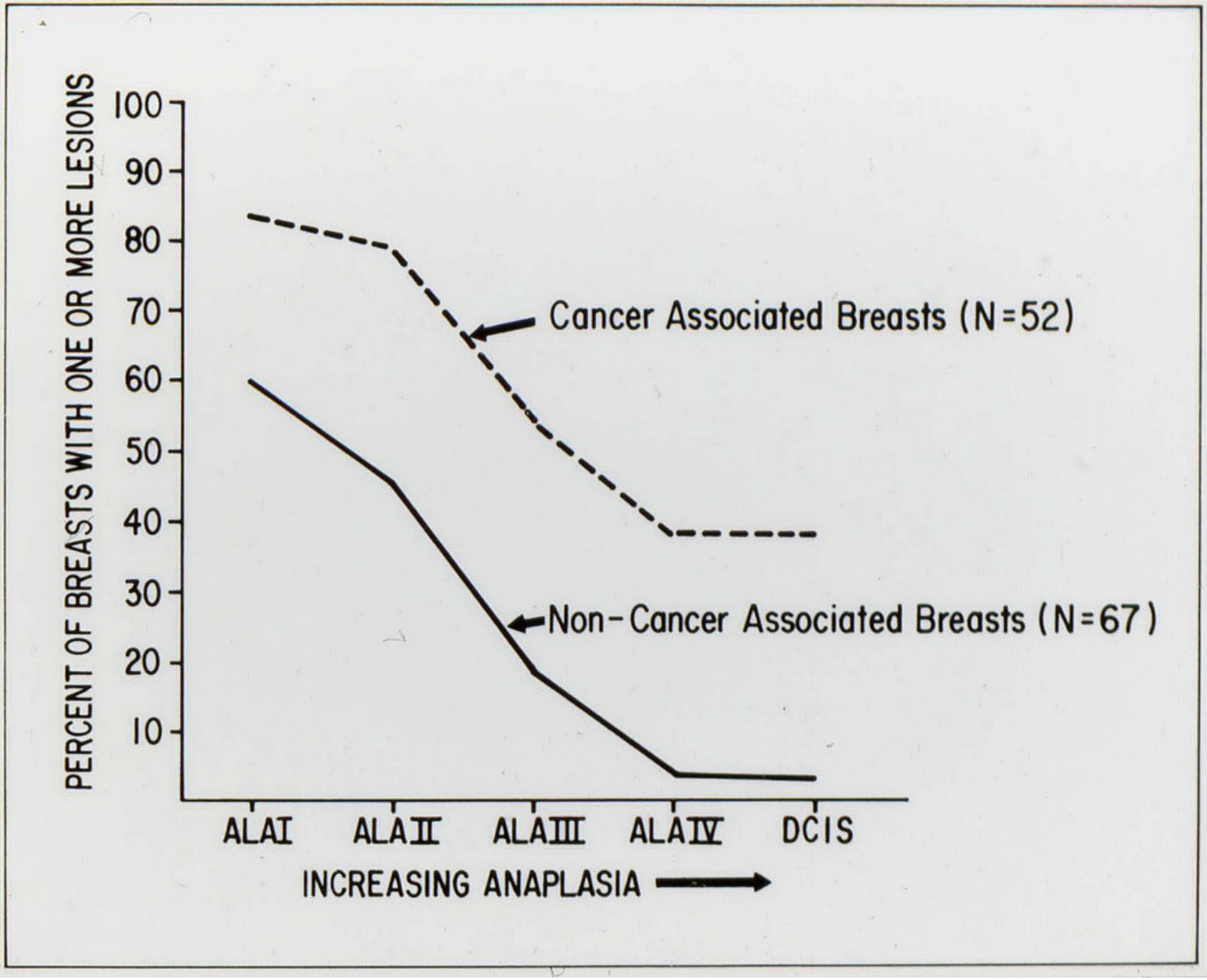
DCIS

Wellings, S.R and Jensen, H. M. On the Origin and Progression of Ductal Carcinoma in the Human Breast . JNCI, 1973, Vol 50, pp 1111 -1118.

Foulds, L. *Neoplastic Development* 1975. Academic Press, London

FEATURES OF PRENEOPLASTIC MAMMARY LESIONS

1. Increase in number with age.
2. Persist after the menopause.
3. More common in patients with breast cancer.
4. Early ovariectomy decreases their number.
5. Hyperplastic
6. Atypical epithelial cell populations grading to carcinoma-in-situ.


PERCENT OF BREASTS WITH ONE OR MORE LESIONS
100
90
80
70
60
50
40
30
20
10
Cancer Associated Breasts (N=52)
Non-Cancer Associated Breasts (N=67)
ALAI
ALAII
ALAIII
ALAIV
DCIS
INCREASING ANAPLASIA

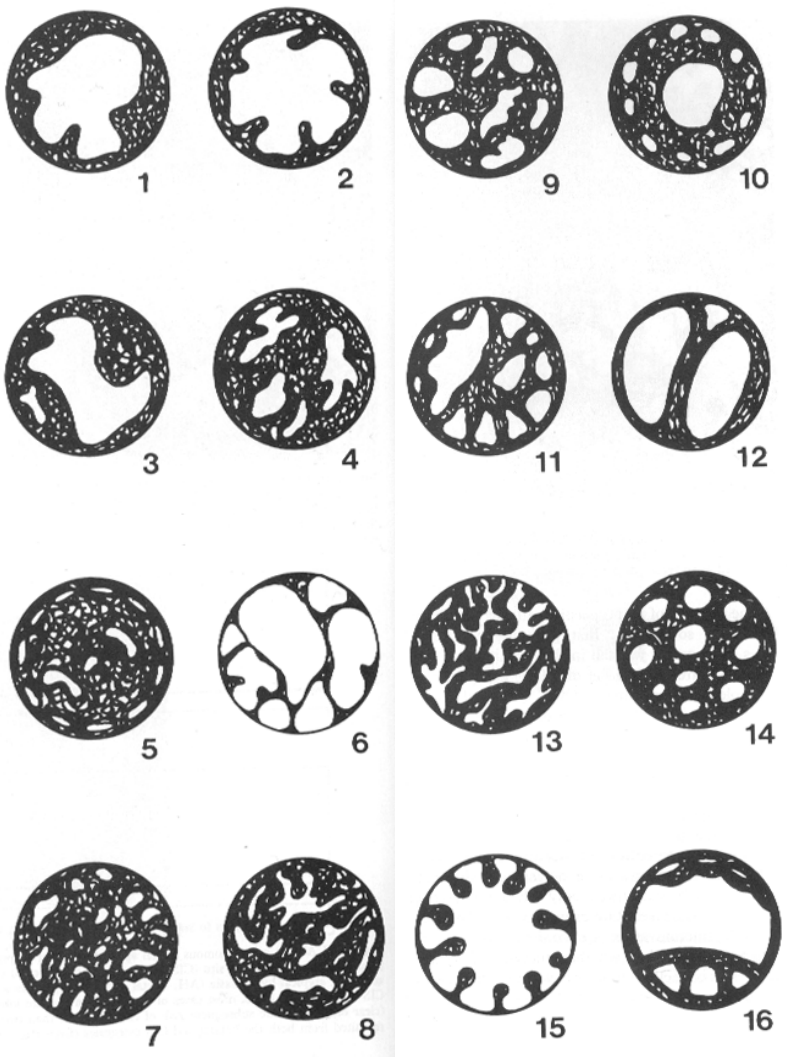
Risk factors for breast cancer in women with proliferative breast disease

