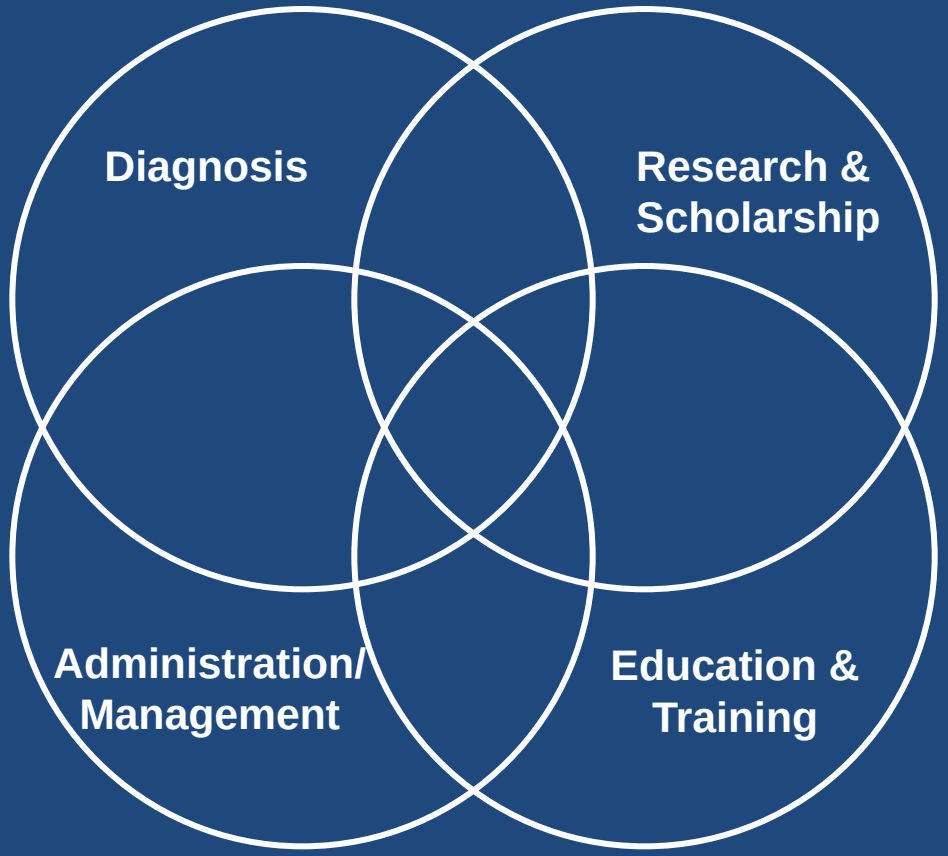
# Gynaecological Pathology: past, present and future

Mike Wells
Professor of Gynaecological Pathology
University of Sheffield

President, British Division,
International Academy of Pathology
2012 - 2014

# A Pathologist's Career



**“… I have had the ideal of service. While it is important for those properly qualified to spend time on research for the benefit of future generations, it is of great importance to provide for the generation now in existence. I have therefore devoted much of my time in trying to be of service to those who must recognize and treat tumors and tumor-like lesions.”**

**Arthur Purdy Stout**

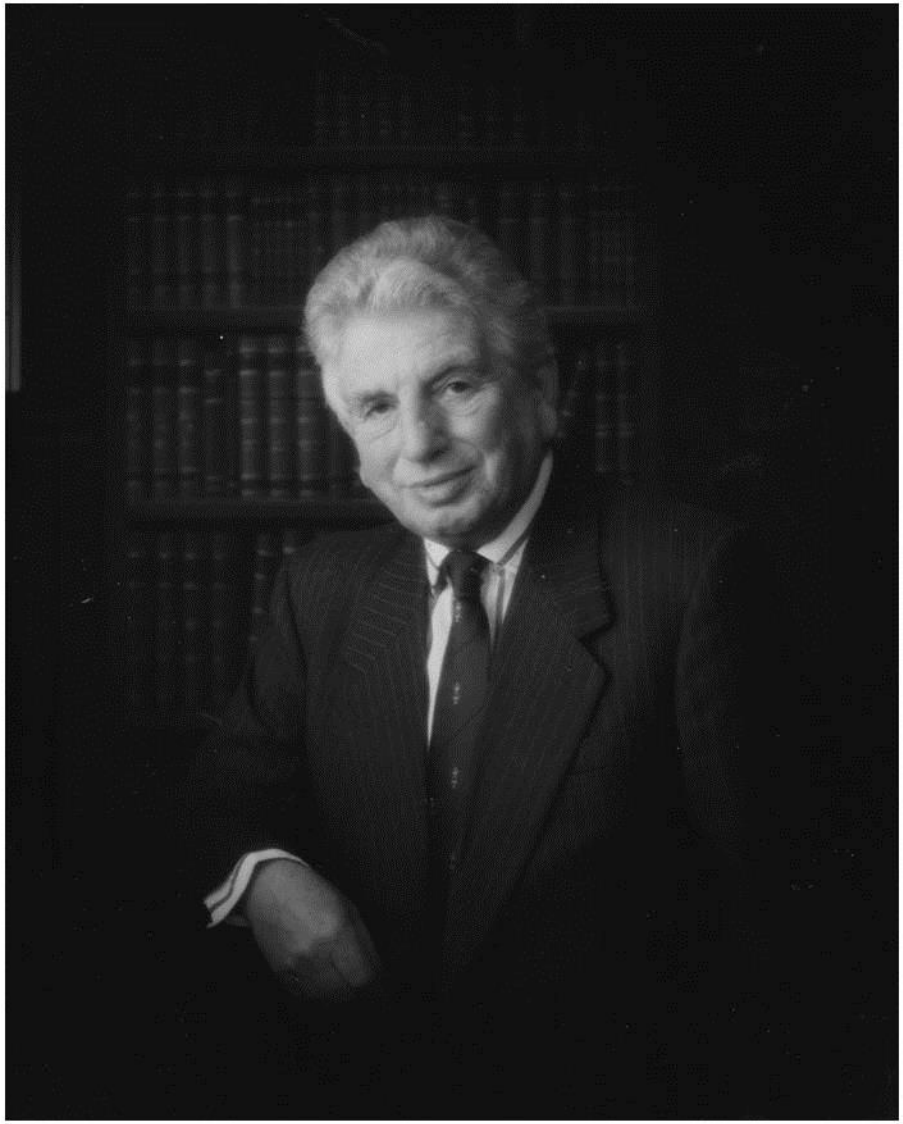
Late Professor of Surgery & Pathology

College of Physicians and Surgeons

Columbia University

**~400 invited talks, lectures and slide seminars in 57 countries over 30 years**

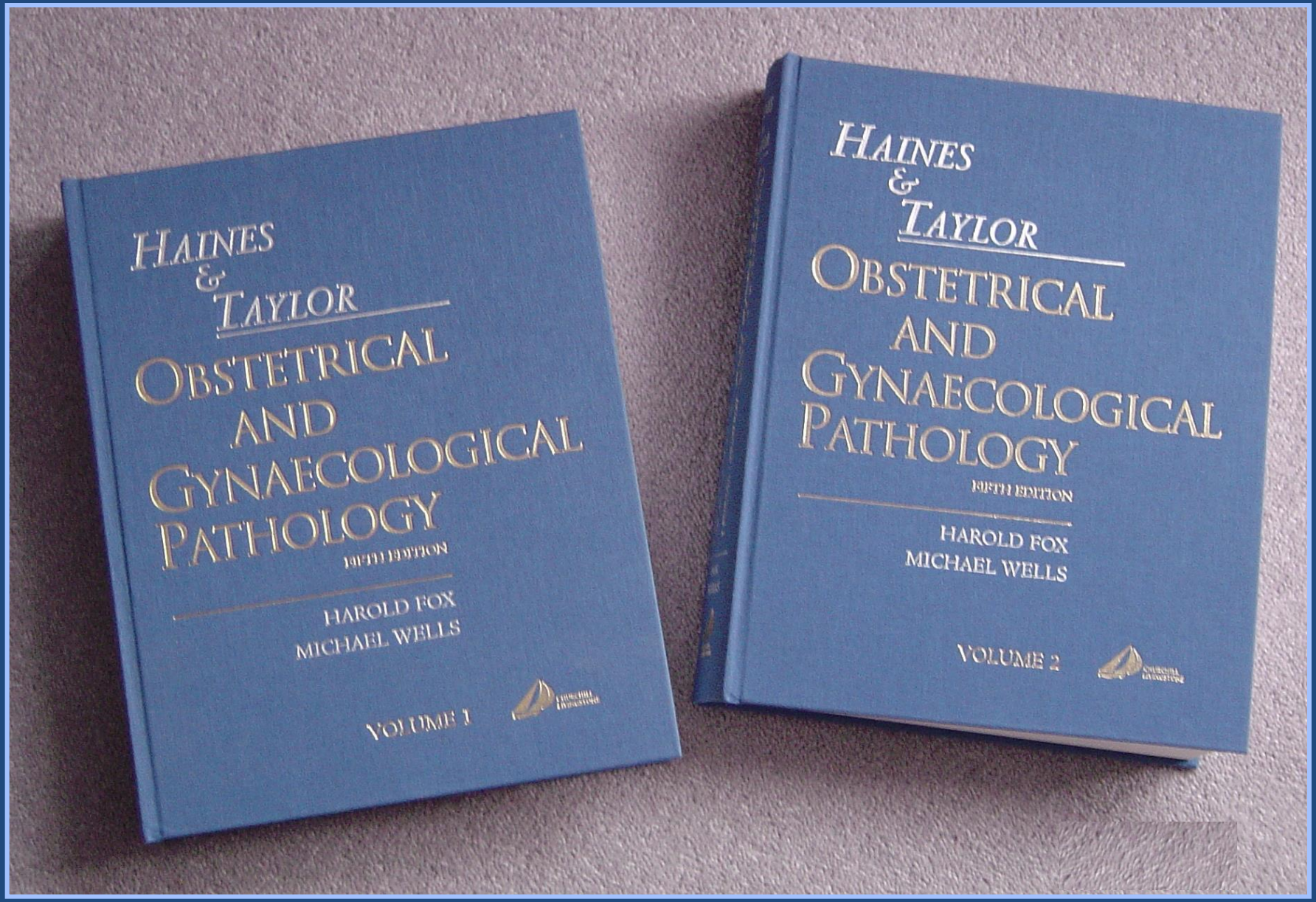

Sheffield



# Harold Fox

1931 – 2012

Professor of Reproductive Pathology, University of Manchester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OBSTETRICAL AND GYNAECOLOGICAL PATHOLOGY
FIFTH EDITION
HAROLD FOX
MICHAEL WELLS
VOLUME 1
HAINES & TAYLOR
OBSTETRICAL AND GYNAECOLOGICAL PATHOLOGY
FIFTH EDITION
HAROLD FOX
MICHAEL WELLS
VOLUME 2

*British Journal of Obstetrics and Gynaecology*
August 1985, Vol. 92, pp. 867–869

# Zollinger–Ellison syndrome due to a gastrin secreting ovarian mucinous cystadenoma. Case report

D. R. MORGAN *Registrar*, M. WELLS *Lecturer and Honorary Consultant*, R. C. MACDONALD *Lecturer and Honorary Senior Registrar** & D. JOHNSTON *Professor**, *Departments of Pathology and *Surgery, Leeds General Infirmary, Leeds LS1 3EX*

## Case report

A 35-year-old woman presented with epigastric pain and diarrhoea for 3 months and vomiting for 1 month with an associated weight loss of 16 kg. There was no significant gynaecological history. Barium meal examination and upper gastrointestinal tract endoscopy showed multiple ulcers in the second part of the duodenum, coarse gastric mucosal folds and gastric outlet obstruction. At this time a diagnosis of Zollinger–Ellison syndrome was suspected. The syndrome is characterized by intractable peptic ulceration and diarrhoea often accompanied by steatorrhoea and hypokalaemia. It is associated with hypergastrinaemia and is usually due to a gastrin secreting tumour of the pancreas (Zollinger & Ellison 1955). Subsequent selective arteriography and abdominal ultrasound did not localize a tumour mass. Assays for spontaneous (basal) acid output, peak acid response to pentagastrin and peak acid response to insulin were found to be raised (Table 1).

Serum gastrin was estimated by radioimmunoassay using $^{125}$I gastrin 17 (Becton Dickinson, London) and antibody 4562 (Courtesy of Professor J. Rehfeld, Copenhagen). The fasting serum gastrin levels were raised, being 680–940 pg/ml, increasing to 1075 pg/ml after infusion of secretin. Values of serum vasoactive intestinal polypeptide, pancreatic polypeptide, glucagon and somatostatin were within the normal range and assessments of thyroid, parathyroid, pituitary and adrenal function were also normal. At this point deficits of water, sodium and potassium were corrected and additional losses reduced by giving intravenous cimetidine 400 mg four times daily in preparation for a laparotomy.

At operation there was severe ulceration and stenosis of the second part of the duodenum and marked gastric hypertrophy. Careful palpation of the pancreas did not reveal a tumour mass, but a right ovarian cyst was found and the right fallopian tube and ovary were removed. In addition a highly selective vagotomy was performed and the duodenal stenosis treated by duodenoduodenostomy and gastrojejunostomy.

As a result of the operation the gastric acid secretion returned to normal (Table 1) and the postoperative gastrin levels fell to between 20 and 80 pg/ml. The patient remains clinically well and is receiving no treatment 3½ years later.

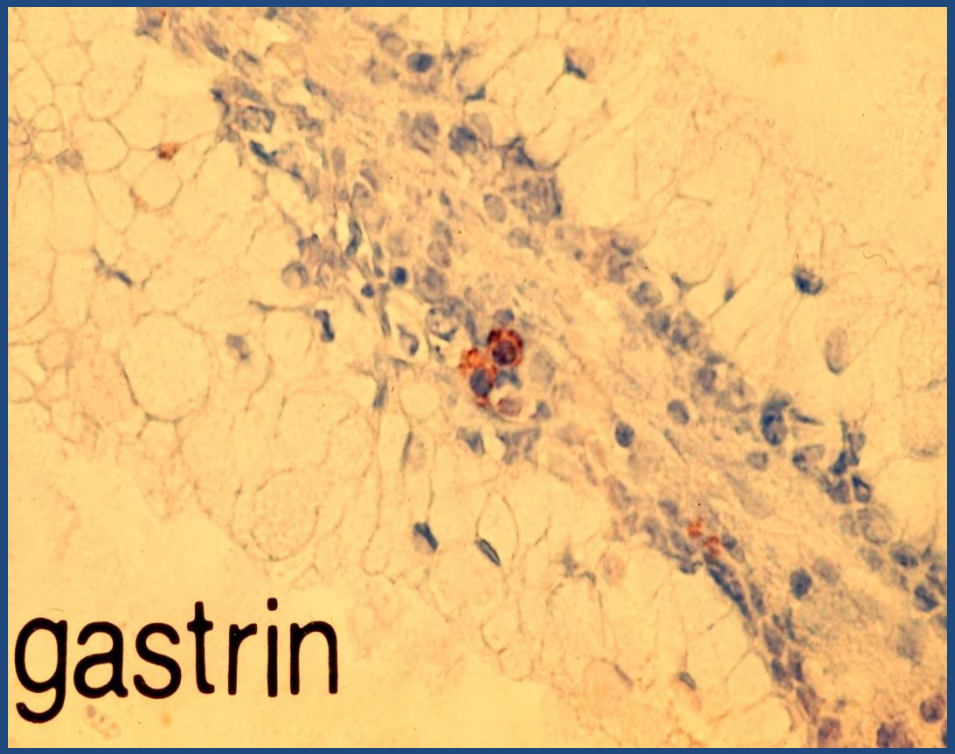
Pathological examination revealed a right ovarian cyst measuring 30 cm × 11 cm × 9 cm and weighing 700 g. Its external surface was smooth and the fallopian tube and fimbriae were attached; it was filled with thick brown mucinous material. There were two large tumour masses measuring 10 cm × 6 cm × 5 cm and 7 cm × 4 cm × 3·5 cm. The centre of the tumour contained further viscous fluid. The level of immunoreactive gastrin in the cyst fluid was 500 pg/ml.

