Milestones of the Division of Women's and Perinatal Pathology

Department of Pathology,
Brigham and Women's Hospital
Boston, Massachusetts

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Edited by George L. Mutter
Boston, 2013

Introduction and Dedication

The Women's and Perinatal (W&P) Division was established in 1931 at the Boston Lying-In Hospital by Arthur Tremain Hertig, who had graduated from Harvard Medical School the year before. Thus began a continuous and progressively branching lineage of faculty and trainees that in 1980 became a division of the Department of Pathology within the newly formed Brigham and Women's Hospital. Commemorated in this portfolio of images are seminal advances in the field by W&P staff. It is representative but not exhaustive, and legends are explanatory rather than documentary. The many colleagues and collaborators that contributed to this work are too numerous to list here, but are a matter of public record that can be gleaned from the roster of coauthors in relevant published reports. We dedicate this portfolio to each and every member of the Department of Pathology, as these are the people who support and inspire us daily.

Faculty of the Women's and Perinatal Pathology Division
December, 2012

Timeline of the Women's and Perinatal Pathology Division, BWH

1832: Boston Lying-In Hospital founded

1875: Free Hospital for Women founded

1931: Pathology Laboratory at Boston Lying-In Hospital founded by AT Hertig

1938: AT Hertig becomes Pathologist in Chief at the Free Hospital for Women (Assistant Pathologist since 1934)

1964: Merger of the Boston Lying-In Hospital and Free Hospital for Women as the Boston Hospital for Women.

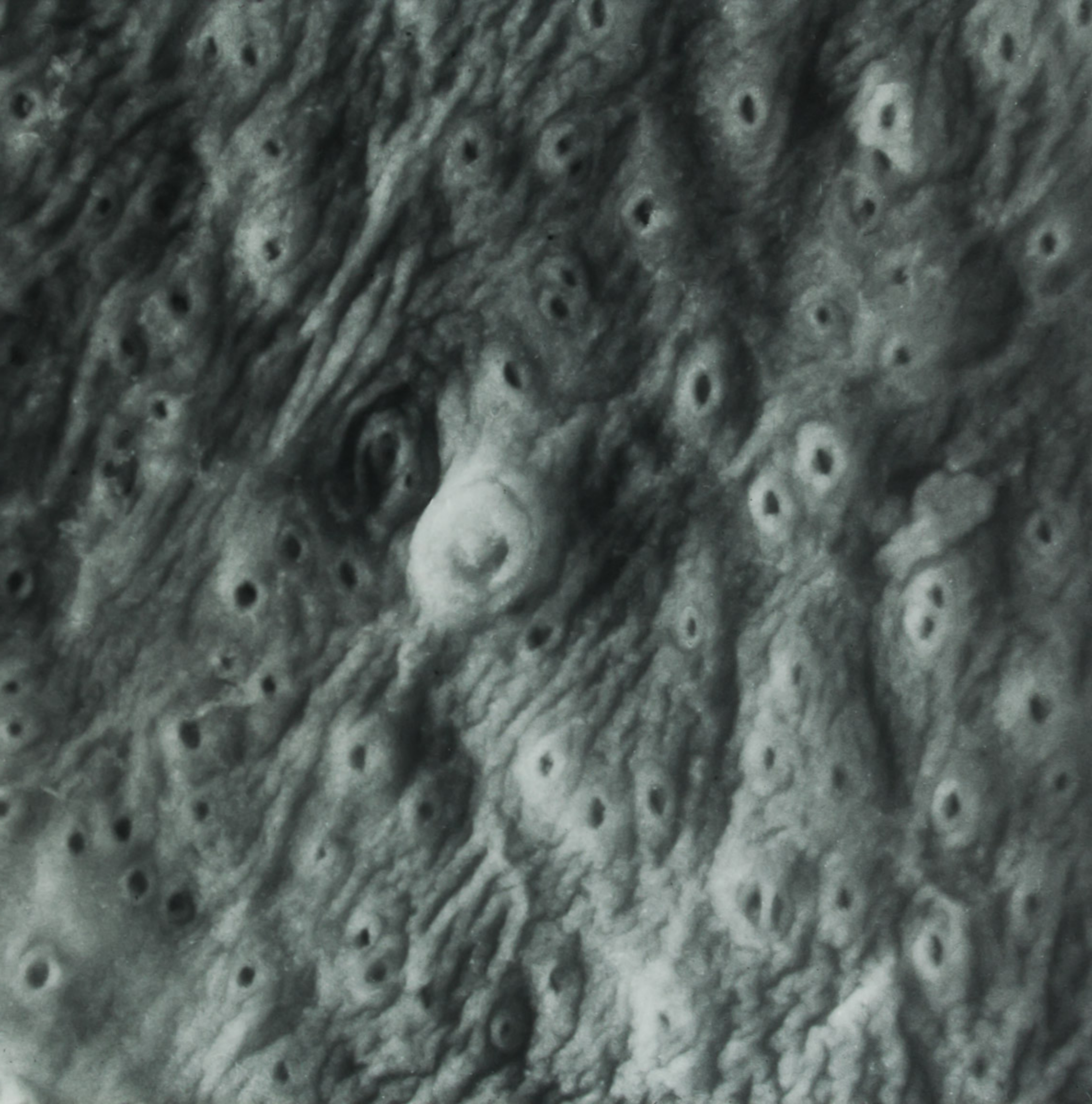
1980: Brigham and Women's Hospital opens, incorporating the Boston Hospital for Women, the Peter Bent Brigham Hospital and the Robert Breck Brigham Hospital.

References:
Cappers, EO. History of the Free Hospital for Women, 1875-1975. Published by Boston Hospital for Women, 1975.
Gore H, Benirschke K. Founders of pediatric pathology: Arthur Tremain Hertig. Perspectives in Pediatric Pathology. 15: 1-10, 1991.

Comprehensive Description of Preimplantation and Early Embryonic Development

1938-1953

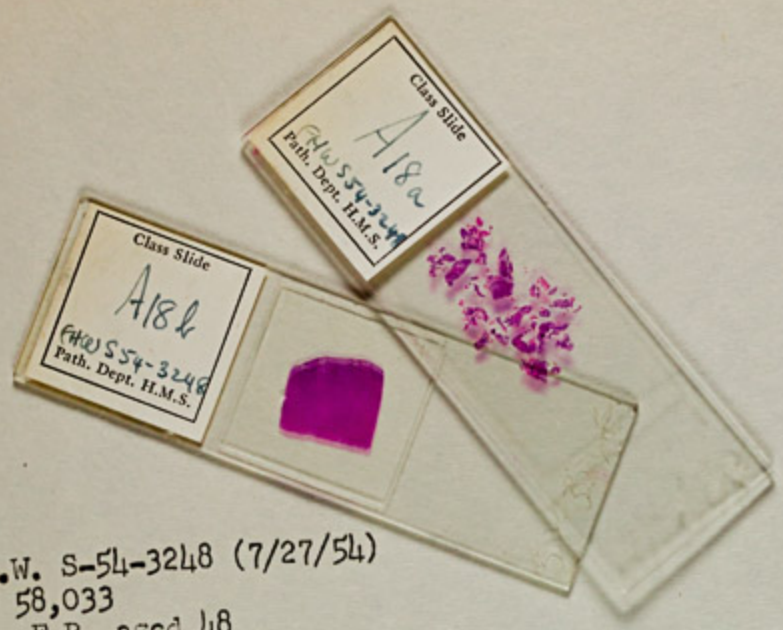
A systematic photographic record of early embryogenesis, including preimplantation and early implantation stages, was the foundation for "Carnegie staging" of early human development. Seminal contributions under support of the Carnegie Institute were made by gynecologist John Rock and Arthur Tremain Hertig, first Chief of Women's and Perinatal Pathology at the Boston Lying-In Hospital and the Free Hospital For Women (later merged to become the BWH Division of W&P Pathology). This is an implantation of a 7 day human embryo (0.09 mm) seen from the uterine lining, as photographed in 1944. Pores on the surface are endometrial gland openings.