W D Dupont, D L Page

. 1985 Jan 17;312(3):146-51.

•PMID: 3965932

(N=17,000)



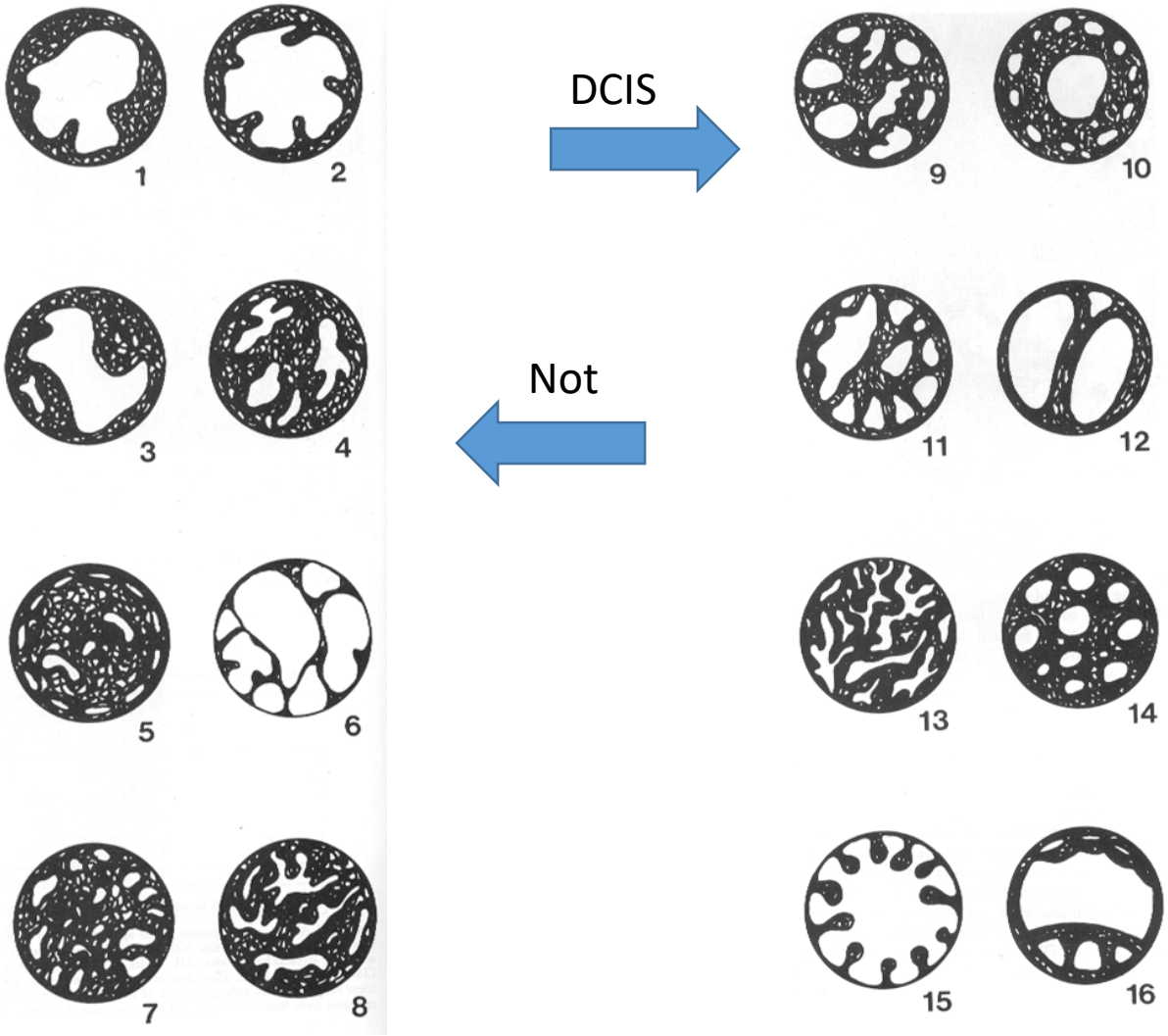
Evidence Based Medicine 1980s Style

David Page

Am J Epidemiol. 1987 May;125(5):769-79. doi: 10.1093/oxfordjournals.aje.a114594.

Breast cancer risk associated with proliferative disease, age at first birth, and a family history of breast cancer

W D Dupont, D L Page



DCIS is associated with an adjacent BrCa…

NIH NATIONAL CANCER INSTITUTE

Español

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PUBLICATIONS

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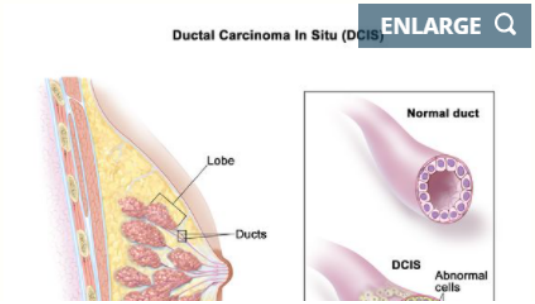
- Fact Sheets
- NCI Dictionaries
  - **Dictionary of Cancer Terms**
  - Drug Dictionary
  - Dictionary of Genetics Terms
- Blogs and Newsletters

DCIS

A condition in which abnormal cells are found in the lining of a breast duct. The abnormal cells have not spread outside the duct to other tissues in the breast. In some cases, DCIS may become invasive breast cancer and spread to other tissues. At this time, there is no way to know which abnormal cells could become invasive. Also called ductal carcinoma in situ and intraductal breast carcinoma.