Histology showed a mucinous cystadenoma of borderline malignancy with numerous complex cystic spaces lined in many areas by a serrated mucin secreting epithelium showing some nuclear stratification (Ovarian Tumour Panel of Royal College of Obstetricians and Gynaecologists 1983). Immunoperoxidase (PAP) staining using gastrin antibody showed many gastrin producing cells within the epithelium of the tumour (Figure 1).

## Comment

The diagnosis of Zollinger–Ellison syndrome was established in this patient by a history of multiple duodenal ulcers, diarrhoea, gastric

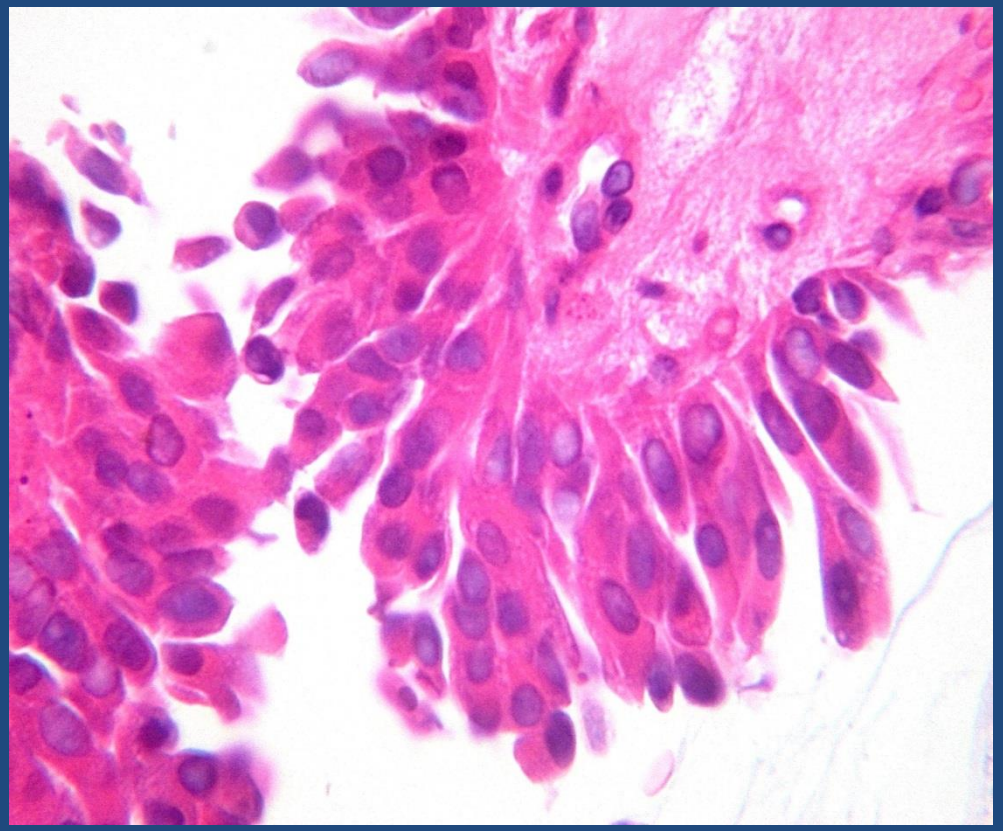




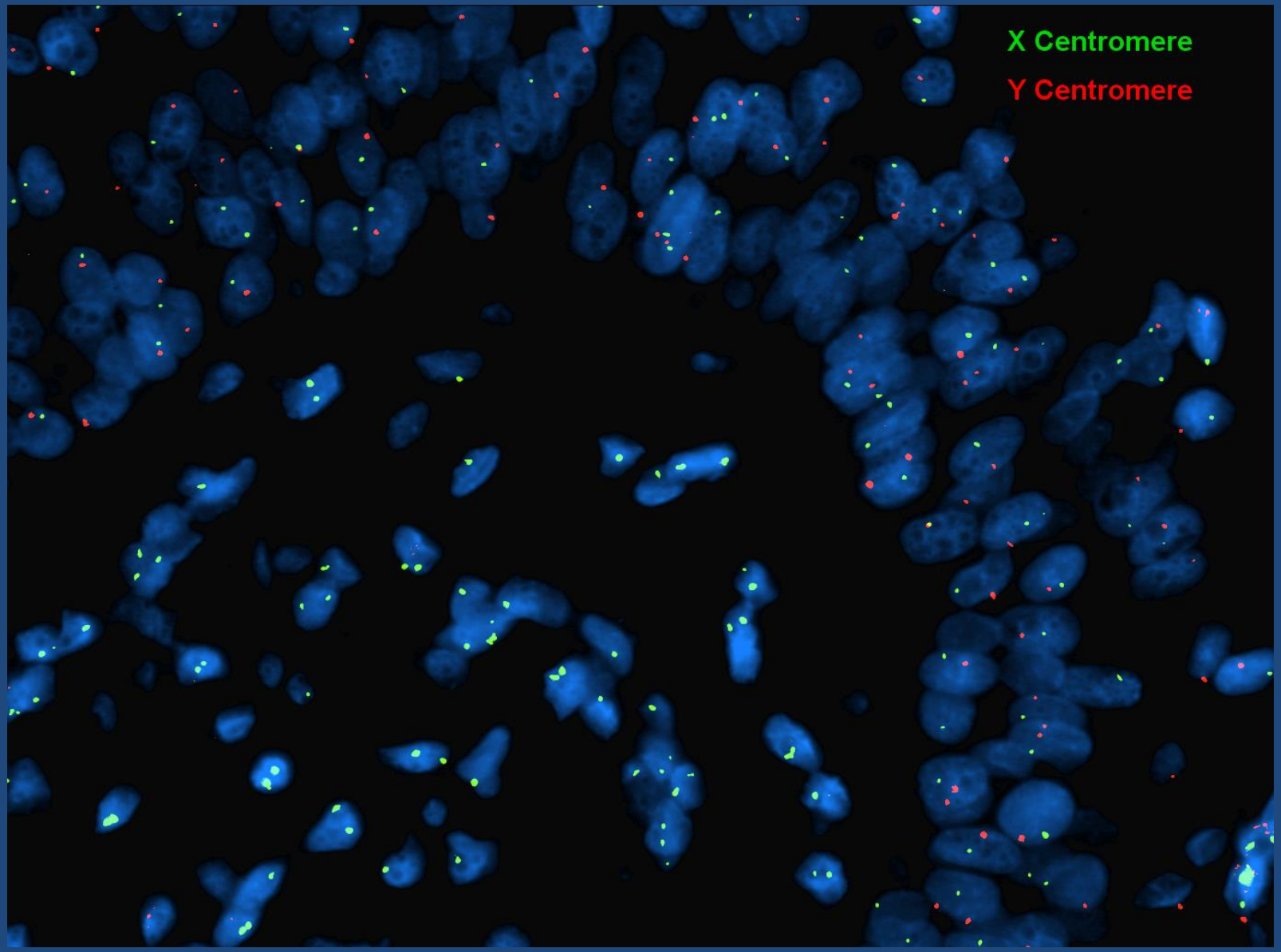
July 2011:
74 years old female: postmenopausal bleeding.

Endometrial biopsy: pale and haemorrhagic tissue fragments.

Patient referred to the Sheffield Gynaecological Cancer Centre.

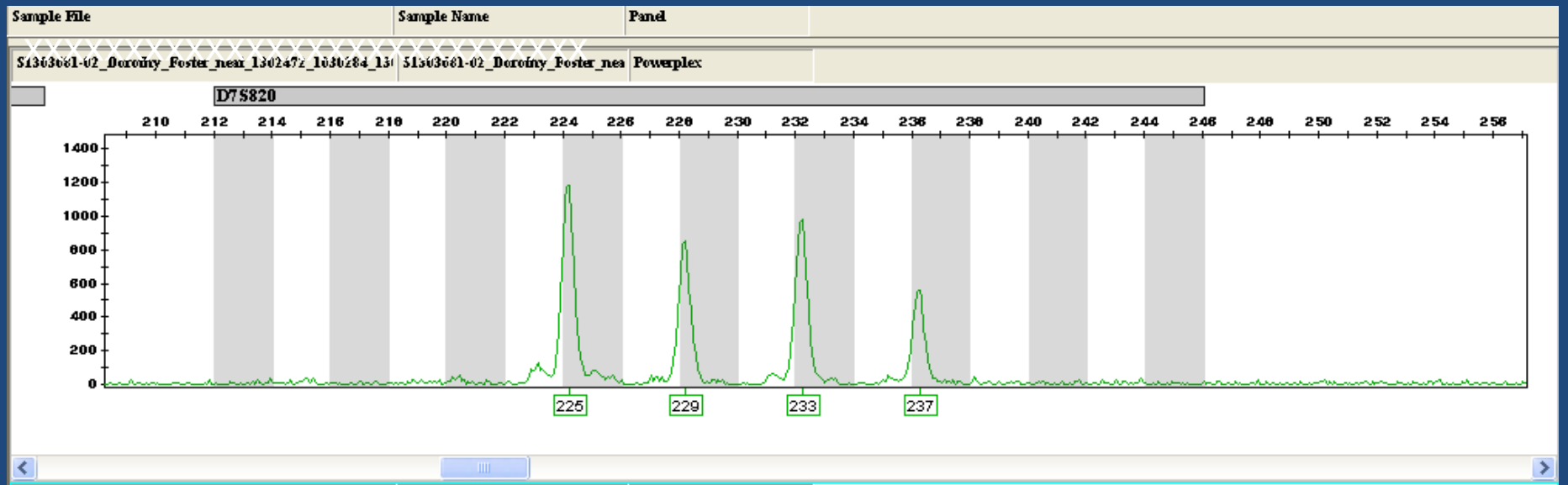


Patient’s husband 74 years old husband diagnosed with Grade 2 papillary transitional cell carcinoma with early invasion of superficial lamina propria (STAGE PT1) in October 2010. He died in January 2012.

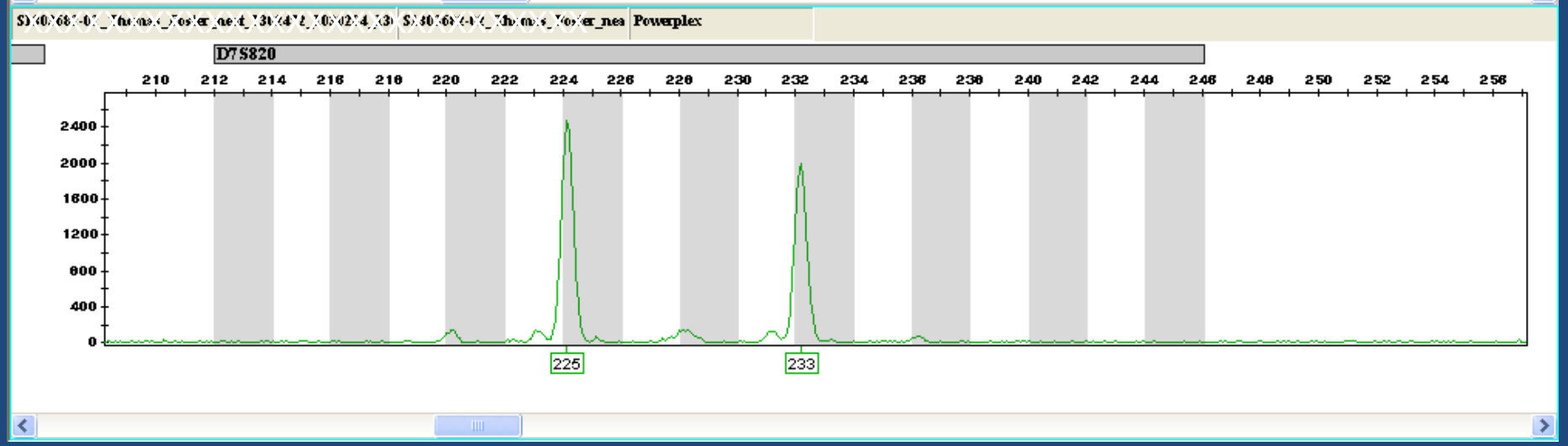



FISH image showing:
Female cells with two green X signals
Male cells with one green X and one red Y signal

a




b



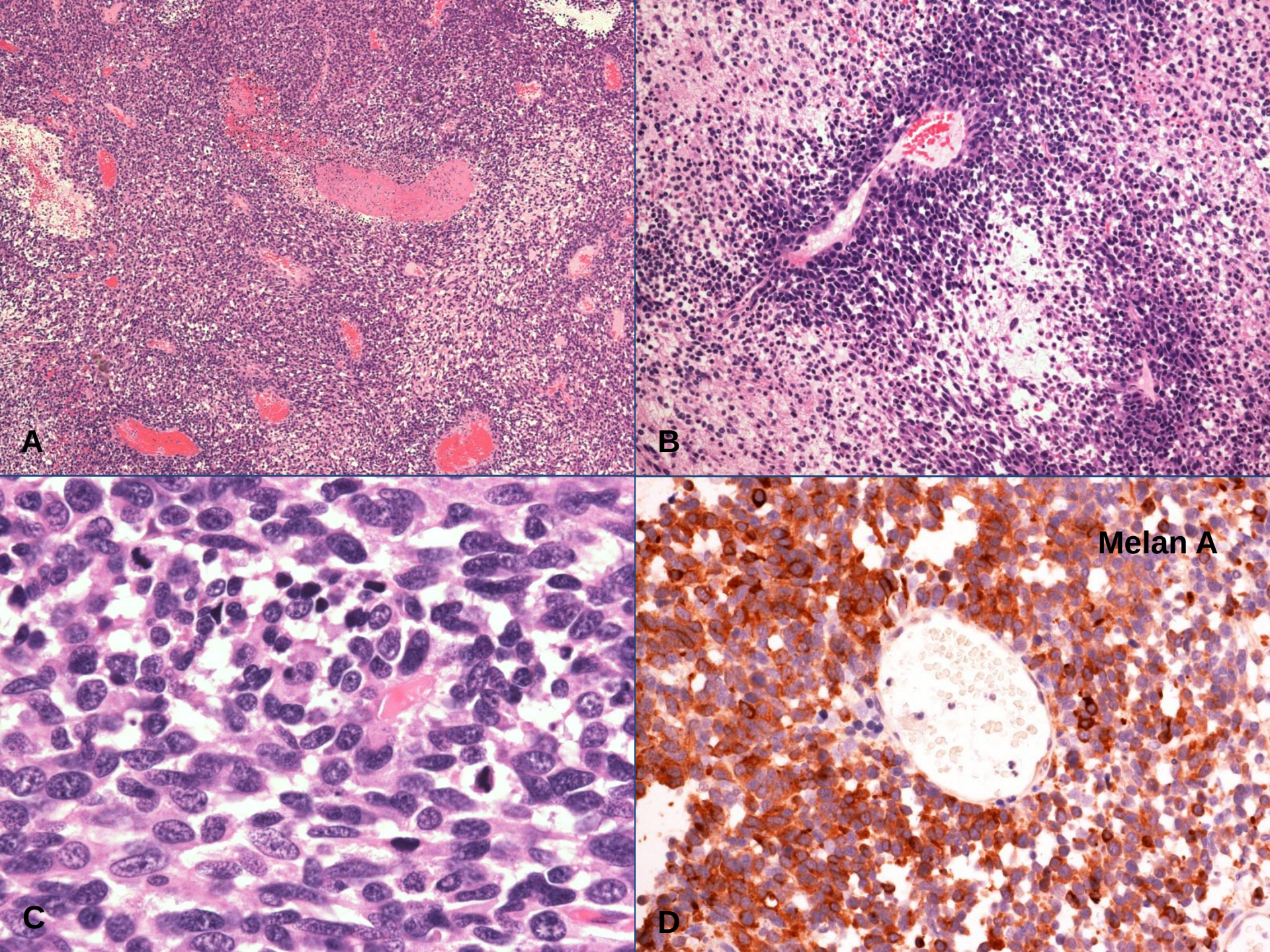

**Genemapper traces for marker D7S820 (PowerPlex® 16)**

a) Sample from D F (wife) (4 alleles: 225, 229, 233 and 237)

b) Sample from T F (husband) (2 alleles: 225 & 233)