Standardization of Endometrial Cycle Dating

1950

Histologic dating of menstrual cycle stage in endometrial biopsies was systematized by a clinical fellow, Robert W. Noyes, under the supervision of Arthur T. Hertig (faculty). What began as a trainee research project became one of the most highly cited papers in gynecologic pathology, and introduced criteria and terminology still in use today. Within just a few years, it became general practice and was taught to all incoming trainees using slide sets such as that shown. The decorative background is the lining of the notebook supplied by Dr. Hertig to students.



A 18 (a&b)

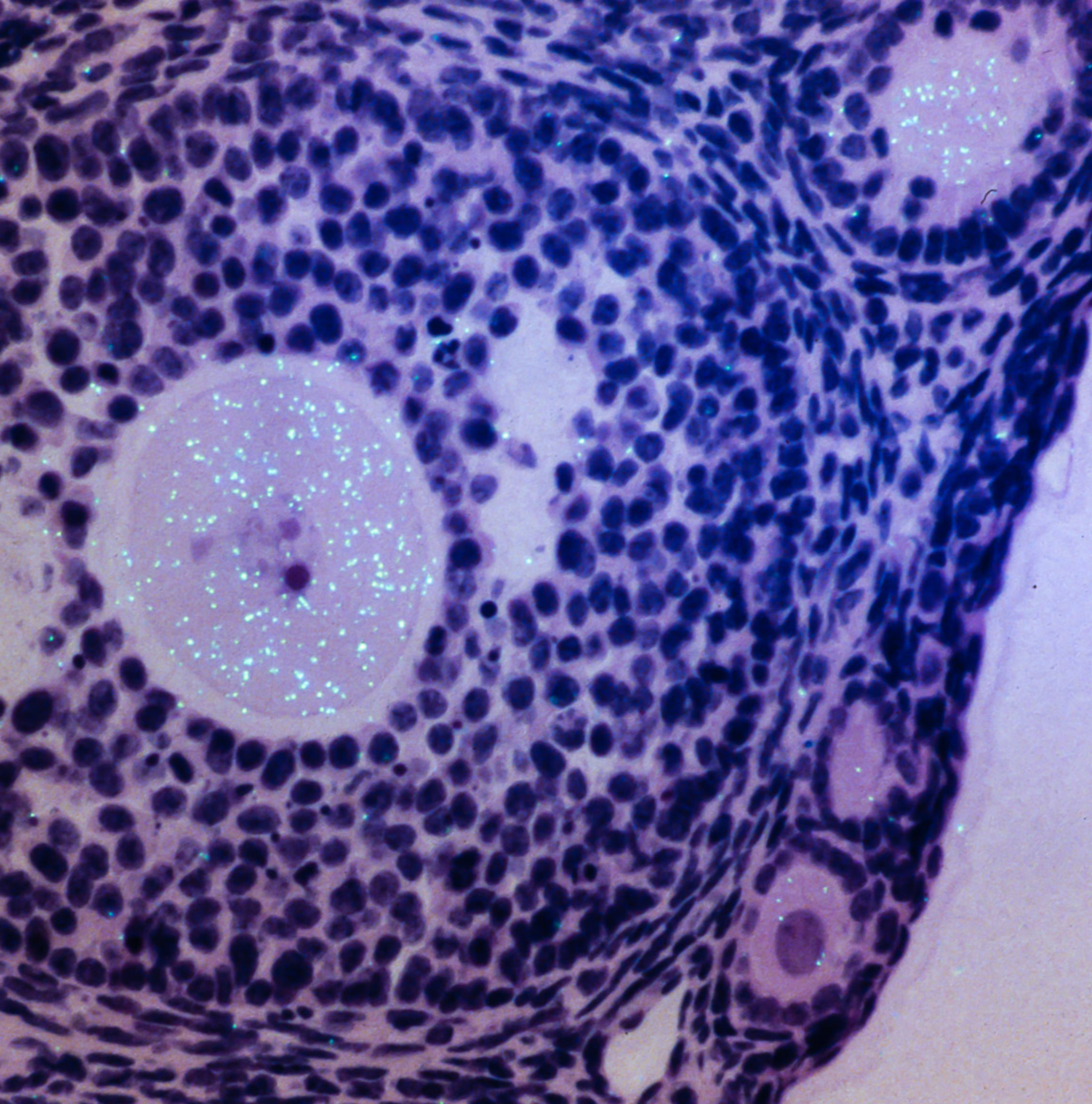
F.H.W. S-54-3248 (7/27/54)
U # 58,033
Mrs. E.B. aged 48

DIAGNOSIS: 18 day secretory endometrium.