OH WELL, YOU CAN'T WIN ALL THE TIME!

BUT

DO NOT FORGET THE BLACK SWAN

CLINICAL VS EXPERIMENTAL REASONING

- Guilt-by-Association: Medical logic is inferential. Based on the evidence, the diagnosis is inferred.

- Test-by-transplantation: Experimental logic requires experiments. In mice, the experiment requires transplantation

The Northern Hemisphere species of swan have pure white plumage

All Swans are white

Swans	
	
Mute Swans (*Cygnus olor*)	
Scientific classification	
Kingdom:	Animalia
Phylum:	Chordata
Class:	Aves
Order:	Anseriformes
Family:	Anatidae
Subfamily:	Anserinae
Tribe:	**Cygnini** Vigors, 1825
Genus:	***Cygnus*** Garsault, 1764

All Swans are not white!

Are all swans white?

Falsifiability or **refutability** of an assertion, hypothesis or theory is the logical possibility that it can be contradicted by an observation or the outcome of a physical experiment. That something is "falsifiable" does not mean it is false; rather, that *if* it is false, then some observation or experiment will produce a reproducible result that is in conflict with it.

For example, the assertion that "all swans are white" is falsifiable, because it is logically possible that a swan can be found which is not white. Not all statements that are falsifiable in principle are falsifiable in practice.[1] For example, "it will be raining here in one million years" is theoretically falsifiable, but not practically so.

The concept was made popular by Karl Popper, who, in his philosophical criticism of the popular positivist view of the scientific method, concluded that a hypothesis, proposition, or theory talks about the observable only if it is falsifiable.

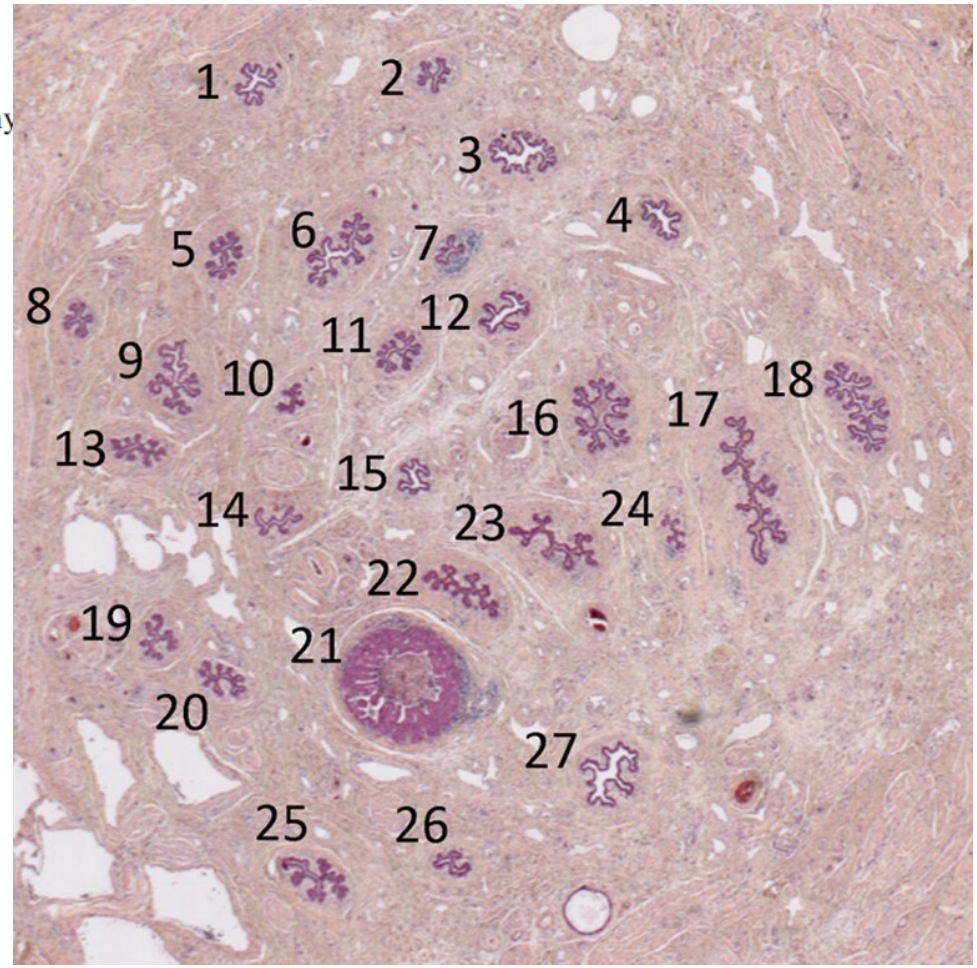
DOI 10.1007/s10549-005-9122-7

Preclinical study

Human breast duct anatomy, the 'sick lobe' hypothesis and intraductal approaches to breast cancer

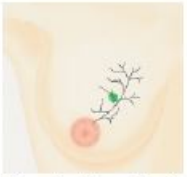
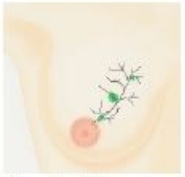
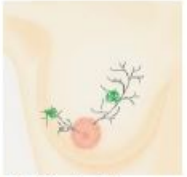
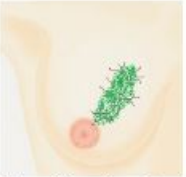
James J. Going[1] and Timothy J. Mohun[2]
[1]*Division of Cancer Sciences and Molecular Pathology, University of Glasgow, Glasgow, Scotland, UK;* [2]*Developmental Biology Division, National Institute for Medical Research, Mill Hill, London, UK*