# Malignant melanoma in the female genital tract – 3 misses in 30 years as a consultant – my bête noire

- primary malignant melanoma of the vulva – **the most serious error of my career**
- malignant melanoma metastatic to the uterus (diagnosed as high grade uterine sarcoma)
- malignant melanoma metastatic to the ovary (diagnosed as high grade endometrioid stromal sarcoma)


A
B
C
Melan A
D

# Advances in service

- immunohistochemistry
- national Gynaecological EQA scheme (BAGP)
- multidisciplinary team meetings
- reporting datasets
- handling of cancer syndrome specimens (BRCA 1 & 2, Lynch)
- molecular pathology

The Royal College of Pathologists

Standards and Minimum Datasets for Reporting Cancers

# Minimum dataset for the histopathological reporting of vulval biopsy specimens and vulvectomy specimens for vulval cancer

March 2001

The Royal College of Pathologists

Standards and Minimum Datasets for Reporting Cancers

# Minimum dataset for the histopathological reporting of atypical hyperplasia and adenocarcinoma in endometrial biopsy and curettage specimens and for endometrial cancer in hysterectomy specimens

March 2001

The Royal College of Pathologists

Standards and Minimum Datasets for Reporting Cancers

# Minimum dataset for the histopathological reporting of cervical neoplasia

March 2001

# International Collaboration on Cancer Reporting (ICCR):

## - development of evidence-based core datasets for pathology cancer reporting

The Royal College of Pathologists
Pathology: the science behind the cure

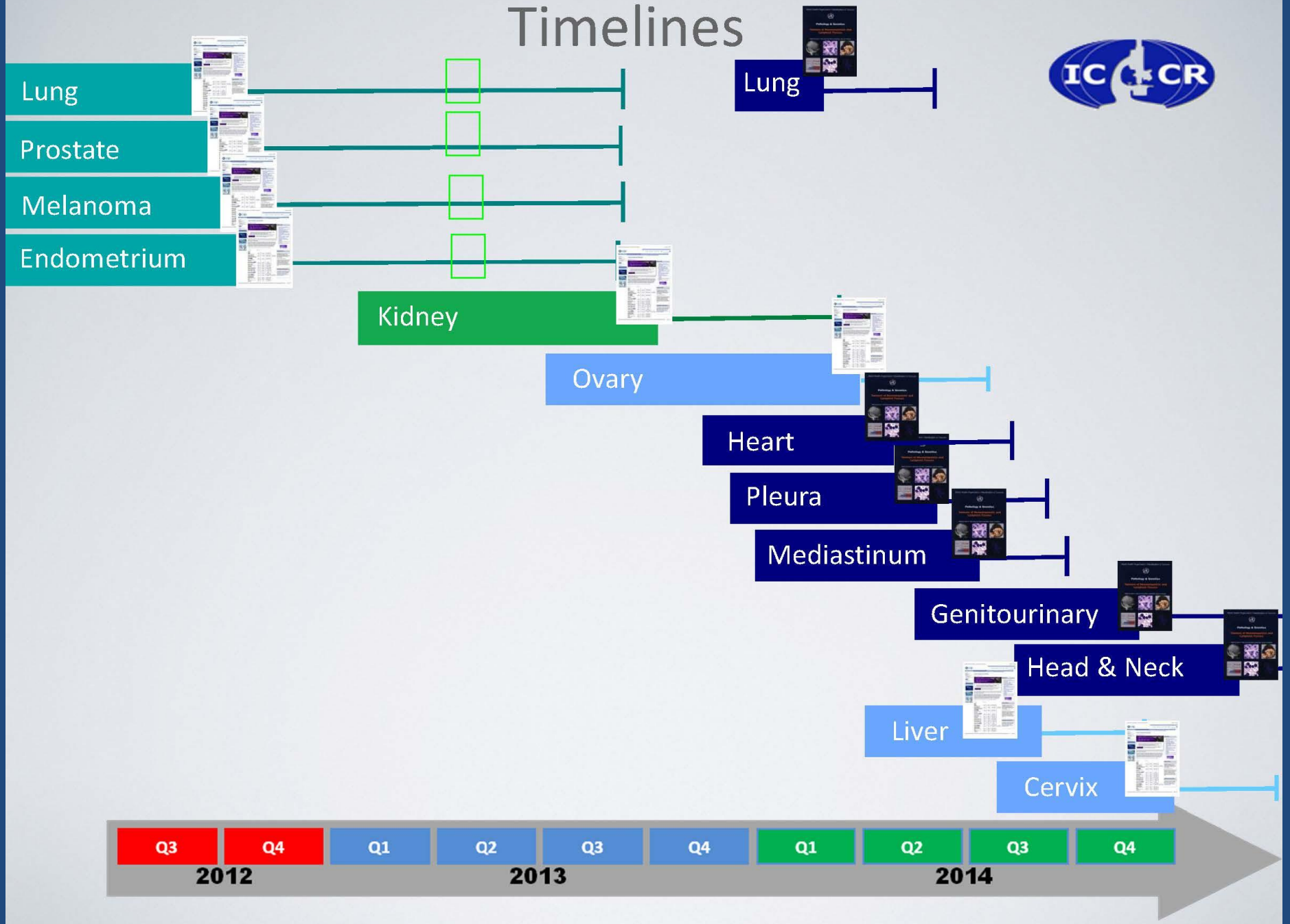
European Society of Pathology

cap

RCPA
The Royal College of Pathologists of Australasia

CANADIAN ASSOCIATION OF PATHOLOGISTS
ASSOCIATION CANADIENNE DES PATHOLOGISTES

# Timelines


Lung
Prostate
Melanoma
Endometrium
Kidney
Lung
Ovary
Heart
Pleura
Mediastinum
Genitourinary
Head & Neck
Liver
Cervix
Q3
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
2012
2013
2014

# Meeting of ICCR, European Congress of Pathology, London, August 2014

# 5 areas of research activity

- trophoblast biology and neoplasia
- HPV and cervical neoplasia
- cervical glandular neoplasia
- p53 in precursor lesions of ovarian cancer
- HRT and the endometrium

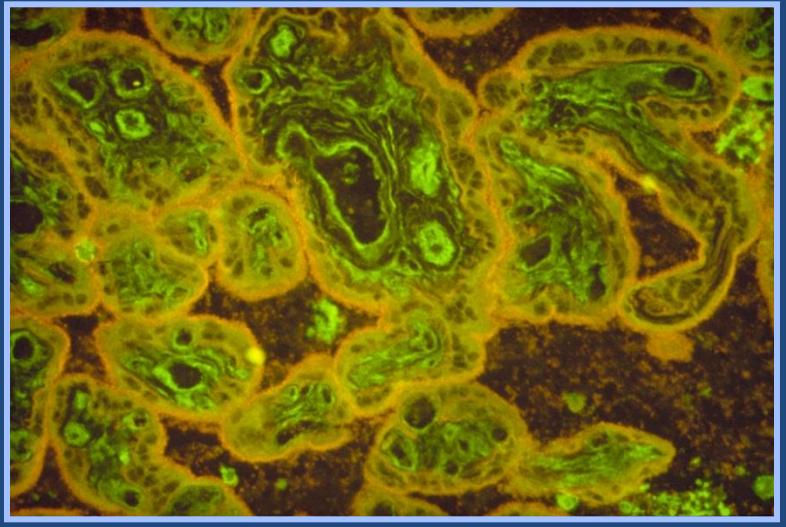
# Trophoblast biology and neoplasia

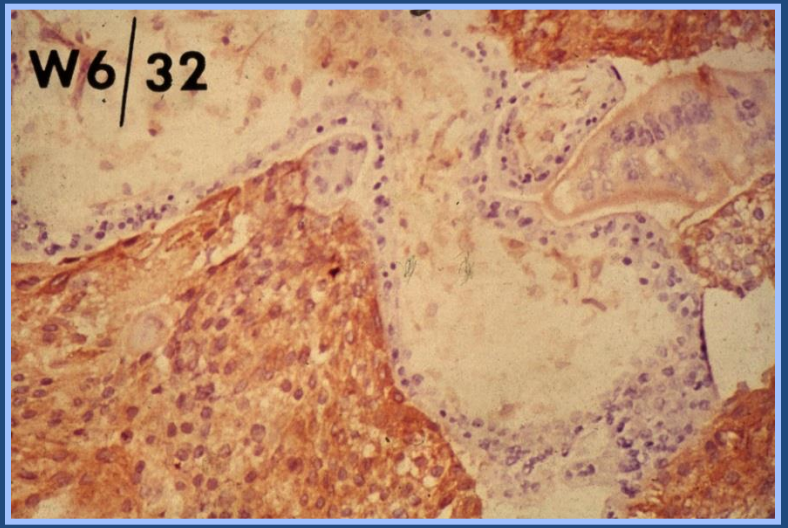
AMERICAN JOURNAL OF REPRODUCTIVE IMMUNOLOGY 6:167–174 (1984)

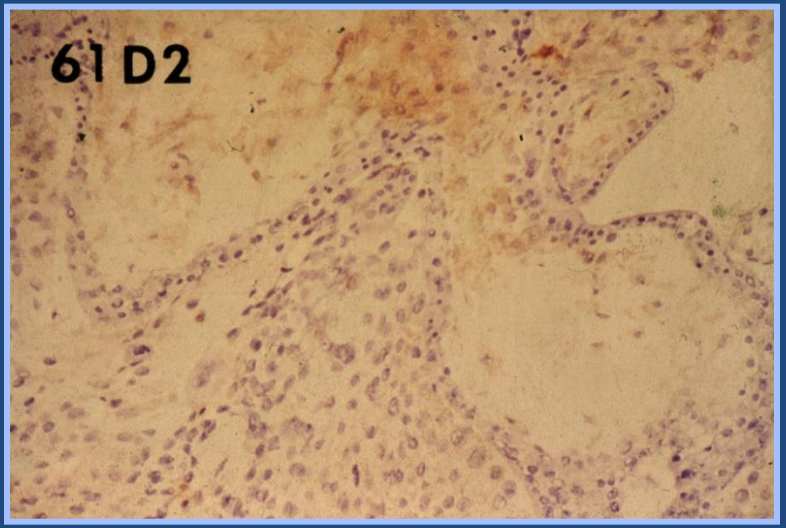

AJRI Pregnancy Immunology

# Class I Antigens of the Major Histocompatibility Complex on Cytotrophoblast of the Human Placental Basal Plate

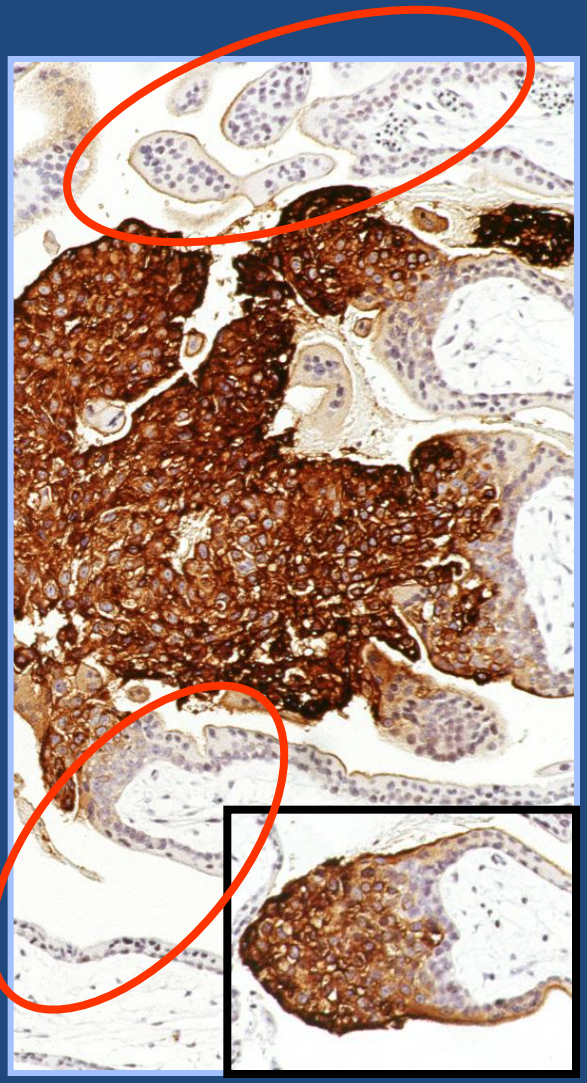
MICHAEL WELLS, BAE-LI HSI, AND W. PAGE FAULK
*Department of Pathology, University of Leeds, Leeds LS2 9JT, England (M.W.) and INSERM U210, Laboratoire d'Immunologie, Faculté de Médecine, Avenue de Vallombrose, 06034 Nice-Cedex, France (B.L.H., W.P.F.)*



