# Una mirada al passat per entreveure el futur

Dr. Miquel Àngel Carrasco
Societat Catalana de Citopatologia
Octubre 2012

# Els inicis de la citologia

- **1838, Johannes Müller** (1801-1858). Patòleg berlinès. Realitza les primeres extensions citològiques de tumors per raspat de les superfícies tumorals

- **1843, Gottlieb Gluge** publica les primeres imatges citològiques d'un càncer cervical obtingudes per raspat

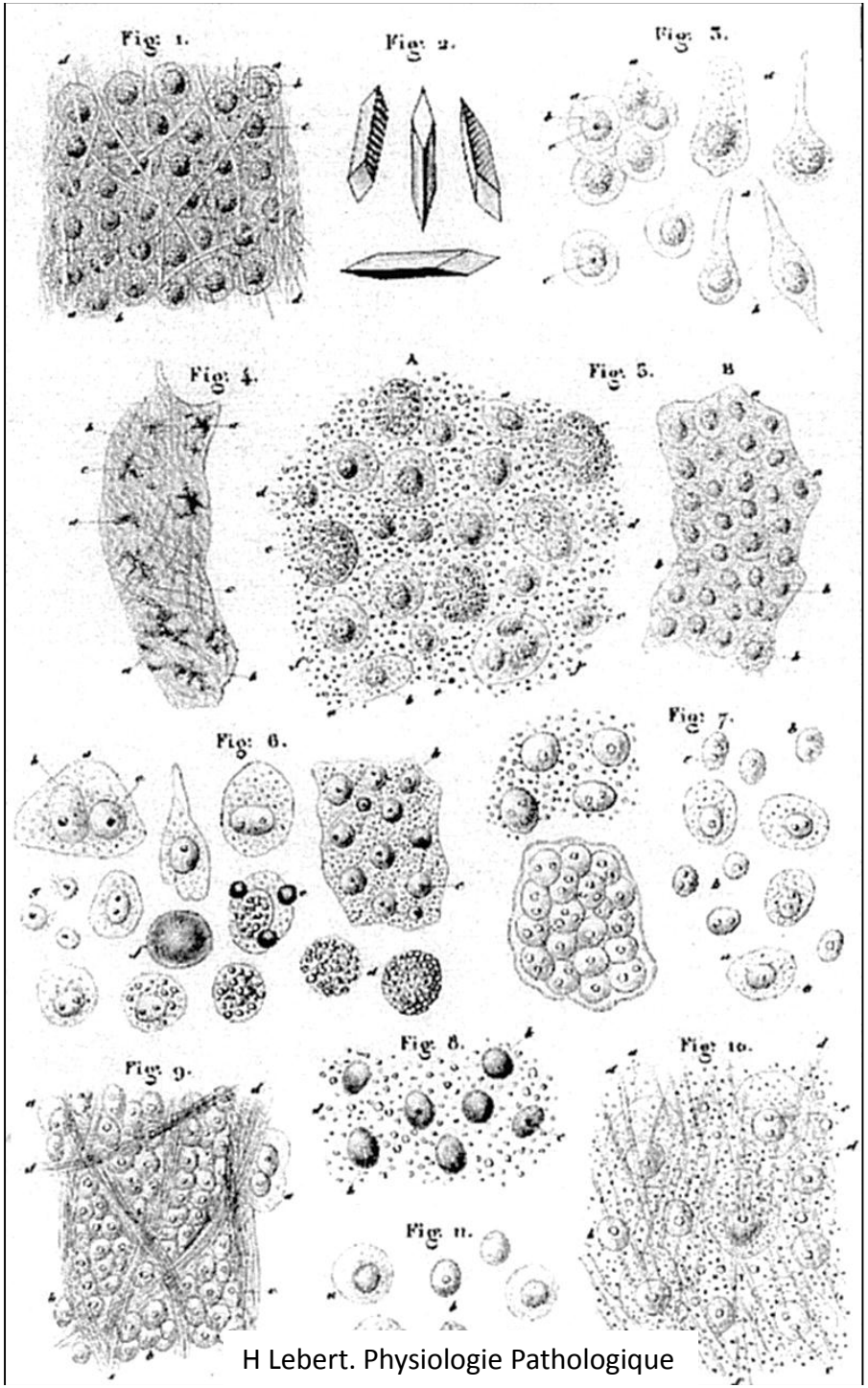
- **1843-1846, WH Walshe** publica imatges de càncer mama, sarcomes i les primeres cèl·lules neoplàstiques en un esput

"IF THE CANCER HAVE SOFTENED, THE MICROSCOPICAL CHARACTERS OF THAT PRODUCT MAY BE FOUND SOMETIMES IN THE SPUTA."

W.H. Walshe
London, 1851

# Els inicis de la citologia

- **1845, Hermann Lebert** (1813-1878). Patòleg francès nascut a Alemanya publica un atles de patologia amb més de 250 imatges, moltes d'elles citològiques

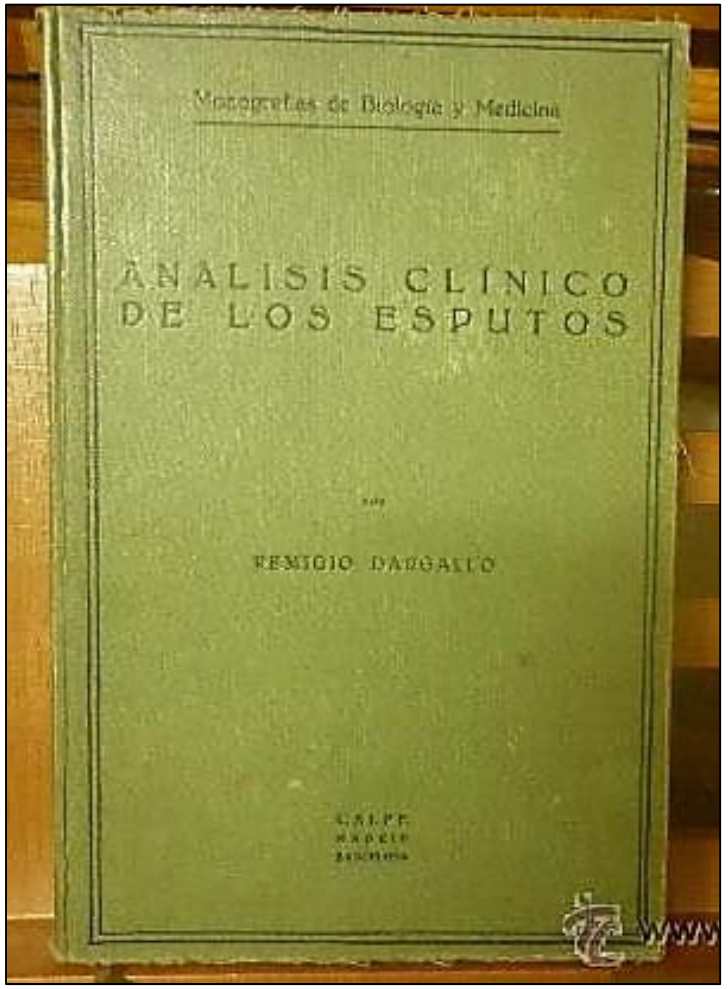


H Lebert. Physiologie Pathologique

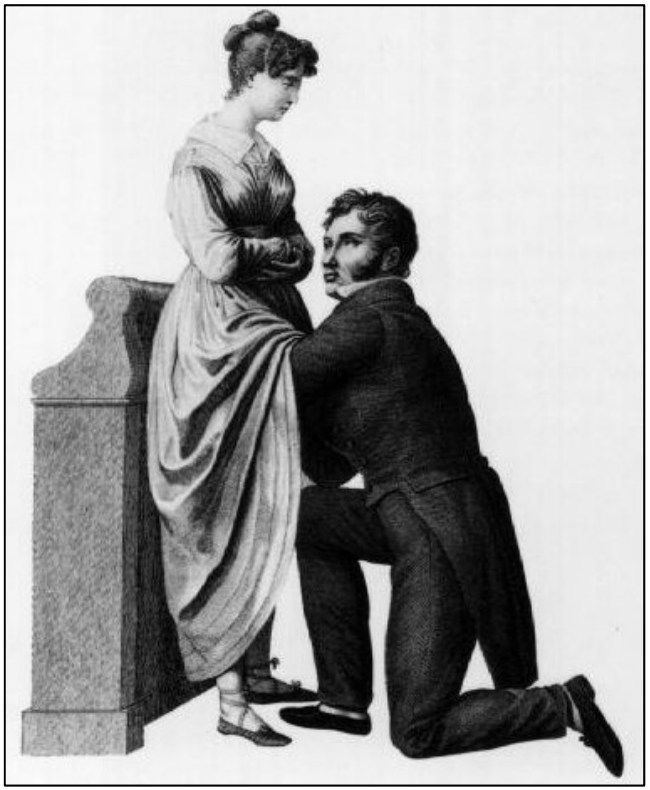
# Els inicis de la citologia

- **1853, James Paget** presenta les primeres imatges de citologia per punció aspiració d'un tumor mamari
- **1856 i 1869, D. Lambl i WH Dickinson** publiquen imatges de tumors en orina
- **1890's**
  - **Orines**
  - **Esputs**
  - **Líquids ascítics...**

- **1920, Remigio Dargallo** publica en Espanya la primera monografia en citologia clínica (Análisis Clínico de los Esputos)

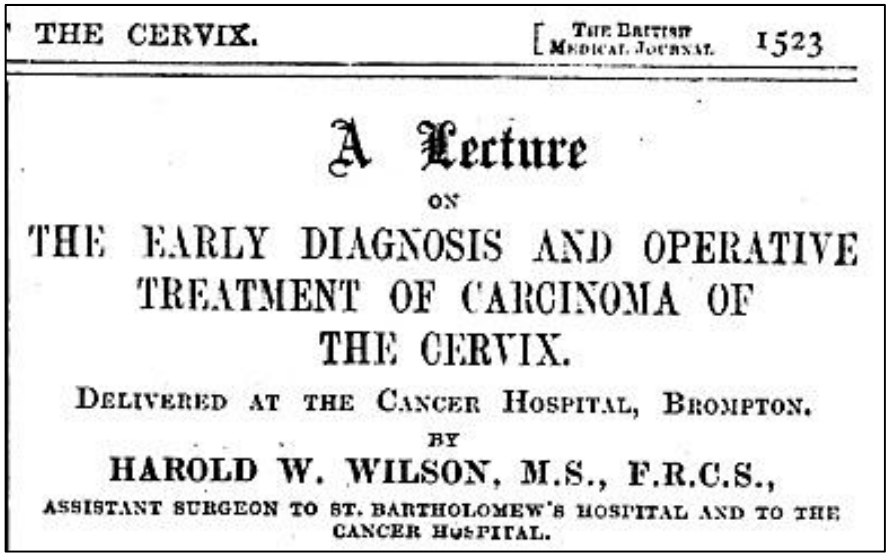


# La ginecologia

# Diagnòstic precóç del carcinoma de cèrvix. 1913

- Formes clíniques
  - Papil·lifera
  - Infiltrant
  - Ulcerativa
- Formes de diseminació
  - Cèrvix vaginal
    - Cap a la vagina
    - Cap als parametris
  - Cèrvix supravaginal – canal
    - Cap al cos uterí



THE CERVIX. [THE BRITISH MEDICAL JOURNAL 1523

A Lecture

ON

THE EARLY DIAGNOSIS AND OPERATIVE TREATMENT OF CARCINOMA OF THE CERVIX.

DELIVERED AT THE CANCER HOSPITAL, BROMPTON.

BY

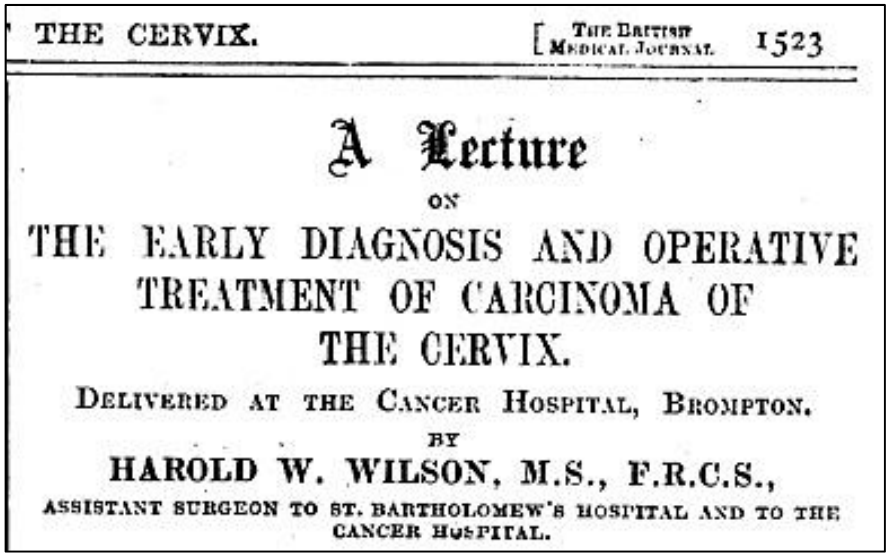
HAROLD W. WILSON, M.S., F.R.C.S.,

ASSISTANT SURGEON TO ST. BARTHOLOMEW'S HOSPITAL AND TO THE CANCER HOSPITAL.

Wilson HW. A Lecture ON THE EARLY DIAGNOSIS AND OPERATIVE TREATMENT OF CARCINOMA OF THE CERVIX: Delivered at the Cancer Hospital, Brompton. Br Med J. 1913 Dec 13;2(2763):1523-6

# Diagnòstic precóç del carcinoma de cèrvix. 1913

- Simptomatologia
  - Hemorràgies coitals
  - Metrorràgies postmenopausa
  - Secrecions serohemàtiques
- Signes
  - Augment consistència i mida del cèrvix
  - Ulceracions i friabilitat
- Diagnòstic histològic
  - Curetatge de la superfície del cèrvix per obtenir petites peces de teixit



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# Càncer cervical als inicis del segle XX