Key words: anatomy

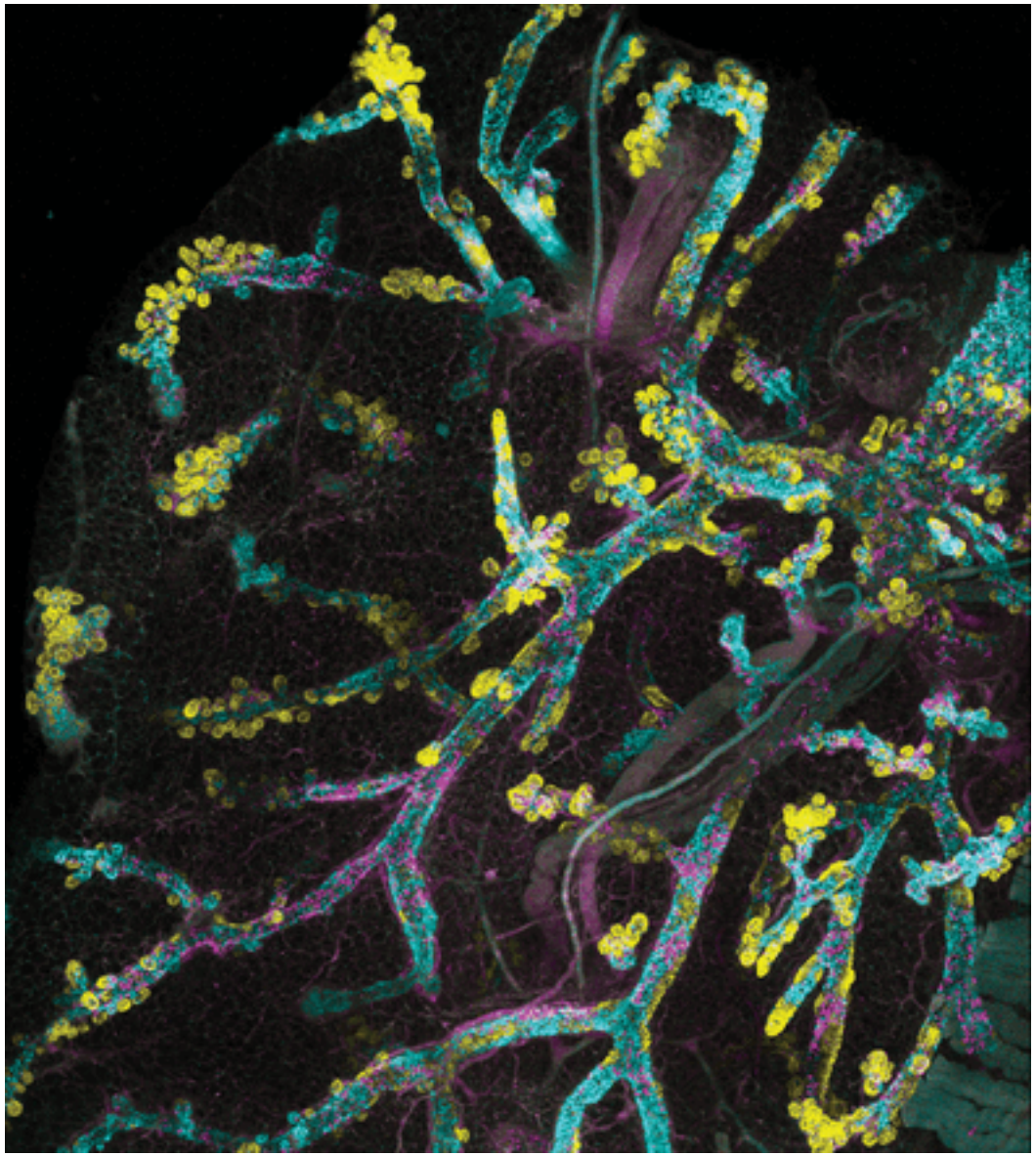



Are all swans white?

Table 1 Treatment options by aggregate (*in situ* & invasive) tumour distribution categories, according to t

Treatment phase	Classification			
	Unifocal	Multifocal	Multicentr	
Pattern of tumour presentation	Well-circumscribed single focus of *in situ* cancer only, invasive cancer only or both *in situ* and invasive cancer within the same focus	Well-circumscribed multiple foci of *in situ* and/or invasive cancer or both	Well-circumscribe multiple foci of *in* invasive cancer distributed in more than one lobe	l growth /asive cancer or both
Preoperative planning	 Single lobe, limited extent	 Single lobe, greater of resection	 Multiple lobes, multisegment resection	 Significant extent of tissue involvement
Surgical resection	Single segment/standard BCS with negative margins	Single segment/more extensive resection, possibly with oncoplastic techniques to achieve negative margins and acceptable cosmesis with BCS	Multisegment resection with negative margins for each individual foci to achieve BCS or mastectomy	Consider primary systemic therapy for downstaging for BCS, or mastectomy
Current adjuvant medical therapy	Guided by molecular subtyping & genomic profiling	Guided by size, molecular subtyping & nodal involvement	Guided by size, molecular subtyping & nodal involvement	Guided by size, molecular subtyping & nodal involvement
Current radiotherapy	Recommended for majority of cases if BCT performed	Recommended if BCT performed	Recommended if BCT performed	Usually aggressive and later stage, RT recommended for both BCT & mastectomy
Present molecular knowledge	Similar genetic alterations in precursor lesions and malignant disease	Greater proportion of tumour foci with homogenous mutations	Heterogenous tumour mutations associated with greater inter-foci tumour distance	–
Future possibilities	Molecular characteristics of epithelial cells in sick lobe or cancerized field may inform surgical margins, provide prognostic and predictive information for medical therapy & radiotherapy			

ORIGINS: THE TDLU



HER2 Isoforms Uniquely Program Intratumor Heterogeneity and Predetermine Breast Cancer Trajectories During the Occult Tumorigenic Phase

Joshua D. Ginzel1, Chaitanya R. Acharya2, Veronica Lubkov1,2, Hidetoshi Mori3, Peter G. Boone1,2, Lauren K. Rochelle1, Wendy L. Roberts1, Jeffrey I. Everitt4, Zachary C. Hartman2,4, Erika J. Crosby2, Lawrence S. Barak1, Marc G. Caron1, Jane Q. Chen3, Neil E. Hubbard3, Robert D. Cardiff3, Alexander D. Borowsky3, H. Kim Lyerly2,5, and Joshua C. Snyder1,2

MOLECULAR CANCER RESEARCH | CELL FATE DECISIONS August 10, 2021

PROGESSION
TO INVASIVE NEOPLASIA

NEXT WEEK

SESSION 4

See you then!

