Correspondence

p53 in human papillomavirus associated anogenital cancers

It was interesting to read the paper by Ogunbiyi *et al*¹ regarding the investigation of p53 protein expression in anal squamous neoplasia in association with human papillomavirus (HPV) 16. A similar study was recently undertaken² addressing the relation between p53 protein expression and HPV infection in cervical neoplasia. Comparison of these two studies reveals several interesting observations with regard to the role of p53 in HPV positive cancers.

Both studies revealed a strong association between the detection of HPV sequences and p53 antigen expression in invasive cancers. p53 immunocytochemistry was positive in 69.5% of HPV 16 positive invasive anal cancers¹ and in 86% of HPV 16/18 positive invasive cervical cancers.²

Both studies showed uniform positive reactions with the panels of antibodies for p53 antigen detection: DO-1, CK-1, DO-7 and PAb 240, DO-7.² However, while p53 protein expression involved almost all tumour cells in the anal cancer group, only focal isolated cells or groups of cells expressed p53 protein in the cervical cancer study. Nevertheless, the immunocytochemical expression of p53 in both HPV positive anal and cervical cancers is inconsistent with the hypothesis that wild-type p53 cell regulating functions are annulled in HPV positive cancers as a consequence of complexing with HPV E6.^{3,4} As p53 regulates entry into the S phase of the cell cycle, disruption of its function by complexing with E6 and subsequent degradation via the ubiquitin system⁵ has been the proposed form of inactivation of p53 in HPV positive cancers.⁴ Hence, the dual detection and co-localisation of p53 antigen and integrated HPV 16 DNA, albeit in isolated cells, in cervical cancers questions this hypothesis.² Alternatively, the reliability of p53 immunocytochemistry may be in doubt.⁶

These findings emphasise the need for further studies elucidating the role of p53 in HPV positive cancers. These studies should combine p53 protein localisation by immunocytochemistry and semiquantitative western blot analysis with p53 gene sequencing in HPV positive and negative anogenital cancers.

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1 Ogunbiyi OA, Scholfield JH, Smith JHF, Polaczar SV, Rogers K, Sharp F. Immunohistochemical analysis of p53 expression in anal squamous neoplasia. *J Clin Pathol* 1993; 46:507-12.

2 Cooper K, Herrington CS, Evans MF, Gatter KC, McGee JO'D. p53 antigen in cervical condylomata, intraepithelial neoplasia, and carcinoma: relationship to HPV infection and integration. *J Pathol* 1993;171:27-34.

- 3 Werness BA, Levine AJ, Howley PM. Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science* 1990;148:76-9.
- 4 Vousden KH, Wrede D, Crook T. Human papillomavirus oncoprotein function: releasing the brakes on cell growth control. *Papillomavirus Rep* 1991;2:1-3.
- 5 Scheffner M, Werness BA, Huijbregste JM, Levine AJ, Howley PM. The E6 oncoprotein encoded by HPV types 16 and 18 promotes the degradation of p53. *Cell* 1990;63:1129-36.
- 6 Wynford-Thomas D. p53 in tumour pathology: can we trust immunocytochemistry? [editorial]. *J Pathol* 1992;166:329-30.

Paget's disease of the breast

O'Sullivan *et al*¹ recently reported a case of Paget's disease of the nipple without associated carcinoma. We have previously studied 11 cases of this disease in women.² To avoid the usual flattening of mammary specimens, they were placed in a net during formalin fixation. Sections were cut parallel to the thoracic wall and not perpendicular to it. Using this method, 17 to 42 ducts were found under the nipple compared with the usual eight to 12.

We found a consistent association between Paget's disease and intraductal eosinophilic cell carcinoma. Three patients had an invasive underlying tumour: in one case it was not anatomically related to the ductal carcinoma, which occupied nine of the 17 ducts found in the nipple; in the other two patients the invasive and ductal tumours were in contact, but many of the ducts, some of which were opposite the tumour, also contained carcinoma. However, according to the traditional view of Paget's disease, as the ducts divide dichotomously, only one or a very small number of ducts should have contained carcinoma.

There was no invasive tumour in the other eight cases. The nipple or areola contained from eight to 35 ducts with in situ carcinoma or comedocarcinoma, sometimes extending deep into the breast.

Paget's cells are cytologically different from the duct carcinoma cells. Moreover, using a mathematical model, we calculated that it would take 115 days for a Paget's cell to move 1 cm in the epidermis which exceeds the life of a cancer cell. Over this period the epidermis would be renewed seven times and Paget's cells would be exfoliated. This suggests that Paget's cells arise in the basal layer of the epidermis. The synchronous ductal carcinoma probably occurs at the epidermal junction of the ducts.

Specimens of mammary (and extra-mammary) Paget's disease should be studied with sections cut parallel to the skin, providing a better view of the ductal lesions.

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1 O'Sullivan ST, McGreal GT, Lyons A, Burke L, Geoghegan JC, Brady MD. Paget's disease of the breast in a man without underlying breast carcinoma. *J Clin Pathol* 1994;47:851-2.

