



INTRADUCTAL PROLIFERATIVE LESIONS OF THE BREAST

Juan Rosai, M.D.

Park City Pathology Workshop
9 February 2015



- **PRECANCEROUS**
- **PREMALIGNANT**
- **PRECURSOR**
- **PREINVASIVE**
- **ATYPICAL HYPERPLASIA**

- **INTRAEPITHELIAL CARCINOMA**
- **CARCINOMA IN SITU (CIS)**





Fred Stewart



ATLAS OF TUMOR PATHOLOGY

Section IX—Fascicle 34

TUMORS OF THE BREAST

by

Fred W. Stewart, M. D.

Pathologist to Memorial Hospital

Professor of Pathology

Cornell University Medical School

Attending Pathologist of New York Hospital, New York City

1950



PRECANCEROUS LESIONS

“Personally, I do not think in terms of ‘precancerousness’ [...] I do not feel that I possess any exact information on where the stage of irreversibility begins. One thing is probable, and that is that it begins before the microscope can detect it.

Really, I do not know what “precancerous” means.

F W Stewart (1950)



HOW SHALL WE NAME THEM ?

- **PRECANCEROUS**
- **PREMALIGNANT**
- **PRECURSOR**
- **PREINVASIVE**
- **ATYPICAL HYPERPLASIA**

- **INTRAEPITHELIAL CARCINOMA**
- **CARCINOMA IN SITU (CIS)**



Human Pathology (2007) 38, 1447–1453

On being a pathologist

Of tissues, cells, and molecules: reminiscences of an old pathologist

Leopold G. Koss MD

Department of Pathology, Montefiore Medical Center/Albert Einstein, College of Medicine, Bronx, NY 10461, USA



“To my knowledge, the credit for the first clear description of ‘intraepithelial carcinoma’ as a precursor lesion of invasive cancer [...] goes to an obscure gynecologist named Schauenstein from the city of Graz in Austria”

L.G. Koss (2007)



Schauenstein W.

Histologische Untersuchungen über
atypisches Plattenepithel an der Portio
und an der Innerfläche der Cervix
uteri.

Arch Gynak 1908; 85:576



Zur Kenntnis
des
Uteruskarzinoms.

Monographische Studie über Morphologie, Entwicklung,
Wachstum, nebst Beiträgen zur Klinik der Erkrankung.

Carcinoma in situ

Dr. J. Schottlaender und **Dr. F. Kermauner**

a. o. Professor und Vorstand des Laboratoriums
der II. Frauenklinik

Privatdozent

an der Universität Wien.

1912





ALBERT C. BRODERS



JOUR. A. M. A.
Nov. 12, 1932

CARCINOMA IN SITU CONTRASTED
WITH BENIGN PENETRATING
EPITHELIUM

ALBERT C. BRODERS, M.D.
ROCHESTER, MINN.



“Carcinoma in situ is a condition in which malignant cells or their progeny are found in or near positions occupied by their ancestors before the ancestors underwent malignant transformation”

A. C. Broders (1932)



AM J OBST GYNECOL, OCT 1952

A DEBATE

**WHAT IS CANCER IN SITU OF THE CERVIX?
IS IT THE PREINVASIVE FORM OF TRUE CARCINOMA?***

ARTHUR T. HERTIG, M.D., AND PAUL A. YOUNGE, M.D., BOSTON, MASS.

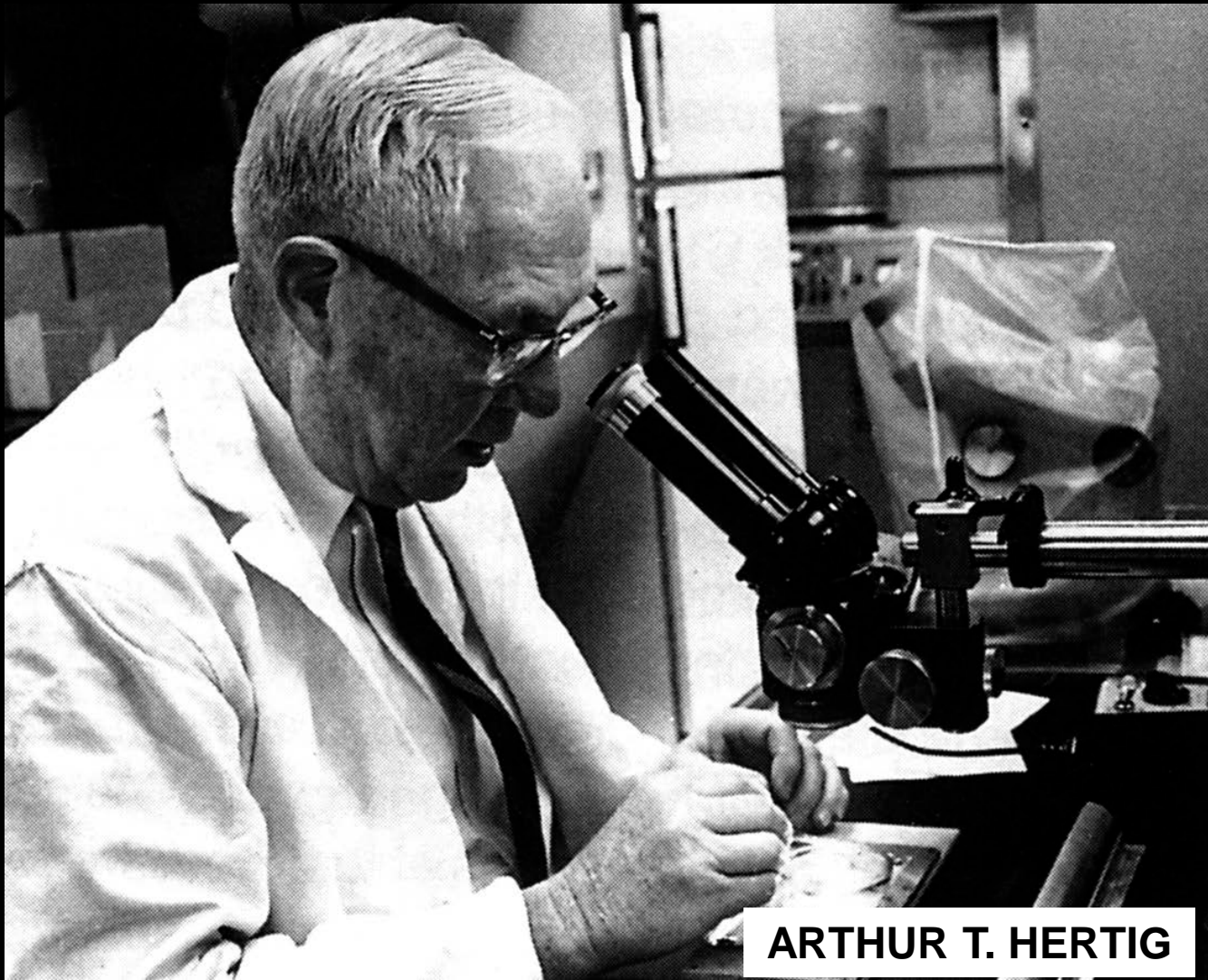
*(From the Departments of Pathology and Gynecology, Harvard Medical School, Boston, and
the Free Hospital for Women, Brookline)*

**CARCINOMA IN SITU OF THE CERVIX: A GENERAL
CONSIDERATION*†**

JOHN L. MCKELVEY, M.D., MINNEAPOLIS, MINN.

(From the University of Minnesota Medical School)





ARTHUR T. HERTIG



CIS

- It is coexistent with
- It precedes
- It is followed by
- It resembles

INVASIVE
CARCINOMA

A. T. Hertig (1952)



“ CIS is the preinvasive stage
of squamous cell carcinoma
of the cervix”

A. T. Hertig (1952)





John L. McKelvey



“To call atypical lesions malignant and treat them as cancer is only to fog our own critical intellectual processes and to harm the patient by putting the fear of cancer permanently in her mind”

J. L. McKelvey (1952)



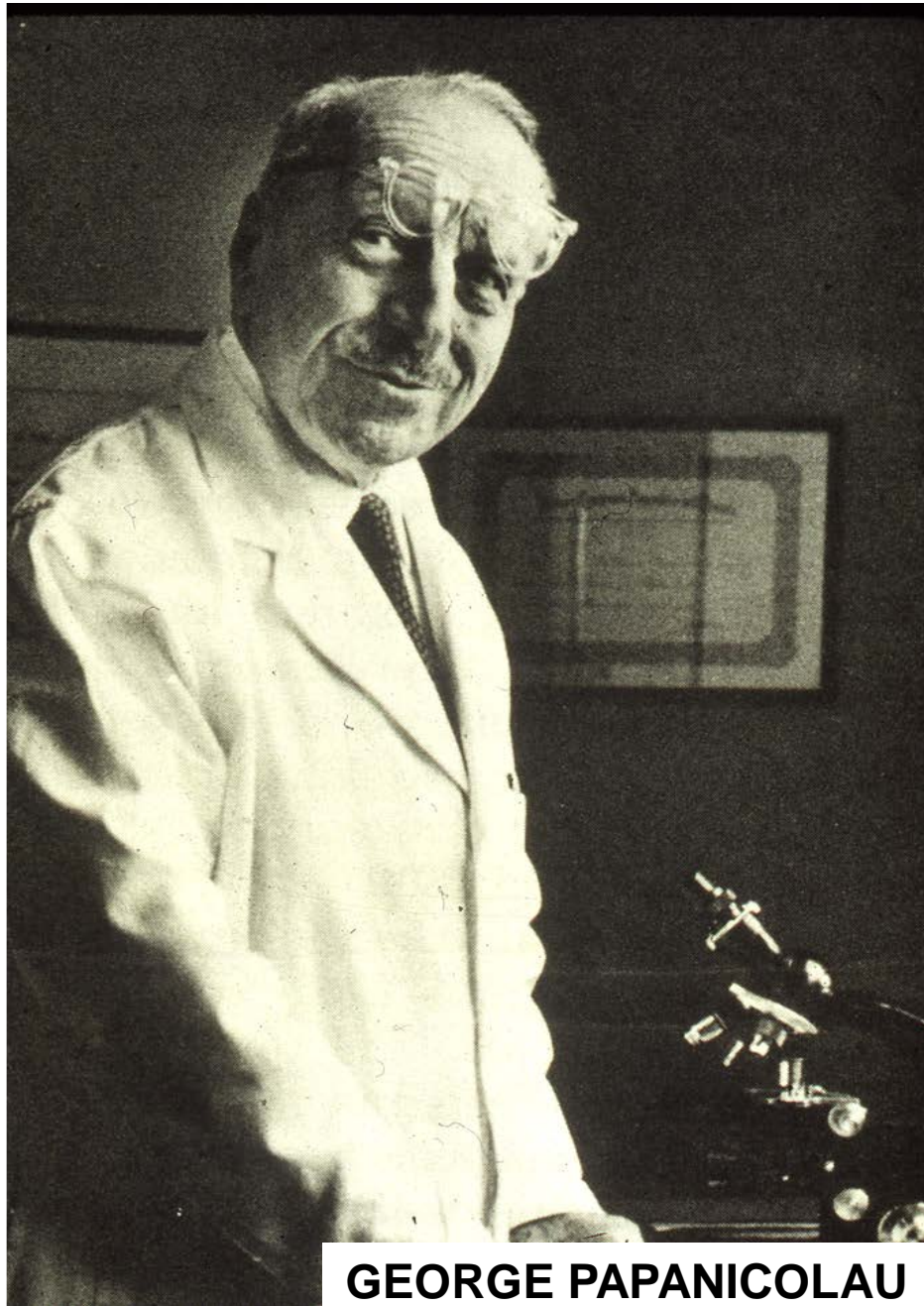
"It would seem wise to drop the term
CIS as it applies to the squamous
epithelial lesions of the cervix"