OVERDIAGNOSIS

DEFINITION: A SETTING IN WHICH DIAGNOSES INCREASE (OFTEN MARKEDLY) IN A POPULATION THAT HAS A STABLE OR DECLINING RATE OF DEATH FROM THAT DISEASE.

Where are we?
How did we get here?
What we have ignored!

Welch, HG and Black, WC. JNCI 102:605-613 (2010). From a presentation by Barry Kramer, NCI

CLINICAL VS EXPERIMENTAL REASONING

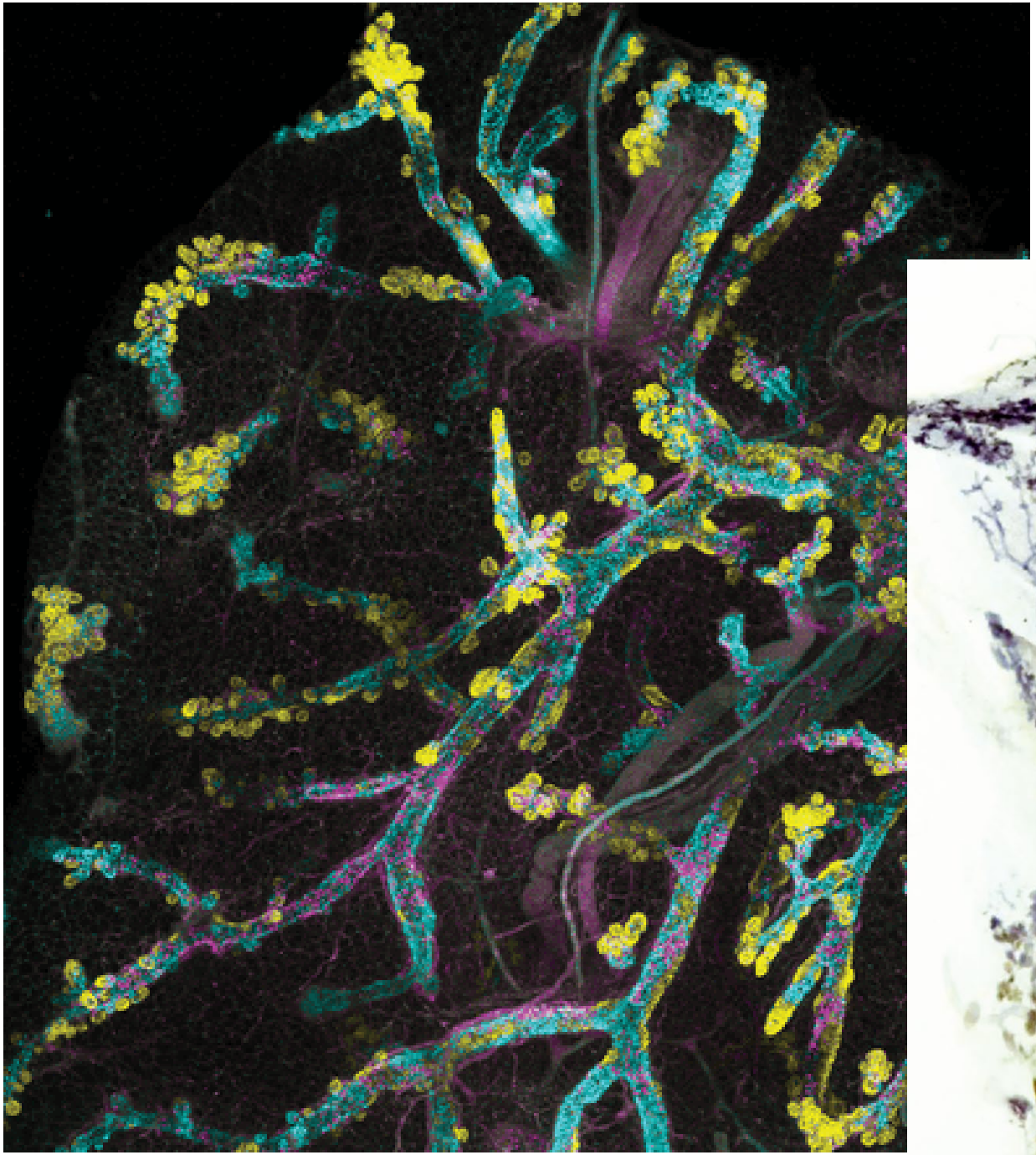
- Guilt-by-Association: Medical logic is inferential. Based on the evidence, the diagnosis is inferred.

- Test-by-transplantation: Experimental logic requires experiments. In mice, the experiment requires transplantation

CLINICAL VS EXPERIMENTAL BIOLOGY

- **Human**: observation, demographics, epidemiology and statistical analysis of heterogeneous populations ***(guilt-by-association)***.
  - Experimental: tissue culture and xenografts.

- **Mouse**: observation, demographics, genetic engineering, and statistical analysis of homogeneous populations.
  - Experimental: Test by transplantation into syngeneic host and orthotopic sites. (***Test-by-transplantation***).