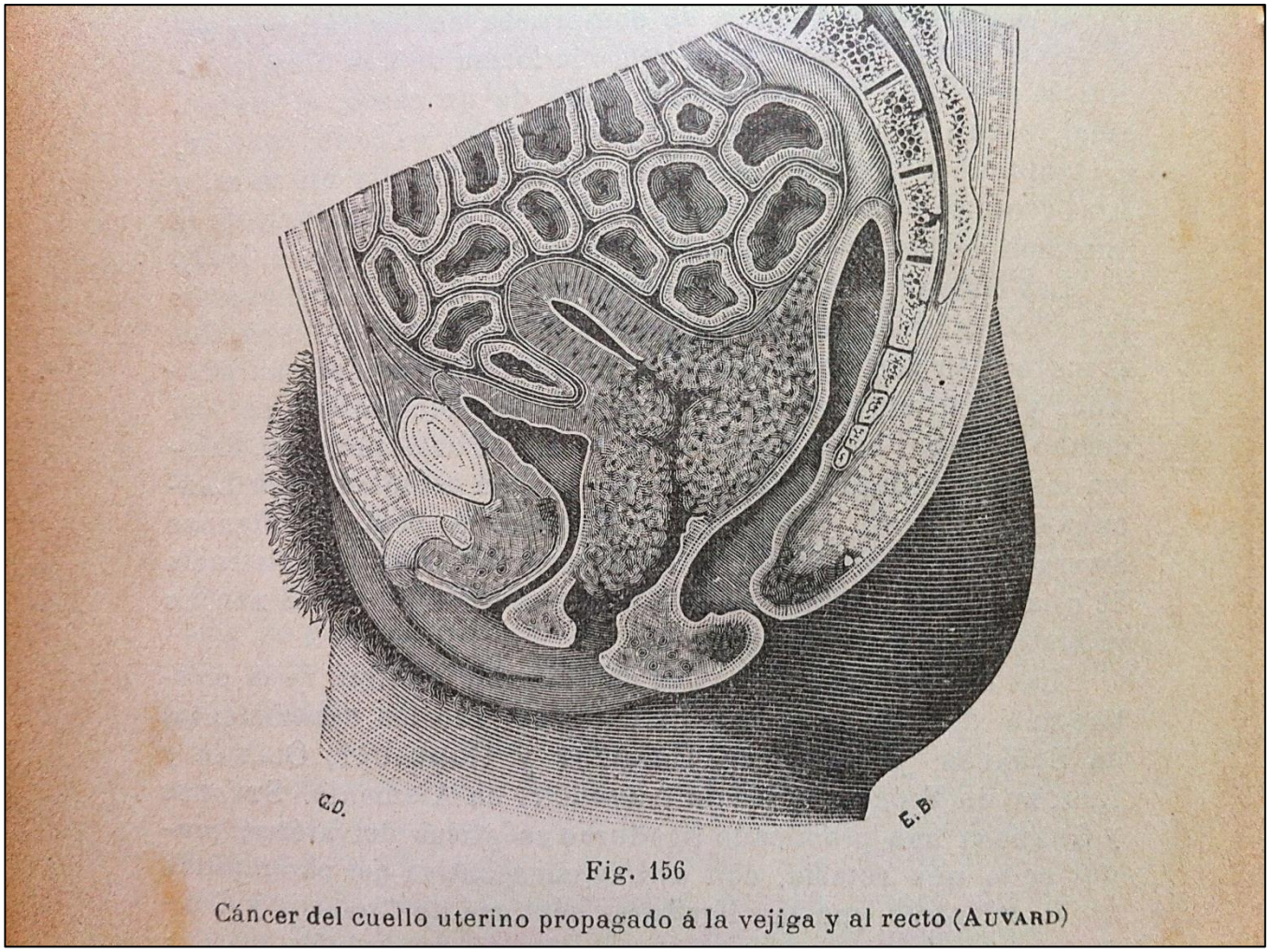


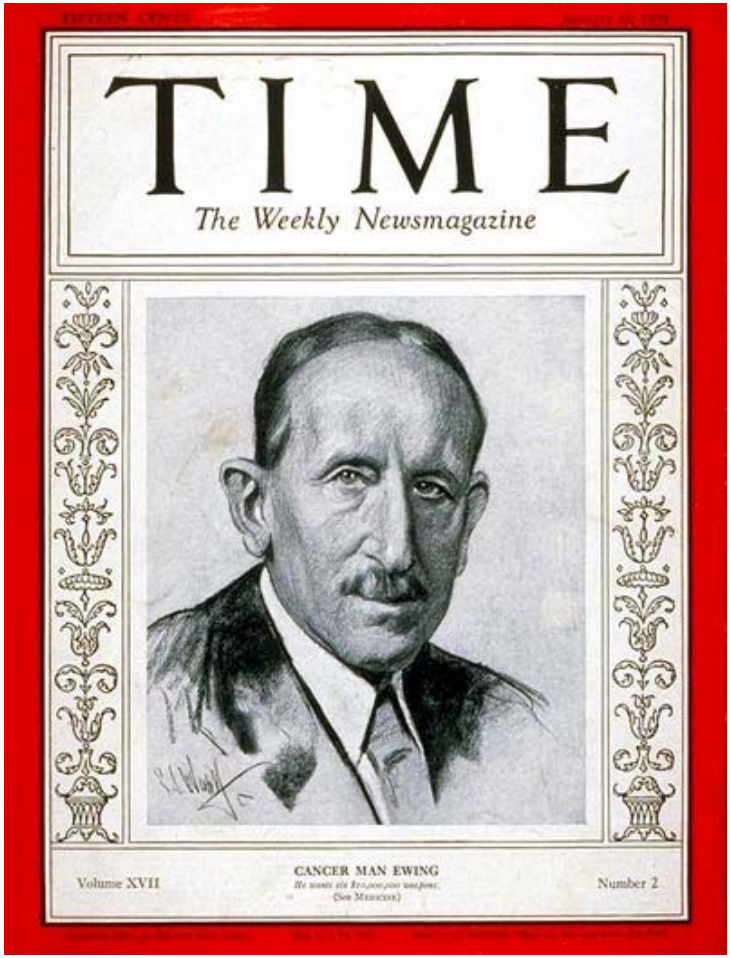

Fig. 156

Cáncer del cuello uterino propagado á la vejiga y al recto (AUVARD)

# Els inicis de la citologia

- **James Ewing (1866-1943)** introdueix la **citologia per aspiració en els 1920's** al Memorial Hospital for Cancer ad Allied Diseases de New York

- 12-1-1931, portada de TIME com el "**Cancer Man Ewing**" per la seva contribució a la Patologia, Oncologia i Citologia



# George N. Papanicolaou (1883-1962)

- 19-X-1913 arriba a Nova York
- Dr. Thomas Hunt Morgan, Univ. Columbia
- Tècnic Dept. Patologia i Bacteriologia Dr. Elser en el New York Hospital Cornell (NYHC)
- **IX-1914 Dept. d'Anatomia del Dr. Charles Stockard (NYHC)**

- Treball d'investigació
- III-1915, Science:

  *"Sex Determination and Sex Control in Guinea Pigs"*
- Necessitava oòcits de les conilletes d'Índies en el moment de l'ovulació
- Menstruació poc evident

# Primers estudis citologics vaginals

- Especulum nasal per inspeccionar in situ la vagina
- Més tard va afegir l'estudi citològic vaginal
- Període 15-16 dies, menstruació 24 hores
- Diferents patrons citològics al llarg del cicle relacionats amb canvis a l'úter i ovaris
- Stockard CR and Papanicolaou GN. A rhytmical "heat period" in the guinea-pig. Science 1917; 46: 1176: 42-44

# THE EXISTENCE OF A TYPICAL OESTROUS CYCLE IN THE GUINEA-PIG—WITH A STUDY OF ITS HISTOLOGICAL AND PHYSIOLOGICAL CHANGES

CHARLES R. STOCKARD AND GEORGE N. PAPANICOLAOU

*Department of Anatomy, Cornell University Medical School, New York City*

ONE TEXT FIGURE AND NINE PLATES

Am. J. Anat 1917, 22:2: 225-283

# Primers passos de la citologia vaginal en dones

- 1920-1925 Papanicolaou pensa realitzar estudis similars en dones

- Inicia estudis amb  la seva dona Mary

- 1925 associació Cornell-H. Dones N.Y.
  - 12 casos, personal de l'hospital
  - Amplia dones casos prequirúrgics

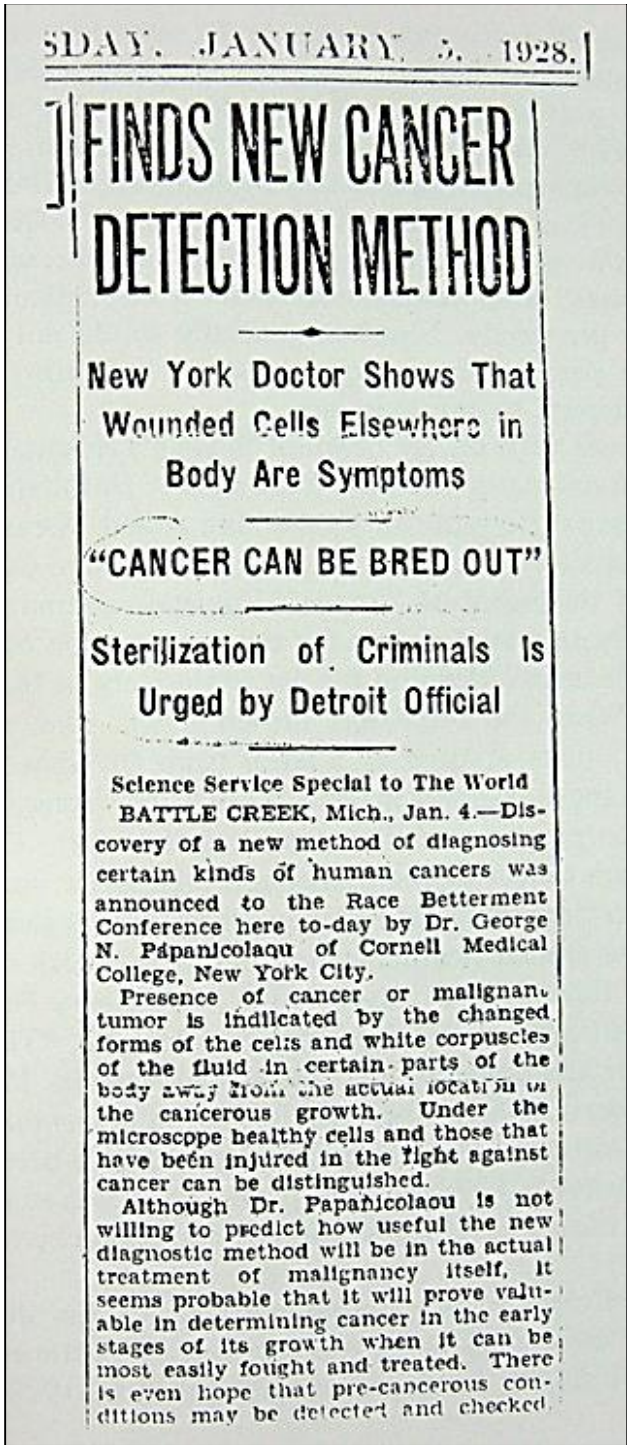
- Primeres observacions de cèl·lules malignes

# Memorial i New York H Cornell en York Avenue


**La milla d’or de la citologia**

# Presentació en societat de la citologia com a nou mètode de diagnòstic del càncer

- Gener 1928
- 3ª Conferència Race Betterment a Battle Creek
  - "New Cancer Diagnosis"
- Poca acceptació entre la classe mèdica: "**El fàcil accés del cèrvix a la biòpsia no fa necessària la citologia**"



SDAY, JANUARY 5, 1928.

## FINDS NEW CANCER DETECTION METHOD

### New York Doctor Shows That Wounded Cells Elsewhere in Body Are Symptoms

### "CANCER CAN BE BRED OUT"

### Sterilization of Criminals Is Urged by Detroit Official

Science Service Special to The World

BATTLE CREEK, Mich., Jan. 4.—Discovery of a new method of diagnosing certain kinds of human cancers was announced to the Race Betterment Conference here to-day by Dr. George N. Papanicolaou of Cornell Medical College, New York City.

Presence of cancer or malignant tumor is indicated by the changed forms of the cells and white corpuscles of the fluid in certain parts of the body away from the actual location of the cancerous growth. Under the microscope healthy cells and those that have been injured in the fight against cancer can be distinguished.

Although Dr. Papanicolaou is not willing to predict how useful the new diagnostic method will be in the actual treatment of malignancy itself, it seems probable that it will prove valuable in determining cancer in the early stages of its growth when it can be most easily fought and treated. There is even hope that pre-cancerous conditions may be detected and checked

## New Cancer Diagnosis

George N. Papanicolaou, M.D.

I will only give a report of some work of mine which may have some bearing on the diagnosis of certain malignant tumors, especially those of the female genital tract.

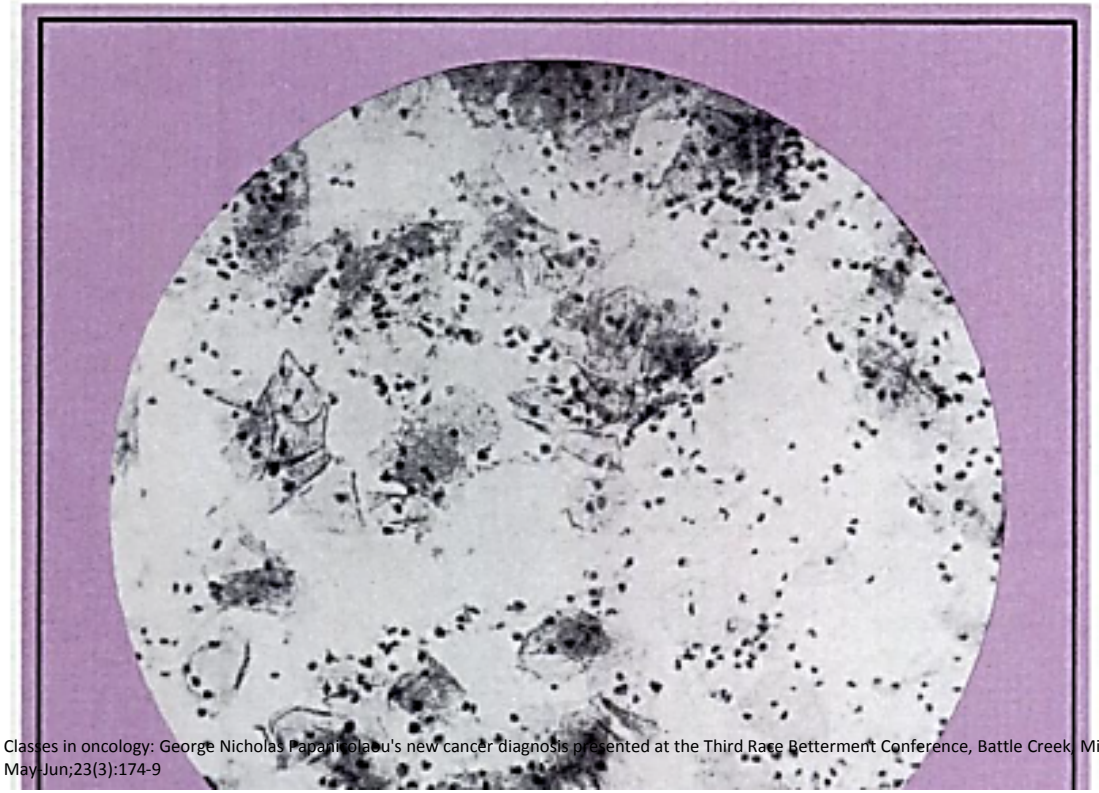
This work was started about two and one-half years ago in the spring of 1925, first in the clinic of Cornell Medical College, then in the Women's Hospital in New York City. First we selected a number of normal women, and we took vaginal smears every day. The technique was very simple. We used a small pipette and took a little fluid from the vagina every day. Our intention was to find out if there was any definite morphological change in the vagina and the vaginal smear that would reveal some of the more important changes that occur in the ovaries and in the uterus.

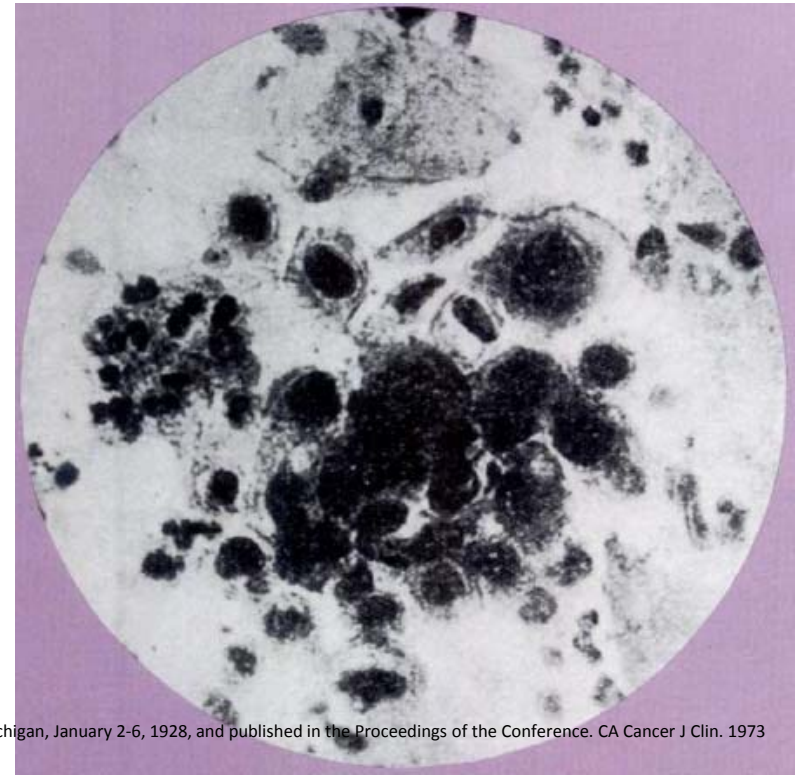
As you probably know, this method has been applied very successfully in other mammals, especially in the rodents, with really surprising results. It has been possible to diagnose or to recognize certain changes in the ovaries and in the uterus. For instance, the time of ovalescence in the ovary may be

This paper was originally presented at the Third Race Betterment Conference, Battle Creek, Michigan, January 2-6, 1928, and published in the Proceedings of the Conference the same year.