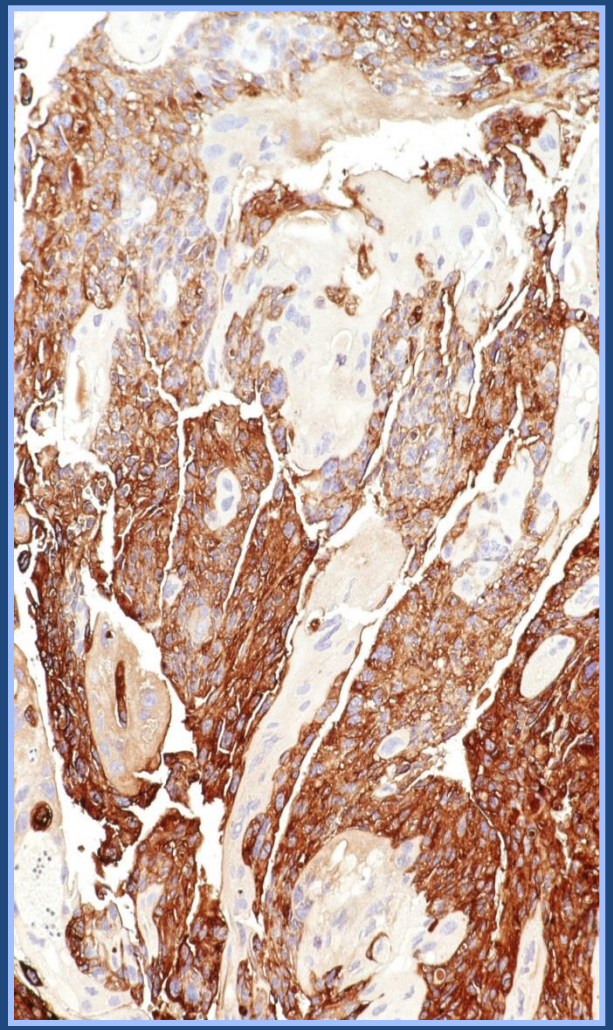


# HLA-G immunoreactivity



Trophoblast column



Choriocarcinoma

**The vast majority of mononucleate trophoblastic cells in choriocarcinoma are villous-type intermediate trophoblast**

*Reprinted from J Clin Pathol* 1987;**40**:615–620

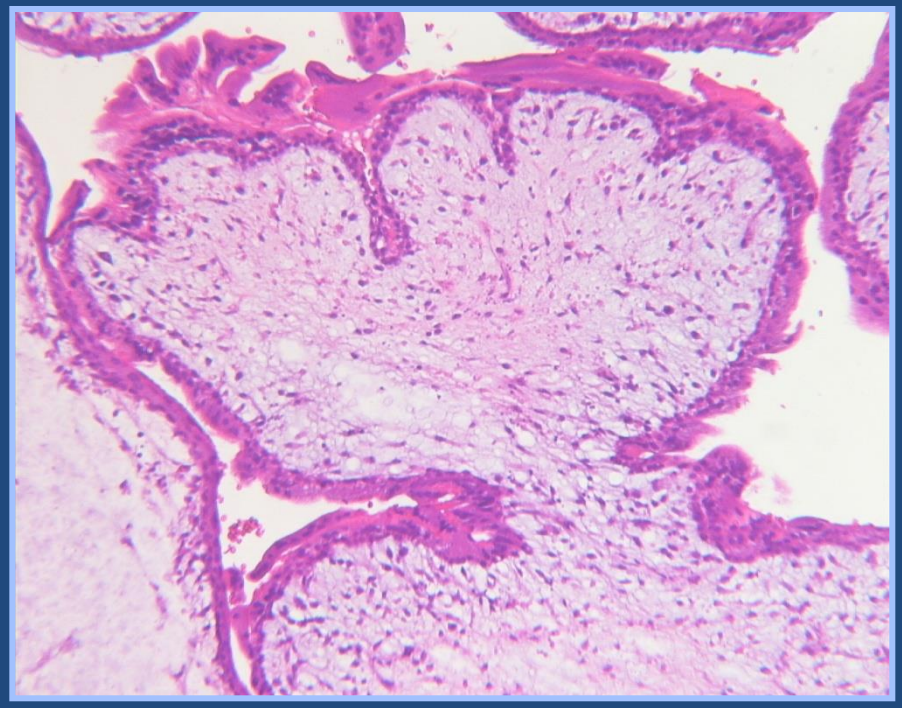

# Diagnosis of molar pregnancy and persistent trophoblastic disease by flow cytometry

J DIANE HEMMING, P QUIRKE, C WOMACK, M WELLS, C W ELSTON, C C BIRD

# Ploidy status and histological diagnosis of molar pregnancies

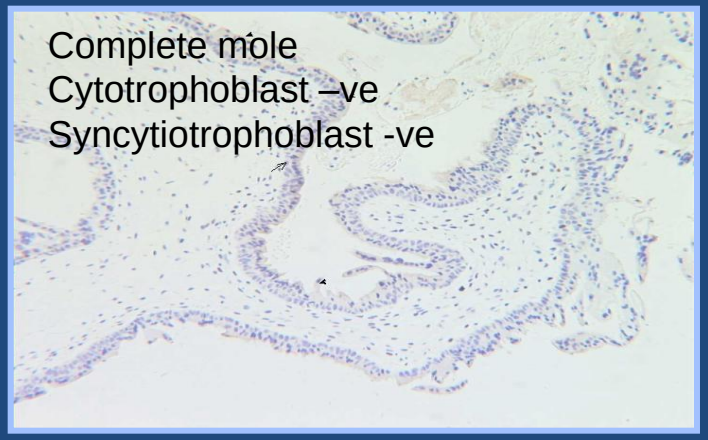
| | | *Histological diagnosis* | | |
|---|---|---|---|---|
| *Ploidy status* | | *Complete mole* | *Partial mole* | *Hydropic abortion* |
| **Diploid** | **59** | **46** | **10** | **3** |
| **Triploid** | **26** | **2** | **20** | **4** |
| **Tetraploid** | **1** | **–** | **1** | **–** |
| **Aneuploid** | **2** | **1** | **1** | **–** |
| ***Total*** | ***88*** | ***49*** | ***32*** | ***7*** |

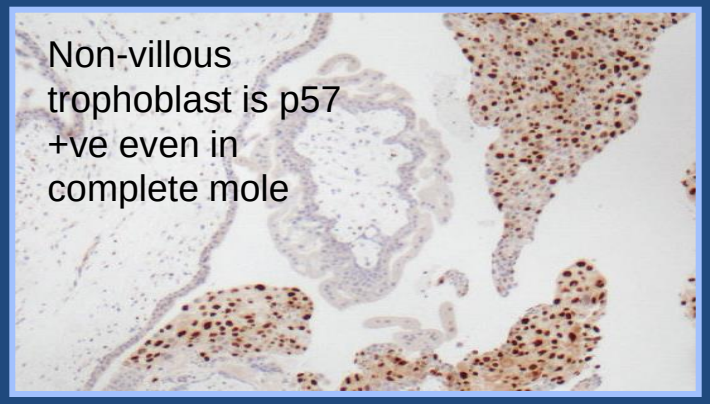
# Early complete mole

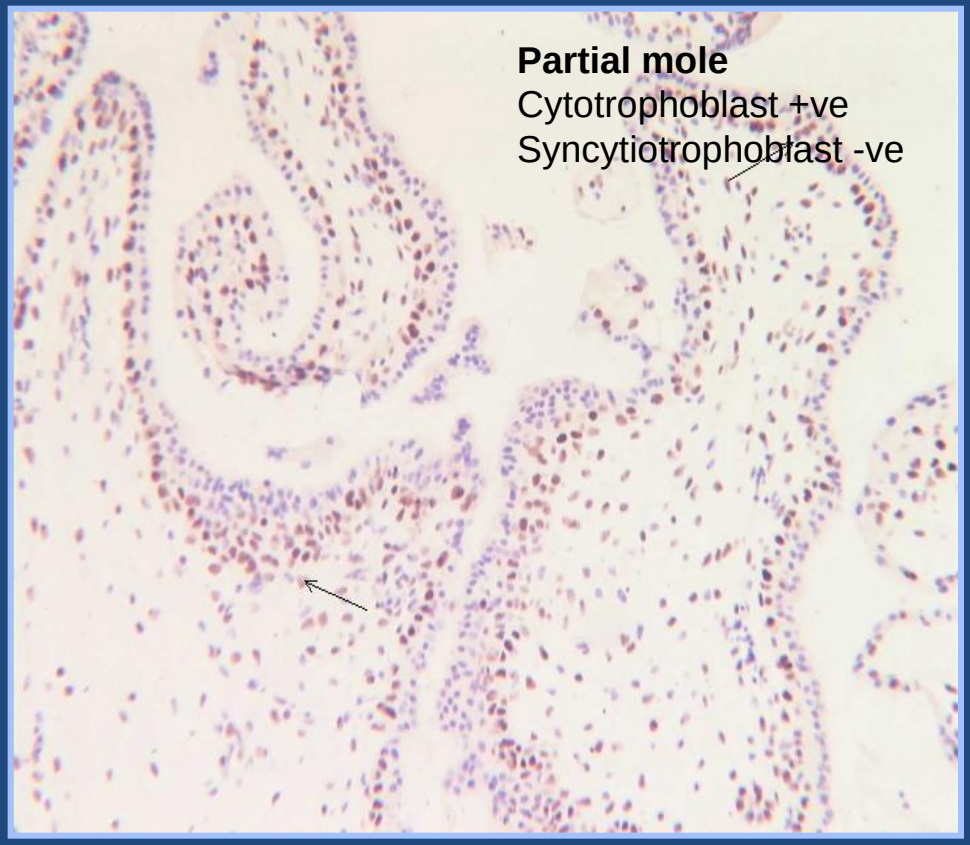


- abnormally shaped villi - branching or polypoid
- stromal mucin
- stromal vessels may be present
- STROMAL NUCLEAR DEBRIS

# $P57^{kip2}$ in hydatidiform mole



*Histopathology* 2003, 43, 363–373

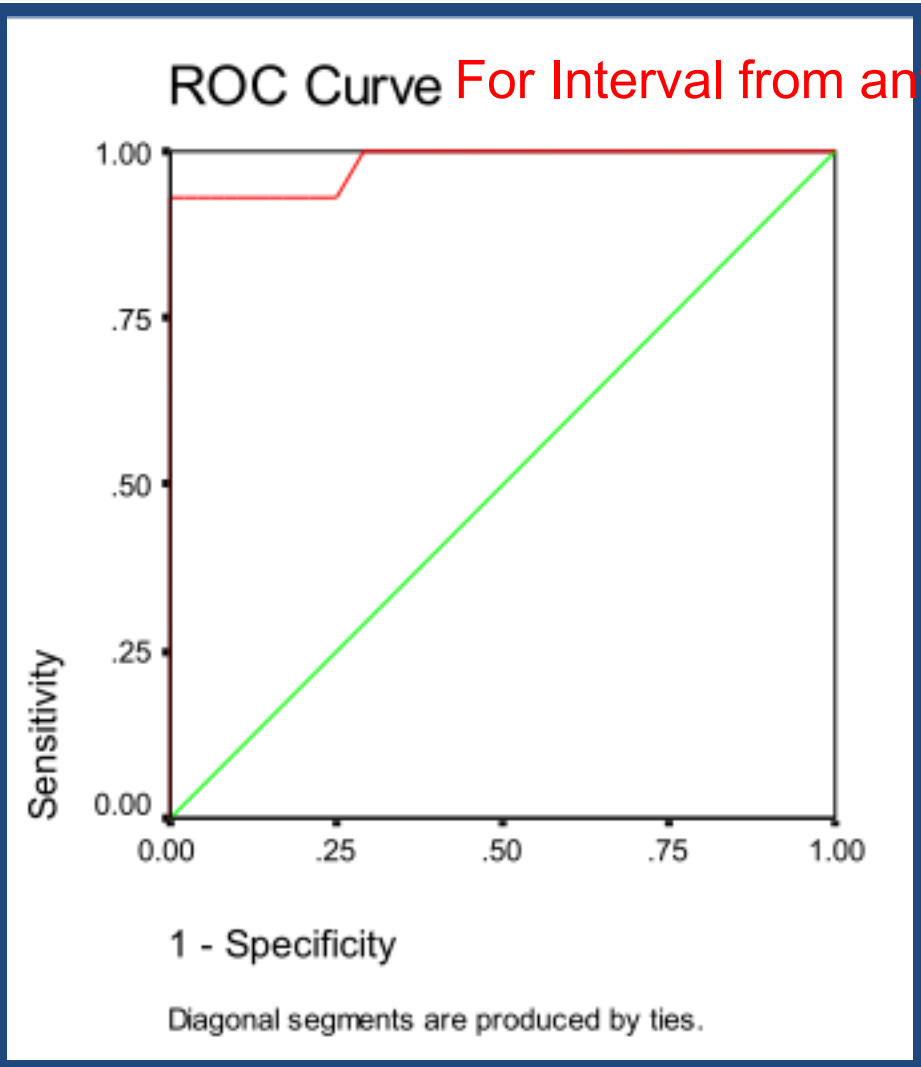
# Refining the diagnosis of hydatidiform mole: image ploidy analysis and p57$^{KIP2}$ immunohistochemistry

H Crisp, J L Burton, R Stewart & M Wells
*Academic Unit of Pathology, Division of Genomic Medicine, University of Sheffield Medical School, Sheffield, UK*

Date of submission 13 February 2003
Accepted for publication 28 May 2003

| Suspected diagnosis | Image cytometry | p57$^{kip2}$ status | Revised diagnosis |
|---|---|---|---|
| Partial mole | Triploid | +ve | Partial mole |
| Complete mole | Triploid | +ve | Partial mole |
| Partial mole | Diploid | -ve | Complete mole |
| Partial mole | Diploid | +ve | Hydropic miscarriage |

# PSTT: 48 months from causative pregnancy is critical

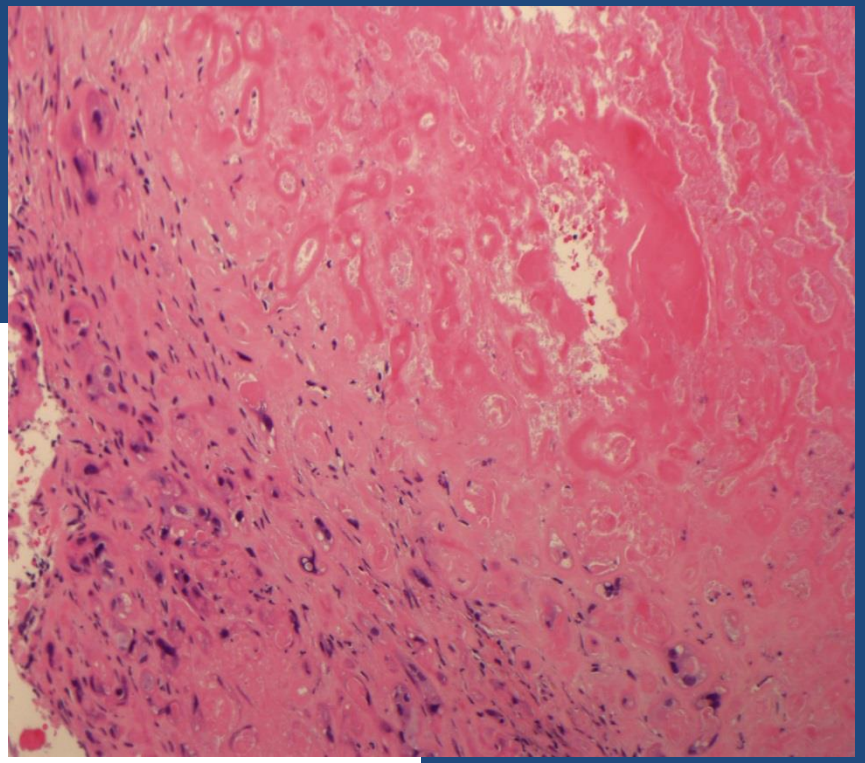



**48 month cut-off**

Specificity 100%
Sensitivity 93%

| Time | Dead | OS |
|---|---|---|
| < 48 | 1/49 | 98% |
| ≥ 48 | 13/13 | 0% |

Schmid P *et al* Lancet 2009, 374: 48-55



*International Journal of Gynecological Pathology*
**00**:1–8, Lippincott Williams & Wilkins, Baltimore


Original Article

# Atypical Placental Site Nodule (APSN) and Association With Malignant Gestational Trophoblastic Disease; A Clinicopathologic Study of 21 Cases

Baljeet Kaur, F.R.C.Path., Dee Short, Rosemary A. Fisher, Ph.D., F.R.C.Path., Philip M. Savage, Ph.D., F.R.C.P., Michael J. Seckl, Ph.D., F.R.C.P., and Neil J. Sebire, F.R.C.Path.

# HPV and cervical neoplasia

JOURNAL OF PATHOLOGY, VOL. 152: 77–82 (1987)

# DEMONSTRATION OF HUMAN PAPILLOMAVIRUS TYPES IN PARAFFIN PROCESSED TISSUE FROM HUMAN ANO-GENITAL LESIONS BY *IN-SITU* DNA HYBRIDISATION

MICHAEL WELLS*, SHARON GRIFFITHS*, FRASER LEWIS* AND COLIN C. BIRD†

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*Received 9 January 1987*
*Accepted 19 February 1987*

## SUMMARY

A sensitive *in situ* hybridization technique for the demonstration of human papillomavirus (HPV) employing a biotin–streptavidin polyalkaline phosphatase complex has been successfully applied to formalin-fixed, paraffin processed tissue obtained from a selected series of patients with ano-genital lesions. Benign condylomata from males and females showed the presence of HPV 6 and 11. Two cases of vulval intraepithelial neoplasia showed HPV 16. Four cases of squamous carcinoma of the anal canal also showed HPV 16 in the tumour or in the adjacent pre-invasive neoplastic epithelium. A case of malignant transformation in a cervical condyloma was associated with HPV 6 and 11. This technique permits the retrospective evaluation of routinely processed material thus widening the investigative spectrum for HPV.

KEY WORDS— Papillomavirus, *in-situ* hybridisation, formalin-fixed tissue.