First RNA in situ Hybridization of Paraffin Tissues

1987

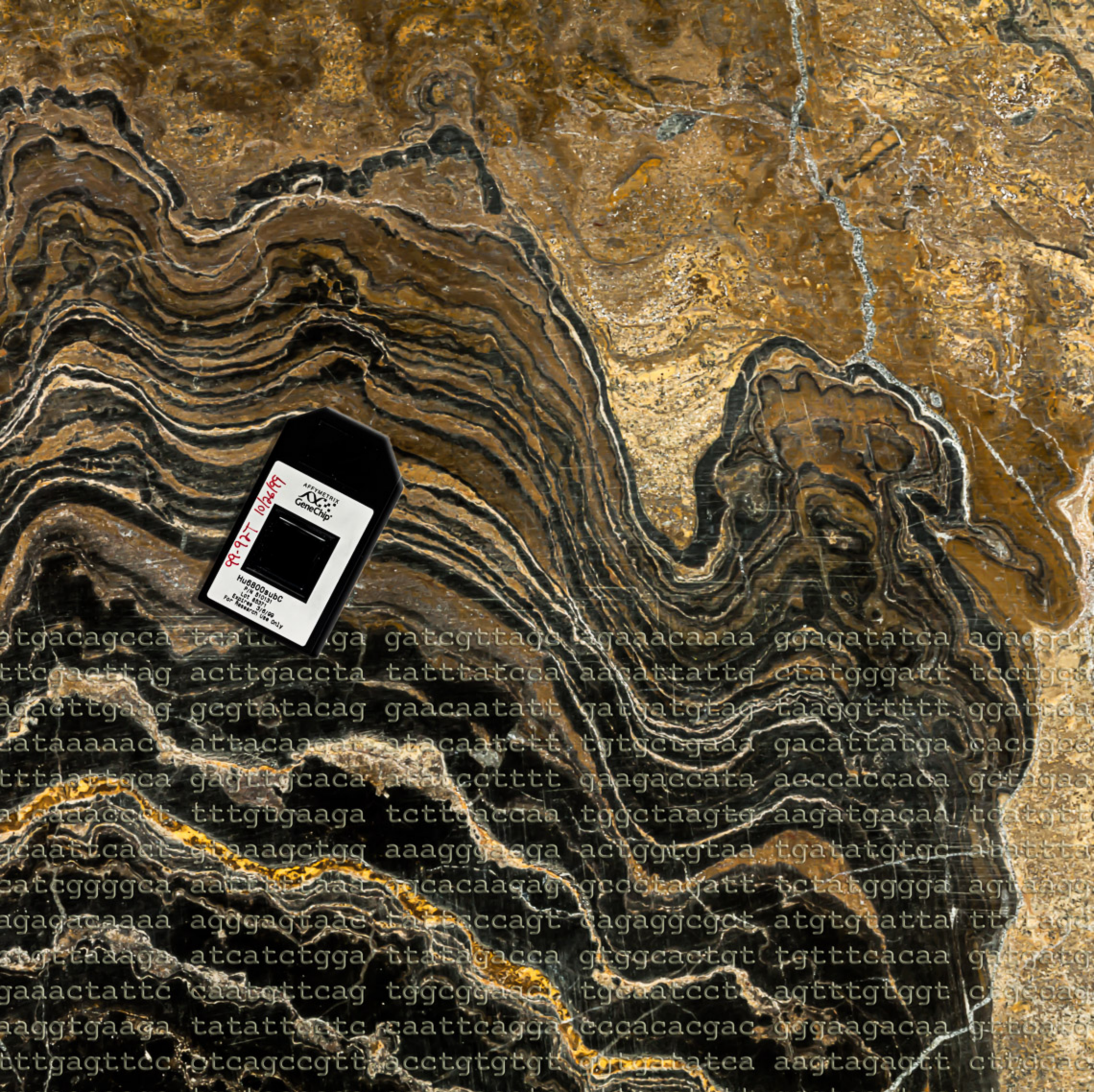
Application of emerging molecular tools to histologic material required development of new approaches amenable to routine archival pathology tissues. In situ hybridization to target tissue mRNAs was initially constrained to frozen sections, as preservation and accessibility of RNAs in paraffin tissues was unknown. The first successful RNA-RNA in situ hybridization in paraffin tissues is shown here. The c-mos proto-oncogene is specifically expressed in oocytes, at levels that increase as they develop. Silver grains of the autoradiographic emulsion are highlighted by epi-illumination. (George L. Mutter, faculty)



Algorithm for Design of Oligonucleotide Targets for the First Commercial Gene Chip

1995-1998

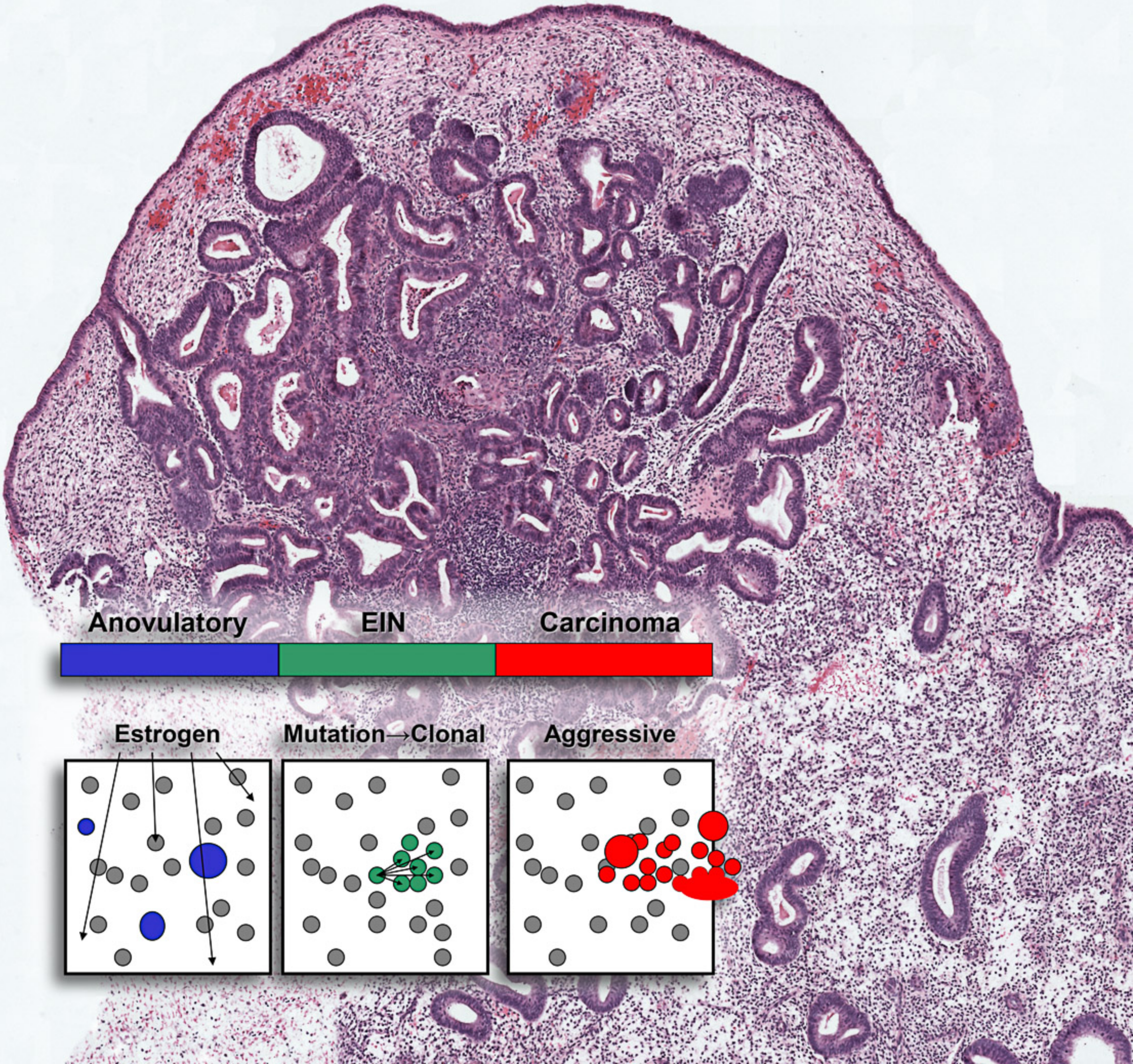
Commercialization of high throughput gene expression analysis became possible in the 1990s, with in situ photosynthesis of microscopic oligonucleotide arrays by the California company Affymetrix using technologies from the integrated circuit industry. A key component was development, by a W&P fellow (Lincoln Stein), of a robust computational algorithm for unique 20-mer oligonucleotide hybridization targets matching all known genomic sequences. The resultant oligos were deployed on the first chips sold by Affymetrix. Contrasting with this "newest" form of synthetic DNA, the background is a 2.2 billion year old fossil stromatolyte from Bolivia, the oldest known living organism on Earth.