Conclusions:

1. Presentaven un nou mètode de diagnòstic de certs tumors malignes, especialment del tracte genital femení
2. El mètode i la tècnica emprada eren molt senzills d'aplicar
3. El reconeixement de les cèls. malignes està basat en el reconeixement d'aquestes cèls. i de la reacció que causa en l'organisme
4. Mètodes similars poden ser emprats en el reconeixement del càncer en altres òrgans

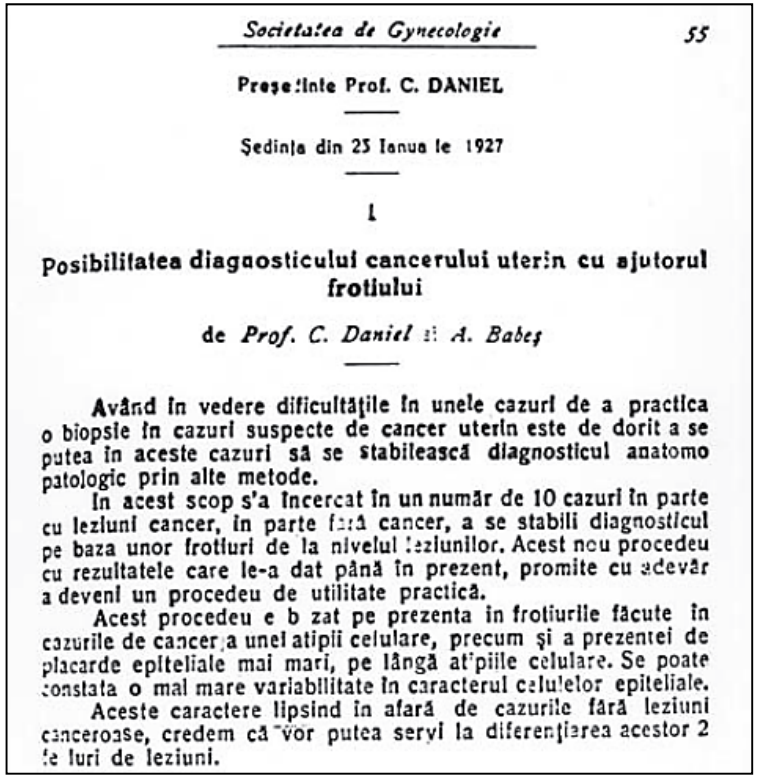




Classes in oncology: George Nicholas Papanicolaou's new cancer diagnosis presented at the Third Race Betterment Conference, Battle Creek, Michigan, January 2-6, 1928, and published in the Proceedings of the Conference. CA Cancer J Clin. 1973 May-Jun;23(3):174-9

# Primers passos a Europa

- **Aurel A. Babeş** i el Professor Constantin Daniel
- Gener i abril del 1927 presenten davant la Societat de Ginecologia de Bucharest:
  - **Diagnòstic del càncer del coll uterí per frotis**



*Societatea de Gynecologie* 55

Președinte Prof. C. DANIEL

Ședința din 25 Ianuarie 1927

I

**Posibilitatea diagnosticului cancerului uterin cu ajutorul frotiului**

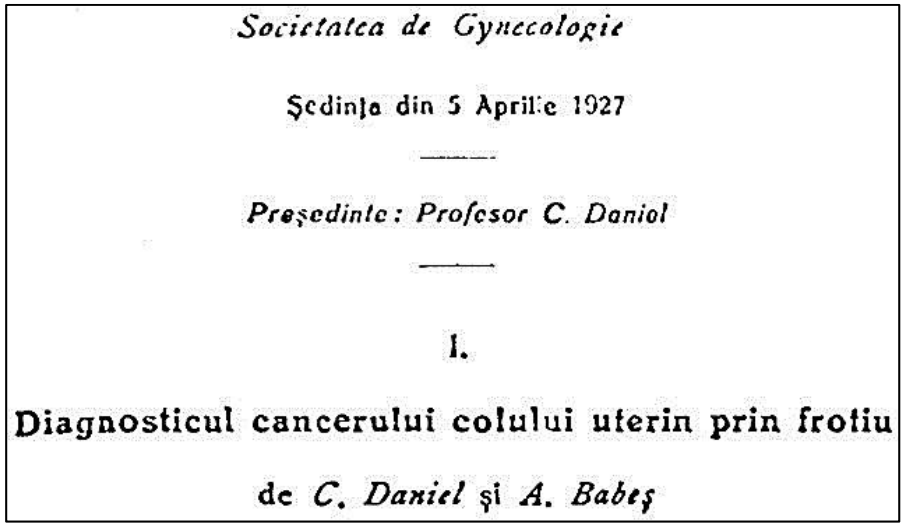
de *Prof. C. Daniel* și *A. Babeș*

Având în vedere dificultățile în unele cazuri de a practica o biopsie în cazuri suspecte de cancer uterin este de dorit a se putea în aceste cazuri să se stabilească diagnosticul anatomo patologic prin alte metode.

În acest scop s'a încercat în un număr de 10 cazuri în parte cu leziuni cancer, în parte fără cancer, a se stabili diagnosticul pe baza unor frotiuri de la nivelul leziunilor. Acest nou procedeu cu rezultatele care le-a dat până în prezent, promite cu adevăr a deveni un procedeu de utilitate practică.

Acest procedeu e b zat pe prezenta în frotiurile făcute în cazurile de cancer a unei atipii celulare, precum și a prezenței de placarde epiteliale mai mari, pe lângă atipiile celulare. Se poate constata o mai mare variabilitate în caracterul celulelor epiteliale.

Aceste caractere lipsind în afară de cazurile fără leziuni canceroase, credem că vor putea servi la diferențiarea acestor 2 feluri de leziuni.



*Societatea de Gynecologie*

Ședința din 5 Aprilie 1927

*Președinte: Profesor C. Daniel*

I.

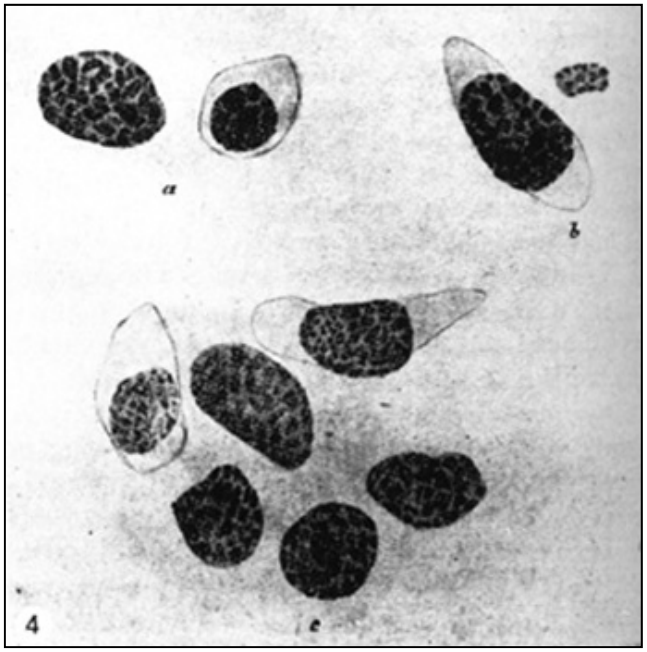
**Diagnosticul cancerului colului uterin prin frotiu**

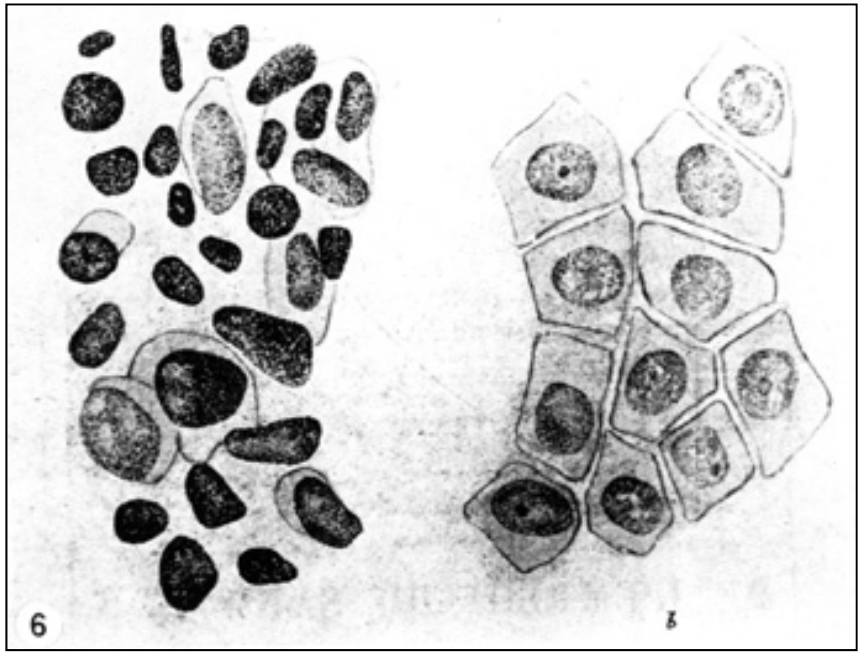
de *C. Daniel* și *A. Babeș*

Naylor B, Tasca L, Bartziota E, Schneider V. In Romania it's the Méthode Babeş-Papanicolaou. Acta Cytol. 2002 Jan-Feb;46(1):1-12

# Primers passos a Europa

- Diagnostic du Cancer de Col Utérin par les Frottis. La Presse Médicale, Wednesday, April 11, 1928 (36: 451-454, 1928)
- Mitjançant una nansa metàl·lica de bacteriologia recullen el material, realitzen el frotis que es fixat a l'aire i tenyit amb Giemsa
- Romania anomena la citologia ginecològica com a "Mètode Babeş-Papanicolaou" en honor del Dr. Babeş



# Aurel Babeş

- Romania 1886-1961
- Fill del professor de química Aurel V. Babes
- Nebot del professor de patologia de la Universitat de Bucarest i Budapest Victor Babes, especialista en microbiologia i malalties infeccioses. Descobridor de l'agent causal de la Babesiosis. Nominat a P Nòbel 1924
- 1915, graduat a l'escola de Medicina de Bucarest, *magna cum laude*. Posteriorment tesi doctoral sobre LCR
- 1921, assistent sènior del Professor Constantin Daniel, cap de Ginecologia Clínica a l'H. Coltea de Bucarest

Naylor B, Tasca L, Bartziota E, Schneider V. In Romania it's the Méthode Babeş-Papanicolaou. Acta Cytol. 2002 Jan-Feb;46(1):1-12

# Aurel Babeş

- Alguns altres dels seus treballs
  - Study of Fine Morphology of Negri Corpuscles
  - The Diagnosis of Epidemic Typhus by Means of the Weil-Felix Reaction with Proteus X19
  - Tractat sobre La Pelagra, amb el seu tiet i el seu pare
  - Text d'Anatomia Patològica General
  - Text d'Endocrinologia
  - Treballs sobre patologia ginecològica, sífilis, tuberculosi, càncer experimental...

Naylor B, Tasca L, Bartziota E, Schneider V. In Romania it's the Méthode Babeş-Papanicolaou. Acta Cytol. 2002 Jan-Feb;46(1):1-12

# Per què el treball d'Aurel Babeş en citologia ginecològica no va tenir continuïtat?

- L'impacte de la publicació en la revista francesa va ser mínim en el mon anglosaxó

- 1931 publica un altre treball "Sur le cancer superficial du col utérin" però amb mínimes referències al mètode diagnòstic per frotis

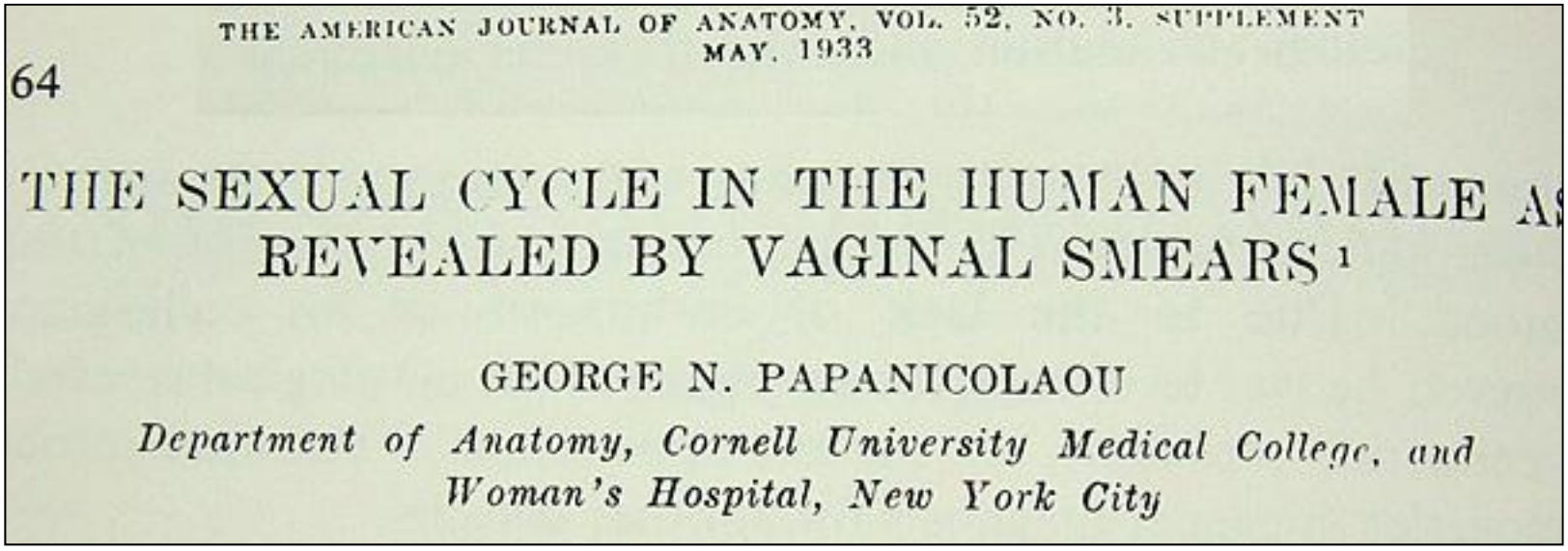
- La gran diversitat d'interessos intel·lectuals

Naylor B, Tasca L, Bartziota E, Schneider V. In Romania it's the Méthode Babeş-Papanicolaou. Acta Cytol. 2002 Jan-Feb;46(1):1-12

# Algú més al mon?

- Odorico Viana
- Verona
- 1928, La Diagnosi precoce del cancro uterino mediante lo stricio. Clin Ostetrica 1928; 30: 781-793

- ...i s'acabà la citologia al càncer cervical a Europa i USA



THE AMERICAN JOURNAL OF ANATOMY, VOL. 52, NO. 3, SUPPLEMENT
MAY, 1933

64

# THE SEXUAL CYCLE IN THE HUMAN FEMALE AS REVEALED BY VAGINAL SMEARS [1]

GEORGE N. PAPANICOLAOU

*Department of Anatomy, Cornell University Medical College, and Woman's Hospital, New York City*

- Papanicolaou amplia estudis dels canvis citològics durant el cicle de la dona
- Millora el mètode de tinció