## INTRODUCTION

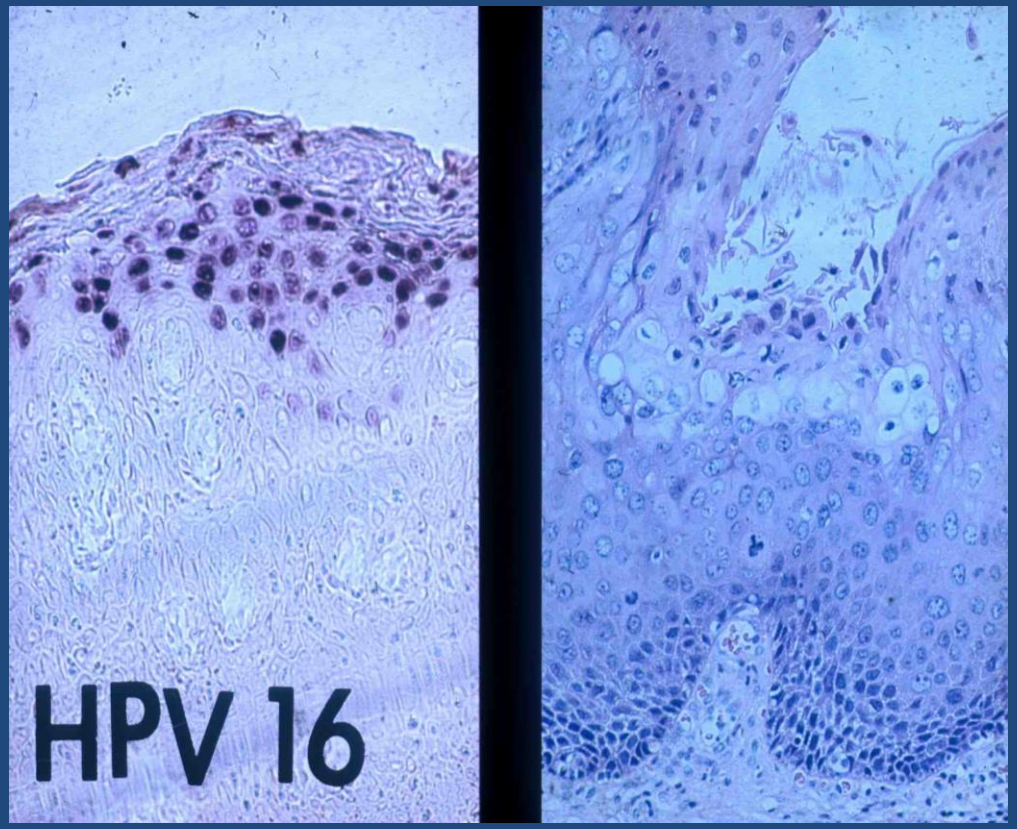
Human papillomaviruses are increasingly implicated as aetiological agents in neoplasia of the ano-genital region, and of the thirty or more types so far described four (HPV 6, 11, 16 and 18) are particularly associated with lesions in this area.[1–4] Electron microscopy[5–8] and immunocytochemistry[8–11] have been employed to demonstrate the virus with disappointing results; even in experienced hands the detection rate in condylomata is only 45–50 per cent. Hybridisation of separated and blotted DNA with radioactively-labelled probes has been used[12–13] but these techniques do not permit the specific localisation of HPV within tissue. More recently specific HPV types have been localised in fixed paraffin embedded tissue by radioactively labelled probes[14] and in fresh tissue by the use of biotinylated probes.[15] The present study reports a technique for the demonstration of HPV types in paraffin processed tissue using biotinylated labelled probes.

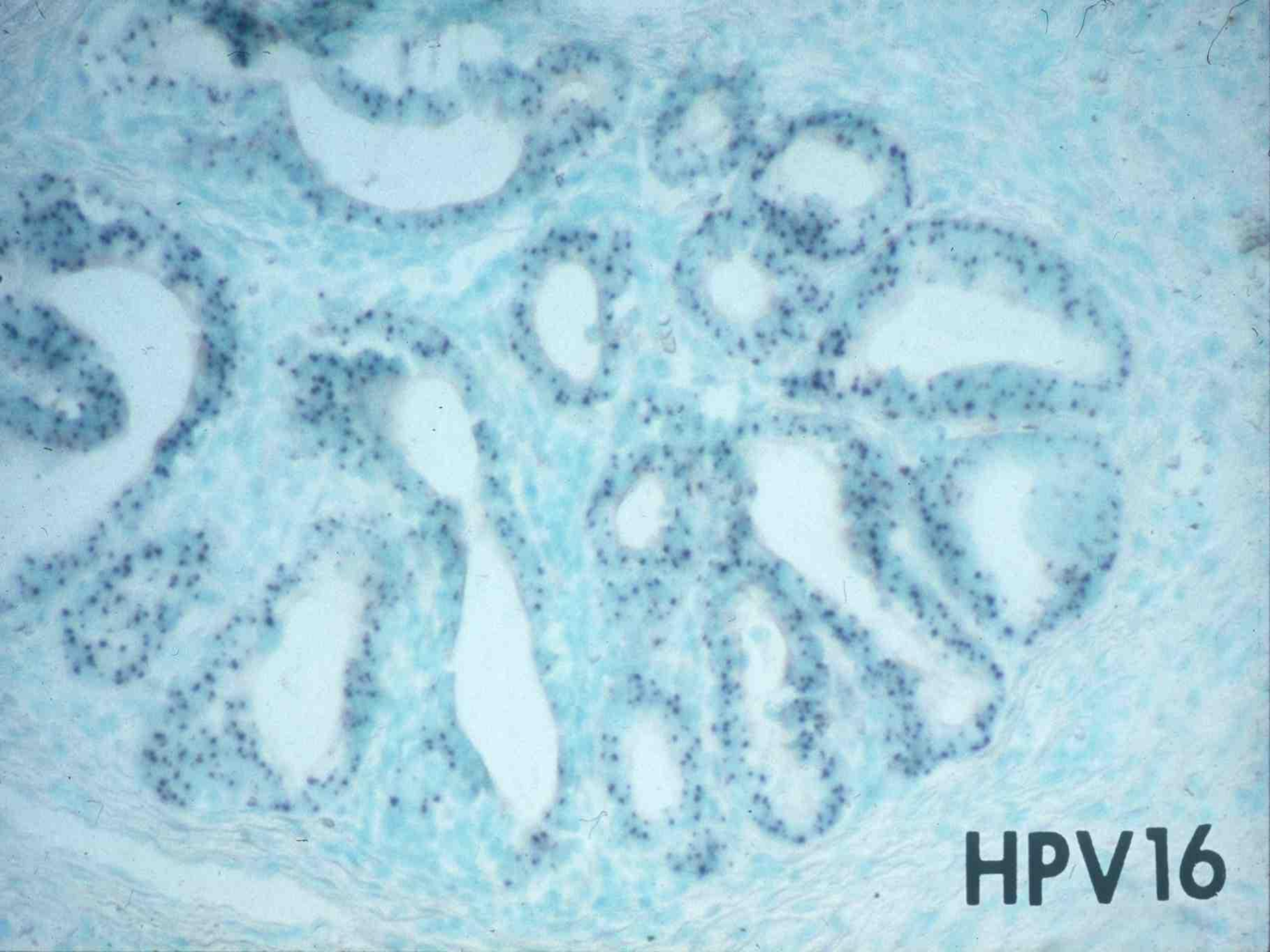
## MATERIALS AND METHODS

Representative tissue blocks of a suitable range of cases believed to be of papillomavirus aetiology or to show morphological features of papillomavirus infection were selected following histological review from the files of the Department of Pathology, University of Leeds. The tissue had been routinely formalin-fixed and embedded in paraffin wax and consisted of substantial biopsy, hysterectomy or resection specimens. The relevant clinical

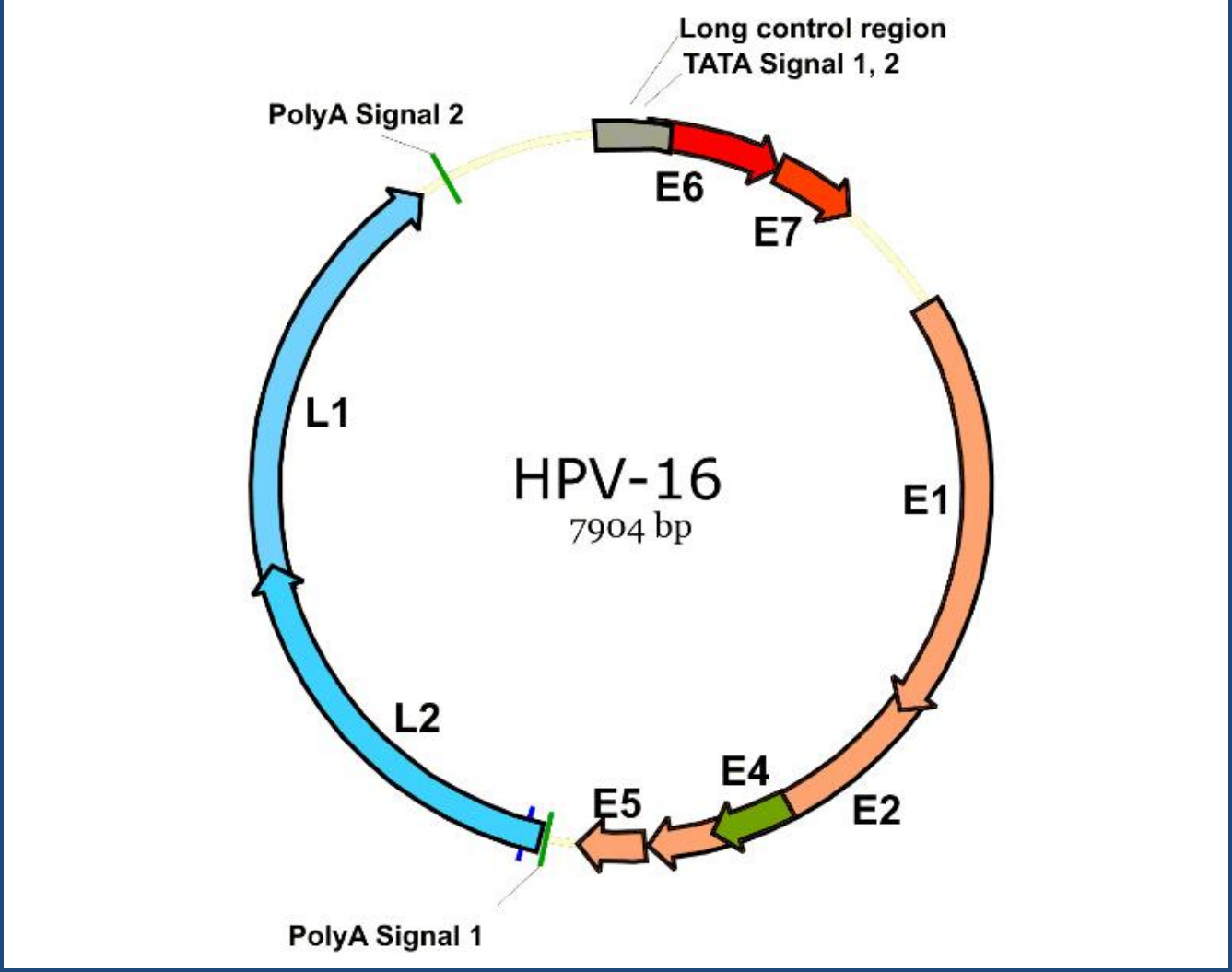
Addressee for correspondence: Dr M. Wells.

0022–3417/87/060077–06$05.00


HPV16

# HPV 16 genome



JOURNAL OF PATHOLOGY
*J. Pathol.* **186**: 275–280 (1998)

# EXPRESSION PATTERNS OF THE HUMAN PAPILLOMAVIRUS TYPE 16 TRANSCRIPTION FACTOR E2 IN LOW- AND HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA

NORMAN J. MAITLAND[1]*, SARAH CONWAY[2], NAFISA S. WILKINSON[2], JANE RAMSDALE[2], JO R. MORRIS[1], CYRIL M. SANDERS[1], JULIE E. BURNS[1], PETER L. STERN[3] AND MICHAEL WELLS[4]

[1]*YCRC Cancer Research Unit, Department of Biology, University of York, York YO1 5DD, U.K.*
[2]*Department of Pathology, St James' University Hospital, Leeds LS9 7TF, U.K.*
[3]*Department of Immunology, Paterson Institute for Cancer Research, Manchester M20 9BX, U.K.*
[4]*Department of Pathology, University of Sheffield Medical School, Sheffield S10 2RX, U.K.*

## SUMMARY

**Specific antibodies against the C-terminus of E2, produced by affinity purification of polyclonal antisera, have been used to identify the cellular populations which express the HPV 16 E2 transcription factor, in a series of formalin-fixed, paraffin-embedded cervical tissues. Cases were selected for both the presence of HPV 16 DNA (confirmed by multiple gene-specific PCR detections) and the presence of multiple grades of cervical intraepithelial neoplasia (CIN). The data indicate that E2 expression is highest in CIN I and in koilocytic lesions. Lower expression was observed in CIN II and little in CIN III lesions. In contrast, there was some restoration of E2 expression in invasive carcinomas, although the intracellular distribution was much more diffuse. The location of E2 expression to the superficial layers of the cervical epithelium, as well as the occurrence of some basal expression in CIN I, suggests that antibodies against HPV 16 E2 could be a useful adjunct to standard histological techniques for the detection of 'at-risk' patients as part of a cervical screening programme.** © **1998 John Wiley & Sons, Ltd.**

KEY WORDS—**HPV 16; cervical cancer; E2 open reading frame**

## INTRODUCTION

Human papillomavirus (HPV) is strongly implicated as a major aetiological agent in carcinoma of the cervix.[1] DNA from the high-risk group of HPVs (which includes HPV 16) can be detected in a large majority of cervical cancers and life-long persistent infection with HPV has recently been identified as a major oncogenic factor in this disease. While DNA detection methods (reviewed by Bosch *et al.*[2]) have emerged as an excellent method of identifying the presence of HPV 16, for which serological studies are still somewhat underdeveloped,[3] the extreme sensitivity of polymerase chain reaction (PCR)-based DNA detection studies can make their interpretation difficult. We have produced domain-specific polyclonal antibodies against both the N- and the C-terminal portions of the HPV 16 E2 protein,[4] which has a domain structure similar to many other transcription factors,[5] consisting of a DNA binding/dimerization C-terminal domain linked by a flexible 'hinge' to a transactivation N-terminal domain. In bovine papillomavirus (BPV), the full length protein can act as a transcriptional activator,[6] whereas in HPV there is evidence in favour of both activation[7,8] and repression[7,9] of viral transcription. Recently, the E2 protein has been shown to repress growth rates of tumour cells, even in the absence of HPV genes or their expression,[10] and can both induce apoptosis[11] and regulate the cell cycle.[12]

In cervical cancers, the HPV genome is frequently integrated into the cell chromosome, resulting in a disruption or, more frequently, deletion of the E2 open reading frame.[13,14] This is in direct contrast to the situation in pre-invasive neoplasia, where episomal circles of HPV DNA are most often observed.[15] However, many tumours also contain multiple copies of episomal, circular, and intact HPV genomes.[16] The distribution of HPV DNA in differentiating epithelium has been extensively studied by *in situ* hybridization[17–19] and shows a defined increase from the basal layers of the epithelium to the superficial layers, and most notably within koilocytes in CIN I and II lesions. Antibodies to viral antigens were unavailable when most of these studies were carried out.[17] Papillomavirus gene expression has been determined, in the absence of sufficiently discriminating antisera for immunohistochemistry,[20] by a number of *in situ* hybridization techniques.[19,21] Expression at the mRNA level appears strongest in the basal and parabasal layers of dysplastic epithelium, i.e., in contrast to the levels of presumably episomal HPV DNA.