AFFYMETRIX
GeneChip
Hu6800subC
P/N 810131
Lot 85571
Expires 3/6/99
For Research Use Only
98-927 10/26/98

EIN, a Monoclonal Endometrial Precancer

1995-2000

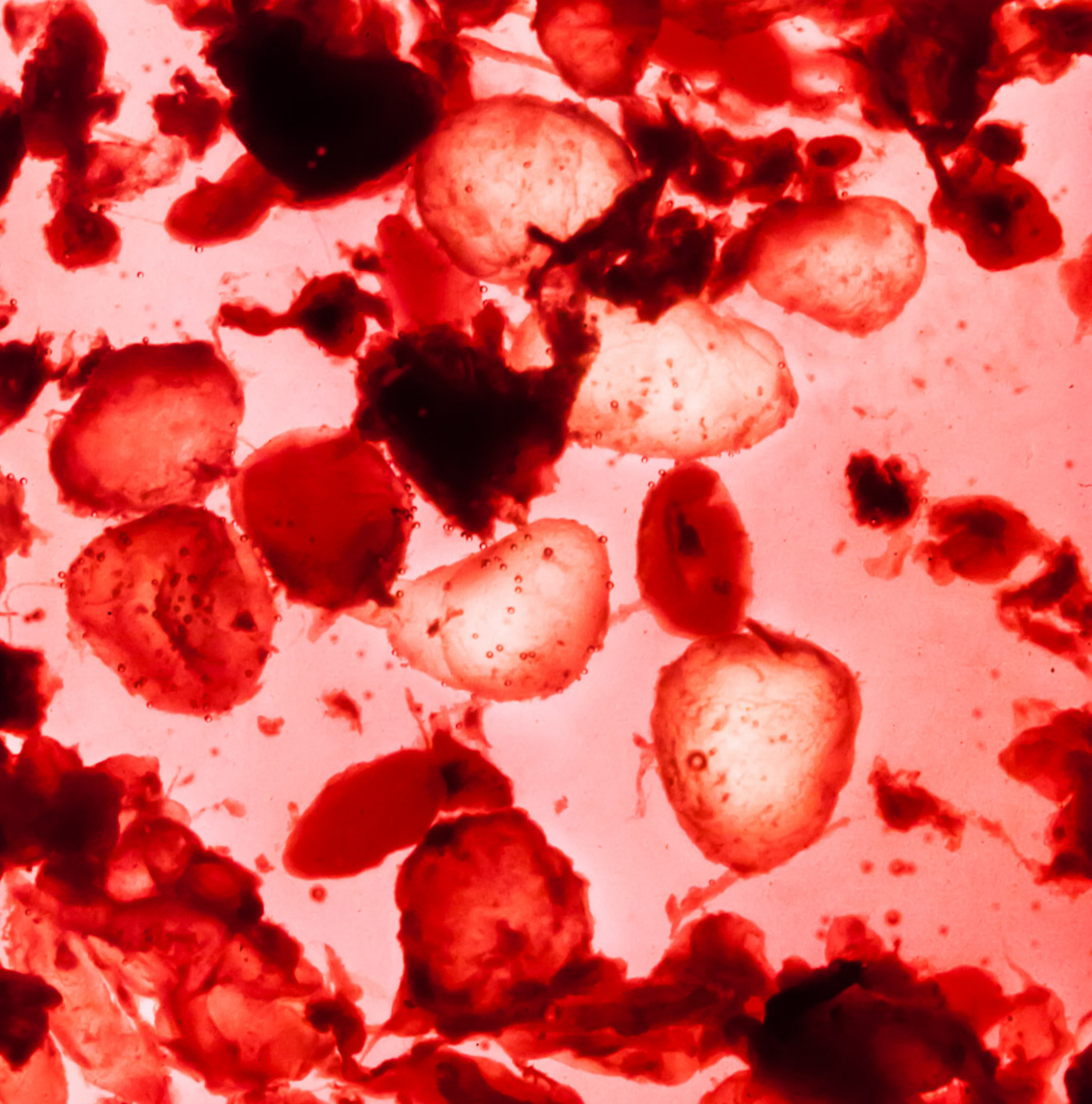
Demonstration of acquired somatic mutation and resultant clonal growth in the earliest endometrial precancers separated high risk lesions from what had been a mixed bag of "hyperplasias." Expansile clonal growth and contrast between lesion and background normal tissues were histologic features that led to improved diagnostic criteria applicable to routinely stained slides under the newly coined moniker of "Endometrial Intraepithelial Neoplasia." EIN was first implemented clinically within the W&P division in 2001, and granted its own ICD9 code by the US Government in 2009. (George L. Mutter, faculty; William Faquin, fellow)


Anovulatory
EIN
Carcinoma
Estrogen
Mutation→Clonal
Aggressive

P57, a Marker for Diagnosis of Complete Hydatidiform Mole

2001

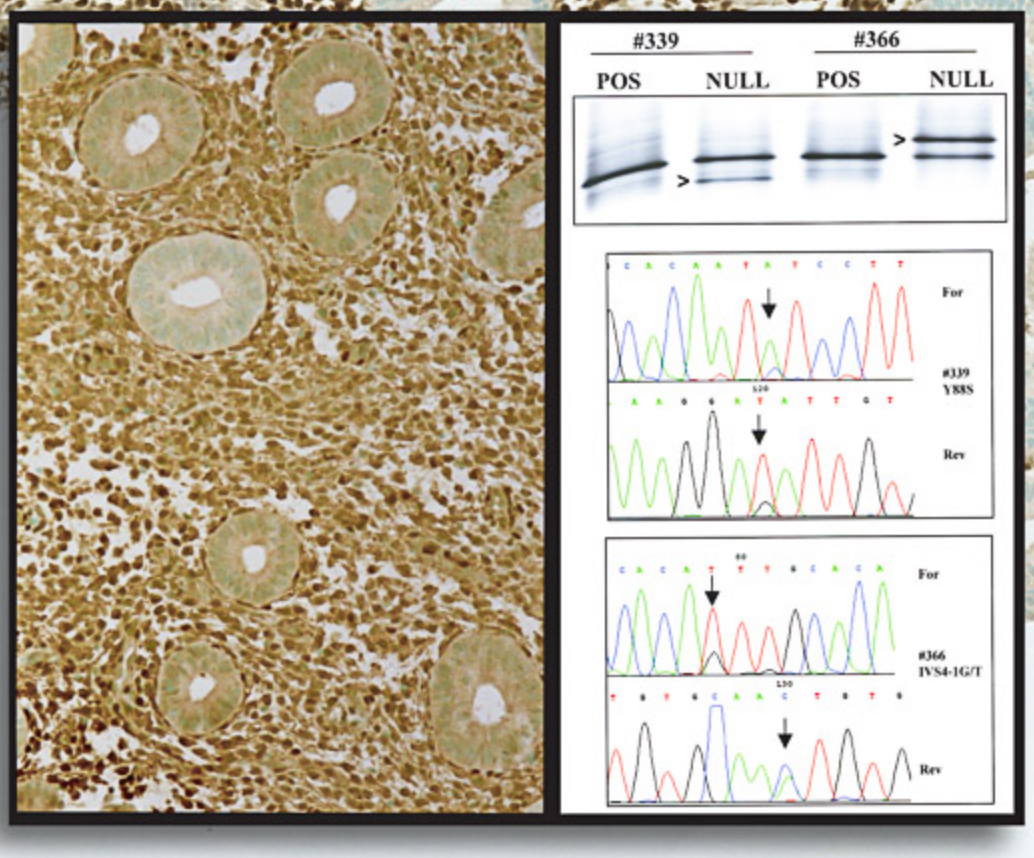
Androgenetic gestations, complete hydatidiform moles, predispose the patient to malignant choriocarcinoma. Diagnosis on pure histologic grounds was a longstanding problem until Diego Castrillon (faculty) and David Genest (faculty) showed that the paternally imprinted gene p57 was aberrantly underexpressed in complete moles. Immunohistochemistry for p57 has become a diagnostic tool in equivocal cases, and provided a gold standard for extrapolation of accurate diagnosis to earlier stages when a full complement of morphologic features has not yet developed.