**Papanicolaou i Traut**

**1939 mor Dr. Stockard i el substitueix el Dr. Joseph Hinsey**

Empenta al diagnòstic citològic del càncer

S'inicia col·laboració amb el Dr. Traut

Estudis citològics a totes les dones que ingressaven al Dept. Ginecologia

El material es recull per aspiració amb pipeta del fons de sac posterior vaginal

Dr. Traut

**Primeres publicacions**

1941, Papanicolaou i Traut presenten a la Societat Obstètrica de N.Y.:

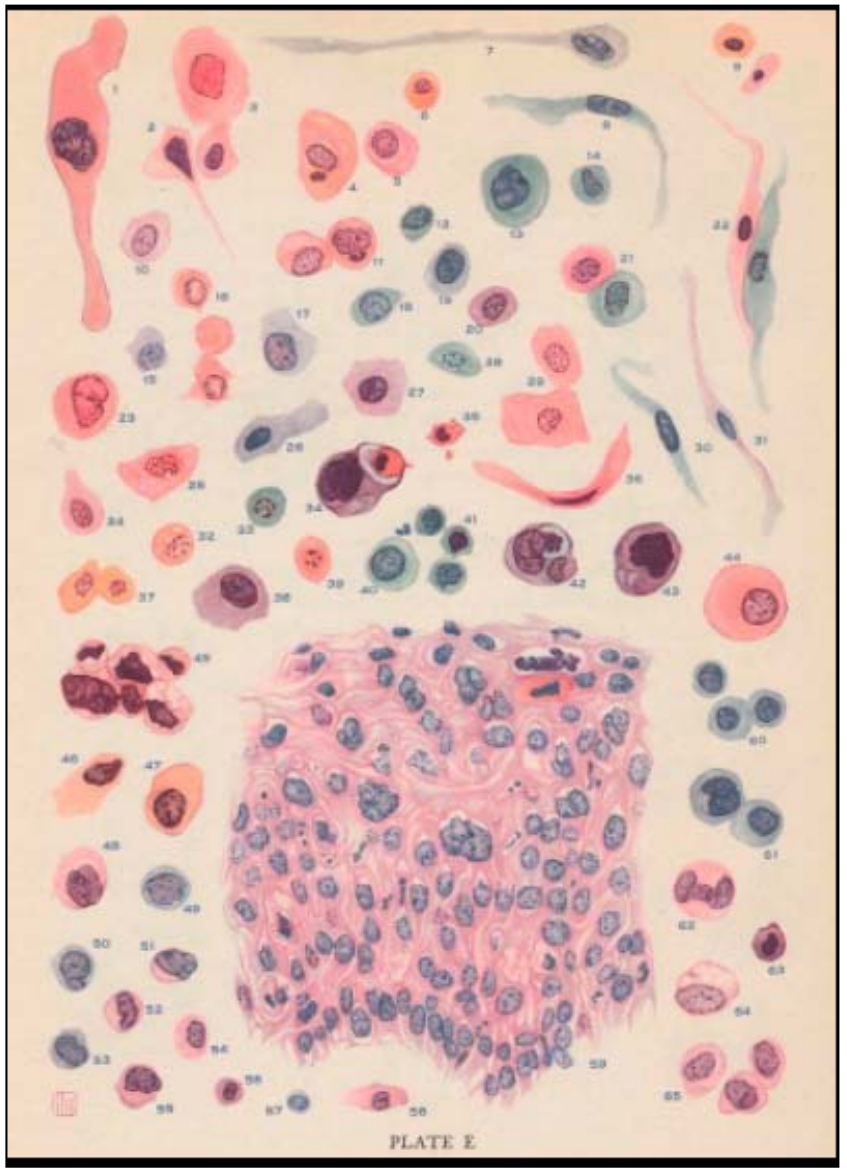
> "*The diagnòstic value of vaginal smears in carcinoma of the uterus*" Am. J. Obst. Gyn

1943, publiquen la monografia:

> "*Diagnosis of Uterine Cancer by Vaginal Smear*"

1944, Dr. E. Ayre presa citològica amb visualització del cèrvix i 1947 inventa espàtula

1947, 1er. Curs de Citologia N.Y. Cornell's H.




Diagnosis of Uterine Cancer by Vaginal Smear

## Millores metodològiques

- Fixació èter-alcohol
- Substitució de l'HE
- **GN Papanicolaou. A new procedure for staining vaginal smears. Science 1942; Vol. 95 no. 2469 pp. 438-439 . DOI: 10.1126/science.95.2469.438**



FOR WORK IN MATHEMATICS

*Dr. John Charles Chenoweth McKinsey*, instructor in mathematics, New York University: Studies of the basic concepts and logical foundations of mathematics, and by *Dr. Alfred Tarski*, the Polish refugee mathematician. Both will work at the Institute for Advanced Study, Princeton, N. J.

# SPECIAL ARTICLES

## A NEW PROCEDURE FOR STAINING VAGINAL SMEARS[1]

IN the course of a study of vaginal smears conducted in cooperation with Dr. Herbert F. Traut, of the Department of Gynecology of Cornell Medical College and of New York Hospital, for the purpose of diagnosing malignant tumors and other pathological conditions of the female genital tract,[2] it was realized that certain modifications and improvements in our procedure of staining vaginal smears were necessary. Methods which proved to be successful in other applications[3,4,5] were not found to be entirely satisfactory in this particular work because of a common disadvantage. The staining of the cells was too deep to permit a sharp definition of their outlines in smears that were relatively thick or contained much blood. In most cases of carcinomas and in many other pathological conditions there is a profuse vaginal discharge frequently mixed with blood which forms a heavy film on the slides. In such rich and bloody smears there is considerable crowding and overlapping of cells which, when deeply stained, can not be well differentiated. This applies more particularly to the small endometrial cells which are often found in menstrual and other uterine bleedings and have a pathognomonic value in the diagnosis of adenocarcinomas of the fundus[2] and of other gynecological conditions. These cells also have great importance in the evaluation of the normal menstrual cycle, of sterility and of estrogenic and other endocrine therapy.

After long experimentation it was found that a much greater transparency and an equally good color differentiation of the cells can be obtained by the use of solutions of stains in 95 per cent. alcohol instead of aqueous solutions. Various alcoholic stains were thus developed, but here only two will be described which are now being used more generally in our laboratory (see Table I).

TABLE I

| | | | Stain EA 36 | Stain EA 25 |
|---|---|---|---|---|
| Light green SF yellowish | National Aniline and Chemical Co. | 0.5 per cent. solution in 95 per cent. alcohol | 45 cc | 44 cc |
| Bismarck Brown | National Aniline and Chemical Co. | 0.5 per cent. solution in 95 per cent. alcohol | 10 cc | 12 cc |
| Eosin yellowish | National Aniline and Chemical Co. | 0.5 per cent. solution in 95 per cent. alcohol | 45 cc | 44 cc |
| Acid phosphotungstic | Merck | | 0.200 gm | 0.170 gm |
| Lithium carbonate, saturated aqueous solution | | | 1 drop | 1 drop |

The 0.5 per cent. alcoholic solutions are first prepared. As the solubility of the stains in 95 per cent. alcohol is low, the solutions are heated at the time of preparation. The solutions are kept in stock without being filtered. Stains EA 36 or EA 25 should, however, be filtered in order to eliminate undissolved particles of stain.

The staining procedure is as follows:

1. Fix smears immediately (before drying) in equal parts of 95 per cent. alcohol and ether for 5 to 15 minutes.[6] Rinse in 70 per cent. and 50 per cent. alcohols and in distilled water.

2. Stain in hematoxylin for 5 to 10 minutes.[7] Rinse

[1] From the Department of Anatomy, Cornell University Medical College, New York, N. Y. Aided by a grant by the Commonwealth Fund.

[2] G. N. Papanicolaou and H. F. Traut, *Jour. Obst. and Gyn.*, 42: 193, 1941.

[3] G. N. Papanicolaou, *Amer. Jour. Anat.*, 52: 519, 1933.

[4] E. Shorr, SCIENCE, 91: 321, 1940; *ibid.*, 91: 579, 1940; *ibid.*, 94: 545, 1941.

[5] G. N. Papanicolaou, *Jour. Lab. and Clin. Med.*, 26: 1200, 1941.

[6] Although smears may be kept in the fixative indefinitely, a prolonged fixation of a week or more affects the staining reaction of the cells.

[7] Staining for only 2 minutes is often sufficient, but, as a rule, better results are obtained with longer staining of 5 to 6 minutes for normal smears and of 8 to 10 for smears used for diagnostic purposes, more particularly for cancer diagnosis. For sections, even longer staining is advised. This timing applies more specifically to Harris Hematoxylin, prepared with domestic hematoxylin and ammonium alum, which is now used in our laboratory. In order to obtain more uniform staining, used hematoxylin should not be discarded, but filtered from time to

1948,Boston. American Cancer Society organitza:

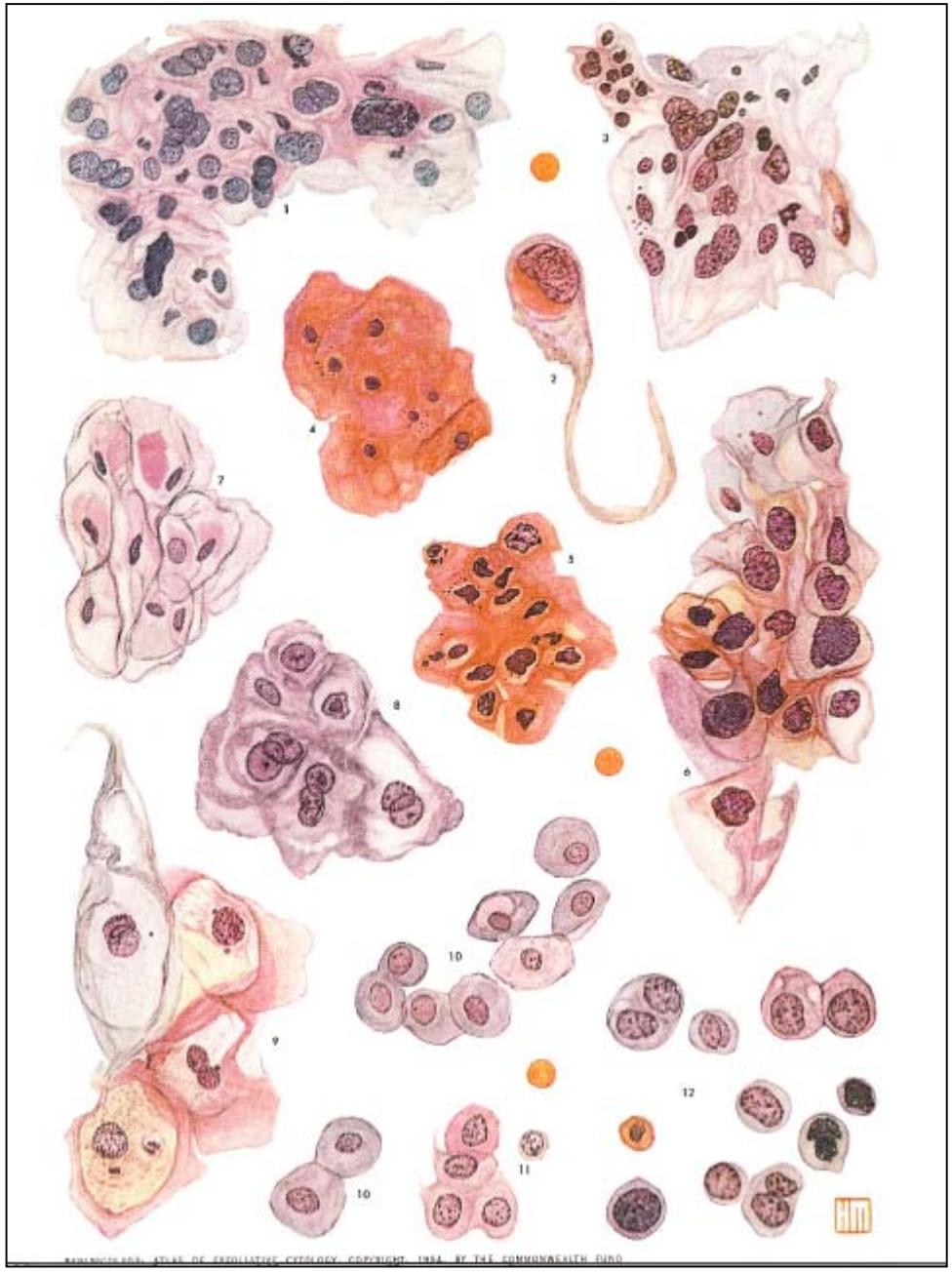
- 1ª Conferència Nacional de Citologia

S'aplica la mateixa tècnica a altres òrgans i mostres

Desenvolupa 5 categories diagnòstiques:

- Classe I Normal
- Classe II Inflamatori
- Classe III Sospitós de malignitat
- Classe IV Altament sospitós de malignitat
- Classe V Maligne

**1954, publica "Atlas of Exfoliative Cytology" $ 18**



Atlas of Exfoliative Cytology

# Present Status and Future Trends of Exfoliative Cytology

*George N. Papanicolaou, M.D.*

Exfoliative cytology is not a new science. It has a long history dating back to the nineteenth century. Since 1847, when Pouchet gave the first description of human vaginal smears, many secretions and fluids of the body have been explored, and many significant observations made by morphologists and pathologists interested in normal and morbid cytology and its diagnostic possibilities. Yet this impressive volume of investigative work did not reach a stage of general recognition for many decades until finally its cumulative force, strengthened by the added impact of newer contributions, caused a break in the dam of inertia and skepticism that had blocked its progressive course. It is only in the last ten years that exfoliative cytology, particularly as applied in the diagnosis of cancer, has received a wide acceptance by the

the study of the abnormal cell. In the same way that pathology has depended for its development on histology, so morbid cytology is fully dependent on a thorough knowledge of normal exfoliative cytology. No one should expect to be proficient in cytological diagnosis without an understanding of the normal cell and its manifold variations. In fact, in many instances, diagnosis is based equally on the evaluation of the normal as well as the abnormal exfoliated elements.

Certain technical improvements have also been contributing factors in the more recent growth of the field. Good preservation by immediate fixation is of paramount importance—and equally as necessary in the study of exfoliated cells as it is in normal and abnormal tissues. Improper fixation or drying of the smear may cause a total

Papanicolaou, G. N. (1952), Present status and future trends of exfoliative cytology. CA: A Cancer Journal for Clinicians, 2: 50–56. doi: 10.3322/canjclin.2.2.50

# Problemes als inicis de la citologia

- Desconeixement de la citologia normal dels diferents òrgans i cavitats
- Desconeixement de les variacions normals cel·lulars
- Fixació deficient de les preparacions dificultaven la seva interpretació
- Desenvolupament d'un bon mètode de tinció
- Tècnica de recollida i transport de les mostres
  - 1947, Ernest Ayre introdueix l'espàtula per obtenir mostres de l'orifici cervical. Important millora en la taxa de falsos negatius.