J. K. McKelvey (1952)



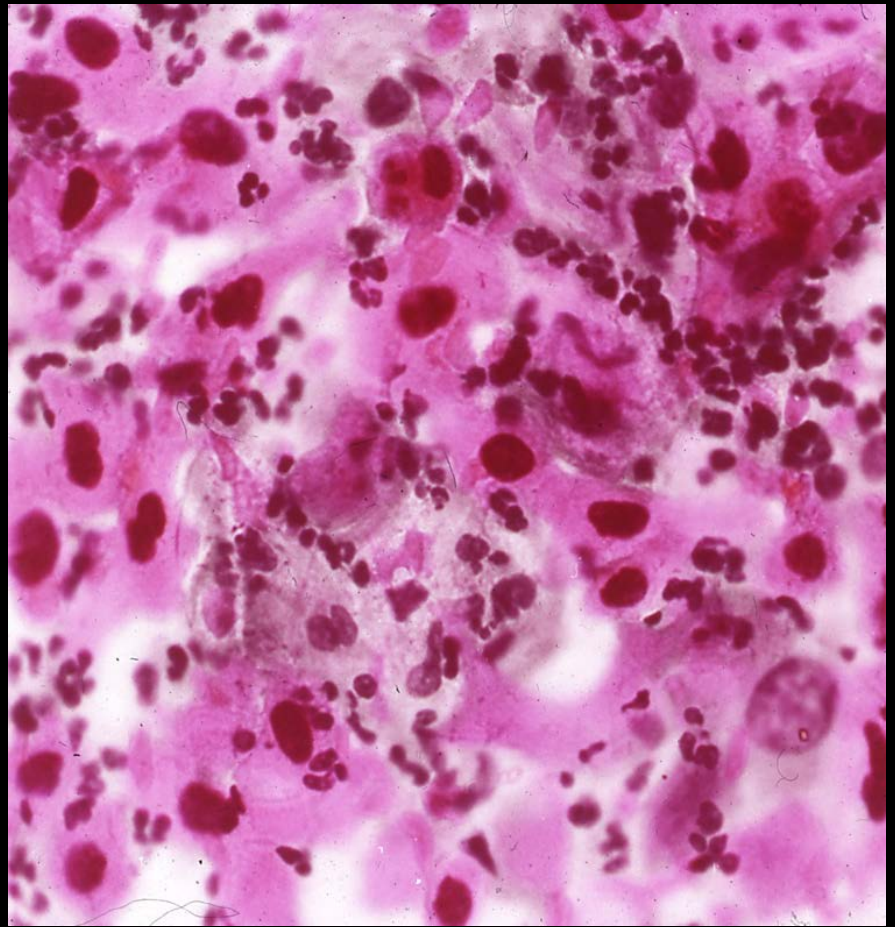
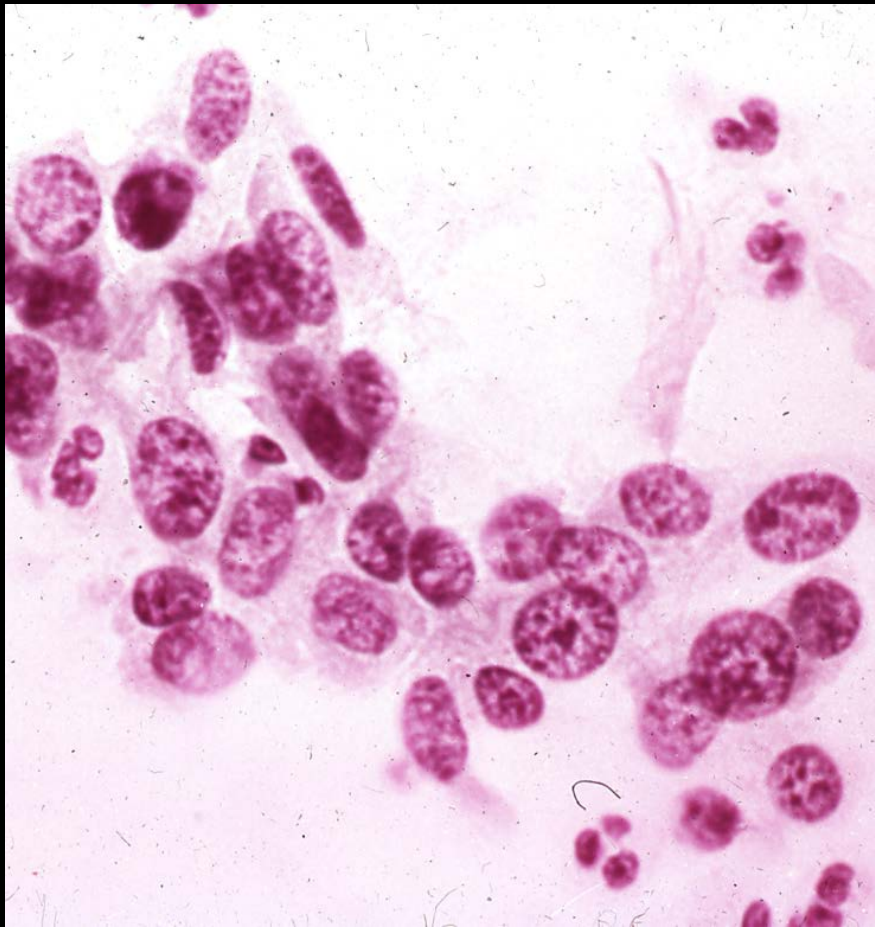
CARCINOMA IN SITU (CIS)

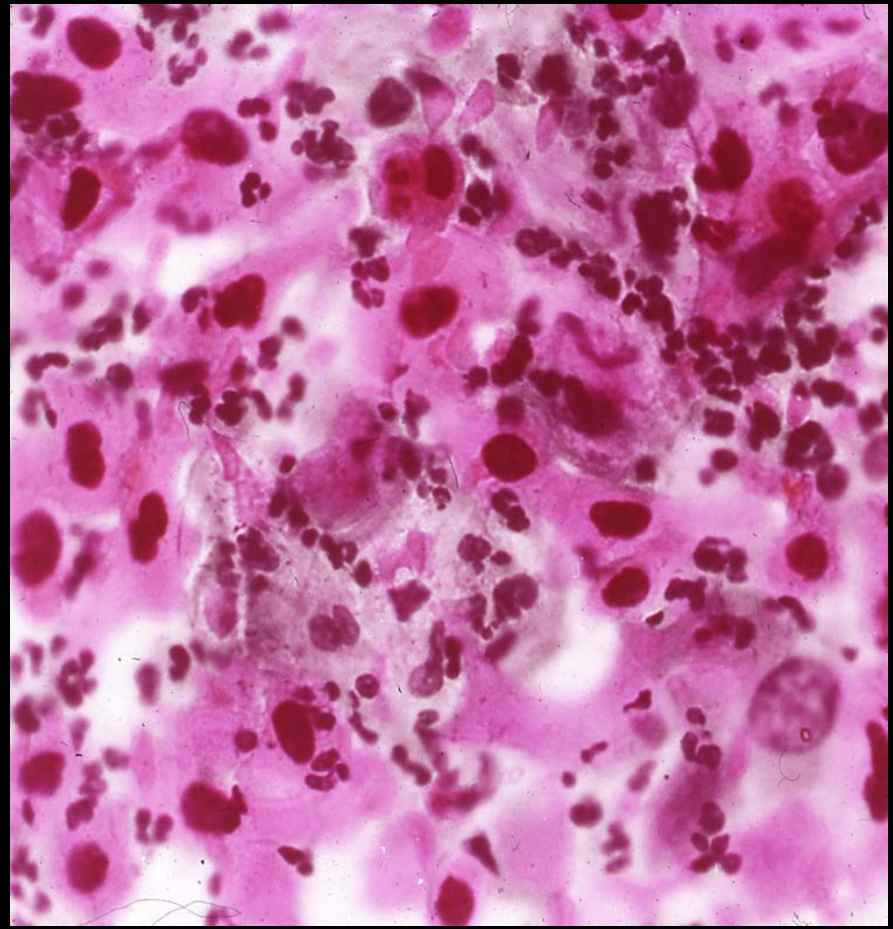
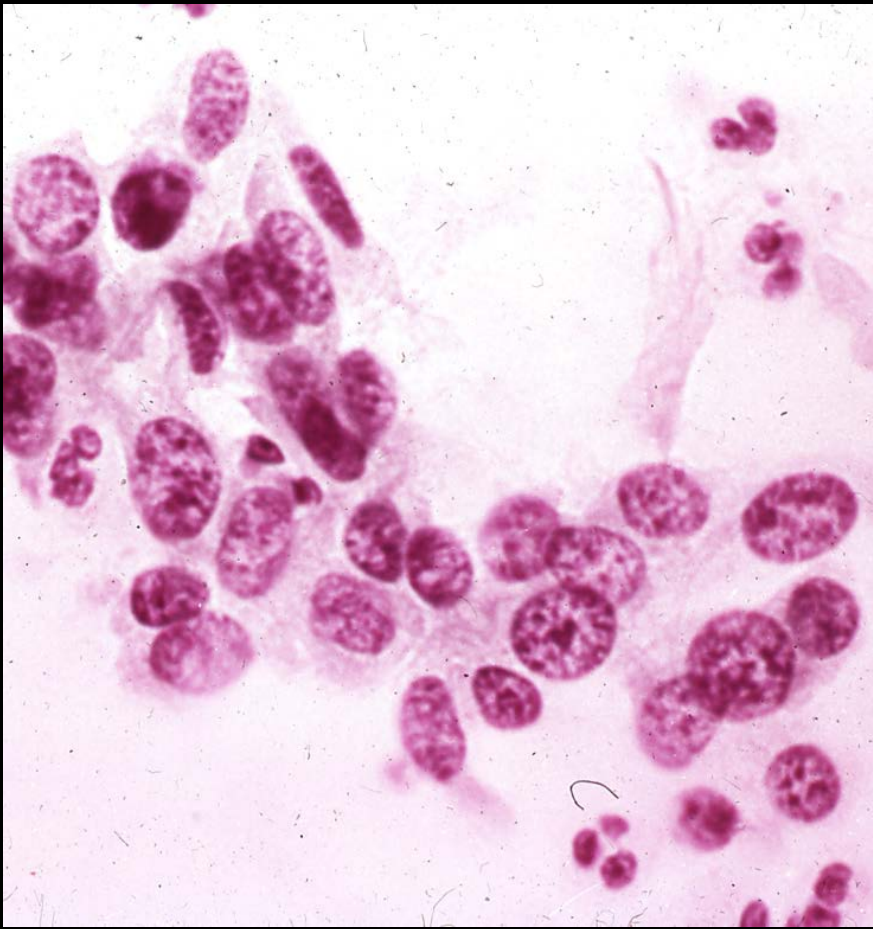




GEORGE PAPANICOLAU







"The term 'carcinoma in situ' or 'intraepithelial carcinoma' should be retained for the first group, whereas the second one should be designated by a new term which would not necessarily suggest malignancy"

G. Papanicolau (1949)



In a recent discussion of this point, the term dysplasia was proposed to specify such cytologic changes as would be suggestive of, but not conclusive, for malignancy."

George Papanicolaou (1949)





WILLIAM OBER



WILLIAM B. OBER

- GHON BUT NOT FORGOTTEN
- FRIEDRICK ZHAN: WHAT IS MY LINE?
- EMIL ZUCKERKANDL AND HIS DELIGHTFUL LITTLE ORGAN
- BOTTOMS UP !