Discovery of Latent Precancers

2001

When loss of function of the tumor suppressor gene PTEN was found to be the most common molecular change in endometrial cancer (~75% of endometrioid tumors), it was soon determined to be present in precursor EIN lesions (background). Using this marker as a beacon for even earlier lesions, somatically acquired PTEN mutation was found in isolated endometrial glands of 40% of normal premenopausal cycling endometrial tissues (inset). These were dubbed "latent precancers" to acknowledge lineage continuity with subsequent carcinoma, while emphasizing that other events are required for progression to clinically actionable disease. (George L. Mutter, faculty; Tan Ince, fellow)



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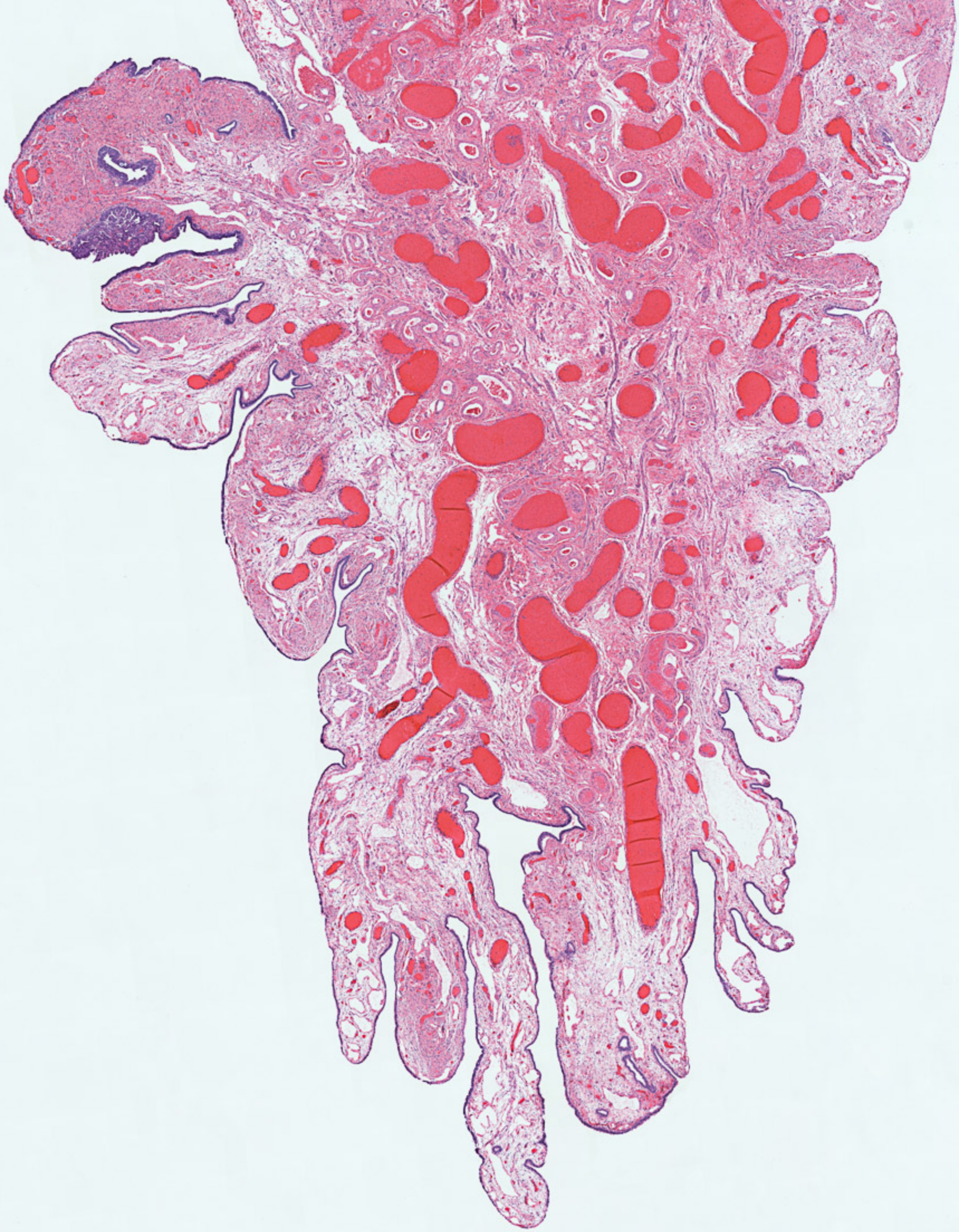
Discovery of the Tubal Origin of Most "Ovarian" Serous Cancers