Espàtula d'Ayre

Papanicolaou, G. N. (1952), Present status and future trends of exfoliative cytology. CA: A Cancer Journal for Clinicians, 2: 50–56. doi: 10.3322/canjclin.2.2.50

# Camps inicials d'aplicació dels estudis citològics en l'àmbit oncològic

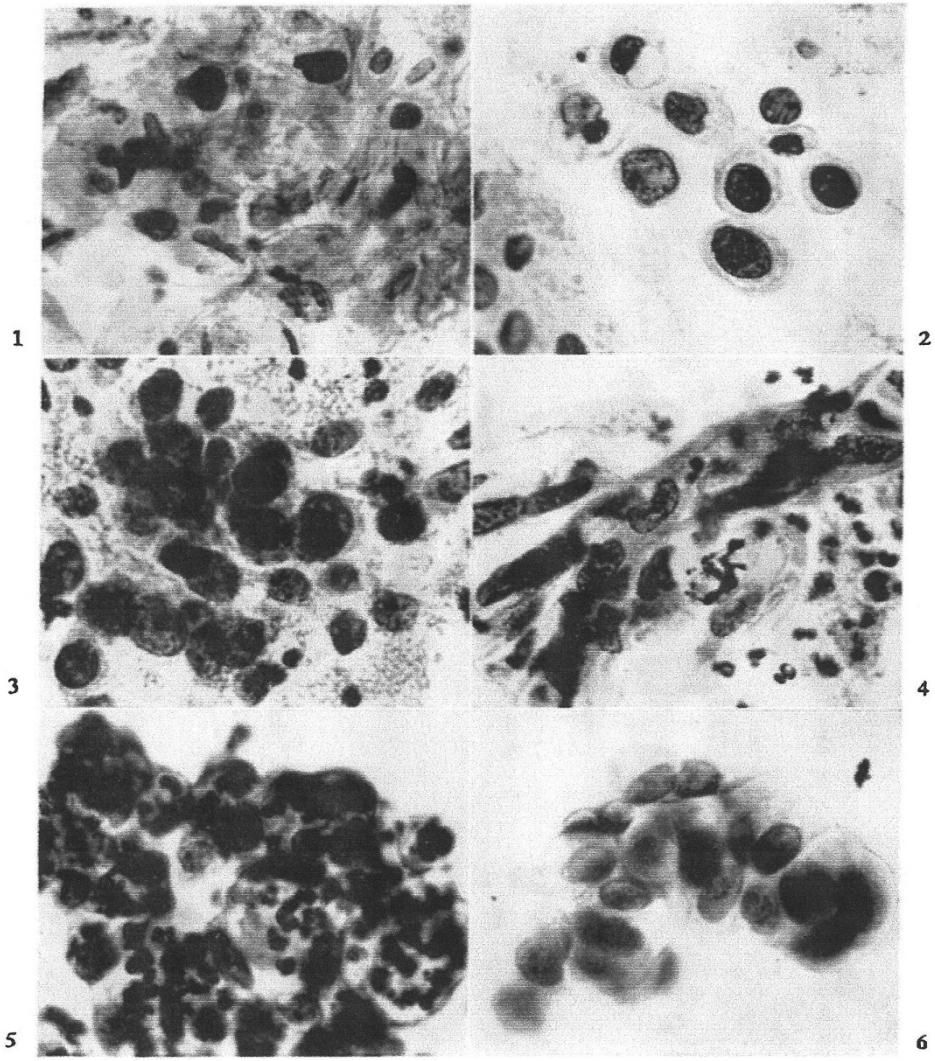
- Càncer de coll uterí
- Càncer de pulmó
- Càncer de bufeta urinària
- Càncer d'estómac
- Càncer de recte i sigma

Papanicolaou, G. N. (1952), Present status and future trends of exfoliative cytology. CA: A Cancer Journal for Clinicians, 2: 50–56. doi: 10.3322/canjclin.2.2.50

# Camps problemàtics en desenvolupament

- Frotis endometrials
- Aspirats ureterals i pèlvics per la marcada atípia present en condicions normals
- Líquids pleurals, peritoneals i pericardíacs per les atípies presents en les cèl·lules mesotelials i histiòcits
- Secrecions mamàries
- Canvis postradiació
- Desconeixement del significat pronòstic dels diferents patrons citològics cervicals preneoplàstics

Papanicolaou, G. N. (1952), Present status and future trends of exfoliative cytology. CA: A Cancer Journal for Clinicians, 2: 50–56. doi: 10.3322/canjclin.2.2.50




Figures 1 to 6. Malignant cells found in smears. (×600.)

Figure 1. Superficial-cell dyskaryosis. Cervical smear. Intraepithelial carcinoma.

Figure 2. Parabasal-cell dyskaryosis. Cervical smear. Intraepithelial carcinoma.

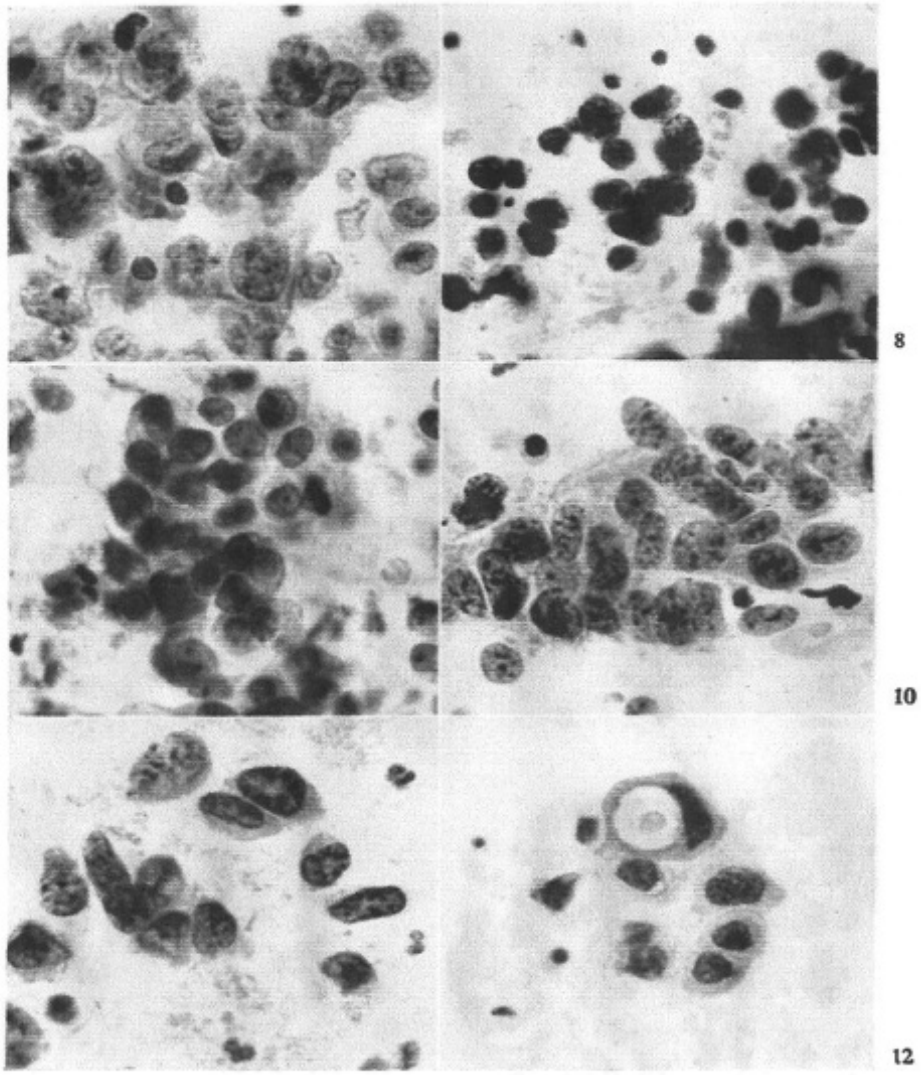
Figure 3. Endocervical-cell dyskaryosis. Cervical smear.

Following the first suspicious smear, biopsy was negative. Two years and two months later, after repeated positive smears and a second inconclusive biopsy, conization of the cervix showed an intraepithelial carcinoma with indications of very early invasion.

Figure 4. Vaginal smear. Squamous-cell carcinoma of the cervix. Grade III.

Figure 5. Vaginal smear. Adenocarcinoma of the endometrium.

Figure 6. Pleural-fluid specimen. Metastatic carcinoma of the breast.




Figures 7 to 12. Malignant cells found in smears. (×600.)

Figure 7. Sputum specimen. Bronchogenic carcinoma, pleomorphic type.

Figure 8. Sputum specimen. Bronchogenic carcinoma, anaplastic type.

Figure 9. Gastric-balloon specimen. Adenocarcinoma of the stomach. Grade II.

Figure 10. Rectal-washing specimen. Carcinoma of the rectum.

Figure 11. Voided-urine specimen. Carcinoma of the bladder.

Figure 12. Catheterized-urine specimen. Carcinoma of the prostate.

Papanicolaou, G. N. (1952), Present status and future trends of exfoliative cytology. CA: A Cancer Journal for Clinicians, 2: 50–56. doi: 10.3322/canjclin.2.2.50

# La citologia als 50's

- La citologia està plenament acceptada entre la comunitat mèdica
- American Board of Pathology inclou la citologia exfoliativa com un dels requeriments per obtenir el títol
- 1951. Fundació de la Societat Americana de Citopatologia. ASC
- Inicialment els diagnòstics van ser molt genèrics (PPCM)
- Els coneixements actuals ja permetien diferenciar entre diferents tipus de càncer i origen
- Dependència del resultat de la biòpsia per a la confirmació d'un càncer

Papanicolaou, G. N. (1952), Present status and future trends of exfoliative cytology. CA: A Cancer Journal for Clinicians, 2: 50–56. doi: 10.3322/canjclin.2.2.50

# Futur de la citologia als 50's

- Detecció del càncer en les seves fases més precoces
- Estudi de les alteracions cel·lulars relacionades amb
  - Medicaments
  - Agents carcinogènics
- Necessitat de creació de programes de formació en citologia

Papanicolaou, G. N. (1952), Present status and future trends of exfoliative cytology. CA: A Cancer Journal for Clinicians, 2: 50–56. doi: 10.3322/canjclin.2.2.50

# Exfoliative Cytology in Mass Screening for Uterine Cancer

## Memphis and Shelby County, Tennessee

*Cyrus C. Erickson, M.D.*

About three years ago, a co-operative project was begun for screening the female population more than 20 years of age for uterine cancer by means of the vaginal-smear test. Approximately one half of this population of 165,000 women has now been screened. One half of these were private patients of physicians in Memphis and Shelby County and the other half were from clinics, health centers, hospitals, and annual industrial clinics.

Positive or suspicious smears were found in 1.9 per cent of the first 70,000 women screened. Biopsies were completed in 81 per cent (1077) of these cases. Biopsy showed 544 (0.78 per cent of 70,000) cancers of the uterus—invasive and intraepithelial. Two hundred eighty-two (0.4 per cent of 70,000) were intraepithelial or noninvasive. Fifteen per cent of the 1077 biopsies showed atypical or inconclusive lesions. Suspicious smears from 293 cases gave negative biopsies, constituting 27 per cent of the biopsy group. False-positive and false-negative reports in this series were less than 0.1 per cent. It is interesting to note that 60 per cent of the 544 invasive and noninvasive cancers found were previously unsuspected—no signs or symptoms—and that this unsuspected group included many of the invasive cancers.

The intensive efforts toward education

Erickson, C. C. (1955), Exfoliative cytology in mass screening for uterine cancer: Memphis and shelby county, tennessee. CA: A Cancer Journal for Clinicians, 5: 63–64. doi: 10.3322/canjclin.5.2.63

# The Gynecologist Views Cytology Past, Present, and Future

*Lewis C. Scheffey, M.D., and A. E. Rakoff, M.D.*

The cytological method for the diagnosis of cancer is by no means a new technique, dating back as it does to as early as 1860, when Beale recognized neoplastic cells in the sputum from a patient with carcinoma of the pharynx.

The earliest reference of which we are aware concerning the use of the cytological method for the diagnosis of gynecological neoplasms is dated 1873, when Thomas M. Drysdale, a Philadelphian and a founding member of the American Gynecological Society, contributed a chapter to a volume of ovarian tumors by Washington L. Atlee, entitled, "Dropsical Fluids of the Abdomen; Their Physical Properties; Chemical Analysis; Microscopic Appearance and Diagnostic Value; Based on the Examination of Several Hundred Specimens." These studies by Drysdale were begun as early as 1853.

follows: "In looking at the apparently barren results of numberless analyses of these organic fluids, practical men of our profession have sneered at such labors as useless; but it is hoped it will be proved in these pages that at least one point has been gained, and that in the chemical examination of these fluids, more particularly when assisted by the microscope, we have a valuable aid to diagnosis, and one nearly infallible."

Howard A. Kelly's comment in the "Dictionary of American Medical Biography" was, "unfortunately the alleged discovery did not stand the test of time as the cell was not pathognomonic."

In 1895, Rieder demonstrated mitoses in smears of ascitic fluid from a case of carcinoma of the ovary. It was not until 1928, however, that cancer cells from the genital tract were recognized

Scheffey, L. C. and Rakoff, A. E. (1952), The gynecologist views cytology past, present, and future. CA: A Cancer Journal for Clinicians, 2: 63–68. doi: 10.3322/canjclin.2.2.63

# 1952. The gynecologist views cytology past, **present**, and future

- Quines són les indicacions de la citologia?
- A totes les dones o a certs grups d'edat?
- Quins intervals entre les citologies?
- Quantes preparacions per dona?
- Cost  1,50-2 $ per pacient
- Estudi a Filadèlfia
  - 4 anys, 12000 citos (5000 dones)
  - Només detecten 7 casos de càncer cervical i només un asimptomàtic
  - 70% de les dones eren jueves
- Massachusetts
  - 8 casos de cc en 1512 dones asimptomàtiques
  - 133 casos de cc  en 1364 dones simptomàtiques

# 1952. The gynecologist views cytology past, present, and future

- American Cancer Society, Boston, 1948
  - Falsos positius de la citologia 8,7-25,3 %
  - Falsos negatius 0-1,2%

- La citologia es recull del fons de sac posterior vaginal

- El % de positius podria augmentar si es realitzessin preses cervicals

# 1952. The gynecologist views cytology past, present, and **future**

- La citologia ha de ser una metodologia estàndard en el cribratge del càncer ginecològic
- La citologia no pot reemplaçar una bona història ginecològica
- Necessitat urgent d'una formació correcta a un nombre suficient de patòlegs i tècnics
- Desig de noves metodologies per al futur

> Excellent as the Papanicolaou staining techniques are, it is to be hoped that the future may produce some new mode of examination that will even more specifically identify the cancer cell.

# Per què no es va atorgar el premi Nòbel a Papanicolaou?

(Professeur C. DANIEL).

## DIAGNOSTIC
## DU CANCER DU COL UTÉRIN
## PAR LES FROTTIS

Par A. BABÈS

Maître de Conférences à la Faculté de Médecine de Bucarest.

Le diagnostic précoce du cancer du col utérin, comme d'ailleurs du cancer en général, est basé sur l'examen histopathologique de la biopsie faite au niveau des lésions.

Dans l'état actuel de nos connaissances, il existe deux caractères histopathologiques permettant le diagnostic précoce du cancer : l'hétérotypie, c'est-à-dire l'envahissement des éléments épithéliaux en profondeur, et l'atypie, la modification des cellules épithéliales.

La Presse Médicale, Wednesday, April 11, 1928 (36: 451-454, 1928)

of carcinoma of the uterine cervix. More important is the question: who did it? Undoubtedly, George Papanicolaou's contribution to the introduction of the technique that he developed in New York City was substantial and epoch making. But it should be recognized that while he presented his smear technique (later named after him as the Pap Smear) at the Third Race Betterment Conference in January 1928, an article was then in press on the same topic. The article was published in the April 1928 issue of La Presse Medicale (Fig. 1). The author of the article was Aurel Babes (1886-1961), a Rumanian gynecology professor of Hungarian origin. In the article [19] he summarized his presentations at the January and April, 1927, meetings of the Gynecologic Society of Bucharest. The published article (Fig. 1) consists of four pages and nine figures illustrating various cytologic findings, including cancer cells, in smears obtained from the cervix and vagina. The priority of Babes' report was the reason behind the Nobel Committee's rejection of George Papanicolaou for consideration for the Nobel Prize.

Steven I. Hajdu. *A Note from History:* Rediscoveries in Pathology and Laboratory Medicine. Ann Clin Lab Sci 2006; 36 (3): 359-361

**Figure 26** Group outside the Papanicolaou Cancer Research Institute in Miami about two weeks before Dr. Papanicolaou died. Front row, from left to right: Drs. Papanicolaou, Philip Archer, Bernard Naylor, Irena Koprowska and John R. McDonald.