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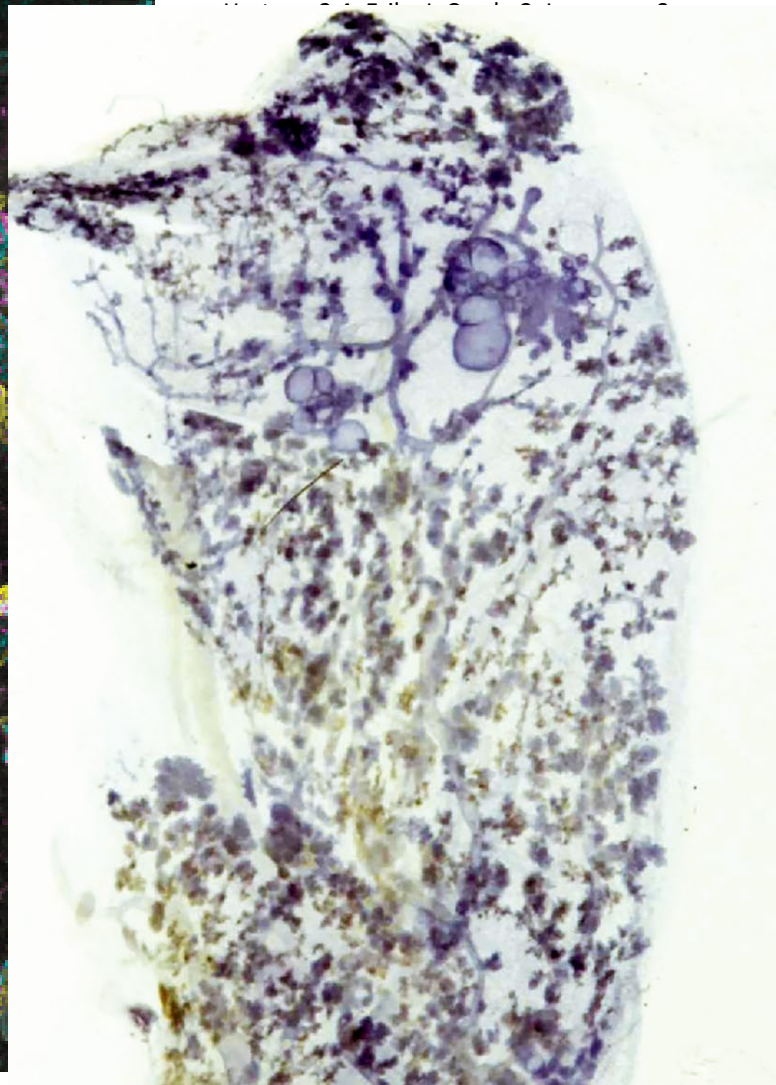

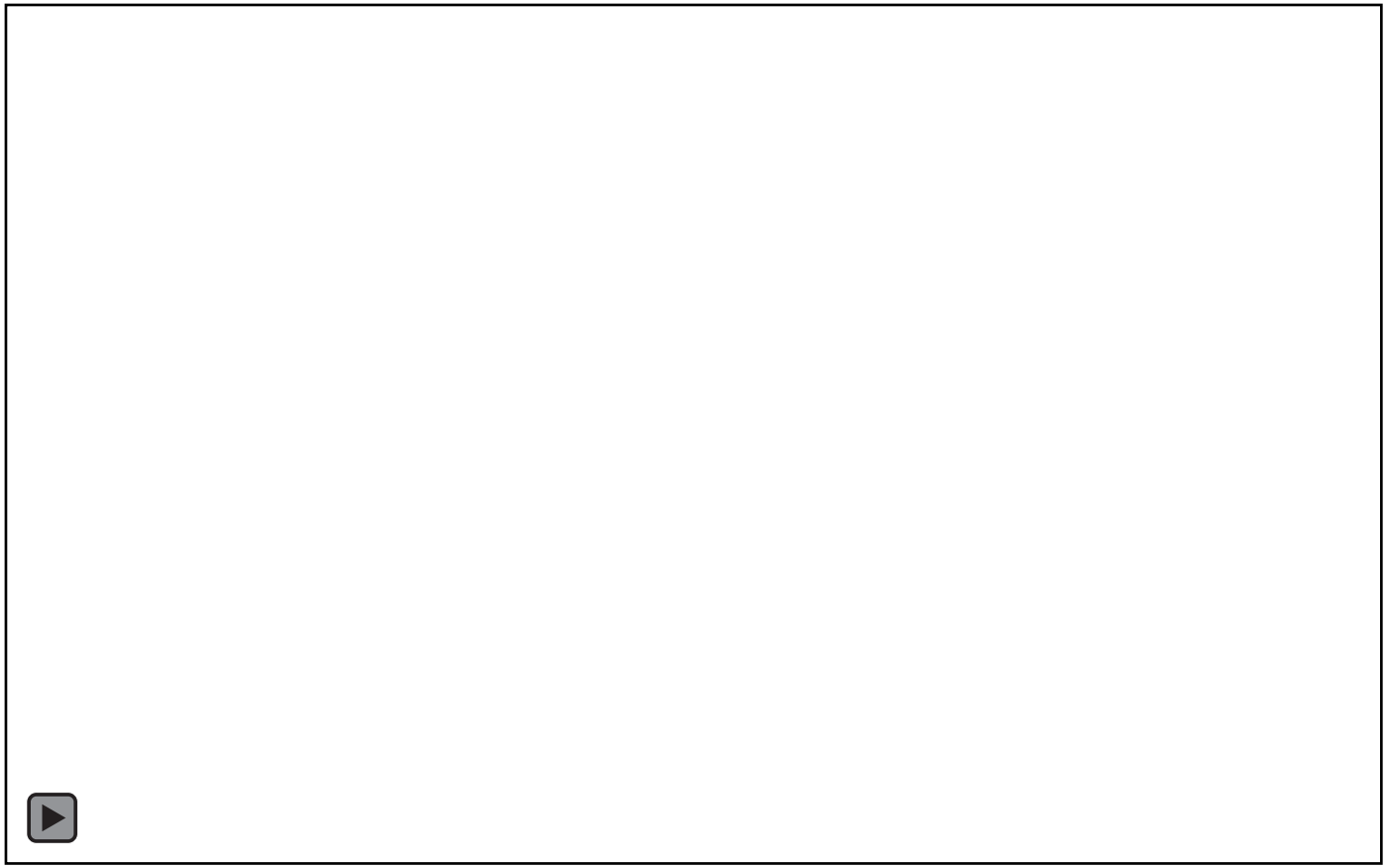

Table 1: Taxonomy of breast cancer based on normal cell phenotype predicts outcome

Table 1
Cellular differentiation states in normal human breast lobules

Cell type		ER	AR	VDR	K5/14/17	Ki67	Cld-4	K7/8/18	CD10/SMA/p63
Luminal									
L1 (HR0)	Ki67$^+$	–	–	–	–	+	+	+	–
L2 (HR0)	K18$^+$	–	–	–	–	–	+	+	–
L3 (HR0)	K5$^+$	–	–	–	+	–	+	+	–
L4 (HR1)	ER$^+$	+	–	–	–	–	+	+	–
L5 (HR1)	AR$^+$	–	+	–	–	–	+	+	–
L6 (HR1)	VDR$^+$	–	–	+	–	–	+	+	–
L7 (HR1)	K5$^+$VDR$^+$	–	–	+	+	–	+	+	–
L8 (HR2)	ER$^+$AR$^+$	+	+	–	–	–	+	+	–
L9 (HR2)	ER$^+$VDR$^+$	+	–	+	–	–	+	+	–
L10 (HR2)	AR$^+$VDR$^+$	–	+	+	–	–	+	+	–
L11 (HR3)	ER$^+$AR$^+$VDR$^+$	+	+	+	–	–	+	+	–
Myoepithelial									
My1	CD10$^+$	–	–	–	–	–	–	–	+
My2	K5$^+$	–	–	–	+	–	–	–	+

