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

- Diagnosis
- Research & Scholarship
- Administration/Management
- Education & Training
“... 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
Harold Fox

1931 – 2012

Professor of Reproductive Pathology, University of Manchester
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, scarce 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 125I gastrin 17 (Becton Dickinson, London) and antibody 4952 (Courtesy of Professor J. Retheil, Copen- hagen). The fasting serum gastrin levels were raised, being 680-940 pg/ml, increasing to 1075 pg/ml after infusion of secretin. Values of serum oesophageal intestinal polypeptide, pancreatic polypeptide, glucagon and somatostatin were within the normal range and assessments of thy- roid, parathyroid, pituitary and adrenal function were also normal. At this point defects of water, sodium and potassium were corrected and addi- tional losses reduced by giving intravenous saline and 400 mg four times daily in prepara- tion for a laparotomy.

At operation there was severe ulceration and stenosis of the second part of the duodenum and marked gastric hyperplasia. 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 addi- tion a highly selective vagotomy was performed and the choledochal stenosis treated by duod- eonehoduodenostomy and gastrojejunostomy.

As a result of the operation the gastrin 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 31 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 tube 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 immunoreac- tive 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 mucous secreting epithelium showing some nuclear stratification (Ovarian Tumour Panel of Royal College of Obstetricians and Gynaecolo- gists 1983). Immunoperoxidase (PAP) staining using gastrin antibody showed many gastrin pro- ducing 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
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)
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
Minimum dataset for the histopathological reporting of vulval biopsy specimens and vulvectomy specimens for vulval cancer

Minimum dataset for the histopathological reporting of atypical hyperplasia and adenocarcinoma in endometrial biopsy and curettage specimens and for endometrial cancer in hysterectomy specimens
International Collaboration on Cancer Reporting (ICCR):

- development of evidence-based core datasets for pathology cancer reporting
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
Class I Antigens of the Major Histocompatibility Complex on Cytotrophoblast of the Human Placental Basal Plate

MICHAEL WELLS, BAE-LI HLS, 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 Veillemobra, 06034 Nice-Cedex, France (B.L.H., W.P.F.)
The vast majority of mononucleate trophoblastic cells in choriocarcinoma are villous-type intermediate trophoblast.
Diagnosis of molar pregnancy and persistent trophoblastic disease by flow cytometry

J DIANE HEMMING, P QUIRKE, C WOMACK, M WELLS, C WELSTON, C C BIRD
## Ploidy status and histological diagnosis of molar pregnancies

<table>
<thead>
<tr>
<th>Ploidy status</th>
<th>Complete mole</th>
<th>Partial mole</th>
<th>Hydropic abortion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diploid</td>
<td>59</td>
<td>46</td>
<td>10</td>
</tr>
<tr>
<td>Triploid</td>
<td>26</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Tetraploid</td>
<td>1</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Aneuploid</td>
<td>2</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>88</strong></td>
<td><strong>49</strong></td>
<td><strong>32</strong></td>
</tr>
</tbody>
</table>
Early complete mole

- abnormally shaped villi
  - branching or polypoid
- stromal mucin
- stromal vessels may be present
- STROMAL NUCLEAR DEBRIS
**P57^{kip2} in hydatidiform mole**

- **Complete mole**
  - Cytotrophoblast -ve
  - Syncytiotrophoblast -ve

- **Partial mole**
  - Cytotrophoblast +ve
  - Syncytiotrophoblast -ve

- **Non-villous trophoblast is p57 +ve even in complete mole**
# Refining the diagnosis of hydatidiform mole: image ploidy analysis and p57<sup>kip2</sup> 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*

<table>
<thead>
<tr>
<th>Suspected diagnosis</th>
<th>Image cytometry</th>
<th>p57&lt;sup&gt;kip2&lt;/sup&gt; status</th>
<th>Revised diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial mole</td>
<td>Triploid</td>
<td>+ve</td>
<td>Partial mole</td>
</tr>
<tr>
<td>Complete mole</td>
<td>Triploid</td>
<td>+ve</td>
<td>Partial mole</td>
</tr>
<tr>
<td>Partial mole</td>
<td>Diploid</td>
<td>-ve</td>
<td>Complete mole</td>
</tr>
<tr>
<td>Partial mole</td>
<td>Diploid</td>
<td>+ve</td>
<td>Hydropic miscarriage</td>
</tr>
</tbody>
</table>
PSTT: 48 months from causative pregnancy is critical

For Interval from antecedent preg

48 month cut-off

Specificity 100%
Sensitivity 93%

<table>
<thead>
<tr>
<th>Time</th>
<th>Dead</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 48</td>
<td>1/49</td>
<td>98%</td>
</tr>
<tr>
<td>≥ 48</td>
<td>13/13</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

HPV and cervical neoplasia
DEMONSTRATION OF HUMAN PAPILLOMAVIRUS TYPES IN PARAFFIN PROCESSED TISSUE FROM HUMAN ANOGENITAL LESIONS BY IN-SITU DNA HYBRIDISATION

MICHAEL WILLS, DIARMID GRIFFITHS, FRASER LEWIS AND COLIN C. BIRT

Department of Pathology; University of Leeds, Leeds LS2 9JT, U.K.