On the morning of Friday, February 16, 1962, I tracked down Babeş article of 1928 in the medical library of the University of Miami and brought it to the institute in Miami where Dr. Papanicolaou had recently taken up the directorship. I briefly told him what I had found and suggested that I show it to him on Monday because he was just about to meet an important visitor who would be his house guest over the weekend. During our very brief exchange, Dr. Papanicolaou gave no intimation of being aware of the existence of Babeş article. By the Monday morning, three days later, when I would have shown him the article, Dr. Papanicolaou had died of a heart attack.

To complete this sketch of Papanicolaou's professional life after his retirement from Cornell University in 1951, he remained there carrying out re-

Bernard Naylor. The Century of Cytopathology. Acta Cytol 2000;44: 709-725

# Els primers citotècnics 1950's

The Cytology Laboratory, University of Tennessee

# 1950’s Citotècniques

# Quina és més antiga?

A

B




1957

# THE COLPOSCOPIC DIAGNOSIS OF EARLY CERVICAL CARCINOMA

*By* J. D. ANDREW, M.A., M.B., B.CH., M.R.C.O.G.

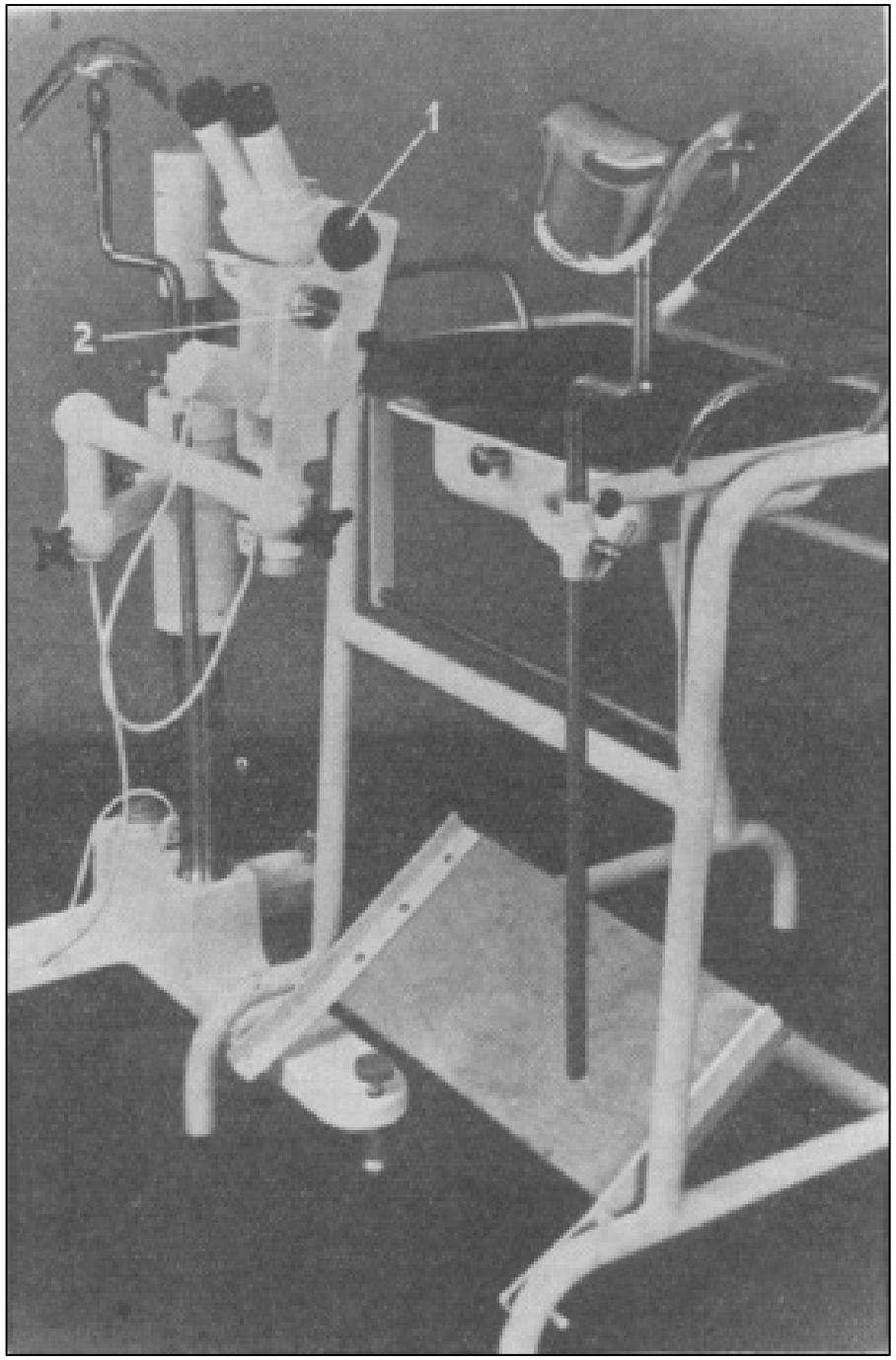
*Late Senior Registrar to the Department of Obstetrics and Gynaecology, St. Bartholomew's Hospital*

Cytological study of the cervix is easy to undertake as far as the clinician is concerned and is inexpensive to perform. As a means of screening out-patients it is perhaps ideal in its simplicity. The method, however, demands the attention of a competent cytologist whose training is to be measured in years rather than months, whose effective output is necessarily limited, and who requires the backing of considerable laboratory facilities and a well-trained technical staff. Furthermore, once a positive diagnosis of cancer cells is reported in a cervical smear by the cytologist, the responsibility for treatment is thrust squarely on the clinician's shoulders. His dilemma only becomes apparent in the early cases, and in particular with the so-called intra-epithelial carrealize their limitations so that they can be overcome. The colposcope provides a way of effecting improvements.

## The Colposcope

This instrument provides a means whereby a three-dimensional study of an illuminated surface can be made under various magnifications. It was originally devised by Hans Hinselman, of Hamburg, in 1925 for the study of the epithelium of the vulva, vagina and cervix. Many varieties of colposcope are now available, some of complex design, although the principle of the procedure remains a very simple one. Up to the present day the colposcope has found little favour amongst British gynaecologists as a diagnostic instrument.

ANDREW JD. The colposcopic diagnosis of early cervical carcinoma. Postgrad Med J. 1956 Nov;32(373):560-3




# The Carl Zeiss Colposcope

WITH OR WITHOUT ELECTRONIC FLASH,

PHOTOGRAPHIC ATTACHMENT

*full details on application to*

**RAYNER**

100 NEW BOND STREET - LONDON W.1

*Grosvenor 5081*

1956

# UNUSUAL PATTERNS OF SQUAMOUS EPITHELIUM OF THE UTERINE CERVIX: CYTOLOGIC AND PATHOLOGIC STUDY OF KOILOCYTOTIC ATYPIA

*By* Leopold G. Koss and Grace R. Durfee

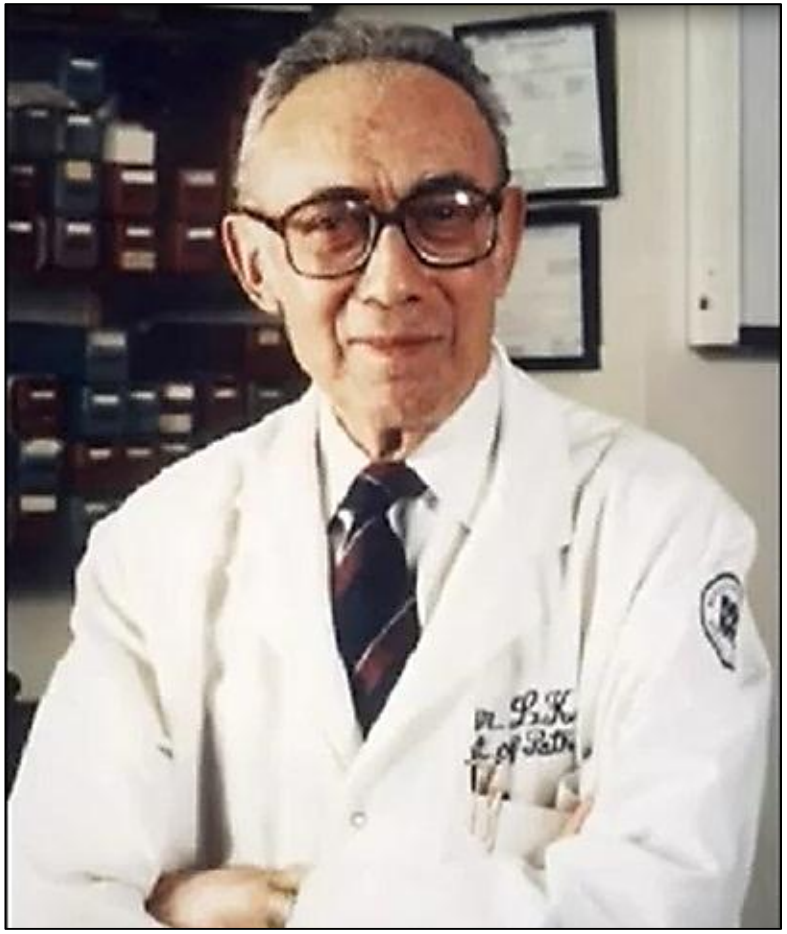
*The Strang Laboratory of Cytology and the Pathology Laboratories, Memorial Center for Cancer and Allied Diseases, New York, N. Y.*

Ann. N.Y. Acad. Sci. 63, 1245-1261, 1956

As a result of long-term study, it appears that one and, possibly, a second tissue pattern of disorderly epithelium can be isolated among these lesions. The first one is characterized essentially by the presence in histologic sections of large cells with relatively small but irregular and hyperchromatic nuclei surrounded by clear and transparent cytoplasm. Thus, the nucleus seems to be suspended in an empty space. For descriptive purposes, we have coined the term *koilocytotic atypia*, from the Greek word "koilos," meaning hollow or cavity, to designate this lesion. Many of these lesions were recognized primarily in smears before their recognition in tissues. The term "warty dyskeratosis" was commonly used in the pathology laboratory when referring to this type of epithelial change.

# Leopold G. Koss

- Patòleg al Memorial Hospital for Cancer ad Allieds Diseases
- Estudiant amb Dr. Papanicolaou
- Dexeible del Dr. Ewing
- 1956, introdueix l'atípia "coilocítica"
- 1961, publica el primer text didàctic en citopatologia amb correlació histopatològica: *"Diagnostic Cytology and its Histopathologic Bases"*



# Relació del "*Koilocyte*" i el VPH

- 1951, JE Ayre menciona la presència de cèls amb halo perinuclear
- 1956, LG Koss anomena per primera vegada el *koilocyte*
- 1968, detecció per ME de partícules virals en els condilomes
- 1976, Meisels i Fortin publiquen en Acta Cytologica els patrons citològics de les lesions condilomatoses del cèrvix i vagina
- 1977, Hausen presenta la possible relació entre VPH i carcinoma escamós
- ...
- 1995. IARC cataloga VPH 16 i 18 com a carcinògens
- 2003. IARC incorpora VPH 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 y 82. Probables 26, 53 y 66

The Link between Koilocytes and Human Papillomaviruses. *Annals of Clinical & Laboratory Science, vol. 36, no. 4, 2006. SI Hadju*

# Dubtes de la relació VPH i càncer cervical

*Br. J. Cancer* (1988) **57,** 1–5



**COMMENTARY**

## Does human papillomavirus cause cervical cancer? The state of the epidemiological evidence

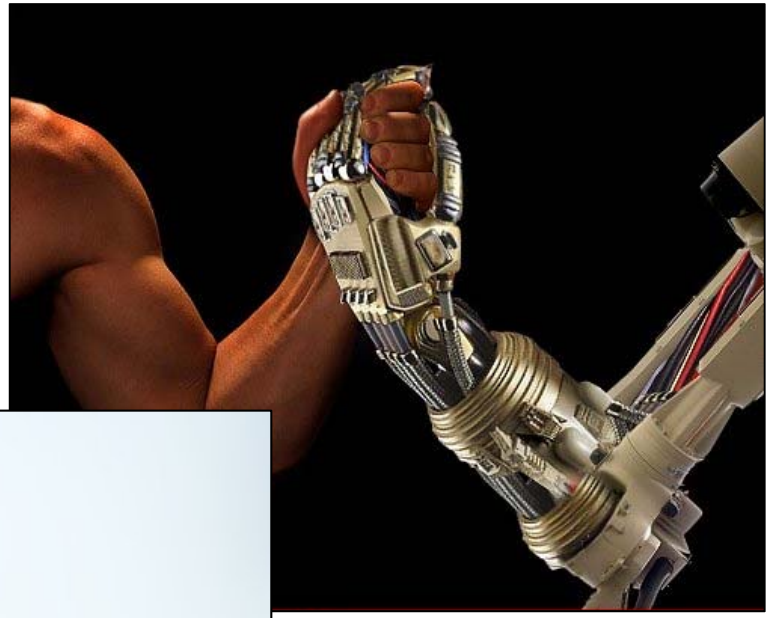
N. Muñoz[1], X. Bosch[1] & J.M. Kaldor[2]

[1]*Unit of Field & Intervention Studies and* [2]*Unit of Biostatistics Research & Informatics, International Agency for Research on Cancer, 150 cours Albert-Thomas, 69372 Lyon Cedex 08, France.*

**Summary** The human papillomavirus has emerged over the past decade as the leading candidate to be the sexually transmitted aetiological factor in cervical cancer. Although it appears that papillomavirus types 16 and 18 are associated with a higher risk of advanced cervical neoplasia, most of the evidence comes from studies which do not satisfy basic epidemiological requirements, and are therefore difficult to interpret. The most significant problems are the small sample size, potentially biased selection of study subjects, the difficulties in cytologically distinguishing precancerous lesions from papilloma infection of the cervix, the unknown specificity and sensitivity of the various hybridisation methods for determining papillomavirus infection status, and the statistical analyses and presentation of results. On the basis of the existing studies, one is forced to conclude that, while experimental data suggest an oncogenic potential for HPV, the epidemiological evidence implicating it as a cause of cervical neoplasia is still rather limited.

# Citologia ginecològica ahir

# Citologia ginecològica avui. VPH




ThinPrep Imaging System

# Citologia ginecològica avui

## Increasing Cytotechnologist Workload Above 100 Slides Per Day Using the ThinPrep Imaging System Leads to Significant Reductions in Screening Accuracy

Tarik M. Elsheikh, MD[1]; Joseph L. Kirkpatrick, CT (ASCP)[2]; Mackenzie K. Cooper, CT (ASCP)[2]; Mary L. Johnson, CT (ASCP)[2]; Allison P. Hawkins, CT (ASCP)[2]; and Andrew A. Renshaw, MD[3]

**BACKGROUND:** With the current and projected shortage of a cytotechnologist (CT) workforce and the desire to reduce laboratory costs, increased productivity with automated assisted primary screening has become an attractive option for many laboratories. To the best of the authors' knowledge, longitudinal studies examining the effect of increasing workload on the performance of individual CTs have not been performed previously. **METHODS:** Using the ThinPrep imaging system (TIS), the performance of 3 CTs with variable levels of experience were evaluated. Their productivity was noted to increase from an average of 87 to 118 slides per day. The analysis included comparisons of error rates, screening rates, and screening times, including a review of 22 fields of view (FOV). Poststudy interviews of the CTs were also performed. **RESULTS:** Increased workload was found to be proportional to the decreased percentage of cases that underwent full manual review (25.2% to 20.1%; $P < .001$), and decreased actual screening times (7.3 hours/day to 6.7 hours/day, and 5.0 minutes/slideto 3.7 minutes/slide). This resulted in a lower detection of total abnormal findings (10.4% to 8.3%; $P < .001$), atypical squamous cells (6.7% to 4.9%; $P < .001$), and high-grade squamous intraepithelial lesion (0.9 %to 0.7%; $P = .37$), as well as an increased false-negative fraction rate (3.8% to 7.0%; $P = .08$). **CONCLUSIONS:** The results of the current study indicate that an increased average CT workload >100 slides per day with the TIS appears to have been accomplished mostly through a reduction in the amount of time spent reviewing the 22 FOV and the percentage of cases that underwent full manual review, which resulted in a significantly reduced screening performance. ***Cancer (Cancer Cytopathol)* 2010;118:75–82.** 

# Citologia ginecològica avui

**Diagn Cytopathol. 2012 Feb 20. doi: 10.1002/dc.22817. [Epub ahead of print]**

**American society of cytopathology workload recommendations for automated pap test screening: Developed by the productivity and quality assurance in the era of automated screening task force.**

Elsheikh TM, Austin RM, Chhieng DF, Miller FS, Moriarty AT, Renshaw AA.