IHC of normal breast sections from multiple donors (n = 36) with 14 different markers identified multiple normal breast cell subtypes. We grouped the 11 differentiation states in the luminal layer of human breast lobules (L1–L11) into HR0–HR3. All luminal cells expressed K7/8/18 and Cld-4. In the myoepithelial

J Clin Invest DOI: 10.1172/JCI70941

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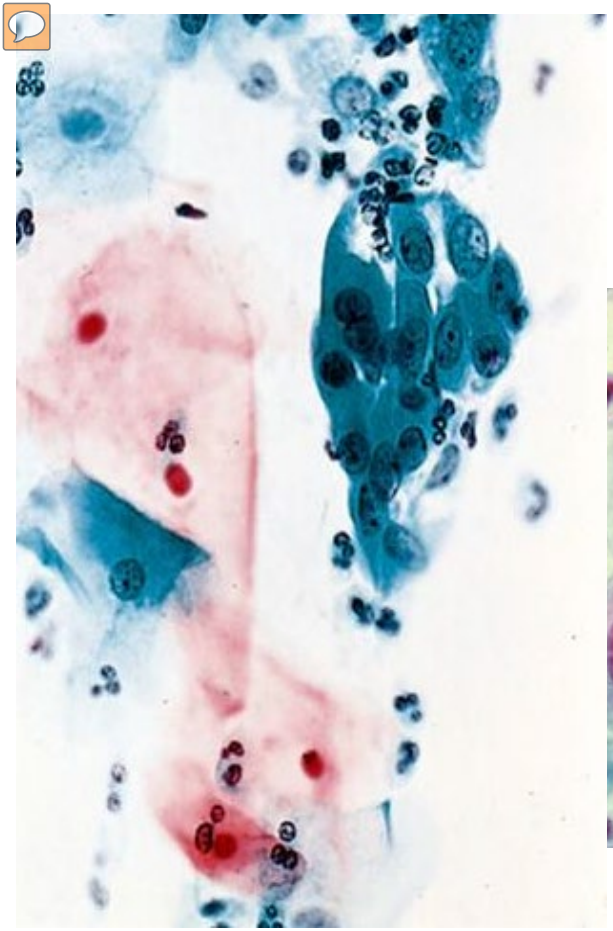
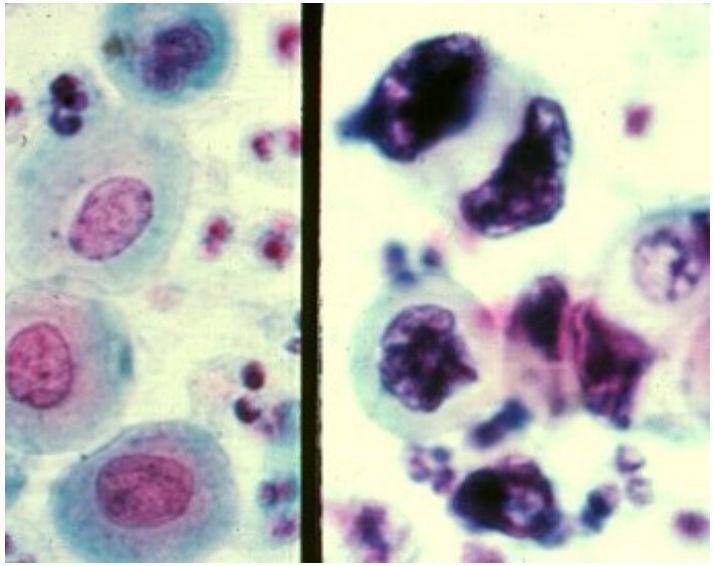
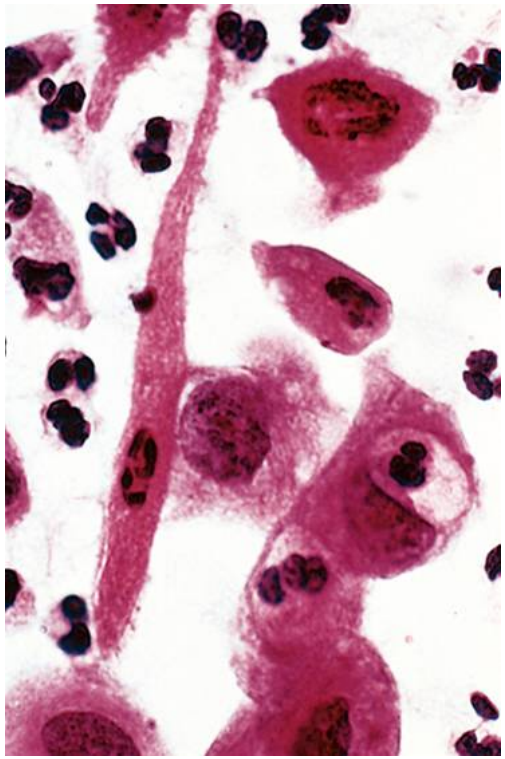
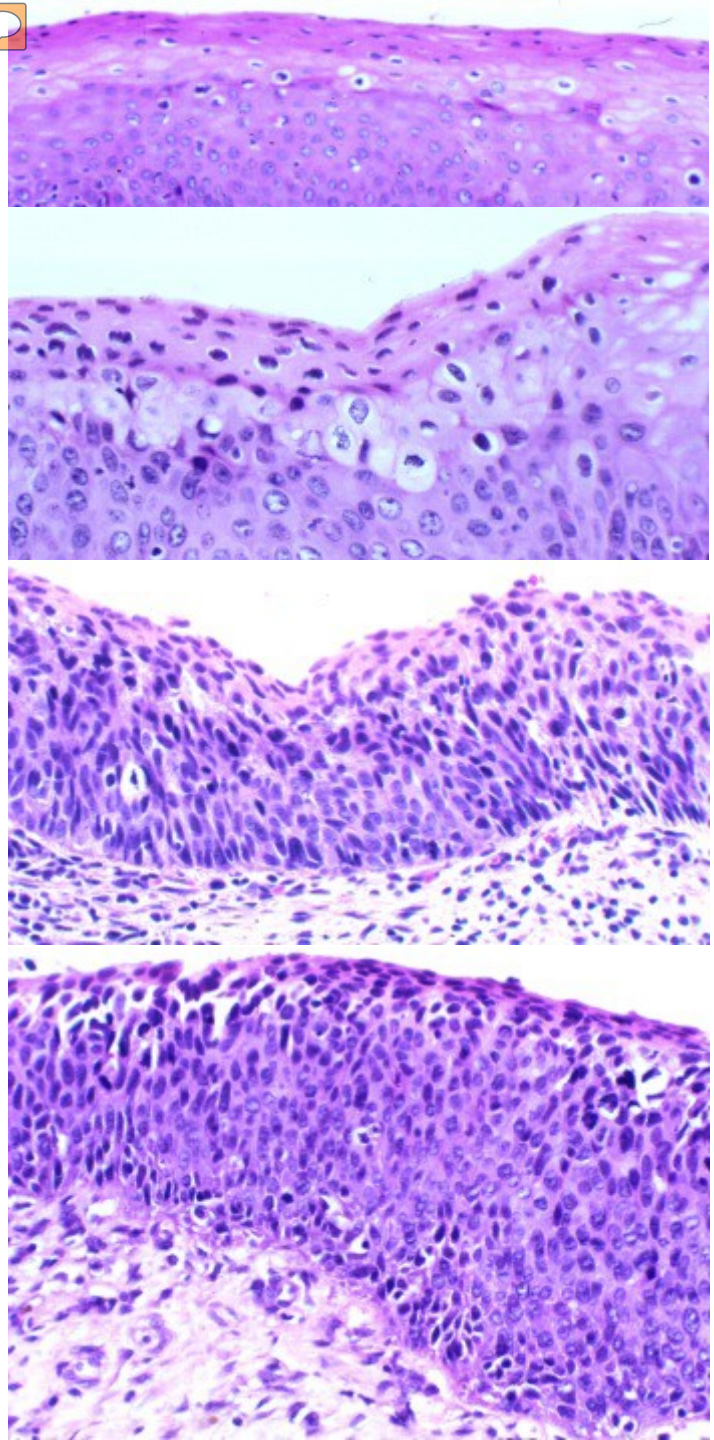