2006-2007

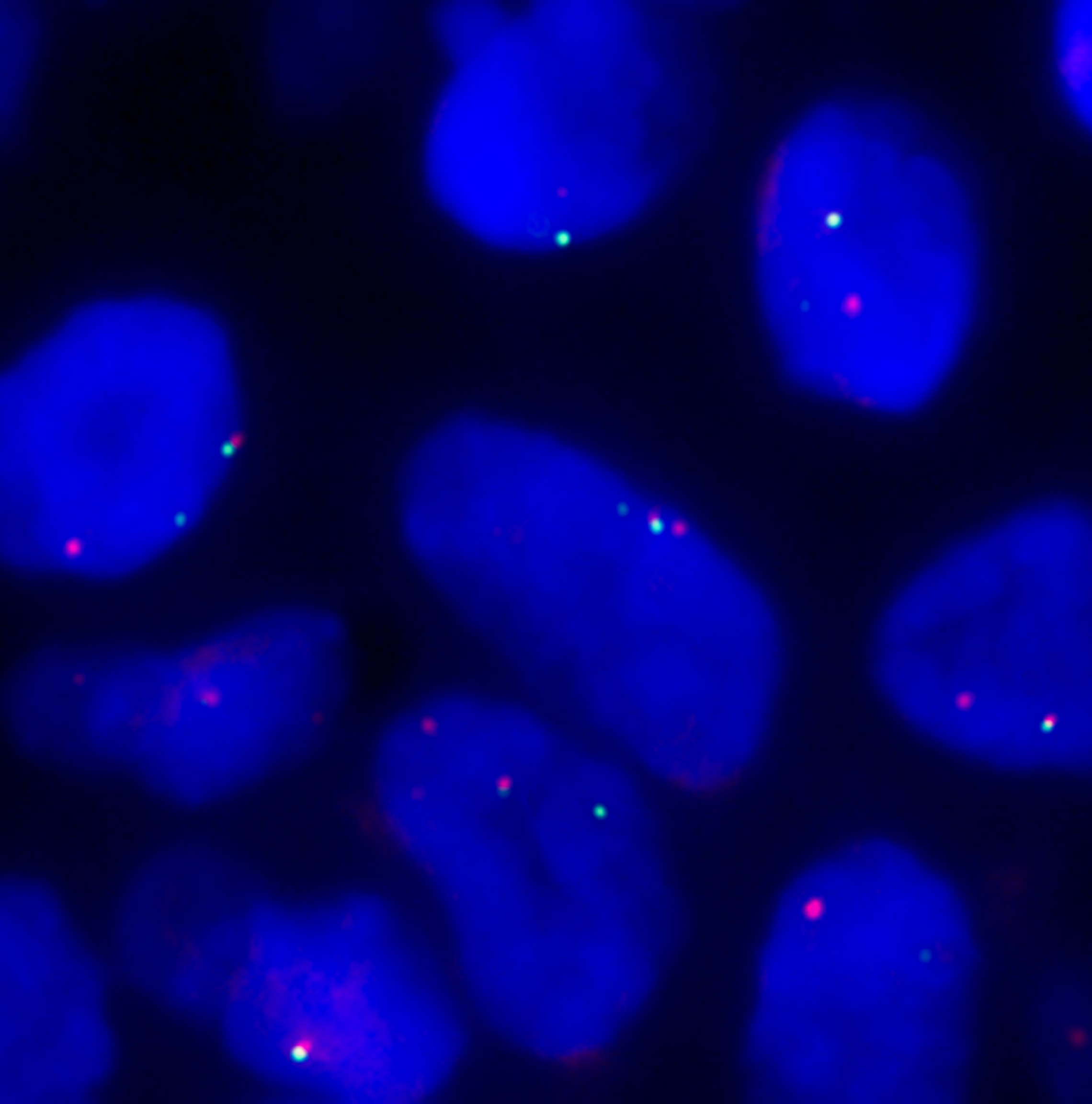
The most common lethal gynecologic malignancy, high grade serous adenocarcinoma, has a mysterious origin that perplexed scientists for decades. Long considered an ovarian tumor based upon the site of greatest tumor bulk at presentation, convincing precursor lesions within the ovary itself were rarely found. The mystery was solved by Christopher P. Crum (faculty) and a lineup of W&P fellows when they discovered P53 mutant cytologically atypical serous lesions in the fallopian tube fimbria designated as serous tubal intraepithelial carcinoma. A sequential cascade of earlier precursor lesions in the fallopian tube has since been elaborated, including latent precancer phases of histologically unremarkable mutated epithelia.



Common Translocations in Endometrial Stromal Neoplasia

2007

Diagnostic translocations which activate transforming genes are much more common in mesenchymal than epithelial neoplasia. When present, they can be informative in identifying underlying pathogenetic mechanisms and clinically useful as diagnostic markers. Marisa R. Nucci (faculty) has shown specific translocations involving chromosomes 7 and 17 in endometrial stromal tumors, shown here for the breakpoint between JAZF1 (chromosome 7,red) and JJAZ1 (chromosome 17,green) in an endometrial stromal nodule. Experiments such as these have defined pathogenetic boundaries between classes of endometrial stromal tumors of previously unknown relationships.



Discovery of the Progenitor Cell of Cervical Squamous Carcinoma

2011

Cervical squamous cell carcinoma is initiated by infection with the human papilloma virus and emergence of a precursor squamous intraepithelial lesion at a particular anatomic site: the transformation zone. Christopher P. Crum (faculty) and collaborators (Frank McKeon, Wa Xian and Michael Herfs) identified a cytokeratin 7 positive (red) population of squamocolumnar junction cells exactly at this site, between glandular endocervix (blue DAPI counterstain) and squamous exocervix (green, cytokeratin 5). Functional and biomarker lineage continuity between these cells, premalignant (CIN) lesions, and resultant squamous carcinoma implicates them in cervical carcinogenesis. The putative progenitor cell offers a novel preventative therapeutic target and potential diagnostic markers in the cervix.

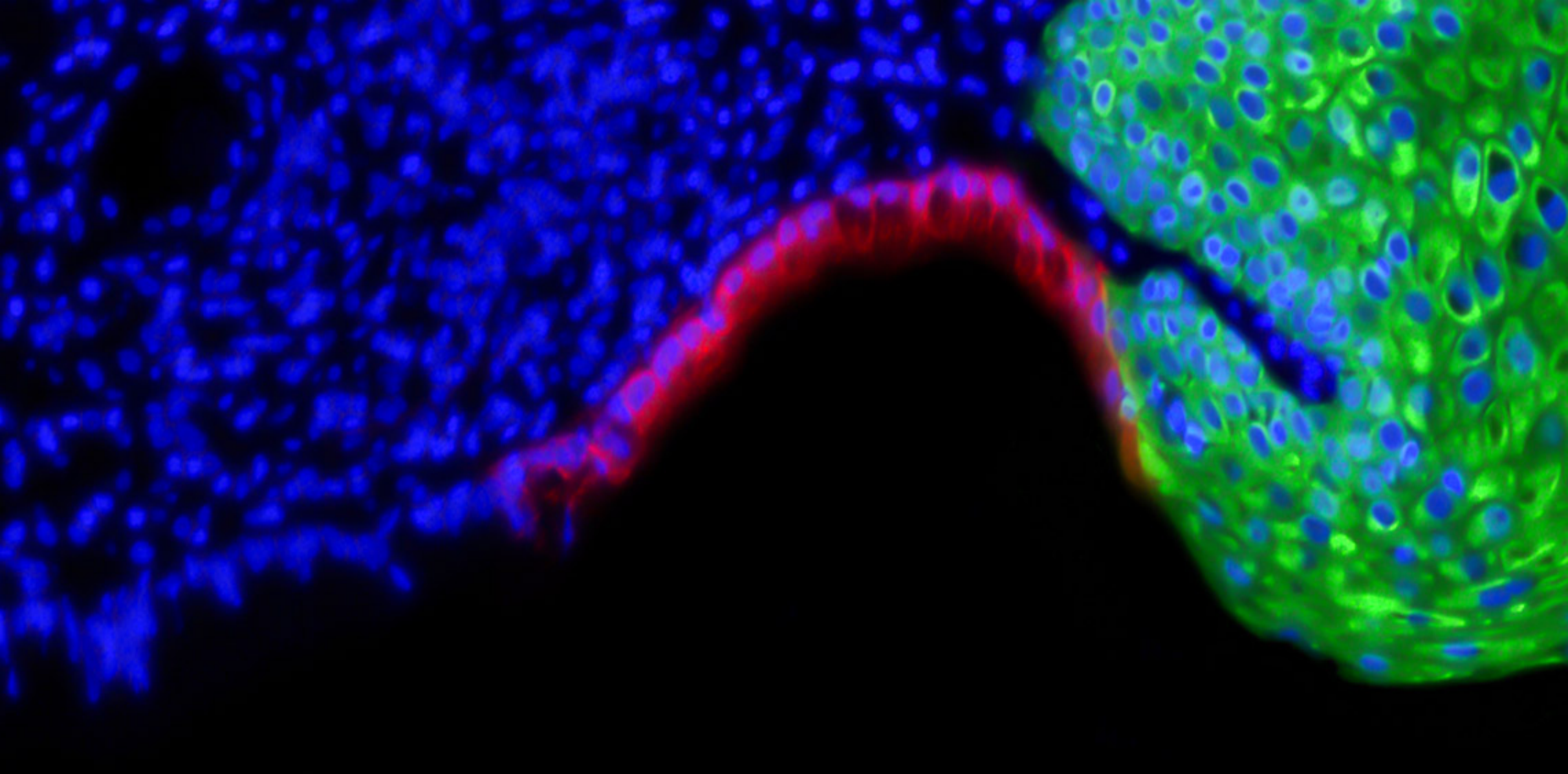
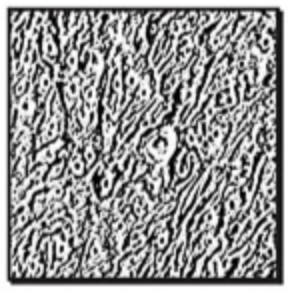