**Abstract**

Based on current literature and the best available research to date, the current FDA workload limits for automated image-assisted screening, including the ThinPrep Imaging System and the FocalPoint GS, of 100 slides/day (imaged only slides counted as 0.5) are extremely high and may be associated with significant reduction in sensitivity. This task force has proposed six recommendations relating to cytotechnologist (CT) workload in automated image-guided Pap test screening, which have already been endorsed by major pathology professional societies. These evidence-based recommendations, however, pertain only to gynecologic specimens with image-assisted screening, as there is no current available data to justify modifying screening practices regarding non-gynecologic specimens. The proposed recommendations are as follow:

**1) CT workday should not include more than 7 hours of Pap test screening in a 24-hr period, and an 8-hr shift day must include at least 2 paid mini-breaks of 15 minutes each and a 30-minute lunch break.**

**2) Future Studies examining CT workload should use actual hours of screening rather than lesser number of hours extrapolated to 8-hour days.**

**3) Average laboratory CT workload should NOT exceed 70 slides/day (slides counted per 2010 FDA bulletin).**

**4) Proportion of imaged slides that undergo full manual review should be at least either 15%, or twice (2×) the epithelial cell abnormality (ECA) rate, whichever is greater.**

**5) ECA-adjusted workload measure is a promising method for calculating and monitoring CT workload, but further studies of this method are necessary before full endorsement.**

**6) CT productivity and workload limits are just one aspect of a good quality assurance program in a cytology laboratory, so other quality indicators to assess CT performance are essential.**

# Citología en base líquida (LBC) vs. VPH test (HC2)

- 2003-2005, 331.818 mujeres, seguimiento 5 a. Kaiser Permanente Northern California
  - Inicio 5,1% HPV + y 3,8% LBC +
- HC2 neg 315.061. Incidencia acumulativa de cáncer 3.8/100.000 año
- LBC neg 319.177. Incidencia acumulativa de cáncer 7.5/100.000 año
- HC2 y LBC negs 306.969. Incidencia acumulativa de cáncer 3.2/100.000 año
- 313.465 (99,5%) HC2 negativa tuvieron LBC negativa

Katki H, Kinney W, Fetterman B et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol 2011; 12: 663–672.

# Cost-Effectiveness of Cervical Cancer Screening With Human Papillomavirus DNA Testing and HPV-16,18 Vaccination


- **Background** The availability of human papillomavirus (HPV) DNA testing and vaccination against HPV types 16 and 18 (HPV-16,18) motivates questions about the cost-effectiveness of cervical cancer prevention in the United States for unvaccinated older women and for girls eligible for vaccination.
- **Methods** An empirically calibrated model was used to assess the quality-adjusted life years (QALYs), lifetime costs, and incremental cost-effectiveness ratios (2004 US dollars per QALY) of screening, vaccination of preadolescent girls, and vaccination combined with screening. Screening varied by initiation age (18, 21, or 25 years), interval (every 1, 2, 3, or 5 years), and test (HPV DNA testing of cervical specimens or cytologic evaluation of cervical cells with a Pap test). Testing strategies included: 1) cytology followed by HPV DNA testing for equivocal cytologic results (cytology with HPV test triage); 2) HPV DNA testing followed by cytology for positive HPV DNA results (HPV test with cytology triage); and 3) combined HPV DNA testing and cytology. Strategies were permitted to switch once at age 25, 30, or 35 years.
- **Results** For unvaccinated women, triennial cytology with HPV test triage, beginning by age 21 years and switching to HPV testing with cytology triage at age 30 years, cost $78000 per QALY compared with the next best strategy. For girls vaccinated before age 12 years, this same strategy, beginning at age 25 years and switching at age 35 years, cost $41000 per QALY with screening every 5 years and $188000 per QALY screening triennially, each compared with the next best strategy. These strategies were more effective and cost-effective than screening women of all ages with cytology alone or cytology with HPV triage annually or biennially.
- **Conclusions: For both vaccinated and unvaccinated women, age-based screening by use of HPV DNA testing as a triage test for equivocal results in younger women and as a primary screening test in older women is expected to be more cost-effective than current screening recommendations.**



Goldhaber JD, Stout NK, Salamon JA, et al. Cost-effectiveness of Cervical Cancer Screening with Human Papillomavirus DNA testing and HPV-16,18 Vaccination. JNCI. 2008;100(5):308-320.

# Cost-effectiveness of human papillomavirus vaccination and screening in Spain.

- Diaz M, de Sanjose S, Ortendahl J, O'Shea M, Goldie SJ, Bosch FX, Kim JJ.
  Eur J Cancer. 2010 Nov;46(16):2973-85.


- **Abstract**
- **BACKGROUND:**
- In Spain, prophylactic vaccination against human papillomavirus (HPV) types 16 and 18 is being offered free-of-charge to one birth cohort of girls aged 11-14. Screening is opportunistic (annual/biannual) contributing to social and geographical disparities.
- **METHODS:**
- A multi-HPV-type microsimulation model was calibrated to epidemiologic data from Spain utilising likelihood-based methods to assess the health and economic impact of adding HPV vaccination to cervical cancer screening. Strategies included (1) screening alone of women over age 25, varying frequency (every 1-5 years) and test (cytology, HPV DNA testing); (2) HPV vaccination of 11-year-old girls combined with screening. Outcomes included lifetime cancer risk, life expectancy, lifetime costs, number of clinical procedures and incremental cost-effectiveness ratios.
- **RESULTS:**
- After the introduction of HPV vaccination, screening will need to continue, and strategies that incorporated HPV testing are more effective and cost-effective than those with cytology alone. For vaccinated girls, 5-year organised cytology with HPV testing as triage from ages 30 to 65 costs 24,350€ per year of life saved (YLS), assuming life-long vaccine immunity against HPV-16/18 by 3 doses with 90% coverage. Unvaccinated girls would benefit from organised cytology screening with HPV testing as triage; 5-year screening from ages 30 to 65 costs 16,060€/YLS and 4-year screening from ages 30 to 85 costs 38,250€/YLS. Interventions would be cost-effective depending on the cost-effectiveness threshold and the vaccine price.
- **CONCLUSIONS:**
- **In Spain, inequitable coverage and overuse of cytology make screening programmes inefficient. If high vaccination coverage among pre-adolescent girls is achieved, organised cytology screening with HPV triage starting at ages 30 to at least 65 every 4-5 years represents the best balance between costs and benefits.**

# Cost-effectiveness of cervical cancer screening: cytology versus human papillomavirus DNA testing.

van Rosmalen J, de Kok IM, van Ballegooijen M. BJOG. 2012 May;119(6):699-709.

**Source**

Department of Public Health, Erasmus MC, University Medical Center, Rotterdam, the Netherlands. j.vanrosmalen@erasmusmc.nl

**Abstract**

**OBJECTIVE:**

To determine the most cost-effective screening programme for cervical cancer.

**DESIGN:**

Cost-effectiveness analysis from a societal perspective.

**SETTING:**

The Netherlands.

**POPULATION:**

Dutch women who have not been invited for human papillomavirus (HPV) vaccination.

**METHODS:**

We calibrated the microsimulation screening analysis (MISCAN) model to Dutch epidemiological data. We used this model to consider nine screening strategies that use: (i) cytological testing with cytology triage for borderline/mildly abnormal smears; (ii) HPV testing with cytology triage for HPV-positive smears; or (iii) cytological testing with HPV triage for borderline/mildly abnormal smears. For each strategy, we varied the number of screening rounds, the time interval, the age of the first screening, and the type of cytological testing (conventional or liquid-based cytology).

**MAIN OUTCOME MEASURES:**

Quality-adjusted life years (QALYs) gained and costs from a societal perspective.

**RESULTS:**

Under the base-case assumptions, primary HPV testing with cytology triage is the most cost-effective strategy. Using cost-effectiveness thresholds of € 20,000 and € 50,000 per QALY gained yields optimal screening programmes with three and seven screening rounds, respectively. The results are sensitive to several uncertain model inputs, most importantly the costs of the HPV test. For women aged 32 years or younger, primary cytology screening is more cost-effective than primary HPV testing.

**CONCLUSIONS:**

**Increasing the interval between screening rounds and changing the primary test from cytology to HPV testing can improve the effectiveness and decrease the costs of cervical cancer screening in the Netherlands.**

# Primary screening for human papillomavirus compared with cytology screening for cervical cancer in European settings: cost effectiveness analysis based on a Dutch microsimulation model.

de Kok IM, van Rosmalen J, Dillner J, Arbyn M, Sasieni P, Iftner T, van Ballegooijen M. BMJ. 2012 Mar 5;344

**Source**

Erasmus MC, University Medical Center, Department of Public Health, PO Box 2040, 3000 CA Rotterdam, Netherlands. i.dekok@erasmusmc.nl

**Abstract**

**OBJECTIVES:**

To investigate, using a Dutch model, whether and under what variables framed for other European countries screening for human papillomavirus (HPV) is preferred over cytology screening for cervical cancer, and to calculate the preferred number of examinations over a woman's lifetime.

**DESIGN:**

Cost effectiveness analysis based on a Dutch simulation model. Base case analyses investigated the cost effectiveness of more than 1500 different screening policies using the microsimulation model. Subsequently, the policies were compared for five different scenarios that represent different possible scenarios (risk of cervical cancer, previous screening, quality associated test characteristics, costs of testing, and prevalence of HPV).

**SETTING:**

Various European countries.

**POPULATION:**

Unvaccinated women born between 1939 and 1992.

**MAIN OUTCOME MEASURES:**

Optimal screening strategy in terms of incremental cost effectiveness ratios (costs per quality adjusted life years gained) compared with different cost effectiveness thresholds, for two levels of sensitivity and costs of the HPV test.

**RESULTS:**

Primary HPV screening was the preferred primary test over the age of 30 in many considered scenarios. Primary cytology screening was preferred only in scenarios with low costs of cytology and in scenarios with a high prevalence of HPV in combination with high costs of HPV testing.

## CONCLUSIONS:

**Most European countries should consider switching from primary cytology to HPV screening for cervical cancer. HPV screening must, however, only be implemented in situations where screening is well controlled**

# American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. 2012

| Population | Page Numbers | Recommended Screening Method* | Management of Screen Results | Comments |
|---|---|---|---|---|
| Aged <21 y | 521-522 | No screening | | HPV testing should not be used for screening or management of ASC-US in this age group |
| Aged 21-29 y | 522-523 | Cytology alone every 3 y | HPV-positive ASC-US† or cytology of LSIL or more severe: Refer to ASCCP guidelines[2]<br>Cytology negative or HPV-negative ASC-US†: Rescreen with cytology in 3 y | HPV testing should not be used for screening in this age group |
| Aged 30-65 y | 523-529 | HPV and cytology "cotesting" every 5 y (preferred) | HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP guidelines[2]<br>HPV positive, cytology negative:<br>Option 1: 12-mo follow-up with cotesting<br>Option 2: Test for HPV16 or HPV16/18 genotypes<br>• If HPV16 or HPV16/18 positive: refer to colposcopy<br>• If HPV16 or HPV16/18 negative: 12-mo follow-up with cotesting<br>Cotest negative or HPV-negative ASC-US: Rescreen with cotesting in 5 y | Screening by HPV testing alone is not recommended for most clinical settingst |
| | | Cytology alone every 3 y (acceptable) | HPV-positive ASC-US† or cytology of LSIL or more severe: Refer to ASCCP guidelines[2]<br>Cytology negative or HPV-negative ASC-US†: Rescreen with cytology in 3 y | |
| Aged >65 y | 529-531 | No screening following adequate negative prior screening | | Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 y |
| After hysterectomy | 531 | No screening | | Applies to women without a cervix and without a history of CIN2 or a more severe diagnosis in the past 20 y or cervical cancer ever |
| HPV vaccinated | 531-533 | Follow age-specific recommendations (same as unvaccinated women) | | |

## Conclusions

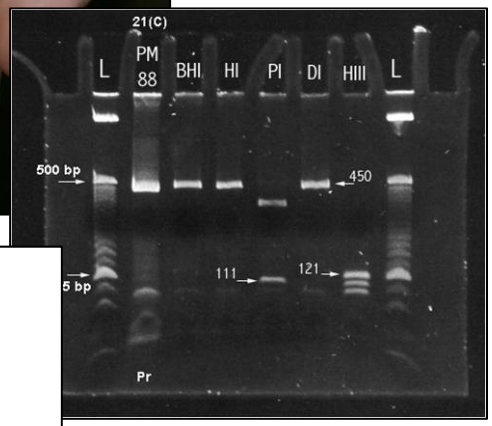
The process used to develop these recommendations represents a transitional stage in guidelines development for the ACS. Previous guidelines have been developed using a con-

**Comparison of seven tests for high-grade cervical intraepithelial neoplasia in women with abnormal smears: the Predictors 2 study.** Szarewski A, Mesher D, Cadman L, Austin J, Ashdown-Barr L, Ho L, Terry G, Liddle S, Young M, Stoler M, McCarthy J, Wright C, Bergeron C, Soutter WP, Lyons D, Cuzick J. J Clin Microbiol. 2012 ; 50: 1867-73.

**1099 pacients referides a colposcòpia per una citologia patològica**

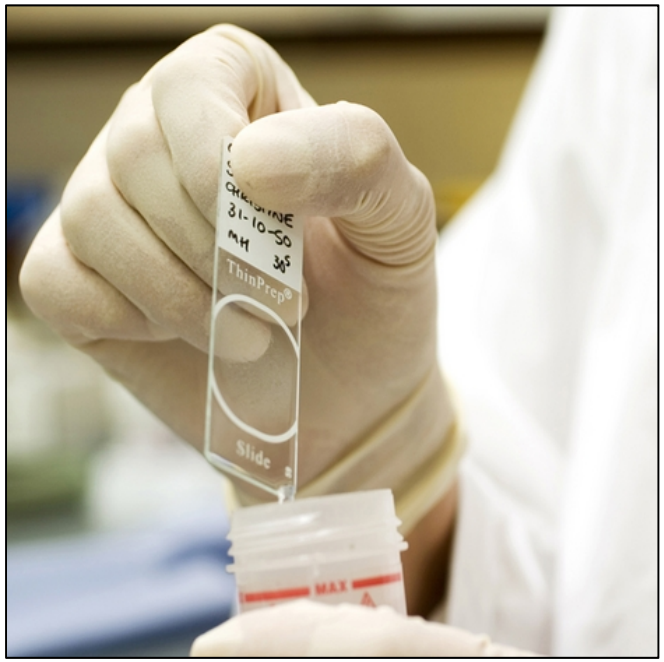
| Test | Sens | Esp | VPP |
|---|---|---|---|
| HC 2 (Qiagen) 13 VPH alt risc | 96,3% | 19,5% | 37,4% |
| Cobas 4800 (Roche) identifica VPH 16 ,18 y 12 (VPH alt risc) | 95,2% | 24% | 37,6% |
| PreTect HPV-Proofer assay (NorChip) identifica mRNA VPH 16, 18, 31, 33 y 45 | 74,1% | 70,8% | 55,4% |
| APTIMA HPV (Gen-Probe) mRNA VPH identifica mRNA VPH 16, 31, 33 y 18-45 (actualment 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) | 95,3% | 28,8% | 39,3% |
| Abbot Real Time identifica VPH 16, 18 i 12 VPH alt risc | 93,3% | 27,3% | 38,2% |
| BD HPV test (BD diagnostics) identifica VPH 16, 18, 31, 45, 51, 52, 59 i agrupats (33, 56, 58, 66) y (35, 39, 68) | 95% | 24,2% | 37,8% |
| CINtec P16 (No CINtec plus) Roche-MTM | 85,7% | 54,7% | 49,1% |
| Citologia | 88,9% | 58,1% | 50,7% |

# Citologia ginecològica demà?




**HPV DNA TEST**

Hybrid Capture II



# Citologia ginecològica demà?

Gynecol Oncol. 2011 May 1;121(2):309-13. Epub 2011 Jan 26.