**LEYDIG, SERTOLI, AND REINKE:
THREE ANATOMISTS WHO WERE ON THE BALL**

WILLIAM B. OBER AND CHE SCIAGURA

Pathol Annu 16 [Pt.1]: 1-13, 1981.



GOLD MEDAL OF THE
MECONIUM SOCIETY



CARCINOMA IN SITU

DYSPLASIA



- **CARCINOMA IN SITU**
- **DYSPLASIA**

Mild

Moderate

Severe





RALPH RICHART



“We wish to propose, on the basis of the present data and other experimental evidence, that the continuous nature of the alterations leading to invasive squamous cell carcinoma be recognized and that the artificial terminologic distinction between dysplasia and CIS be abandoned”

Richard & Barrow (1969)



“Thus, we propose the term ‘cervical intraepithelial neoplasia’, subclassified in class 1 through 3 based on the degree of differentiation, where class 1 would correspond to mild dysplasia and class 3 to CIS”

Richart & Barrow (1969)



CERVICAL INTRAEPITHELIAL NEOPLASIA (C.I.N.)

CIN I

CIN II

CIN III



Buckley, Butler & Fox (1992)

I. It emphasizes the biological and clinical unity of the two apparently discrete conditions of dysplasia and carcinoma in situ



II. It removes from the pathologist the difficult and subjective task of differentiating between dysplasia and carcinoma in situ

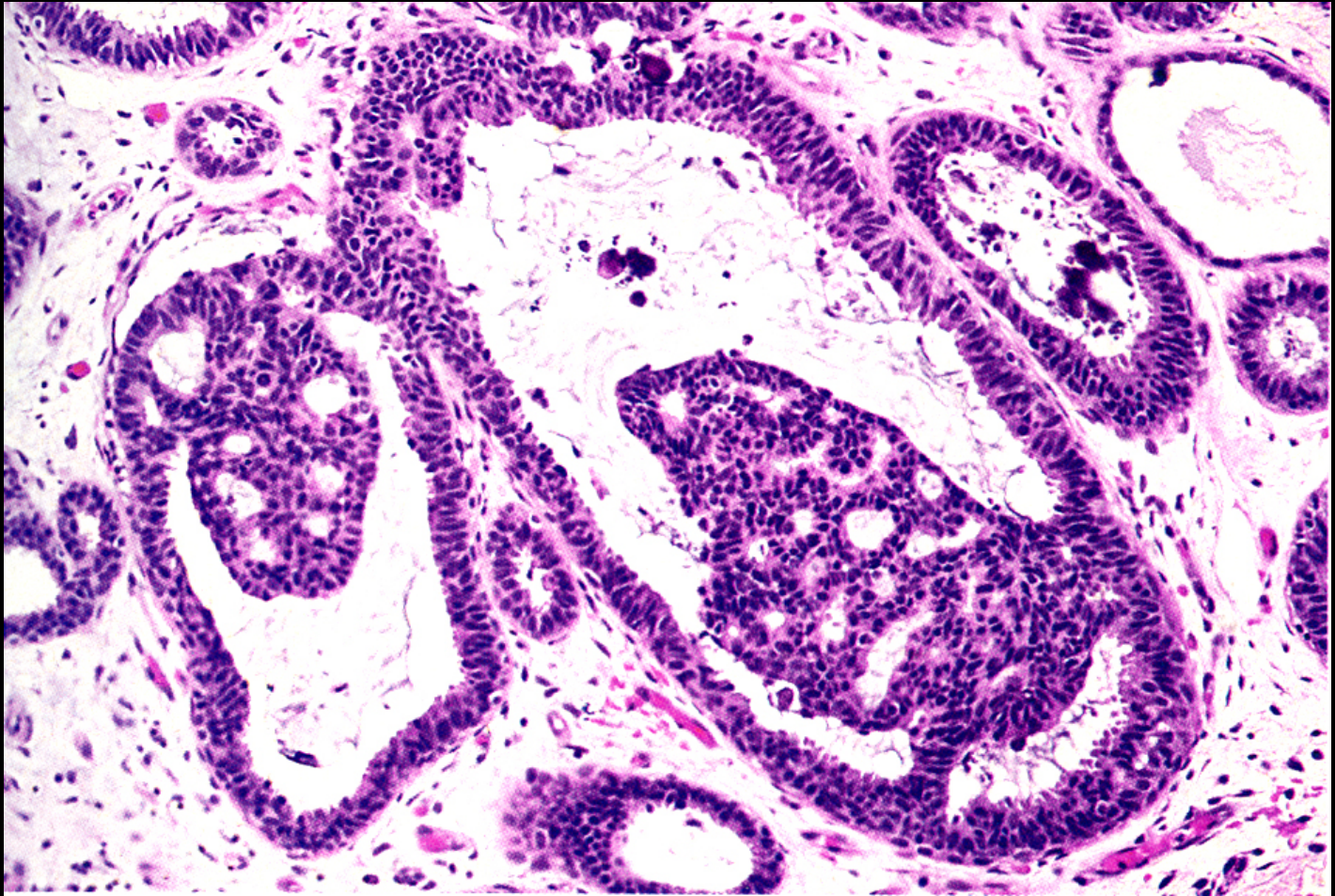


III. It allows for a unity of therapeutic approach and prevents the state of affairs where a diagnosis of CIS is regarded as a definite and often urgent indication for treatment whilst one of dysplasia, often differentiated from CIS on relatively flimsy and uncertain pathologic grounds, is either not treated adequately or ignored



- DYSPLASIA - CIS
- HYPERPLASIA - ATYPICAL H - CIS
- INTRAEPITHELIAL NEOPLASIA









J AZZOPARDI



PROBLEMS IN
BREAST
PATHOLOGY

AZZOPARDI

Volume 11 in the Series

MAJOR PROBLEMS IN PATHOLOGY



Hyperplasia

CIS



“In the vast majority of cases, the distinction can be made and the clinician should be told as unequivocally as possible whether the pathologist considers that the lesion is benign or malignant”

J Azzopardi (1979)



“The problem of where to draw the dividing line is obviously an extremely difficult one, but no less important because of that.”

J. Azzopardi (1979)



“Names like “atypical hyperplasia”
should be avoided as far as possible.
[...] The writer believes that this is
possible in the vast majority of
cases with ductal disease.”

J Azzopardi



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PAUL PETER ROSEN

Rosen's Breast Pathology

Third Edition

Includes
online access
to text and
exam bank



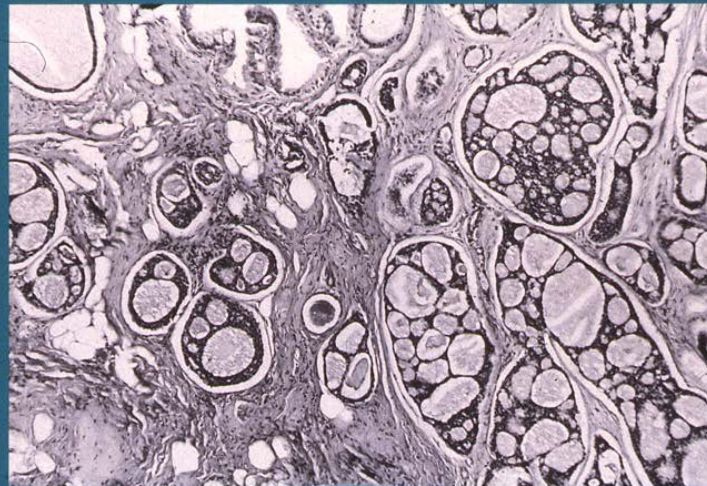
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WILEY & WILSON
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SOLUTION