Normal Human Cervical Cells





Malignant Human Cervical Cells



Cervical Precancer Progression

CIN I

Low Risk HPV Type Infection

ICD

CaCx

CIN 3

CIN 2

CIN 1

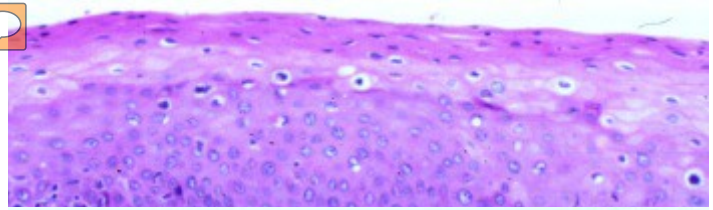
CIN II

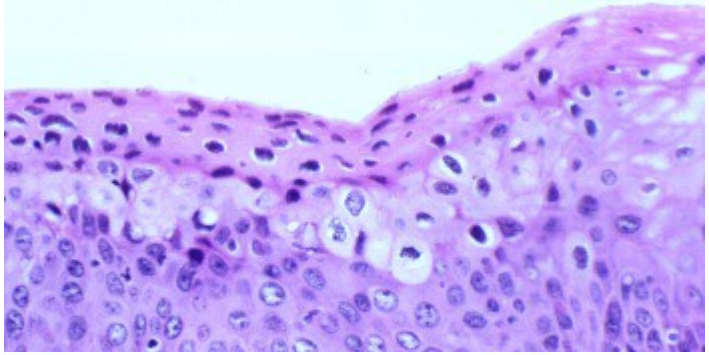
Morphological Continuum

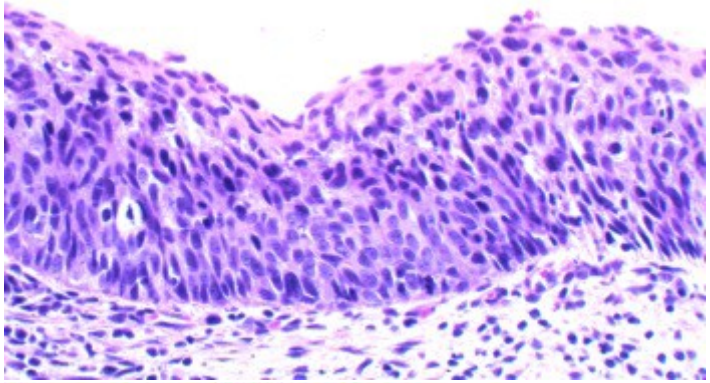
CIN III

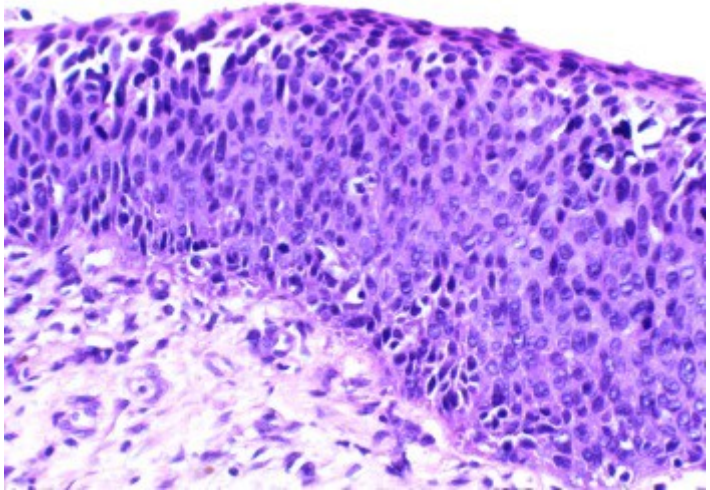
CANCER (Invasion)

Papanicolaou
1929









Cervical Precancer Progression

CIN I

CIN II

CIN III

CANCER (Invasion)

George Papanicolaou

Papanicolaou, G. New Cancer Diagnosis. Proceedings Third Race Betterment Congress, 1928. p. 528.