Photo Credits and Notes

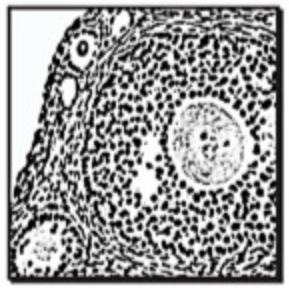


Comprehensive Description of Preimplantation and Early Embryonic Development,1938-1953

Photo Credit: Chester Reather, 1944. Carnegie Institute of Washington.
Carnegie Human Embryo#8225, Carnegie Stage 5a, 1944. Original 3x4" glass lantern slide from the collection of Shirley Driscoll.
Reference:
Hertig AT, Rock J. On a normal human ovum not over 7 1/2 days of age. Anat Rec 91:281, 1945.
Hertig,AT. A fifteen year search for first-stage human ova. JAMA 261:434-435.
Hertig AT, Rock J, Adams EC. A description of 34 human ova within the first 17 days of development. Am J Anat 1956;98:435-494.
Hertig,AT. Forty years in the female pelvis. Obstetrics and Gynecology, 42:907-909, 1973.

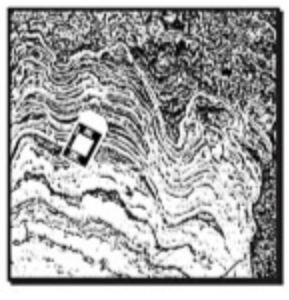
Standardization of Endometrial Cycle Dating. 1950

Photo Credit: George L. Mutter, 2012. Original objects from AT Hertig.
Reference: Noyes RW, Hertig AT & Rock J. Dating the endometrial biopsy. Fert Steril 1:3-25, 1950.
Comment: Noyes reports in a letter of 1980 published in Citation Classics (#14, April 7, 1980) that he was highly grateful for Hertig's generosity in giving him first authorship of the published report.



First RNA *in situ* Hybridization of Paraffin Tissues. 1987

Photo Credit: George L. Mutter, 2012.
Reference: Mutter GL, Wolgemuth DJ. Distinct developmental patterns of c-mos protooncogene expression in female and male mouse germ cells. Proc Natl Acad Sci USA 1987;84:5301-5.
Comment: Columbia Presbyterian Hospital was a key link in transmission of Dr. Hertigs teachings and academic style to BWH. When a former Hertig student (R.Richart) became chief of gynecologic pathology at Columbia Presbyterian Hospital, he in turn trained Drs. Crum and Mutter, who would later return to the BWH as faculty.



Algorithm for Design of Oligonucleotide Targets for the First Commercial Gene Chip. 1995-1998

Photo Credit: George L. Mutter, 2012. The chip cassette is an original pre-market issue (Hu6800 SubA-D) from obtained by G Mutter from Affymetrix under a noncommercial material exchange agreement. Stromatolyte from GL Mutter Collection.
Reference: none published.
Comment: This story was conveyed by L. Stein to G.Mutter in the mid-1990s. Dr. Stein favored open publication of the oligonucleotide sequences at the time, but this was not supported by his Affymetrix associates on the basis that this was confidential company data. Thus the lack of a published citation for this work. In the course of this project, Lincoln Stein was Director of the (1992 - 1997) Informatics Core, MIT Genome Center.

EIN, a Monoclonal Endometrial Precancer. 1995-2000

Photo Credit: George L. Mutter, 2012. Stitched high magnification photomicrograph mosaic.
References: Mutter GL, Chaponot M, Fletcher J. A PCR assay for non-random X chromosome inactivation identifies monoclonal endometrial cancers and precancers. Am J Pathol 1995;146:501-8.
Mutter GL, Baak JPA, Crum CP, Richart RM, Ferenczy A, Faquin WC. Endometrial precancer diagnosis by histopathology, clonal analysis, and computerized morphometry. J Pathol 2000;190:462-9.

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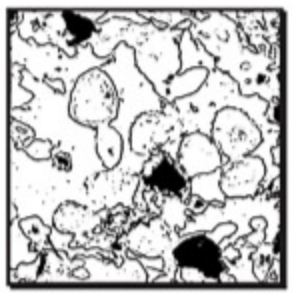
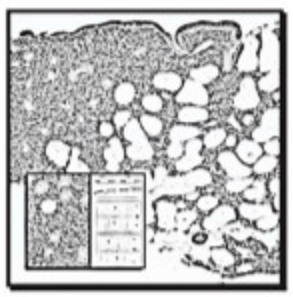


P57, a Marker for Diagnosis of Complete Hydatidiform Mole, 2001

Photo Credit: George L. Mutter, 1986. Molar tissue floated in saline.
Reference: Castrillon DH, Sun D, Weremowicz S, Fisher RA, Crum CP, Genest DR. Discrimination of complete hydatidiform mole from its mimics by immunohistochemistry of the paternally imprinted gene product p57KIP2. Am J Surg Pathol. 2001 Oct;25(10):1225-30.