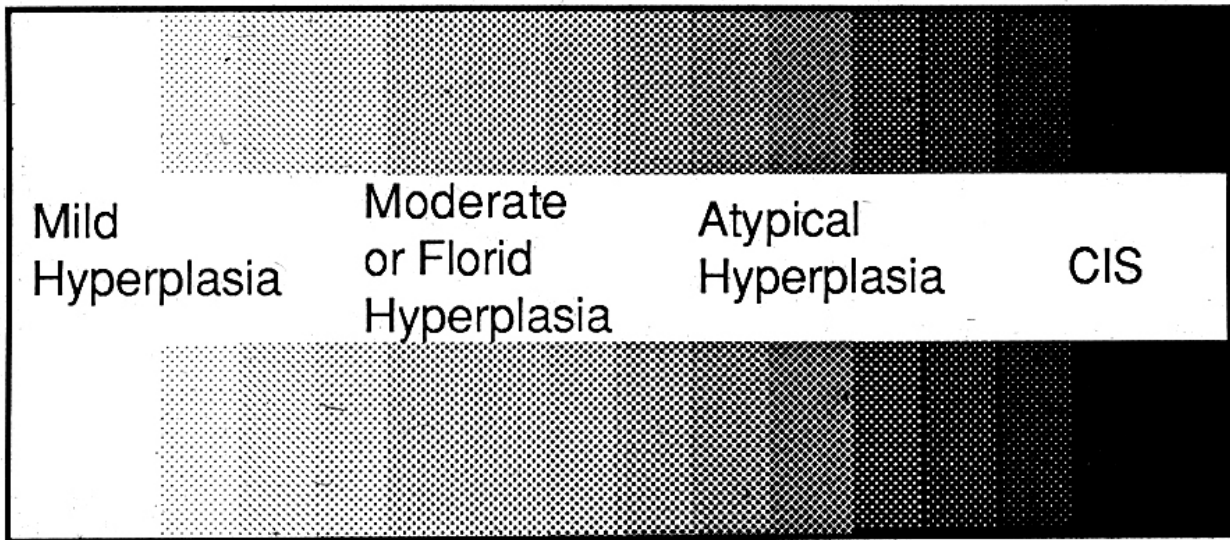
Diagnostic Histopathology of the Breast

DAVID L. PAGE
THOMAS J. ANDERSON



Churchill Livingstone 





Usual hyperplasia
Atypical hyperplasia
Carcinoma in situ



Atypical Hyperplastic Lesions of the Female Breast

A Long-Term Follow-Up Study

DAVID L. PAGE, MD, WILLIAM D. DUPONT PHD,† LOWELL W. ROGERS, MD,*‡
AND MARGARET S. RADOS, RN†
CANCER, 55: 2698 1985

RISK FACTORS FOR BREAST CANCER IN WOMEN WITH PROLIFERATIVE BREAST DISEASE

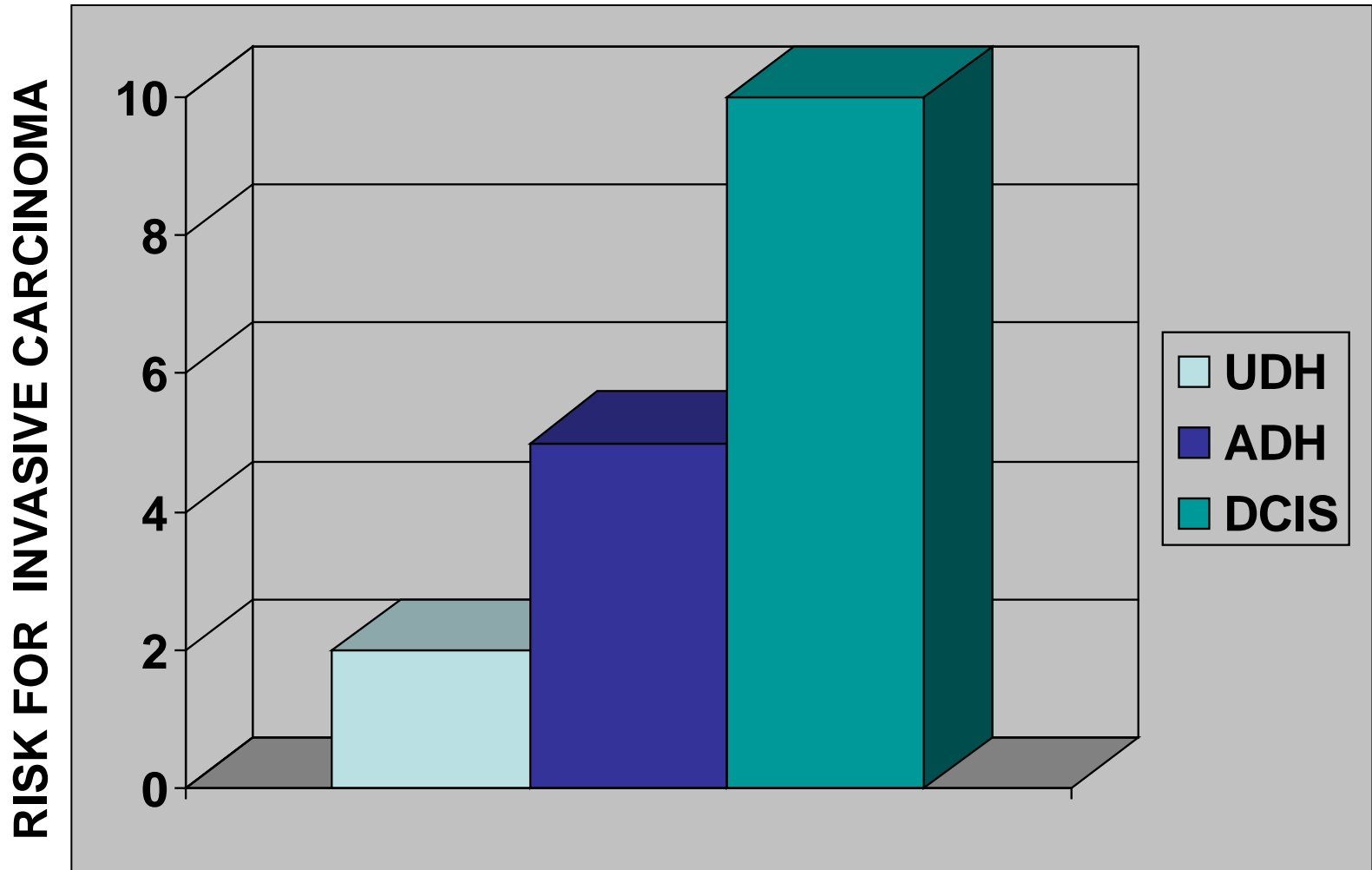
WILLIAM D. DUPONT, PH.D., AND DAVID L. PAGE, M.D.

N. ENGL. J. MED. 312:146, 1985



RELATIVE RISK FOR SUBSEQUENT DEVELOPMENT OF INVASIVE CARCINOMA

(THE CANCER COMMITTEE AF THE COLLEGE OF AMERICAN PATHOLOGISTS)



ARTHUR PURDY STOUT SOCIETY OF SURGICAL PATHOLOGISTS

Sunday, March 4, 1990

8:30 a.m.

GRAND & INDEPENDENCE

BREAST CANCER - WHAT WE NEED TO KNOW TODAY AND TOMORROW

Moderator: Louis Dehner, Washington University School of Medicine, St. Louis, MO

8:30 a.m. **Borderline Epithelial Lesions of the Breast - Juan Rosai, Yale University School of Medicine, New Haven, CT**

9:15 a.m. **Prognosis and Breast Cancer: Recognition of Lethal and Good Prognostic Types - David L. Page, Vanderbilt University School of Medicine, Nashville, TN**

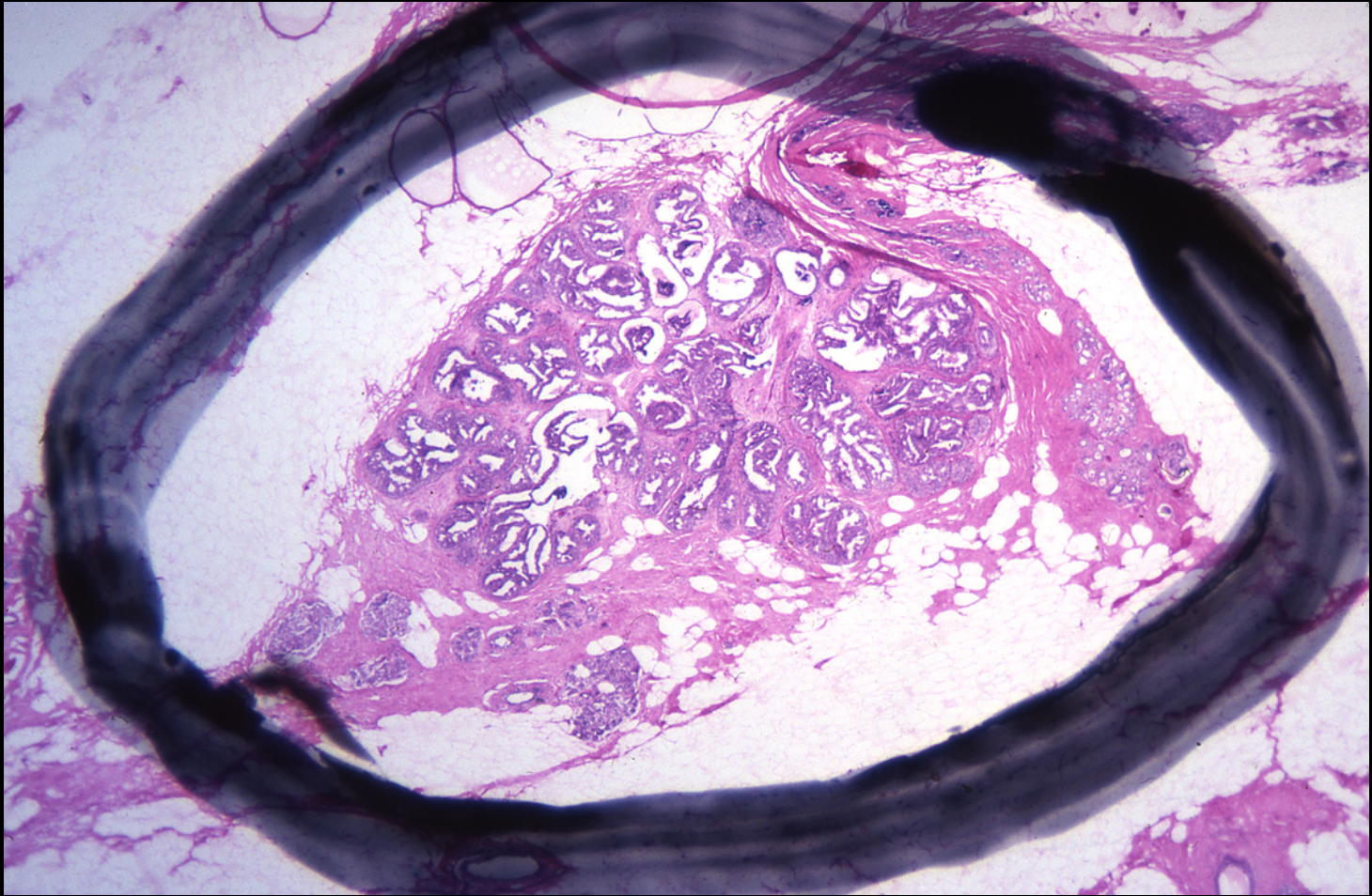
10:00 a.m. RECESS

10:30 a.m. **Prognosis and Cure in "Early" Invasive Breast Cancer: An Assessment of 644 Patients with Median Follow-up of 18 years - Paul Peter Rosen, Memorial Sloan-Kettering Cancer Center, New York, NY**

11:00 a.m. **The Utility of Cell Kinetics in Predicting Probability of Breast Cancer Relapse - Robert W. McDivitt, Washington University School of Medicine, St. Louis, MO**

11:30 a.m. **Is Cystic Disease Related to Breast Cancer ?- Darrow Haagensen, Washington University School of Medicine, St. Louis, MO**





DARRYL CARTER

ROBERT E. FECHNER

RICHARD L. KEMPSON

DAVID L. PAGE

PAUL P. ROSEN



- HYPERPLASIA (H)
- ATYPICAL HYPERPLASIA (AH)
- CARCINOMA IN SITU (CIS)



	A	B	C	D	E	
D1	AH	AH	AH	H	H	
D2	AH	AH	N	H	H	
D3	CIS	CIS	AH	CIS	AH	
D4	CIS	AH	CIS	H	AH	!
D5	AH	AH	H	H	H	
D6	CIS	ALH	CIS	AH	H	!
D7	AH	H	AH	H	H	
D8	AH	H	H	H	H	*
D9	AH	AH	AH	AH	H	*
D10	CIS	AH	H	H	H	!
L1	CIS	AH	AH	AH	H	!
L2	CIS	H	AH	AH	H	!
L3	AH	H	H	AH	H	
L4	CIS	AH	AH	AH	AH	*
L5	CIS	CIS	CIS	AH	AH	
L6	AH	H	AH	H	H	
L7	CIS	H	AH	AH	H	!



	A	B	C	D	E	
D1	AH	AH	AH	H	H	
D2	AH	AH	N	H	H	
D3	CIS	CIS	AH	CIS	AH	
D4	CIS	AH	CIS	H	AH	!
D5	AH	AH	H	H	H	
D6	CIS	ALH	CIS	AH	H	!
D7	AH	H	AH	H	H	
D8	AH	H	H	H	H	*
D9	AH	AH	AH	AH	H	*
D10	CIS	AH	H	H	H	!
L1	CIS	AH	AH	AH	H	!
L2	CIS	H	AH	AH	H	!
L3	AH	H	H	AH	H	
L4	CIS	AH	AH	AH	AH	*
L5	CIS	CIS	CIS	AH	AH	
L6	AH	H	AH	H	H	
L7	CIS	H	AH	AH	H	!



	A	B	C	D	E	
D1	AH	AH	AH	H	H	
D2	AH	AH	N	H	H	
D3	CIS	CIS	AH	CIS	AH	
D4	CIS	AH	CIS	H	AH	!
D5	AH	AH	H	H	H	
D6	CIS	ALH	CIS	AH	H	!
D7	AH	H	AH	H	H	
D8	AH	H	H	H	H	*
D9	AH	AH	AH	AH	H	*
D10	CIS	AH	H	H	H	!
L1	CIS	AH	AH	AH	H	!
L2	CIS	H	AH	AH	H	!
L3	AH	H	H	AH	H	
L4	CIS	AH	AH	AH	AH	*
L5	CIS	CIS	CIS	AH	AH	
L6	AH	H	AH	H	H	
L7	CIS	H	AH	AH	H	!



	A	B	C	D	E	
D1	AH	AH	AH	H	H	
D2	AH	AH	N	H	H	
D3	CIS	CIS	AH	CIS	AH	
D4	CIS	AH	CIS	H	AH	!
D5	AH	AH	H	H	H	
D6	CIS	ALH	CIS	AH	H	!
D7	AH	H	AH	H	H	
D8	AH	H	H	H	H	*
D9	AH	AH	AH	AH	H	*
D10	CIS	AH	H	H	H	!
L1	CIS	AH	AH	AH	H	!
L2	CIS	H	AH	AH	H	!
L3	AH	H	H	AH	H	
L4	CIS	AH	AH	AH	AH	*
L5	CIS	CIS	CIS	AH	AH	
L6	AH	H	AH	H	H	
L7	CIS	H	AH	AH	H	!