Our aim in this study was to examine the expression patterns of E2 protein in single paraffin-embedded sections of cervical tissues, in which the HPV 16 E2 gene status was known, using an antibody which is specific for the E2 C-terminal domain.[4]

*Correspondence to: Professor Norman J. Maitland, YCRC Cancer Research Unit, Department of Biology, University of York, PO Box 373, York YO1 5YW, U.K. E-mail: njm9@york.ac.uk

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CCC 0022–3417/98/110275–06 $17.50


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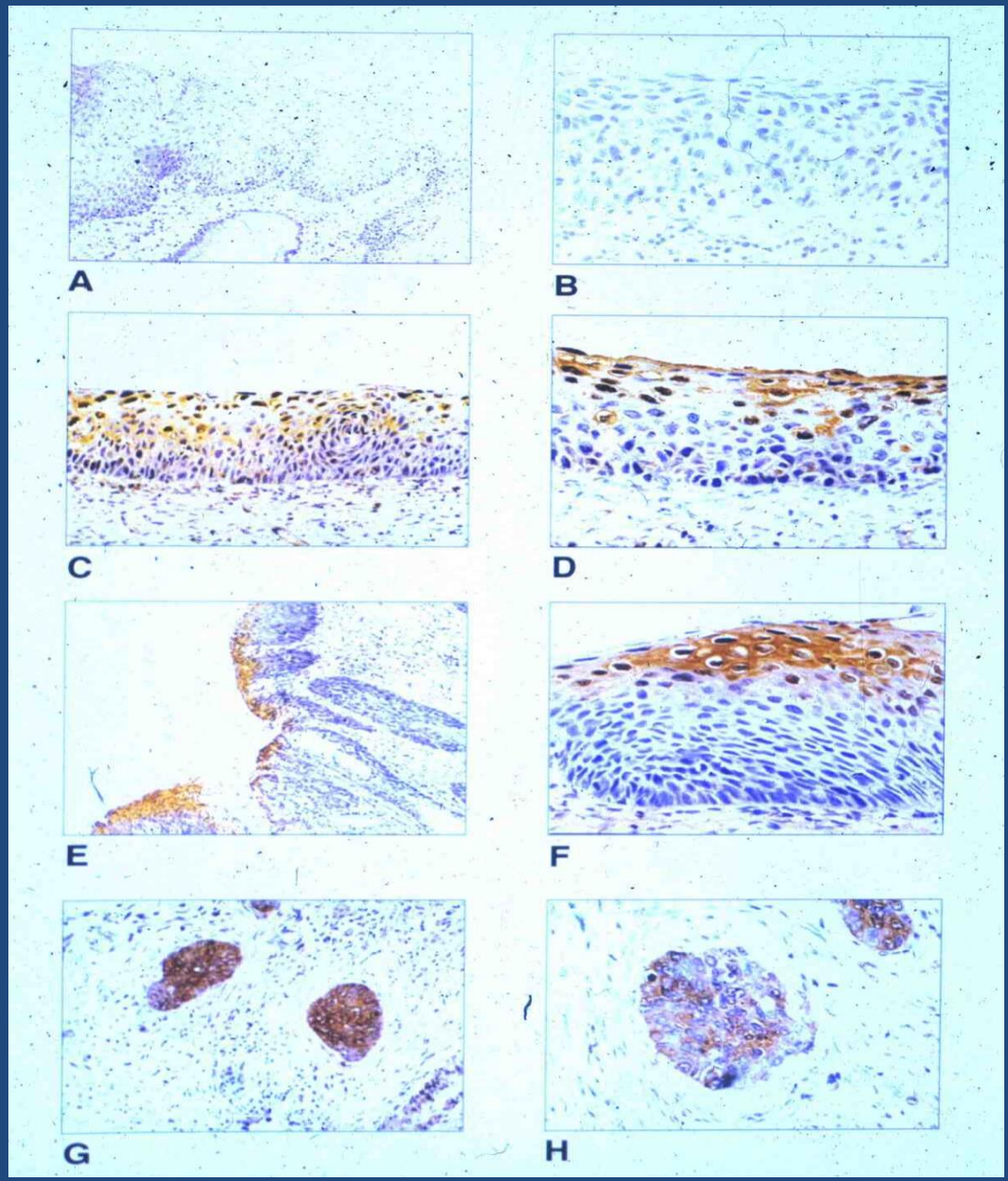
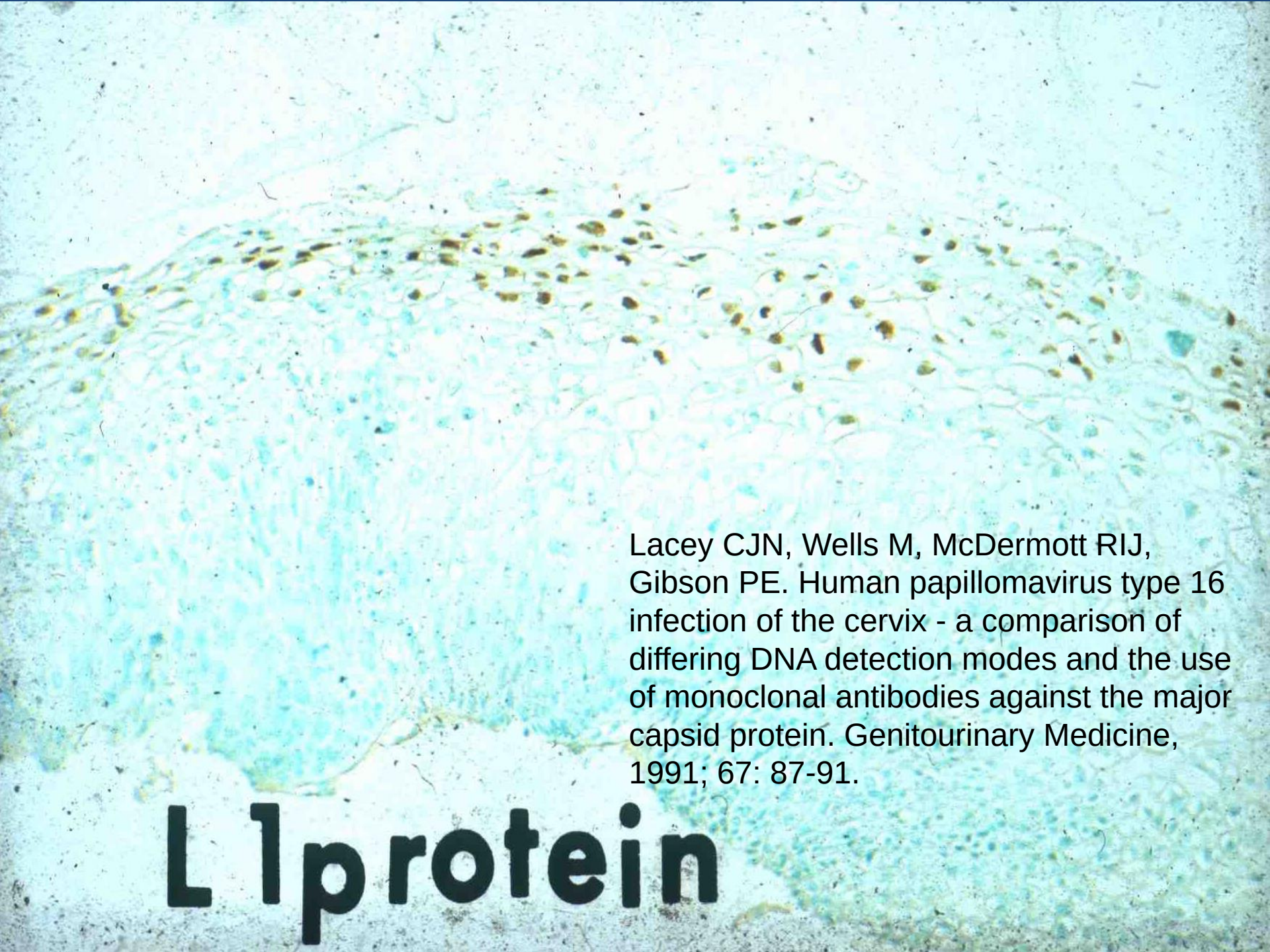
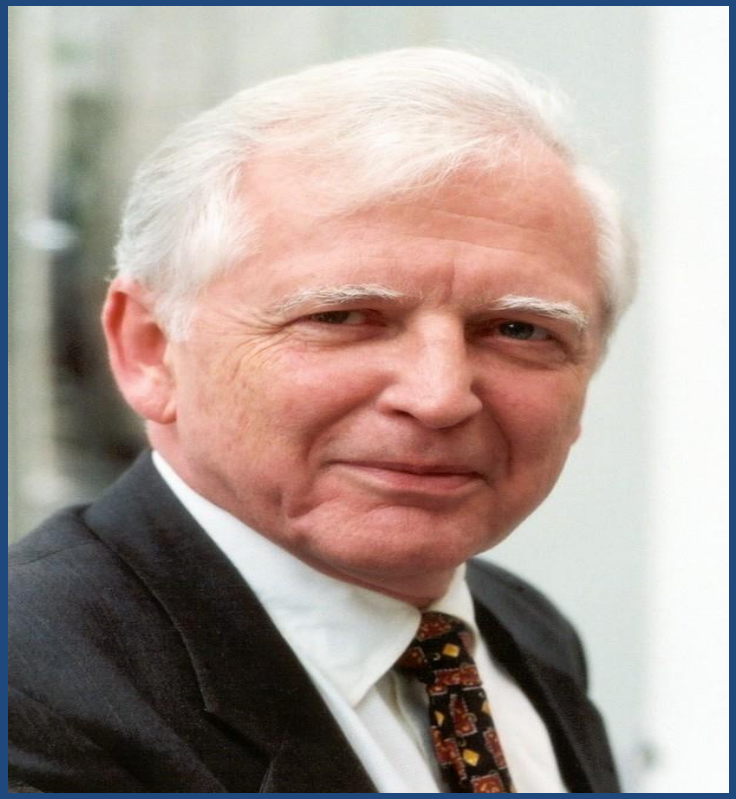
*Revised 3 March 1998*
*Accepted 26 May 1998*





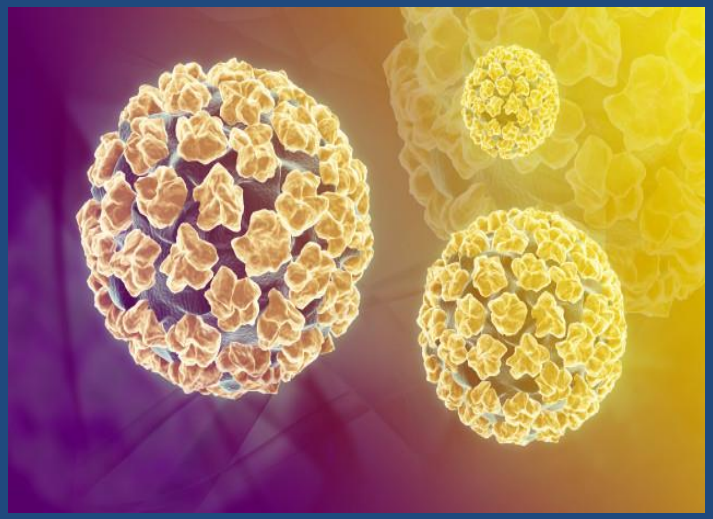

Lacey CJN, Wells M, McDermott RIJ, Gibson PE. Human papillomavirus type 16 infection of the cervix - a comparison of differing DNA detection modes and the use of monoclonal antibodies against the major capsid protein. Genitourinary Medicine, 1991; 67: 87-91.

# Human papillomavirus vaccination



Harald zur Hausen
Nobel prize for
Medicine 2008

Probably the most significant research outcome in female genital tract health in the last 30 years



# HPV vaccination

The HPV major capsid protein, L1, can spontaneously self-assemble into virus-like particles (VLPs) that resemble authentic HPV virions. Vaccine contains recombinant VLPs assembled from the L1 proteins of HPV types 6, 11, 16 and 18.

# The global burden of cervical cancer: a preventable disease

- 528 000 new cases every year
- fourth most common cancer affecting women worldwide, after breast, colorectal, and lung cancers
- most notable in the lower-resource countries of sub-Saharan Africa
- fourth most common cause of cancer death (266 000 deaths in 2012) in women worldwide
- ~ 70% of the global burden falls in areas with lower levels of development
- > one fifth of all new cases are diagnosed in India