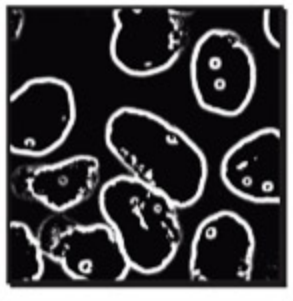


Discovery of Latent Precancers, 2001

Photo Credit: George L. Mutter, 2012. Stitched high magnification photomicrograph mosaic.
Reference: Mutter GL, Ince TA, Baak JPA, Kust G, Zhou X, Eng C. Molecular identification of latent precancers in histologically normal endometrium. Cancer Res 2001;61:4311-4.

Discovery of the Tubal Origin of Most "Ovarian" Serous Cancers, 2006-2007

Photo Credit: George L. Mutter, 2012. Stitched high magnification photomicrograph mosaic.
Reference: Medeiros, F., Muto, M. G., Lee, Y., Elvin, J. A., Callahan, M. J., Feltmate, C., Garber, J. E., Cramer, D. W., & Crum, C. P. 2006, "The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome", Am J Surg Pathol, 30:230-236.
Lee, Y., Miron, A., Drapkin, R., Nucci, M. R., Medeiros, F., Saleemuddin, A., Garber, J., Birch, C., Mou, H., Gordon, R. W., Cramer, D. W., McKeon, F. D., & Crum, C. P. 2007, "A candidate precursor to serous carcinoma that originates in the distal fallopian tube", J Pathol, 211:26-35.



Common Translocations in Endometrial Stromal Neoplasia, 2007

Photo Credit: Marisa R. Nucci, 2007
Reference: Nucci MR, Harburger D, Koontz J, DalCin P, Sklar J. Molecular analysis of the JAZF1-JJAZ1 gene fusion by RE-PCR and Fluorescence in situ hybridization in endometrial stromal neoplasms. Am J Surg Path 31:65-70, 2007.
Koontz JI, Soreng AL, Nucci M, et al. Frequent fusion of the JAZF1 and JJAZ1 genes in endometrial stromal tumors. Proc Natl Acad Sci USA. 2001;98:6348–6353.

Discovery of the Progenitor Cell of Cervical Squamous Carcinoma, 2011

Photo Credit: Michael Herfs, 2011.
Reference: Herfs M, Yamamoto Y, Laury A, Wang X, Nucci MR, McLaughlin-Drubin ME, Münger K, Feldman S, McKeon FD, Xian W, Crum CP. "A discrete population of squamocolumnar junction cells implicated in the pathogenesis of cervical cancer". Proc Natl Acad Sci USA. 2012;109:10516-21

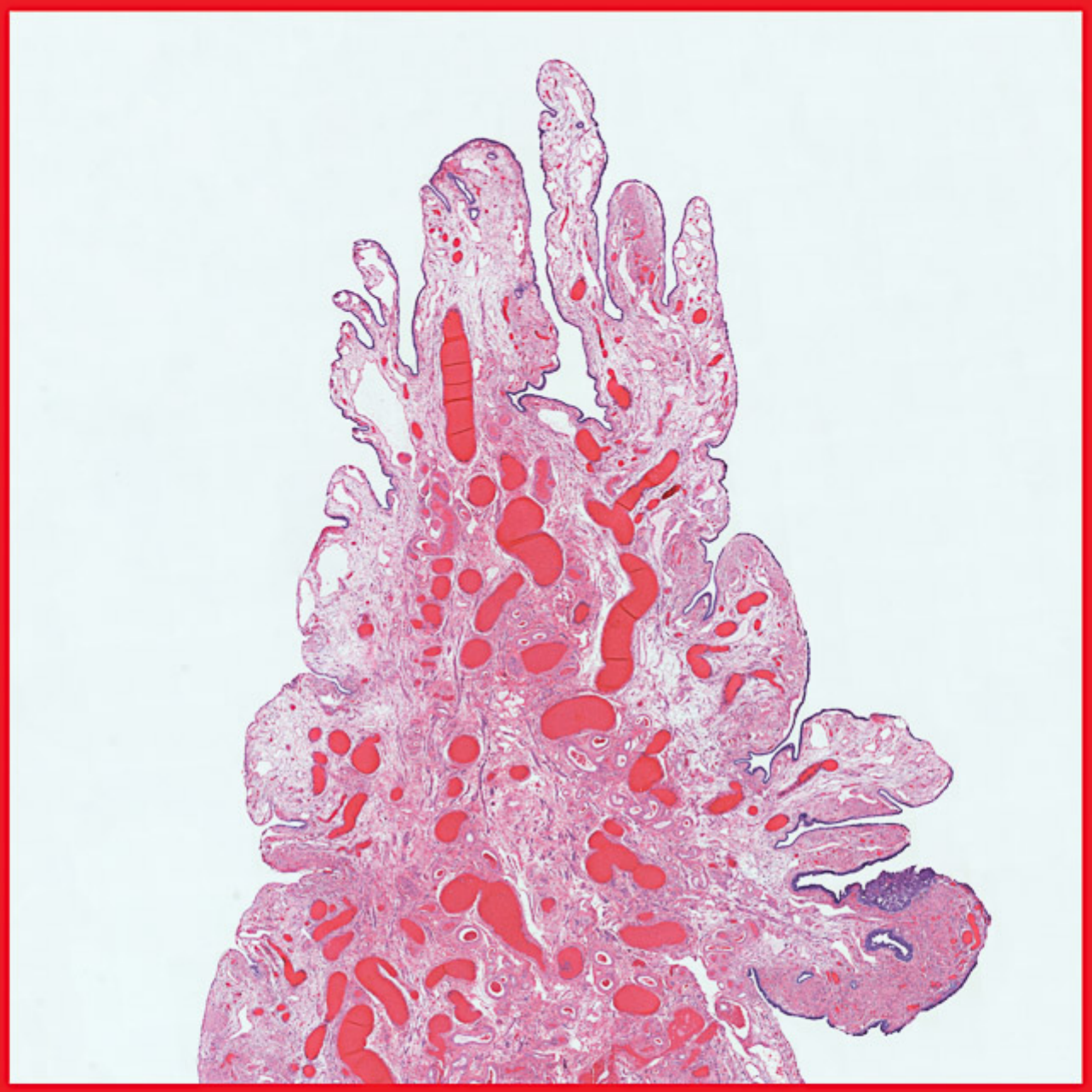
Faculty of the Women's and Perinatal Pathology Division
June, 2013

Christopher P. Crum, Chief
Fred Bieber
Theonia Boyd
Eleanor Chen
Daniela Dinulescu
Michelle Hirsch
Kenneth Lee
George L. Mutter
Marisa R. Nucci
Bradley Quade
William Welch

Exhibition:
Women's and Perinatal Pathology Gallery
Department of Pathology
Brigham and Women's Hospital
75 Francis St, Boston, MA, 02115

Installed Amory Building, 3rd Floor
December, 2012

Chair, Department of Pathology: Jeffrey A. Golden
W&P Division Chief: Christopher P. Crum
Project Manager: George L. Mutter



1832: Boston Lying-In Hospital founded
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