INTRAEPIHELIAL NEOPLASIA

- CERVICAL (CIN)
- ORAL (OIN)
- PROSTATIC (PIN)
- VULVAR (VIN)
- PANCREATIC (PanIN)



MAMMARY INTRAEPITHELIAL NEOPLASIA (MIN)





Fattaneh Tavassoli, MD



Rosai:

**MAMMARY INTRAEPITHELIAL
NEOPLASIA (MIN)**

Tavassoli:

**DUCTAL INTRAEPITHELIAL
NEOPLASIA (DIN)**

**LOBULAR INTRAEPITHELIAL
NEOPLASIA (LIN)**



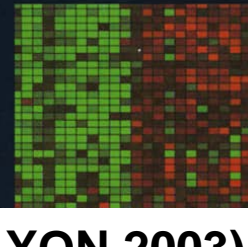
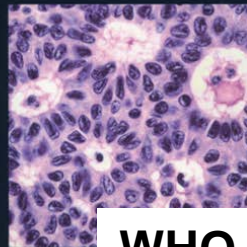
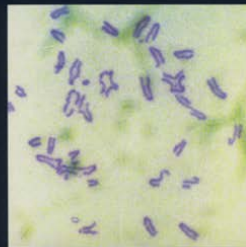
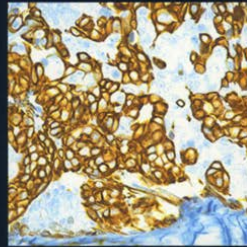
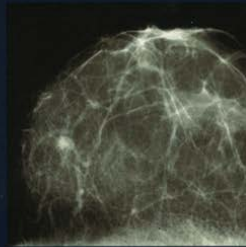
World Health Organization Classification of Tumours



Pathology & Genetics

Tumours of the Breast and Female Genital Organs

Edited by Fattaneh A. Tavassoli & Peter Devilee



WHO (LYON, 2003)



Table 1.11

Classification of intraductal proliferative lesions.

Traditional terminology	Ductal intraepithelial neoplasia (DIN) terminology
Usual ductal hyperplasia (UDH)	Usual ductal hyperplasia (UDH)
Flat epithelial atypia	Ductal intraepithelial neoplasia, grade 1A (DIN 1A)
Atypical ductal hyperplasia (ADH)	Ductal intraepithelial neoplasia, grade 1B (DIN 1B)
Ductal carcinoma in situ, low grade (DCIS grade 1)	Ductal intraepithelial neoplasia, grade 1C (DIN 1C)
Ductal carcinoma in situ, intermediate grade (DCIS grade 2)	Ductal intraepithelial neoplasia, grade 2 (DIN 2)
Ductal carcinoma in situ, high grade (DCIS grade 3)	Ductal intraepithelial neoplasia, grade 3 (DIN 3)



Stuart Schnitt, MD



Interobserver Reproducibility in the Diagnosis of Ductal Proliferative Breast Lesions Using Standardized Criteria

Stuart J. Schnitt, M.D., James L. Connolly, M.D.,
Fattaneh A. Tavassoli, M.D., Robert E. Fechner, M.D.,
Richard L. Kempson, M.D., Rebecca Gelman, Ph.D. and
David L. Page, M.D.

The American Journal of Surgical Pathology 16(12): 1133-1143, 1992



EXPERTS

ROSAI'S STUDY

D. Carter

R.E. Fechner

R.L. Kempson

D.L. Page

P.P. Rosen

SCHNITT'S STUDY

R.E. Fechner

R.L. Kempson

D.L. Page

S.J. Schnitt

J.L. Connolly

F.A. Tavassoli



RESULTS

ALL 6 AGREED 58%

> 5 AGREED 71%

> 4 AGREED 92%



Ductal carcinoma *in situ* (DCIS): pathological features, differential diagnosis, prognostic factors and specimen evaluation

Sarah E Pinder

Breast Research Pathology, Research Oncology, Division of Cancer Studies, King's College London, Guy's Hospital, London, UK



Intraductal proliferative lesions of the breast: morphology, associated risk and molecular biology

Ian O Ellis

Department of Histopathology, University of Nottingham, Molecular Medical Sciences, Nottingham City Hospital, Nottingham, UK





EXTRA
VOL 27, NO 1
FEBRUARY 2010

Seminars in Diagnostic Pathology

DANIEL J. SANTA CRUZ, MD
Editor

Problems in Breast Pathology Revisited

Ian O. Ellis, MD, FRCPath
Vincenzo Eusebi, MD, FRCPath
Stuart J. Schnitt, MD
Guest Editors



The NEW ENGLAND
JOURNAL *of* MEDICINE

VOL. 372 NO. 1

ESTABLISHED IN 1812

JANUARY 1, 2015

NEJM.ORG

SPECIAL REPORT

**Atypical Hyperplasia of the Breast — Risk Assessment
and Management Options**

Lynn C. Hartmann, M.D., Amy C. Degnim, M.D., Richard J. Santen, M.D.,
William D. Dupont, Ph.D., and Karthik Ghosh, M.D.



Ductal Carcinoma *In Situ*: Introduction of the Concept of Ductal Intraepithelial Neoplasia

F.A. Tavassoli, M.D.

Department of Gynecologic and Breast Pathology, Armed Forces Institute of Pathology, Washington, D.C.

Mod Pathol 1998;11(2):140–154



DILEMMAS IN BREAST DISEASE

Mammary Intraepithelial Neoplasia: A Translational Classification System for the Intraductal Epithelial Proliferations

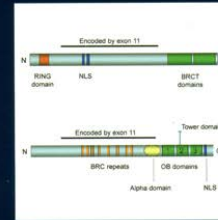
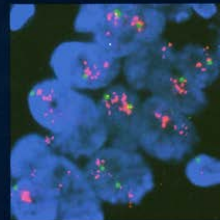
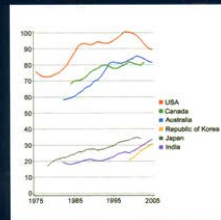
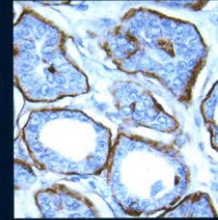
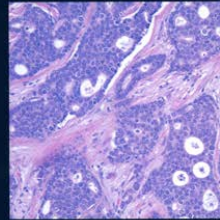
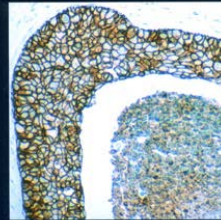
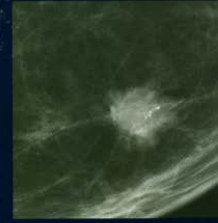
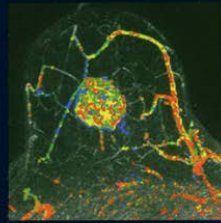
Consultant: Fattaneh A. Tavassoli, M.D.

*Department of Gynecologic and Breast Pathology, Armed Forces Institute of Pathology,
Washington, D.C.*



WHO Classification of Tumours of the Breast

Edited by Sunil R. Lakhani, Ian O. Ellis, Stuart J. Schnitt, Puay Hoon Tan, Marc J. van de Vijver



WHO (LYON, 2012)



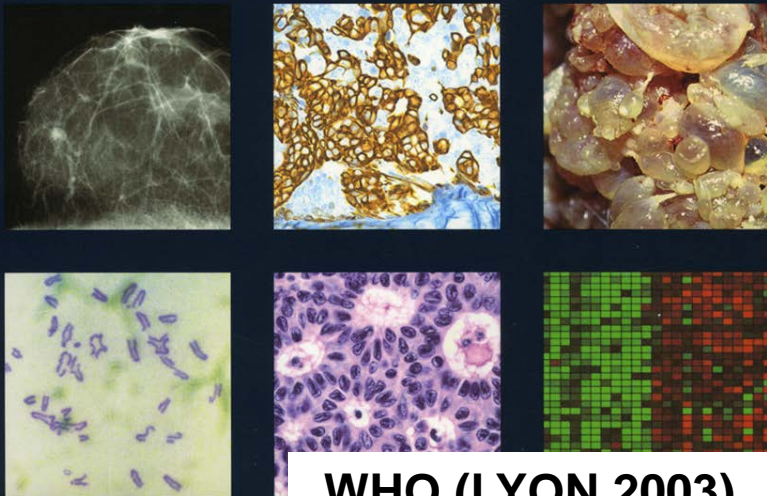
World Health Organization Classification of Tumours



Pathology & Genetics

Tumours of the Breast and Female Genital Organs

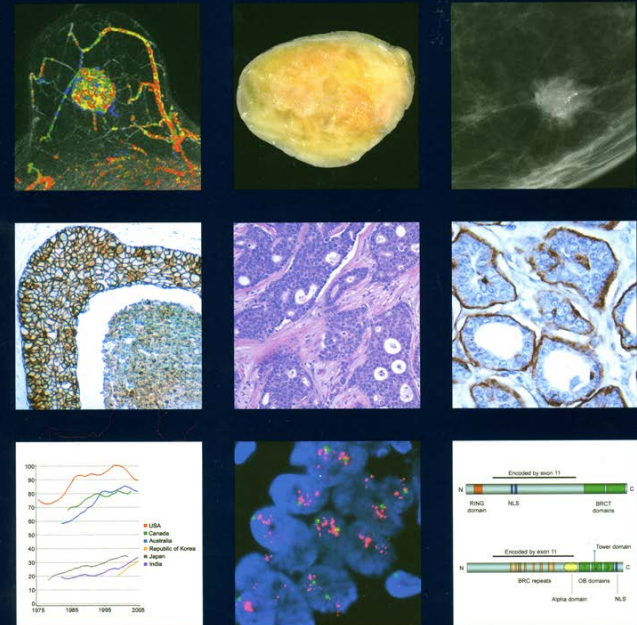
Edited by Fattaneh A. Tavassoli & Peter Devilee



WHO (LYON,2003)

WHO Classification of Tumours of the Breast

Edited by Sunil R. Lakhani, Ian O. Ellis, Stuart J. Schnitt, Puay Hoon Tan, Marc J. van de Vijver



WHO (LYON, 2012)



CHAPTER 5

Intraductal proliferative lesions

Introduction and overview

Usual ductal hyperplasia

Columnar cell lesions

Atypical ductal hyperplasia

Ductal carcinoma in situ

WHO (LYON,2012)



Table 5.01 Morphological characteristics useful in distinguishing ADH from UDH and from low-grade DCIS

Characteristic	UDH	ADH	DCIS (low grade)
Architecture	Cellular swirling and streaming; stretched or twisted epithelial bridges; peripheral, irregular, and slit-like fenestrations.	Rigid cellular bars; bulbous micropapillae; round, punched out spaces.	Rigid cellular bars; bulbous micropapillae; round, punched out spaces.
Cytology	Multiple cell types; uneven distribution and overlapping of cells and nuclei; indistinct cell borders.	Cellular uniformity; even cell placement; distinct cell borders; residual normally polarized cells.	Cellular uniformity; even cell placement; distinct cell borders; no residual normally polarized cells.
Extent	Variable, ranging from one to multiple TDLUs.	Partial involvement of multiple spaces; complete involvement of < 2 spaces or ≤ 2 mm in extent (see text).	Complete involvement of ≥ 2 spaces or > 2 mm in extent (see text).
Risk of developing breast cancer; laterality of risk	Slight risk; generalized bilateral risk.	Moderate risk; generalized bilateral risk.	High risk; regional ipsilateral risk.

ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; TDLU, terminal-duct lobular unit; UDH, usual ductal hyperplasia.

“Some members of the Working Group proposed that the traditional terminology be replaced by ductal intraepithelial neoplasia (DIN) [but] the majority of the participants was in favour of maintaining the traditional terminology”

WHO (Lyon, 2012)



ARGUMENTS AGAINST THE DIN TERMINOLOGY

- No new diagnostic criteria are used
- Will not improve inter-observer variability
- Different molecular profile

• *"Molecular analysis should help to improve upon the traditional classification"*

• WHO (Lyon, 2012) 

CHAPTER 5

Intraductal proliferative lesions

Introduction and overview

Usual ductal hyperplasia

Columnar cell lesions

Atypical ductal hyperplasia

Ductal carcinoma in situ

WHO (LYON,2012)



The characteristic genetic alterations
seen in ADH and low-grade CIS
are not found in UDH



There are no consistent genetic alterations associated with UDH



CHAPTER 5

Intraductal proliferative lesions

Introduction and overview

Usual ductal hyperplasia

Columnar cell lesions

Atypical ductal hyperplasia

Ductal carcinoma in situ

WHO (LYON,2012)



COLUMNAR CELL LESIONS

Columnar cell change

Columnar cell hyperplasia

Flat epithelial atypia



COLUMNAR CELL LESIONS

Columnar cell change

With atypia

Columnar cell hyperplasia

With atypia



COLUMNAR CELL LESIONS

Columnar cell change

With atypia (FEA)

Columnar cell hyperplasia

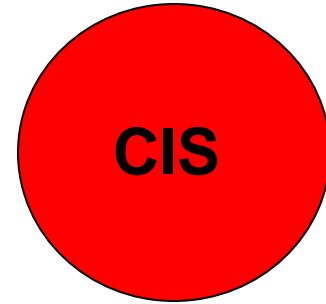
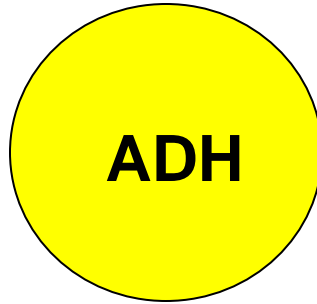
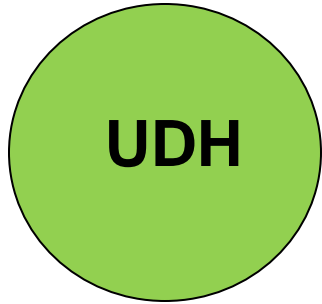
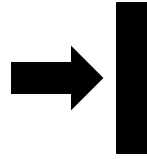
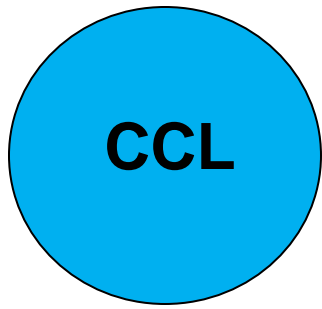
With atypia (FEA)

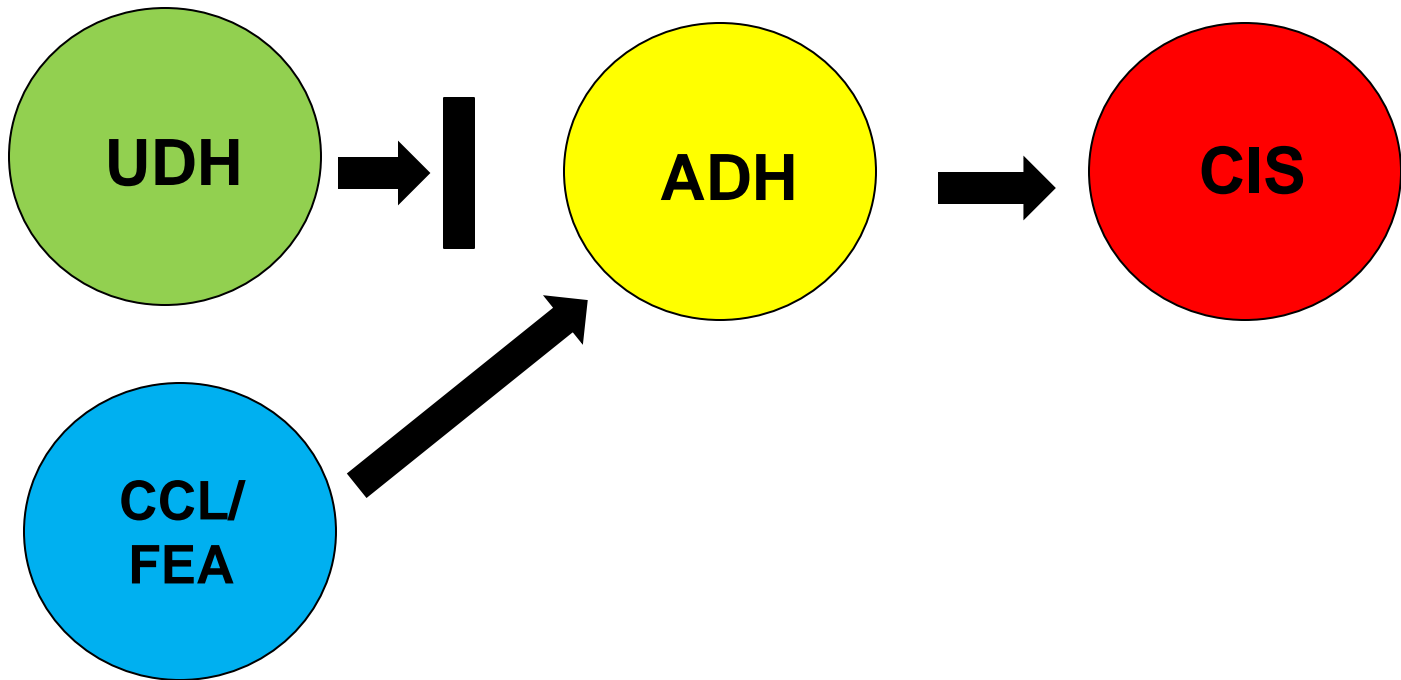
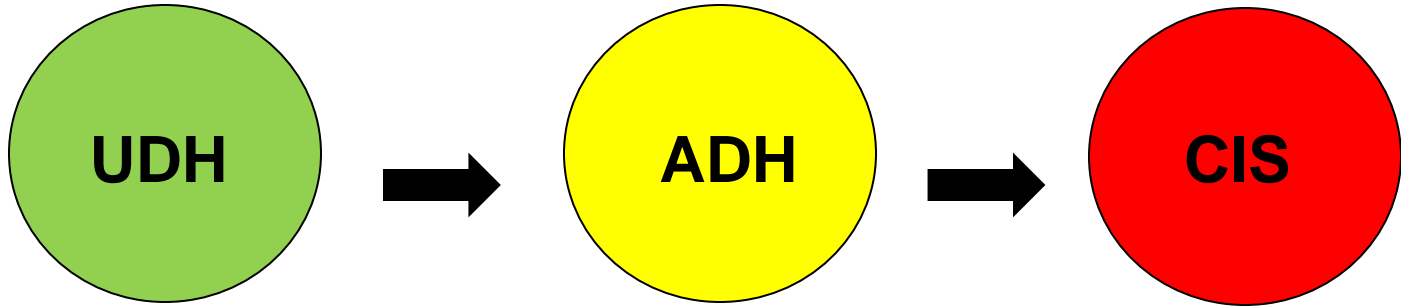


The term columnar cell change for non-atypical lesions and that of flat epithelial atypia for those with atypia has become the preferred term for such lesions

• Ellis, IO (2010)







Genetic alterations have been found in normal breast tissue away from the carcinoma

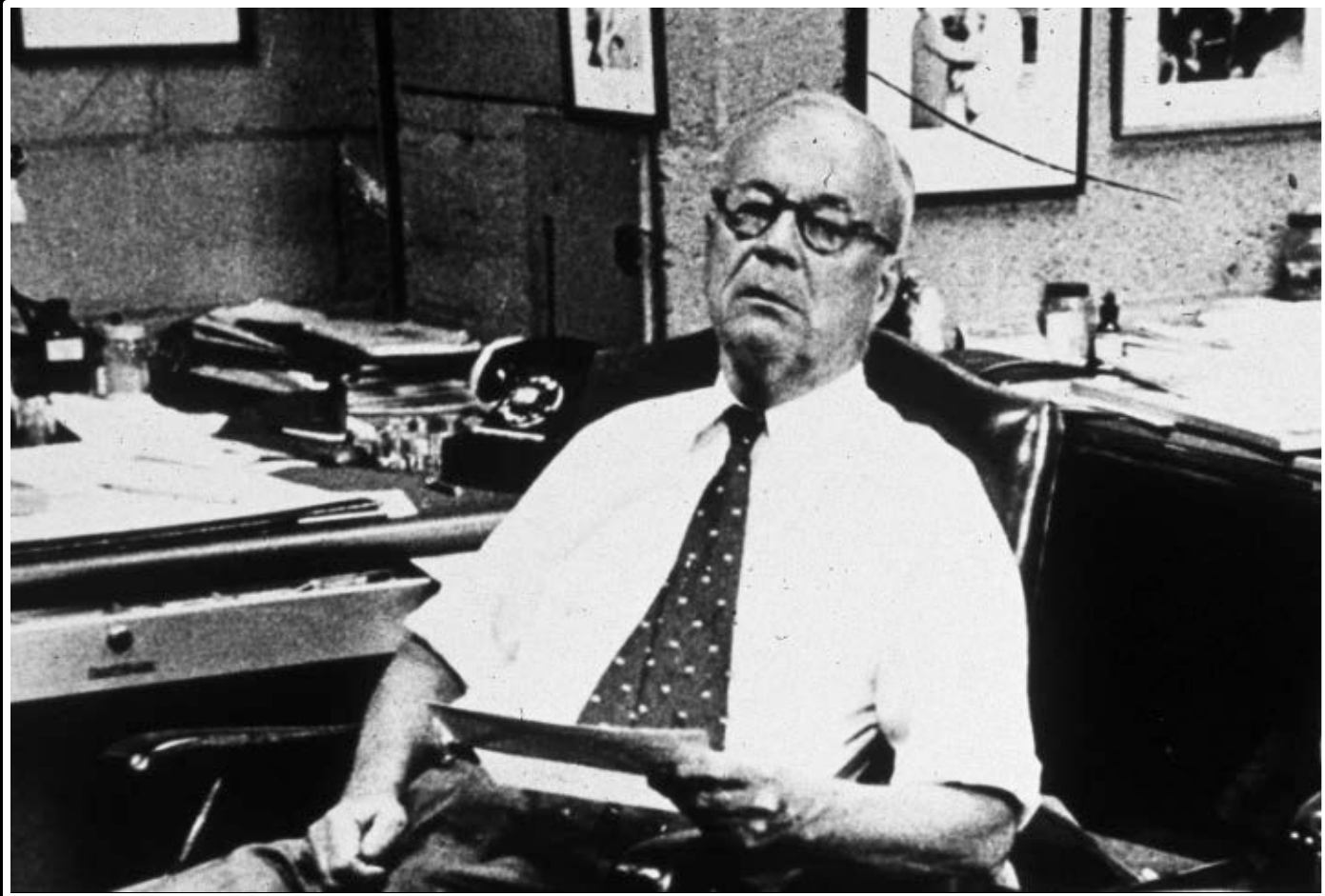
WHO (Lyon, 2012)



Genetic alterations have been seen in the mammary stroma in patients with malignancy