# Cervical glandular neoplasia

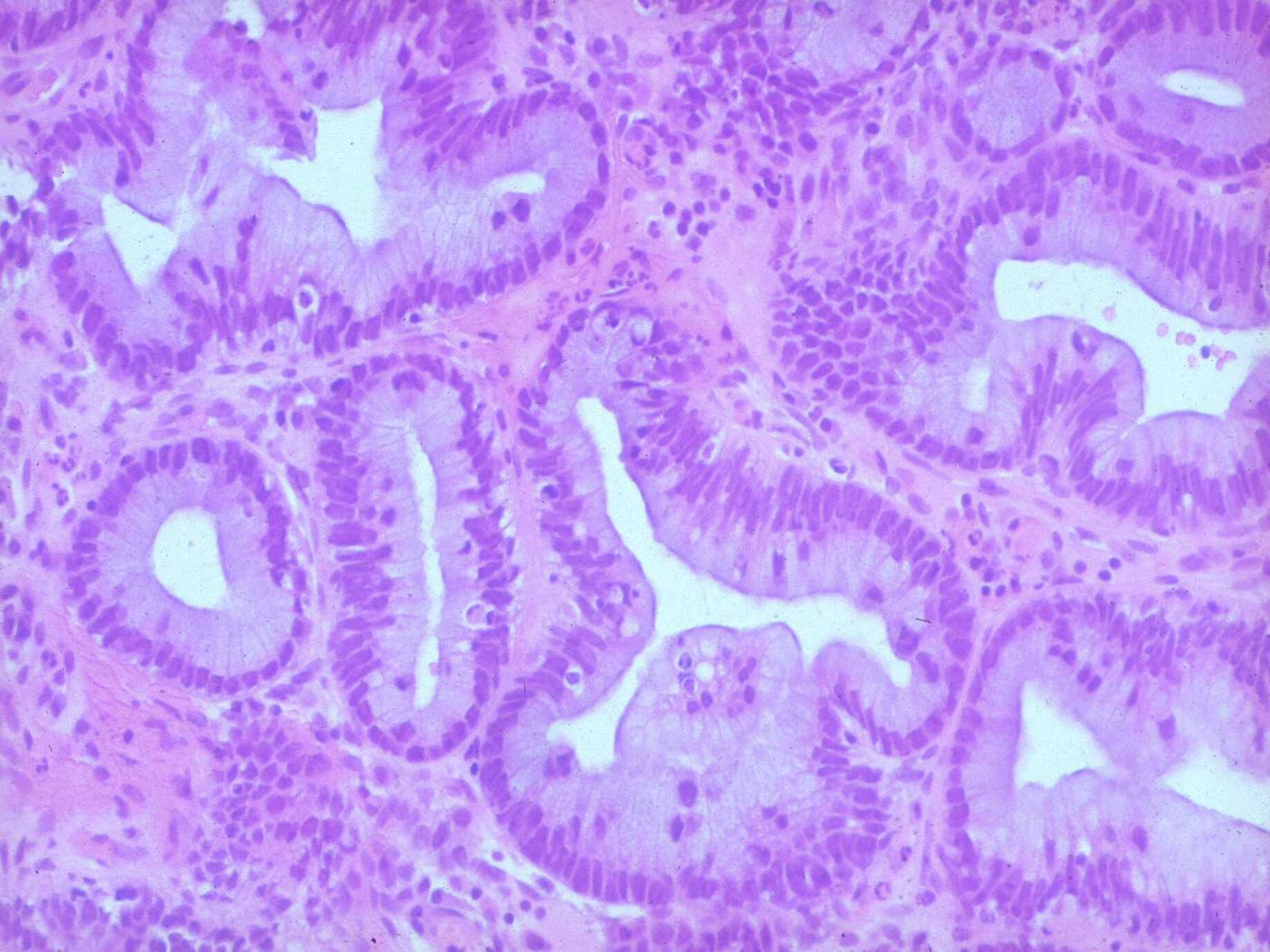
*J Clin Pathol* 1986;**39**:22–28

# Cervical glandular atypia associated with squamous intraepithelial neoplasia: a premalignant lesion?

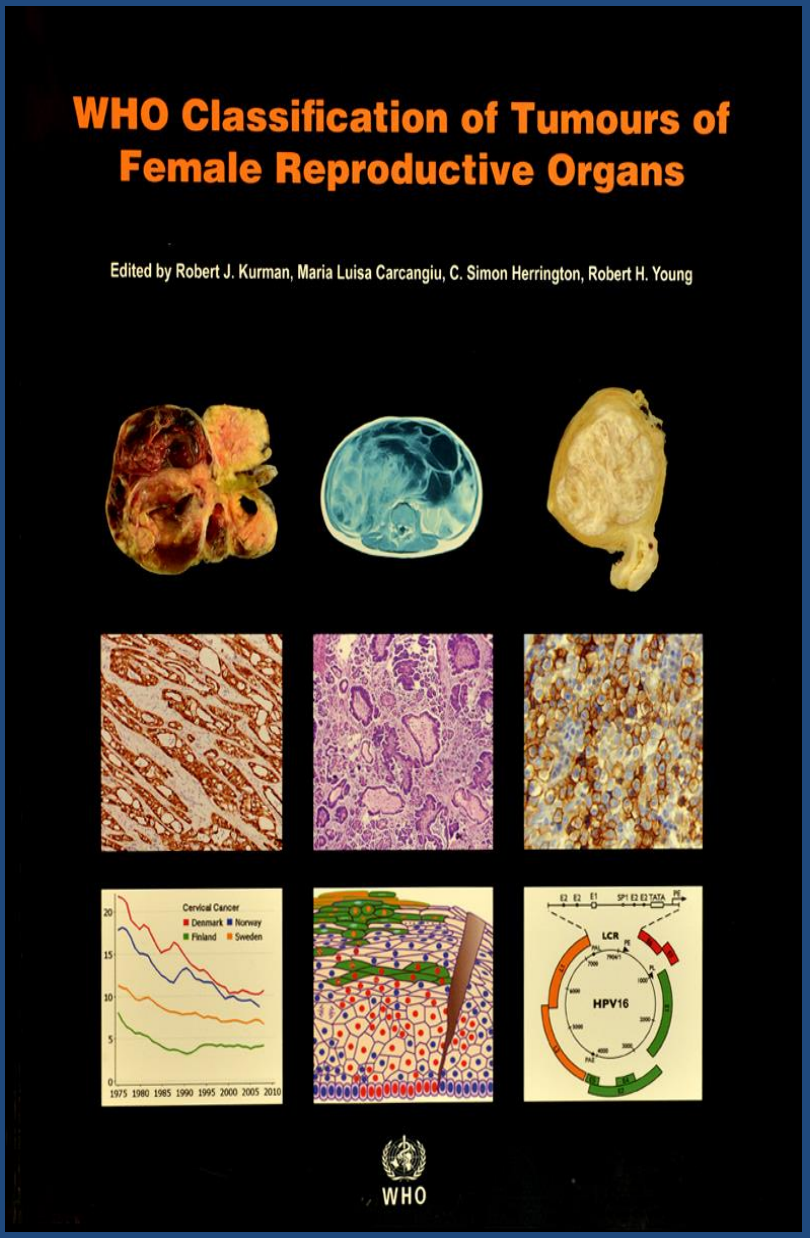
LJR BROWN, M WELLS

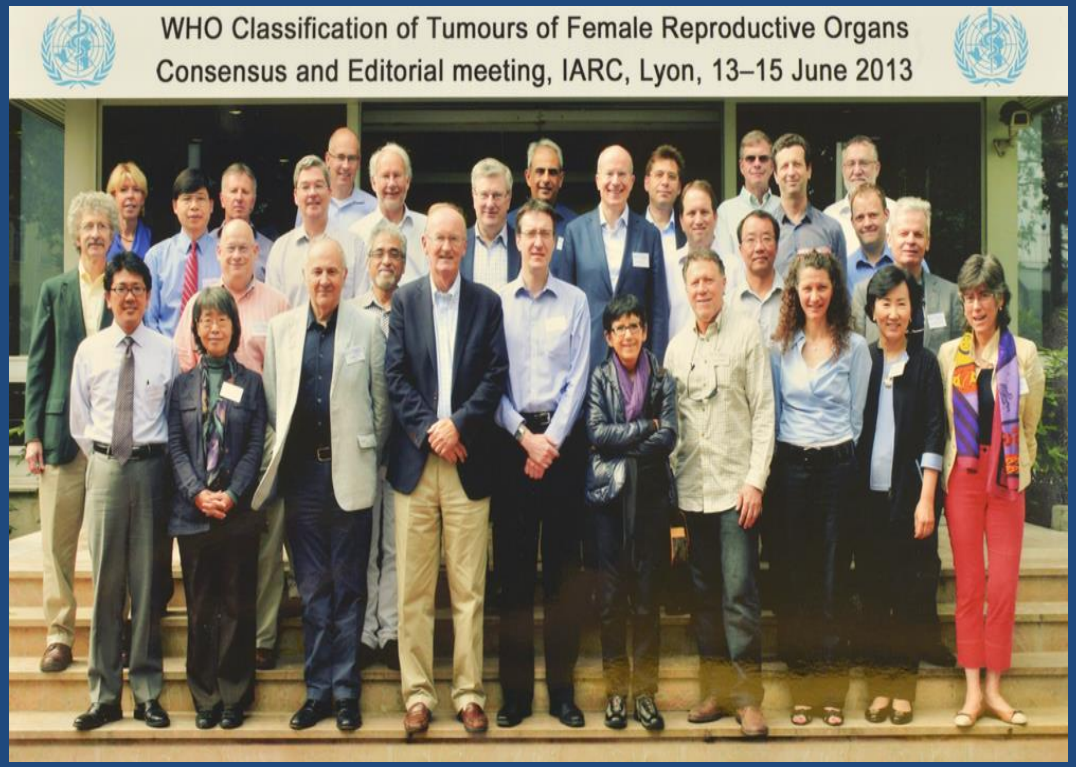
*From the Department of Pathology, University of Leeds, Leeds*

SUMMARY Recent studies have described premalignant changes in the endocervical epithelium, but morphological criteria for the diagnosis of cervical glandular atypia of lesser severity than adenocarcinoma in situ have not been established. Adenocarcinoma in situ is often associated with cervical intraepithelial neoplasia (CIN). The endocervical mucosa in 105 cases of CIN grade III was evaluated and compared with that of 100 controls. Sixteen cases of cervical glandular atypia and one case of adenocarcinoma in situ were identified, and it was possible to discriminate between these and a range of benign glandular lesions. Interestingly, the control series included two patients with cervical glandular atypia, one of whom on review had had a cone biopsy for CIN. The progression of cervical glandular atypia through adenocarcinoma in situ to invasive adenocarcinoma is known, but the natural history of cervical glandular atypia is as yet uncertain.



# CD44 *v*5



WHO Classification of Tumours of Female Reproductive Organs
Edited by Robert J. Kurman, Maria Luisa Carcangiu, C. Simon Herrington, Robert H. Young
Cervical Cancer
Denmark
Norway
Finland
Sweden
1975 1980 1985 1990 1995 2000 2005 2010
LCR
HPV16
WHO


WHO Classification of Tumours of Female Reproductive Organs
Consensus and Editorial meeting, IARC, Lyon, 13–15 June 2013

# EGD (endocervical dysplasia); low grade CGIN

"This is a poorly reproducible diagnosis for which criteria are not well defined. Minimal nuclear atypia with hyperchromasia and slightly increased mitoses or apoptotic bodies are sometimes cited as criteria. Ancillary studies are helpful in further clarifying these atypias, as diffuse, strong p16 reactivity, high ki-67 proliferation index, and lack of hormone receptor expression support interpretation as poorly sampled or morphologically incomplete AIS/HG-CGIN. Lesions showing these immunohistochemical characteristics should be classified as AIS/HG-CGIN for management purposes".

# p53 in precursor lesions of ovarian cancer

# *p53* mutation

- Mutation absent:
  - low grade lesions
  - relatively good prognosis
- Includes:
  - endometriosis
  - low grade serous
  - endometrioid
  - mucinous

- Mutation present:
  - high grade lesions
  - poor prognosis
  - high grade serous

*Histopathology* 1995, 27, 367–371

# p53 protein expression in putative precursor lesions of epithelial ovarian cancer

R.HUTSON, J.RAMSDALE & M.WELLS
*Department of Pathology, St James's University Hospital, Leeds, UK*

Date of submission 13 March 1995
Accepted for publication 19 June 1995

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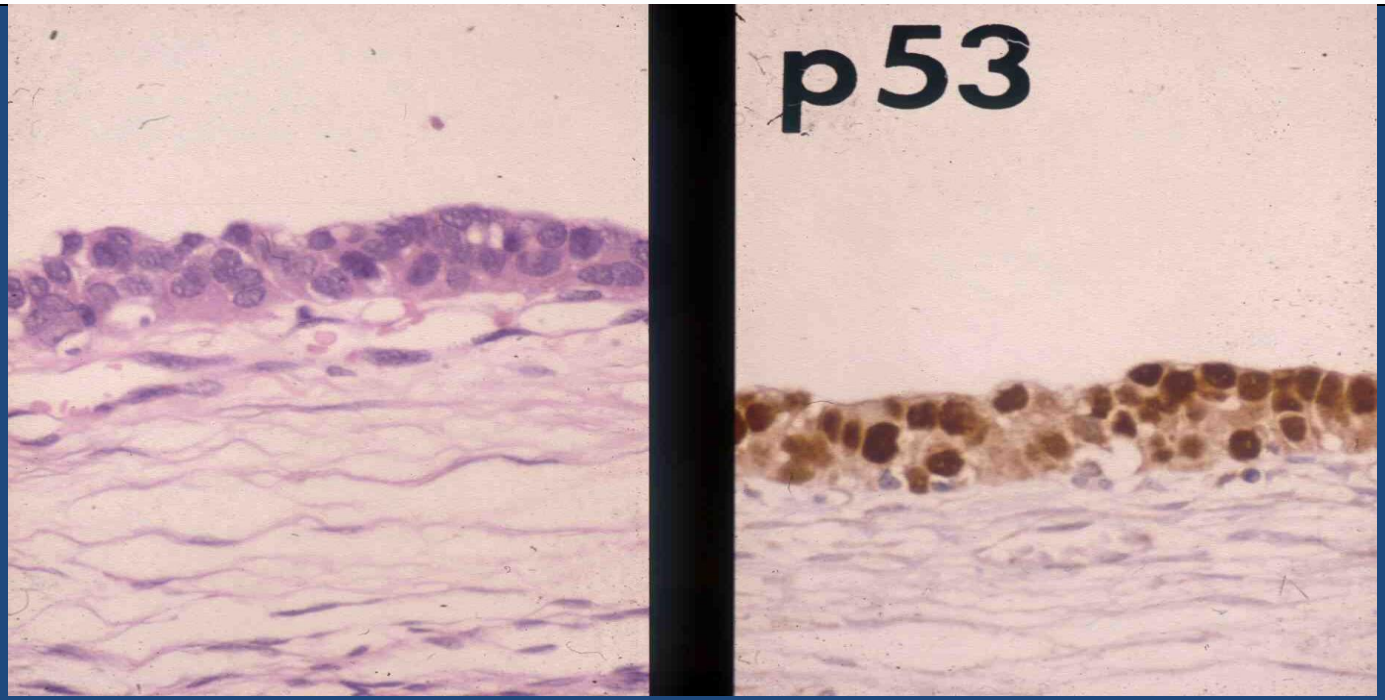
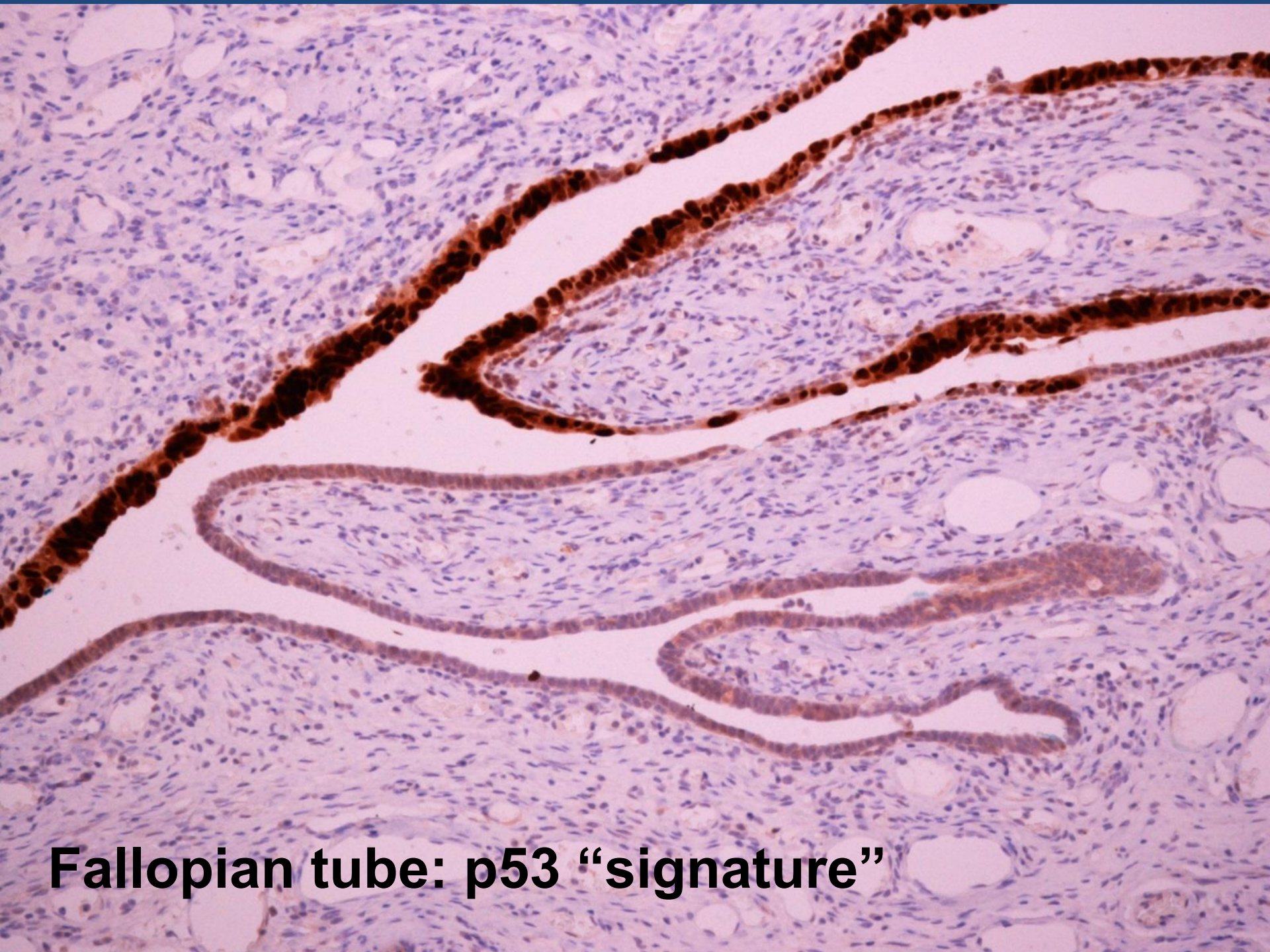
HUTSON R., RAMSDALE J. & WELLS M.
(1995) *Histopathology* **27**, 367–371

**p53 protein expression in putative precursor lesions of epithelial ovarian cancer**




Fallopian tube: p53 “signature”

# Hormone replacement therapy (HRT) and the endometrium

THE LANCET

# Is the timing of withdrawal bleeding a guide to endometrial safety during sequential oestrogen-progestagen replacement therapy?

*David W Sturdee, David H Barlow, Lian G Ulrich, Michael Wells, Helge Gydesen, Michael Campbell, Karen O'Brien, Martin Vessey for the UK Continuous Combined HRT Study Investigators**

**Summary**

Current regimens of sequential hormone replacement therapy are based on data that show a protective effect on the endometrium of at least 10 days of progestagen. In clinical practice, onset of bleeding on or after day 11 of the progestagen phase is taken as reassurance of a normal endometrium.