SUMMARY

A sensitive in situ hybridization technique for the demonstration of human papillomavirus (HPV) employing a biotin- streptavidin and alkaline 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 carcinomas 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 condyloma was associated with HPV 6 and 11. This technique permits the retrospective evaluation of routinely processed material thus widening the investigative spectrum for HPVs.

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

INTRODUCTION

Human papillomaviruses are increasingly implicated as aetiologic 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.1-3 Electron microscopy4-6 and immunocytochemistry7-9 have been employed to demonstrate the virus with disappointing results; even in experienced hands the detection rate in condylomata is only 45-50 percent. Hybridisation of separated and blotted DNA with radioactively-labelled probes has been used10,11 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 12 and in fresh tissue by the use of biotinylated probes.13 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
HPV 16 genome
EXPRESSION PATTERNS OF THE HUMAN PAPILLOMAVIRUS TYPE 16 TRANSCRIPTION FACTOR E2 IN LOW- AND HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA

NORMAN J. HJELEDA,** FRANK CAMPO,** NATHA X. XIE,** SUNDI D.” ROUNSE,** JULIUS H. SANFORD,*** JULIE C. BERGMAN,** PETRA L. MARCO,** AND MICHAEL WELLS

**TBCRC Cancer Research Unit, Department of Biology, University of York, U.K.
***Department of Pathology, University of Minnesota, Minneapolis, MN, U.S.A.
****Department of Pathology, University of Birmingham, Birmingham, U.K.

SUMMARY

Specific antibodies against the C-terminus of E2, produced by affinity purification of polyvalent antiserum, have been used to identify the subcellular location of the protein in cervical tissues. None were observed in the presence of HPV 16 DNA (determined by multiple-gene-specific PCR detections) and in the presence of multiple grades of cervical intraepithelial neoplasia (CIN). The data indicate that E2 expression is highest in CIN I and in keratinocyte lesions. Lower expression was observed in CIN II and little in CIN III lesions. In contrast, there were some reservations 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 active 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 program.

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

INTRODUCTION

Human papillomavirus (HPV) is strongly implicated as a major etiological agent in carcinoma of the cervix. DNA from the high-risk group of HPVs which includes HPV-16 can be detected in a large majority of cervical cancers and lifelong persistent infection with HPV has recently been identified as the major etiologic factor in this disease. While DNA detection methods (reviewed by Bosch et al.) have emerged as a powerful method of identifying the presence of HPV 16, for which serological studies are still somewhat underdeveloped, the excellent sensitivity of polymerase chain reaction (PCR)-based DNA detection studies can make them insensitive (8-10). We have produced domain-specific polyclonal antibodies against both the N- and the C-terminal portions of the HPV 16 E2 protein, which has a domain structure similar to many other transcription factors, consisting of a DNA binding/multiplication domain linked to a flexible hinge in a transcription/Nuclear domain. In human papillomavirus (HPV), this full-length protein acts as a transcription factor in vitro in favour of both activation (16) and repression (17) of viral transcription. Recently, the E2 protein has been shown to suppress growth rates of tumour cells, even in the absence of HPV genes or their expression, and can block cell cycle (18) and regulate the cell cycle (19).

In cervical cancers, the HPV genome is frequently integrated into the cell chromosome, resulting in a dysregulated, more frequently, deletion of the E2 open reading frame (20). This is in contrast to the situation in preinvasive neoplasia where most early stage of HPV DNA are most often observed, indicating that a substantial fraction of HPV DNA is differentiating epithelial cells has been extensively reviewed in vivo hybridization (21, 22) and there is a defined increase from the basal layers of the epithelium to the superficial layers, and most notably within keratinocytes in CIN I and II lesions. Antibodies to viral antigens were uniquely specific for most of these antigens were carried out. Papillomavirus gene expression has been determined, in the absence of sufficiently discriminating antisera for immunohistochemistry, by a number of in-situ hybridization techniques (23). Expression in the mAb level appears strongest in the basal and parabasal layers of keratinocytes, 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.24

Received 29 April 1997
Revised 1 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

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

Harald zur Hausen
Nobel prize for Medicine 2008
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
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 v5

normal

hCGIN
WHO Classification of Tumours of Female Reproductive Organs

Edited by Robert J. Kurman, Mariia Luisa Carcangiu, C. Simon Herrington, Robert H. Young

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
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

p53 protein expression in putative precursor lesions of epithelial ovarian cancer
Fallopian tube: p53 “signature”
Hormone replacement therapy (HRT) and the endometrium
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.

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
“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

- PIK3CA: 30%
- FGFR2: 10-20%
- PTEN: 30-60%
- Beta-catenin: 28-35%
- Microsatellite instability: 20-30%
- K-ras: 10-30%

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, 5, 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
Successful bid to host the 2020 IAP/ESP Congress in Glasgow

Bangkok, October 2014
“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”.