WHO (Lyon, 2012)





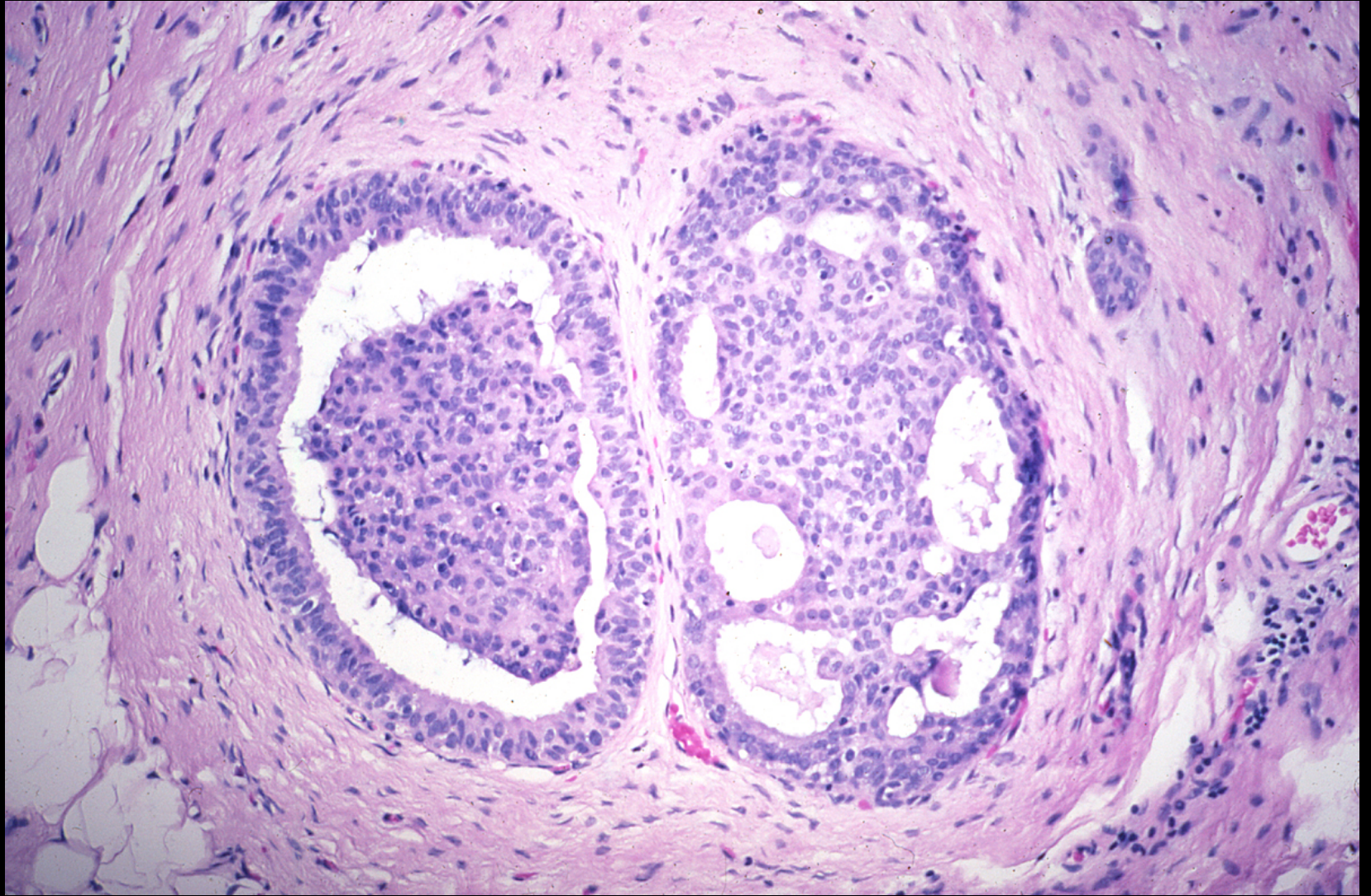
"One thing is probable, and that is that precancerousness begins before the microscope can detect it"

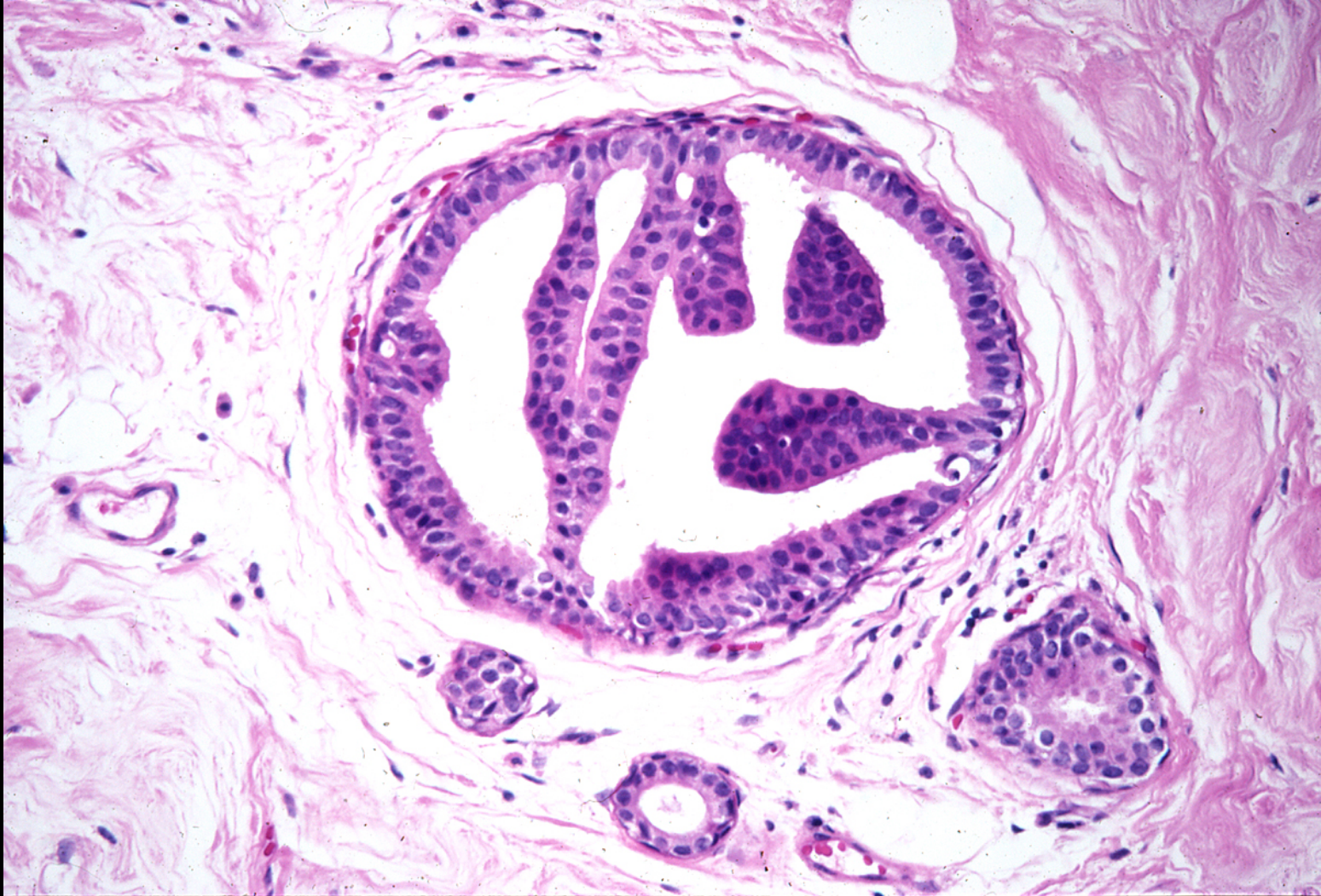
Fred Stewart (1950) 💡

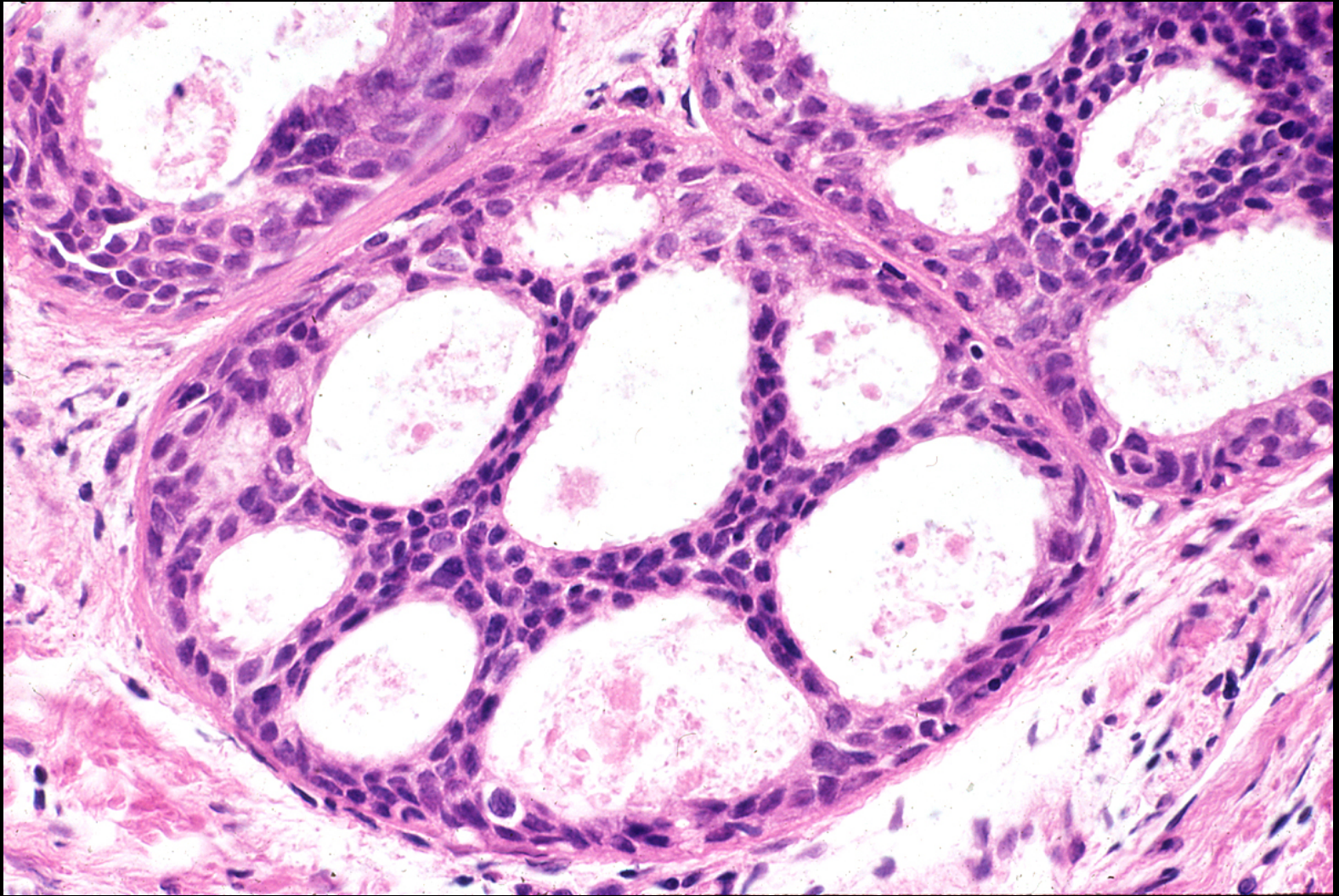
“The classification of intraductal proliferative lesions should be viewed as an evolving concept that may be modified as additional molecular genetic data become available”.