# Characteristics of 44 cervical cancers diagnosed following Pap-negative, high risk HPV-positive screening in routine clinical practice.

Kinney W, Fetterman B, Cox JT, Lorey T, Flanagan T, Castle PE.

**Source**

Division of Gynecologic Oncology, Kaiser Permanente Medical Care Program, Oakland, CA, USA.

**Abstract**

**OBJECTIVE:**

To characterize the cervical cancers diagnosed following a Pap-negative, high risk human papillomavirus (HPV)-positive (Pap-/HPV+) screen in routine clinical practice.

**METHODS:**

Using data from Kaiser Permanente Northern California, we investigated the cases of cervical cancer diagnosed between January, 2003 and January, 2009 following Pap-/HPV+ screen. Two cervical specimens were routinely collected for cervical cancer screening, one for conventional cytology and the other for high risk HPV testing using Hybrid Capture 2 (Qiagen).

**RESULTS:**

Forty-four women (median age at diagnosis=44years) were diagnosed with primary invasive cervical cancer with a recent history of one or more Pap-/HPV+ screens. Twenty-six women had one Pap-/HPV+ screen preceding the diagnosis of cancer, 15 had two, and three had three. There were 16 squamous cancers, one small cell cancer, 24 adenocarcinomas, 2 adenosquamous carcinomas, and one case with separate invasive squamous and adenocarcinoma. FIGO Stage was IA in 11 women, IB in 31 women and IIA in 2 women. Treatment included a pelvic node dissection in 30, 2 (6.7%) of whom had positive nodes.

**CONCLUSIONS:**

**HPV testing contributes to early cervical cancer diagnosis detection in women with negative Pap tests. Most women in this cohort have early stage, node negative, treatable and potentially curable disease. Adenocarcinoma predominated as might be expected because cytology misses these cancers and their precursors. The majority of cancers were diagnosed following a single Pap-/HPV+ screen, suggesting that effective triage to colposcopy of women with a Pap-/HPV+ screen would be preferable to retesting in one year as currently recommended.**

| | All women | No biopsy or <CIN2 | CIN2 | CIN3/AIS | AIS | Squamous carcinoma | Adenocarcinoma | Total cancers |
|---|---|---|---|---|---|---|---|---|
| Total | 331 818 (100%) | 329 508 (100%) | 1476 (100%) | 747 (100%) | 70 (100%) | 49 (100%) | 27 (100%) | 87 (100%) |
| Baseline HPV | | | | | | | | |
| Negative | 315 061 (94·9%) | 314 589 (95·5%) | 322 (22%) | 123 (16%) | 14 (20%) | 18 (37%) | 6 (22%) | 27 (31%) |
| Positive | 16 757 (5·1%) | 14 919 (4·5%) | 1154 (78%) | 624 (84%) | 56 (80%) | 31 (63%) | 21 (78%) | 60 (69%) |
| Baseline Pap | | | | | | | | |
| Pap negative | 319 177 (96·2%) | 318 093 (96·5%) | 687 (47%) | 354 (47%) | 42 (60%) | 15 (31%) | 23 (85%) | 43 (49%) |
| Total Pap positive | 12 641 (3·8%) | 11 415 (3·5%) | 789 (53%) | 393 (53%) | 28 (40%) | 34 (69%) | 4 (15%) | 44 (51%) |
| ASC-US | 8517 (2·6%) | 8106 (2·5%) | 283 (19%) | 123 (16%) | 12 (17%) | 4 (8%) | 1 (4%) | 5 (6%) |
| LSIL | 2527 (0·76%) | 2208 (0·67%) | 253 (17%) | 61 (8%) | 1 (1%) | 4 (8%) | 0 (0%) | 5 (6%) |
| AGUS/NOS | 764 (0·23%) | 705 (0·21%) | 26 (2%) | 27 (4%) | 7 (10%) | 1 (2%) | 2 (7%) | 6 (7%) |
| ASC-H/HSIL/SCC | 833 (0·25%) | 396 (0·12%) | 227 (15%) | 182 (24%) | 8 (11%) | 25 (51%) | 1 (4%) | 28 (32%) |
| Baseline HPV/Pap | | | | | | | | |
| HPV negative/Pap negative | 306 969 (92·5%) | 306 597 (93·0%) | 258 (17%) | 96 (13%) | 11 (16%) | 10 (20%) | 6 (22%) | 18 (21%) |
| HPV negative/Pap positive | 8092 (2·4%) | 7992 (2·4%) | 64 (4%) | 27 (4%) | 3 (4%) | 8 (16%) | 0 (0%) | 9 (10%) |
| HPV positive/Pap negative | 12 208 (3·7%) | 11 496 (3·5%) | 429 (29%) | 258 (35%) | 31 (44%) | 5 (10%) | 17 (63%) | 25 (29%) |
| HPV positive/Pap positive | 4549 (1·4%) | 3423 (1·0%) | 725 (49%) | 366 (49%) | 25 (36%) | 26 (53%) | 4 (15%) | 35 (40%) |
| Baseline HPV/ASC-US | | | | | | | | |
| HPV negative/ASC-US | 6496 (2·0%) | 6455 (2·0%) | 25 (2%) | 14 (2%) | 1 (1%) | 2 (4%) | 0 (0%) | 2 (2%) |
| HPV positive/ASC-US | 2021 (0·6%) | 1651 (0·5%) | 258 (17%) | 109 (15%) | 11 (16%) | 2 (4%) | 1 (4%) | 3 (3%) |

Total cancers includes squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and cervical cancer of unknown histology. CIN3/AIS includes 13 histologies that were either CIN3 or AIS, but precisely which is unknown. Pap positive is ASC-US or worse cytology. CIN2=cervical intraepthelial neoplasia grade 2. CIN3/AIS=cervical intraepthelial neoplasia grade 3 or adenocarcinoma in situ. HPV=human papillomavirus test. ASC-US=atypical squamous-cells of undetermined significance. LSIL=low-grade squamous intraepithelial lesion. AGNUS/NOS=atypical glandular cells of undetermined significance or not otherwise specified. ASC-H=atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion. HSIL=high-grade squamous intraepithelial lesion. SCC=squamous cell carcinoma.

*Table 1:* **Distribution of worst histological diagnosis by enrolment HPV test and Pap smear**

# Considerations for Adding Molecular Testing to Your Lab

The Papanicolaou (Pap) screening test has long been proven effective in early detection and diagnosis of cervical cancer and precancerous lesions. In the 1990s, liquid-based cytology changed the Pap test in terms of collection and evaluation. The past decade has seen molecular testing move from a reference test to an in-house test in many laboratories. Many laboratories are now wondering whether they can effectively and efficiently bring in molecular testing. Depending on state regulations, the types of molecular tests, staff abilities, and administration support, the answer is a definitive YES.

High-risk HPV testing has grown in the past few years to stand with the Pap test as an integral part of cervical cancer screening. It appears to be here to stay, and is positioned for continued growth into the foreseeable future**. The question isn't whether your cytology lab can afford to bring HPV testing in-house; it is whether you can afford not to. If you don't, someone else will.** Wait too long and you may find yourself trying to win back your clients from another lab, or you may face political battles with other departments, such as microbiology, within your (affiliated) hospital.

## Conclusion

**Don't be afraid of change, embrace it. This is a time of transition and opportunity. What you do during this time will impact your laboratory for many years to come.**

AMERICAN SOCIETY FOR CYTOTECHNOLOGY

Working Together. Shaping Our Future.

- **The future of cytotechnology.**
- Since the inception of modern cytology in the 1950's (thanks to the work of Dr. George Papanicolaou), the field of cytology had seen little change. Only in the past 15 years have technological advances led to the integration of molecular diagnostics, immunocytochemistry, flow cytometry and automation in the field of cytology.
- Automation has been one of the most significant changes in cytotechnology practice. Automation in cytopreparation and computer-assisted screening has contributed to an increase in the number of abnormal cases detected as compared to conventional practice and methods. Other benefits to automation include increased productivity, consistency and decreased turn-around time.[2]
- The advent of molecular diagnostic testing has also improved the detection of clinically relevant infections common to cervical cancer. It also has the potential for tailored intervention of therapeutic modalities.[3]Molecular diagnostics similarly utilizes microscopic analysis and interpretation. **There are few cytotechnologists already directly involved in performing and analyzing molecular tests. The impact of these changes to the cytotechnologist's traditional scope of practice is unclear but surely one that will certainly have an impact. Many cytotechnologists have already enhanced their skills in molecular diagnostics.** Cytotechnology training programs are also integrating molecular diagnostics in their curriculums. The American Society for Clinical Pathology (ASCP) currently offers certification in molecular biology for cytotechnologists as well as other medical laboratory scientists.

# Immunocytochemistry: an indispensable technique in routine cytology.

- Immunocytology is today accepted as an indispensable adjunct to cytomorphology. It has led to a dramatic increase in diagnostic accuracy and also allowed the identification of markers both for prognosis and targeted therapies. Most commercially available antibodies will perform in a reproducible and reliable way provided that the cytological specimen has been prepared and fixed properly. In this review various aspects of immunocytochemistry such as preparation of cytological specimens, fixation and choice of antibodies will be discussed. The specificity of the most commonly used antibodies is summarized and staining panels for various tumours are suggested. In addition, the use of markers for targeted therapy and theranostics is discussed, as well as a brief section on the identification of infectious agents.

- Cytopathology. 2011 Aug;22(4):215-29.**Immunocytochemistry: an indispensable technique in routine cytology.** Skoog L, Tani E.

AMERICAN SOCIETY FOR CYTOTECHNOLOGY

Working Together. Shaping Our Future.

- **Job opportunities for the cytotechnologist**

- There are plenty of opportunities for current and aspiring cytotechnologists, despite the impact of automation. Staffing practicing cytotechnologists and the contributions of molecular diagnostics to pathology practice. **Cytotechnologists need to keep themselves abreast of future changes, embrace technology and adapt appropriately.**

# Telecitologia

The second issue regards the actual benefit of preventing time from being spent away from routine office duties. For the telepathology method when summing the pre-screen time, scan time, and diagnosis time, an average total of 12 minutes is needed to perform a telepathology rapid diagnosis. An average of 7.5 minutes of this total is actually spent by the cytopathologist in rendering a rapid diagnosis through telepathology. This is much shorter than the time spent for the cytopathologist who must travel to the site and wait during the dead time between aspirations, which can total to average over 30 minutes. Also, with the time saved by the telepathology cytopathologist, routine office work can continue with improved time management.

**Screening for the Prevention of Cervical Cancer in the Era of Human Papillomavirus Vaccination: An Australian Perspective.**

Farnsworth, A. Acta Cytologica, 2011; 55 (4): 307 - 312

Australia has a unique and highly successful screening program for cervical cancer which is **based on the conventional Pap smear**. Since its introduction in 1991 there has been a decline in both the incidence of and mortality from this disease. Part of the success of this program has been the introduction of Pap test registers and strict quality assurance measures for cervical cytology, including compulsory key performance indicators for laboratories. Using these measures, nationwide calculations give **cervical cytology in Australia a sensitivity of 78% for high-grade lesions and a positive predictive value (PPV) of 78%.** Australia was the first country to introduce a widespread government-funded human papillomavirus (HPV) vaccination program in 2007. ***Because of the high accuracy of Australian cytology, HPV testing alone, given its low PPV and high cost, is unlikely to be a viable alternative to cytology for primary screening in this country.*** Australia therefore faces unique issues and choices in integrating its extensive vaccination program with a successful cervical screening program.

# Futur citologia ginecològica al nostre país

- Depèn únicament de nosaltres
- Tenim a un costat epidemiòlegs només treballant per demostrar la superioritat dels test de VPH i la necessitat de la seva implantació en el cribratge del càncer cervical
- Aprofitar aquests temps de crisi econòmica per demostrar la vàlua real (Sensitivitat i VPP) de la citologia catalana
- Proposta de treball multicèntric a Catalunya

# XX anys de la creació de la Societat Catalana de Citopatologia. 1992


I sense més coses per a discutir s'aixeca la sessió de la que es fa la present acta fundacional, que és firmada com aprovació, per a tots els assistents.

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# VI Congrés Català de Citopatologia

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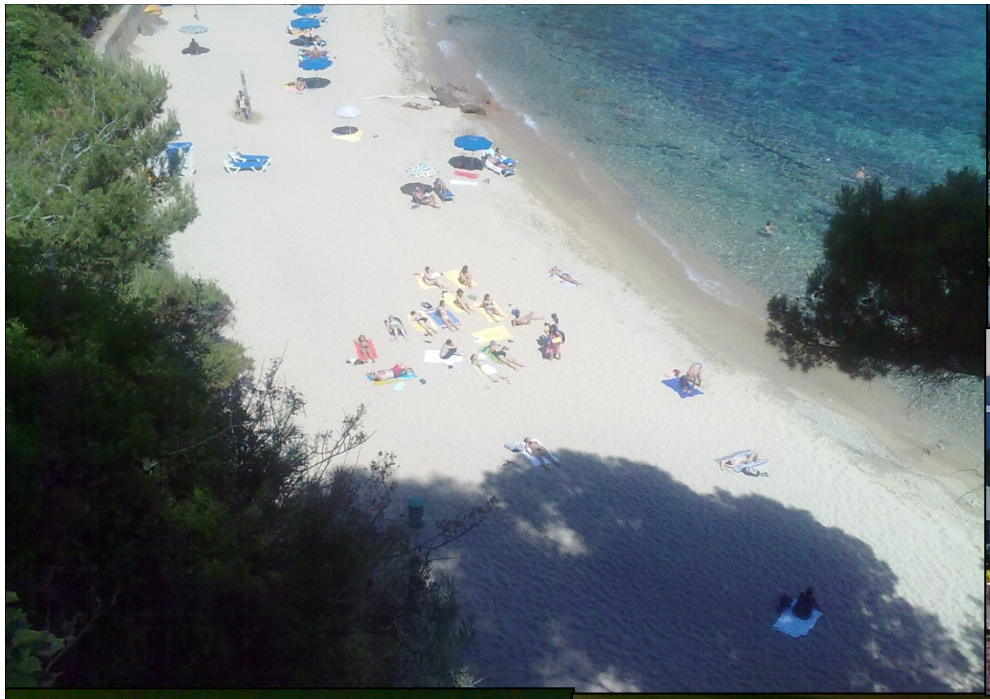





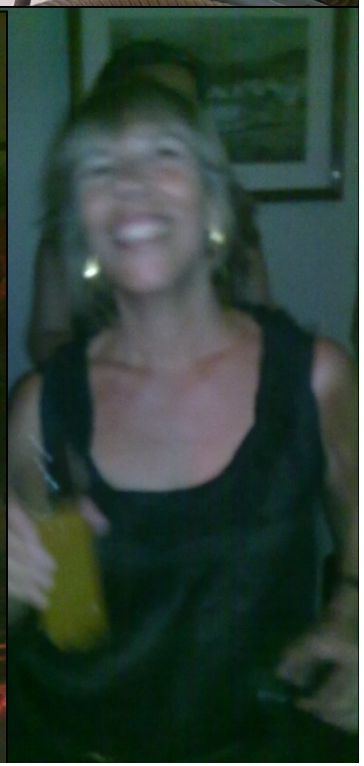

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The Human Cell And The Cytotechnologist (1957)

# Gràcies

Hashime Murayama