413 postmenopausal women taking oestrogen-progestagen hormone replacement therapy with 10 or 12 days of progestagen per cycle completed bleeding diaries for 3 months before endometrial biopsy. For most women, bleeding started around the 13th day after starting progestagen. There was no correlation between endometrial histology and timing of onset of bleeding. 11 (2·7%) women had complex endometrial hyperplasia. The presence of hyperplasia was 2·4% with onset of bleeding after 10 days of progestagen and 2·8% after 12 days.

The timing of onset of withdrawal bleeding during oestrogen-progestagen HRT does not predict endometrial hyperplasia.

*Lancet* 1994; **343:** 979–82

*BMJ* 2002;325:239 ( 3 August )

**Papers**

# Effect on endometrium of long term treatment with continuous combined oestrogen-progestogen replacement therapy: follow up study

**Michael Wells**, *professor* [a], **David W Sturdee**, *consultant* [b], **David H Barlow**, *professor* [c], **Lian G Ulrich**, *consultant* [d], **Karen O'Brien**, *clinical research consultant* [e], **Michael J Campbell**, *professor* [f], **Martin P Vessey**, *professor* [g], **Anthony J Bragg**, *medical director* [e], for the UK Continuous Combined Hormone Replacement Therapy Study Investigators.

# HRT and the endometrium (1)

- an “unassessable” biopsy is not an “inadequate” biopsy if the uterine cavity has been entered
- endometrial histology cannot be predicted by the bleeding pattern
- endometrial hyperplasia can be diagnosed effectively in outpatient biopsy samples

# HRT and the endometrium (2)

- long term use of sequential oestrogen-progestogen replacement therapy increases the risk of endometrial cancer
- continuous combined HRT regimens are safe and effective in the short term treatment of postmenopausal women and improve endometrial safety when used in the long term

Histopathology awarded a centenary Gold Medal by the IAP – Montreal, 2006

Volume 49 Number 5 November 2006

# Histopathology

Edited by Michael Wells


## In this issue



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ISSN 0309-0167 www.blackwellpublishing.com/his

# “British Pathology” reception USCAP

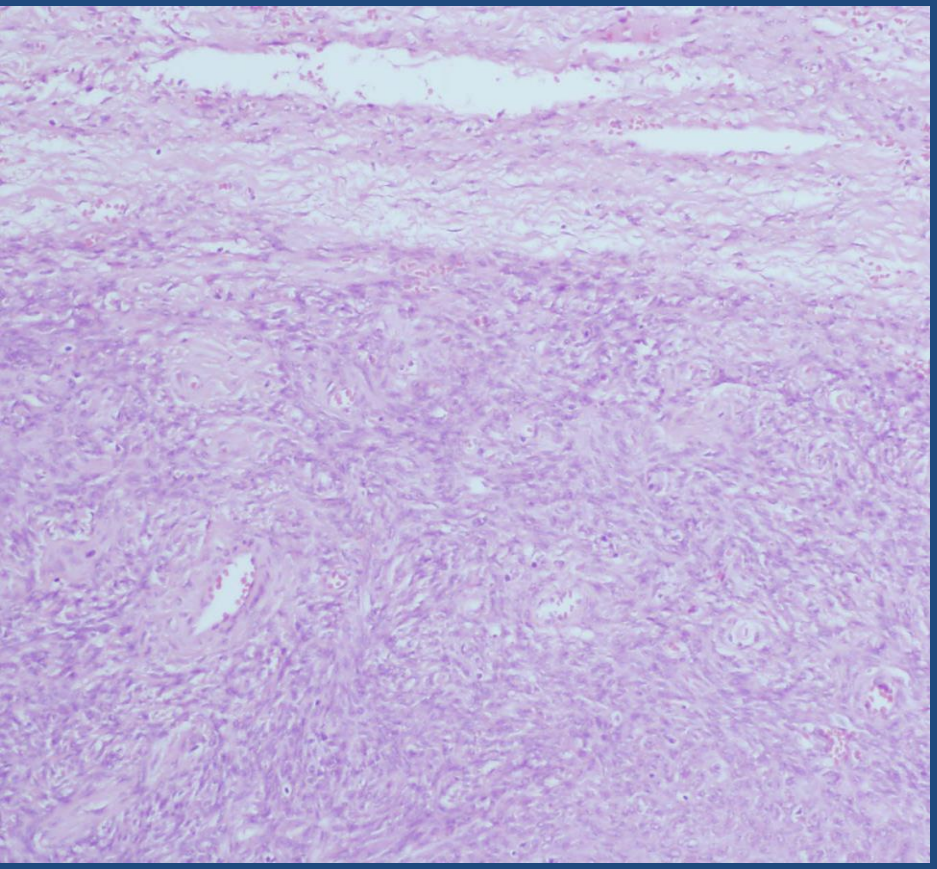
Joint Histopathology/Journal of Pathology reception at USCAP

# The future of gynaecological pathology

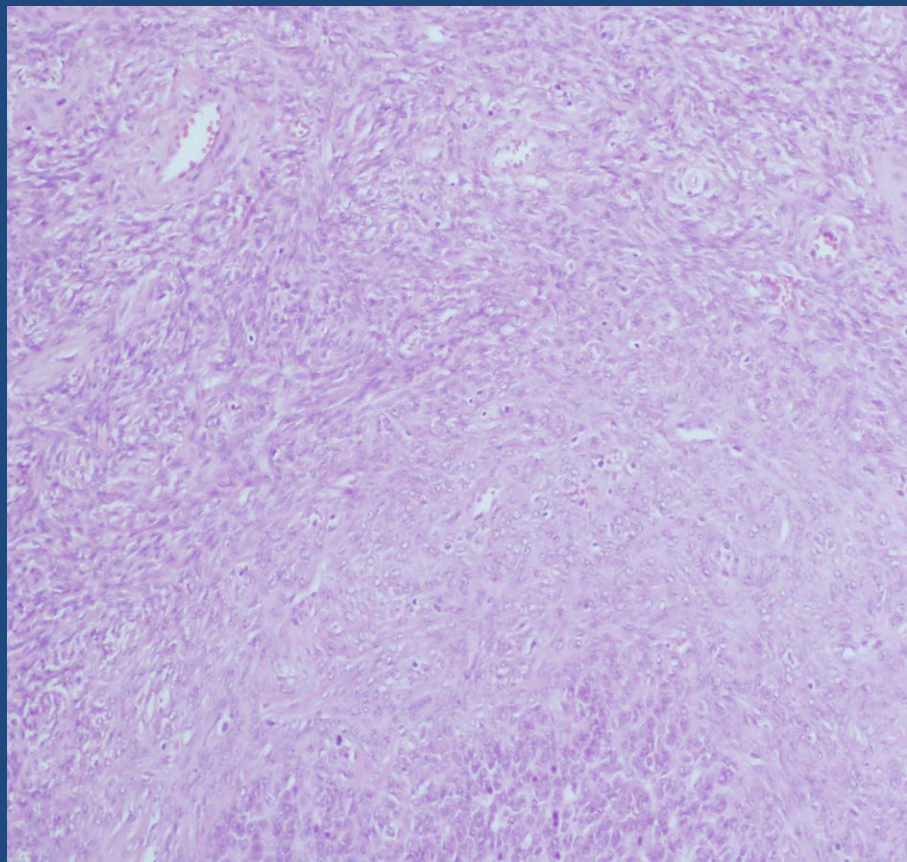
- we need research leaders
- crucial that the pathologist is a key member of the research team
- microscopy will not be supplanted in the foreseeable future
- realise the potential of digital pathology
- molecular pathology will continue to have an incremental impact on tissue diagnosis
- pathologists must retain ownership of the integrated report?

Original diagnosis: “benign fibrothecoma with minor sex cord elements”

Central review: diffuse adult granulosa cell tumour



**Mutation screening of *FOXL2* gene**



Missense mutation c.402C>G, (p.Cys134Trp)

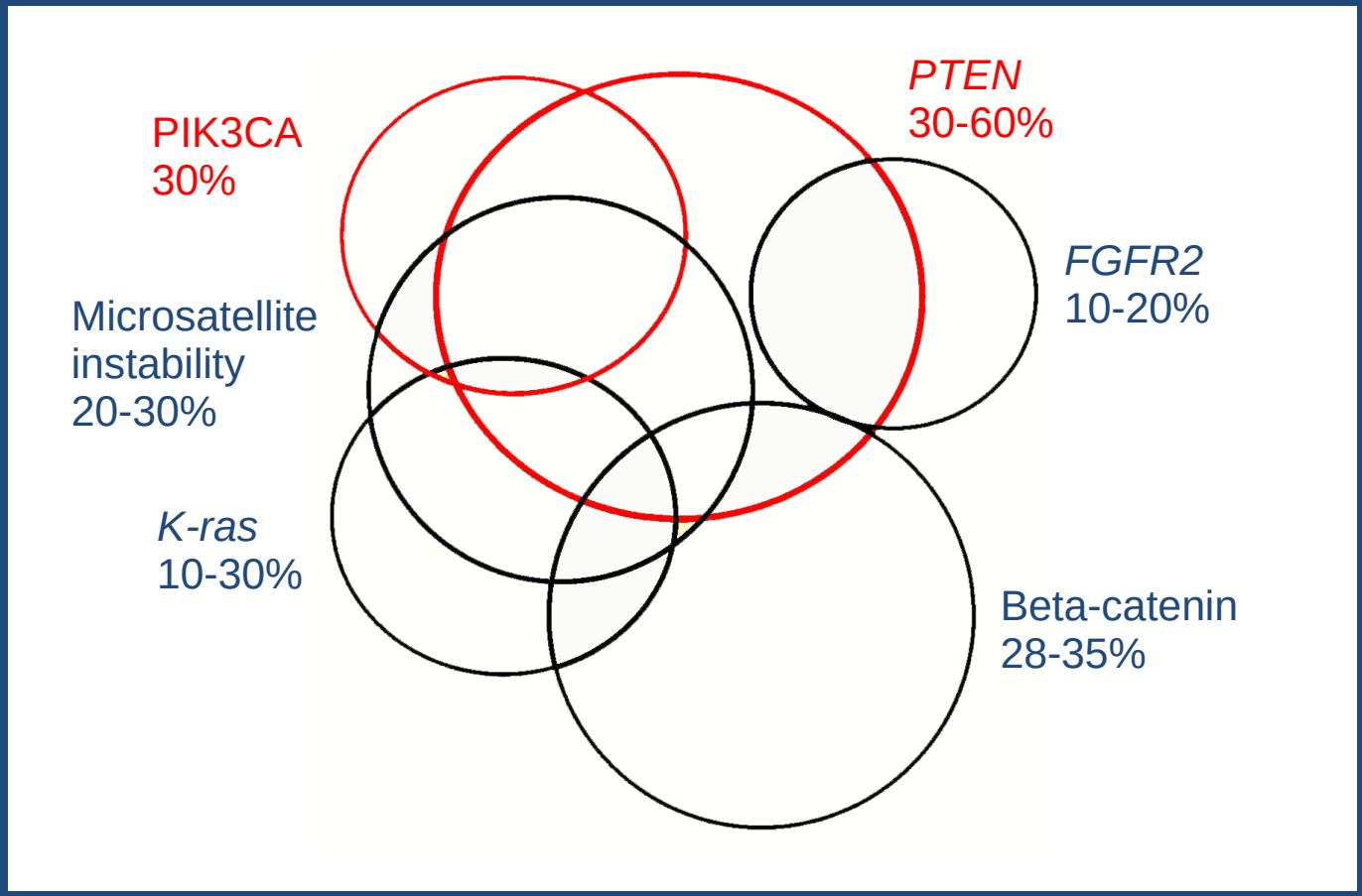
# Gynaecological pathology – future research

- Preventive strategies in endometrial cancer
- Molecular “fingerprint” of individual tumours
- Determination of therapeutic targets – more promising than prognostic markers
- Assessing the effectiveness of therapy

# Endometrioid carcinoma

## Genetic alterations

Courtesy of
Xavier Matias Guiu



- **_RNF43_ is frequently mutated in colorectal and endometrial cancers**
- Marios Giannakis,[1, 2, 3, n1] Eran Hodis,[1, 3, 4, 5, n1] Xinmeng Jasmine Mu,[1, 3,] Mai Yamauchi,[1,] Joseph Rosenbluh,[1, 3,] Kristian Cibulskis,[3,] Gordon Saksena,[3,] Michael S Lawrence,[3,] Zhi Rong Qian,[1,] Reiko Nishihara,[1, 6, 7, 8,] Eliezer M Van Allen,[1, 2, 3,] William C Hahn,[1, 2, 3,] Stacey B Gabriel,[3,] Eric S Lander,[3, 9, 10,] Gad Getz,[3, 11,] Shuji Ogino,[1, 6, 12,] Charles S Fuchs[1, 13,] & Levi A Garraway[1, 2, 3,]
- Nature Genetics Year published:(2014) DOI:doi:10.1038/ng.3127 Received 03 April 2014 Accepted 03 October 2014 Published online 26 October 2014

# Obesity in British women

- 32% UK women BMI > 25
- 24% UK women BMI > 30
- 27% UK women 16-24 years BMI >25
- 68% UK women 55-64 years BMI >25

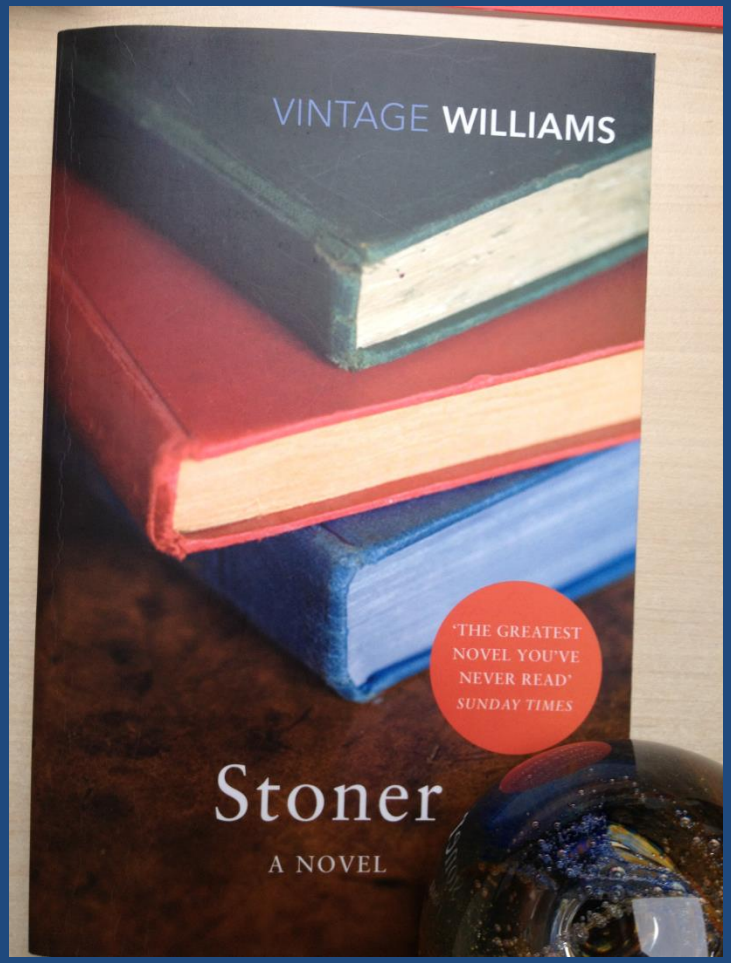
- Prevalence of obesity has trebled since 1985

Health Survey for England 2009


Bangkok,
October 2014

Successful bid to host the 2020 IAP/ESP Congress in Glasgow

# Stoner by John Williams 1965




"An occasional student who comes upon the name may wonder idly who William Stoner was, but he seldom pursues his curiosity beyond a casual question. Stoner's colleagues, who held him in no particular esteem when he was alive, speak of him rarely now; to the older ones, his name is a reminder of the end that awaits them all, and to the younger ones it is merely a sound which evokes no sense of the past and no identity with which they can associate themselves or their careers".