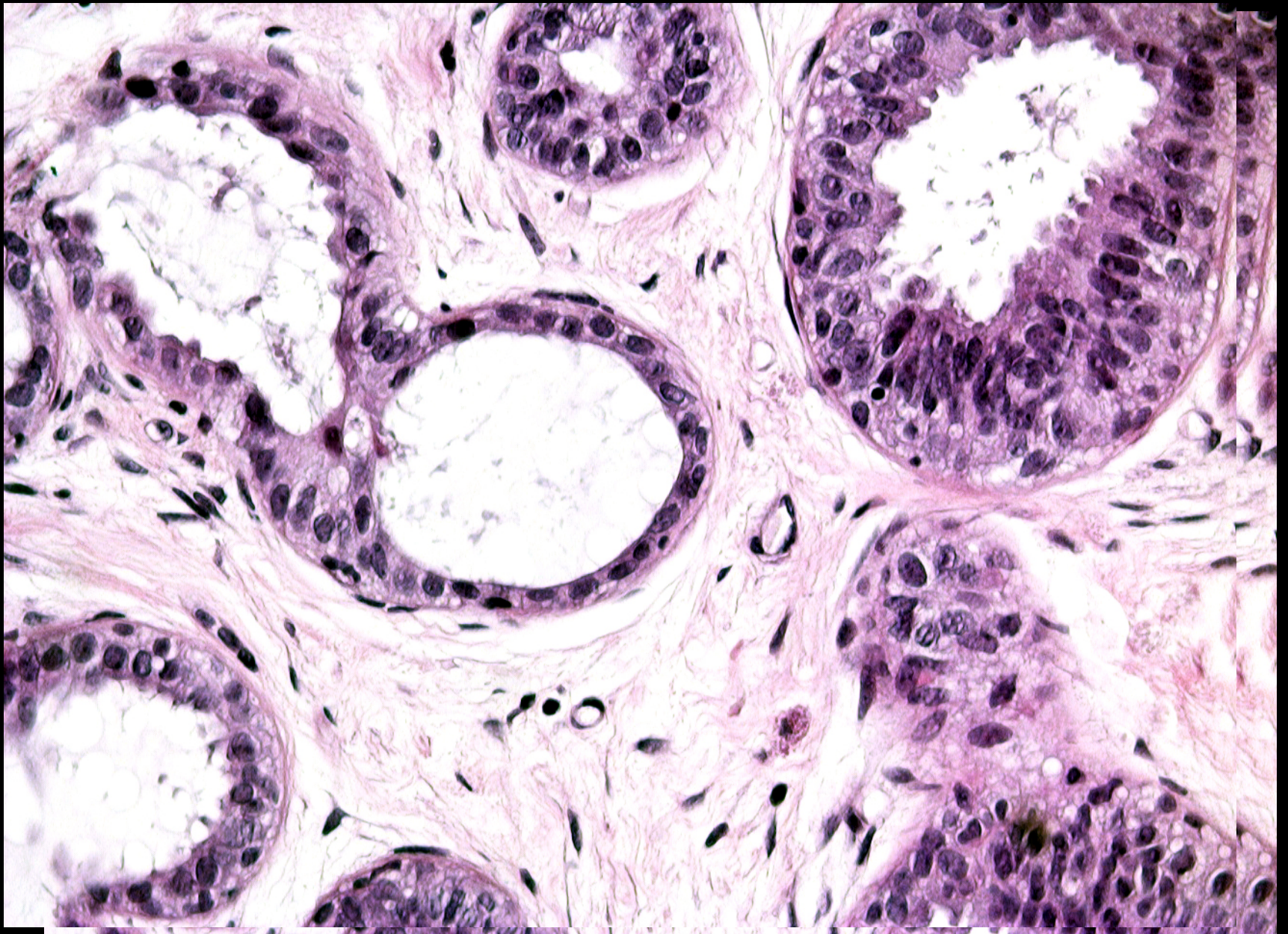
WHO (Lyon, 2003)

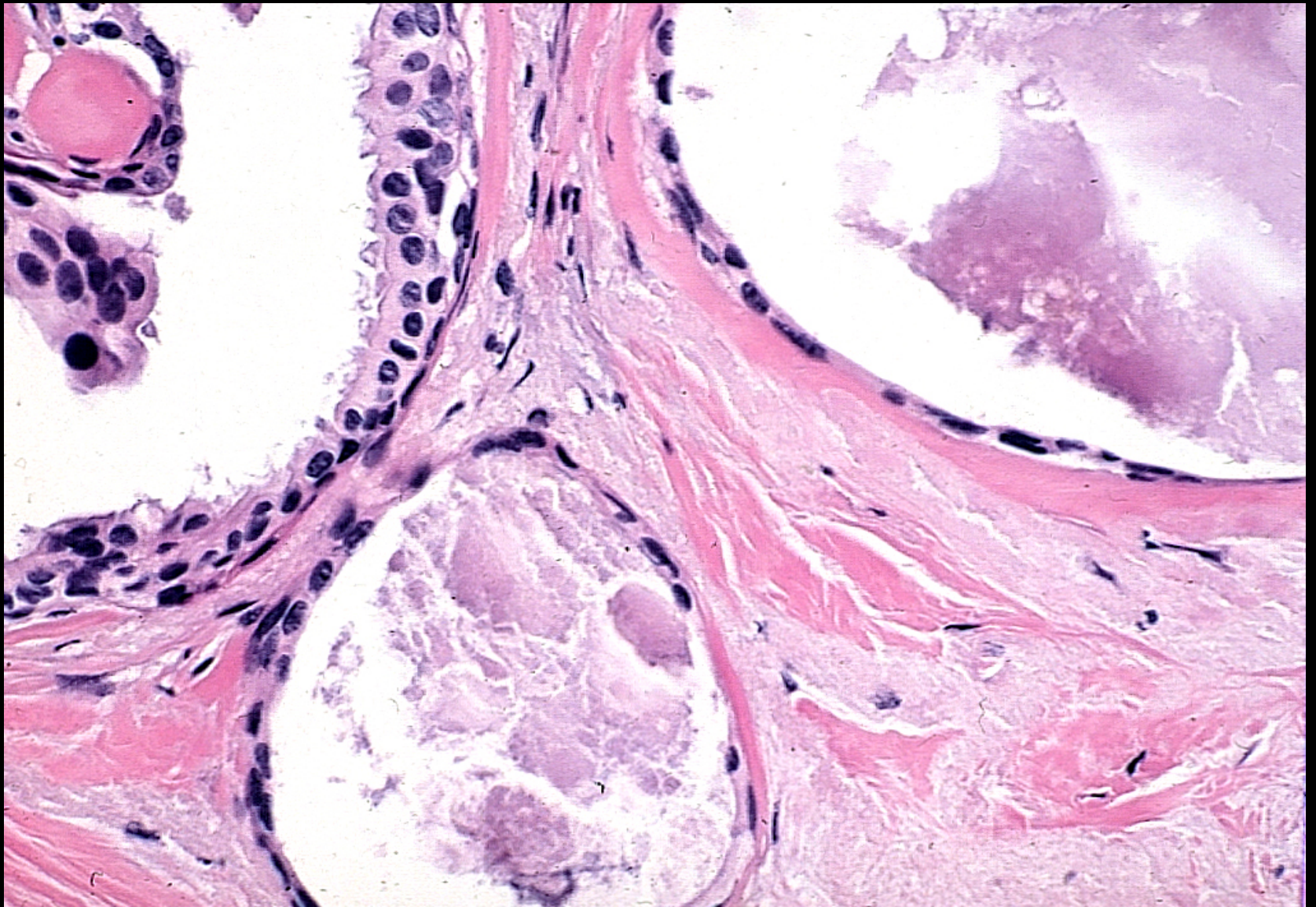


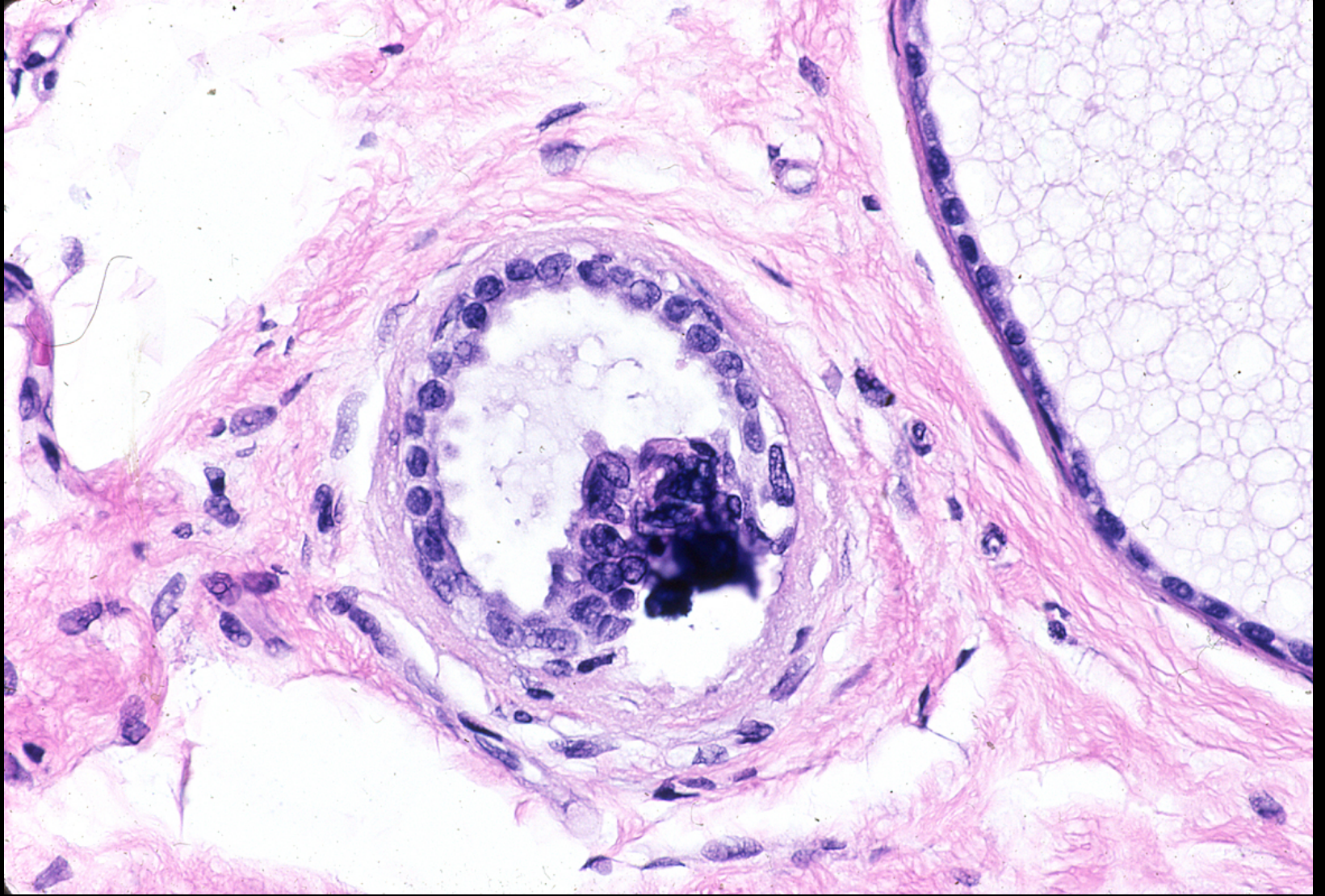












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