2 Warter AL, Padilla N, Le Gal Y. Une nouvelle technique d'examen des pièces d'amputation mammaire. Résultats concernant onze cas de maladie de Paget mammaire. *Ann Pathol* 1984; 4:329-37.

Detection of integrated human papillomavirus 16 DNA in squamous cell carcinoma of the cervix

It was both gratifying and interesting to read the paper by Kristiansen.¹ Gratifying, because an independent laboratory has now conclusively confirmed the previous finding² of the punctate/dot non-isotopic in situ hybridisation signal (NISH type 2) representing integrated human papillomavirus (HPV) 16 DNA in squamous cell carcinoma of the cervix. Interesting, because Kristiansen and colleagues showed a 100% concordance between NISH signal patterns (representing episomal and integrated virus) and the gold standard for determining the physical state of HPV DNA, two-dimensional gel electrophoresis; Southern blot analysis with PstI digestion demonstrated integrated HPV 16 DNA in only 54% of squamous cell carcinomas of the cervix.

This raises interesting questions about the sensitivity of Southern blot analysis in determining the physical state of HPV DNA, as junction fragments essential for determining integrated virus may be masked by episomal virus. As several previous studies (using Southern blot analysis) have not demonstrated integrated virus in all HPV positive cervical cancers, a role for viral integration in cervical carcinogenesis has somewhat waned. The findings of Kristiansen and coworkers certainly strengthen the role of HPV DNA integration in cervical neoplasia and suggests that this physical state may still be crucial. It also clearly questions the methodology that should be used to determine the integrated physical state of HPV DNA in cervical cancer.

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1 Kristiansen E, Jenkins A, Holm R. Coexistence of episomal and integrated HPV 16 DNA in squamous cell carcinoma of the cervix. *J Clin Pathol* 1994;47:253-6.

2 Cooper K, Herrington CS, Strickland JE, Evans MF, McGee JO'D. Episomal and integrated human papillomavirus in cervical neoplasia shown by non-isotopic in situ hybridisation. *J Clin Pathol* 1991;44:990-6.

Book review

Diseases of the Liver and Biliary Tract: Standardization of Nomenclature, Diagnostic Criteria, and Prognosis. Eds CM Leevy, S Sherlock, N Tytgstrum, R Zetterman. (Pp 219; \$50.50.) Raven Press. 1994. ISBN 0-7817-0211-9.

If you were asked to guess to whom the credit for this book is largely due, you probably would not spring to say that it was the late Sammy Davis Jr. Yet the manuscript is the culmination of a process initially begun by an ad hoc International Hepatology Informatics Group who met under the auspices of the National/International Liver

Institute in Newark, USA, which had been founded by the celebrated actor/singer/comedian. The intention was to revise and update the "brown book" *Standardization of Nomenclature, Diagnostic Criteria and Diagnostic Methodology for Diseases of the Liver and Biliary Tract*, published in 1976. Work on the second version started in 1986 and subsequently involved some 114 international experts whose names are listed: a truly formidable assembly. Each disease is characterised as to its definition, clinical and laboratory criteria, radiology, histological appearances, aetiology, and prognosis. The first six chapters describe physical examination, laboratory investigation and currently available tests, imaging techniques and their usefulness, morphological findings that may be encountered, show tabulation of aetiologies, and discuss prognosis and decision analysis. Chapters 7 to 15 deal with specific disease groupings. Some of these are based on clinical presentation—for example, hepatitis or cholestasis, others on pathology such as fatty liver, vascular disorders or tumours, or a mixture of both. Consequently, many entities turn up in more than one chapter or are oddly placed like passive congestion, sickle cell disease, and cholangiocarcinoma under cholestasis. However, cross referencing is abundant and the index lists all sites of entry. The outdated terminology of chronic persistent and chronic aggressive hepatitis is no longer used and chronic liver diseases are dealt with according to their aetiology. Under congenital and perinatal disorders, the concept of ductal plate maldevelopment, which links a group of cystic/biliary/fibrotic conditions together, is not fully elucidated and mesenchymal haematoma [sic] appears in the chapter on tumours. Spelling mistakes are not infrequent and should have been corrected as in Tables 4.1, 4.2, and 5.1. Other, minor criticisms concern understatement like "hepatocellular carcinoma can develop in HBV carriers" or lack of detail—for example, "antimitochondrial antibodies are present in 93% of patients" (with primary biliary cirrhosis) and tabulation of drugs commonly associated with particular types of liver injury would have been useful. All in all, the book may have suffered from too much advice from too many contributors and this has resulted in some lack of organisation. However, all main aspects of liver and biliary diseases (including those of the gall bladder) have been well covered in a succinct and usable form, and the book will serve as a standard for years to come. It is recommended to hepatologists whatever their specialty.

P P ANTHONY

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Notices

**Oxford Regional Cytology Training School,
John Radcliffe Hospital
presents the
Non-gynaecological & fine
needle aspiration cytology course**

5–9 June 1995

This one week course is suitable for trainee medical and MLSO staff. Some accommodation is available.

Course fees: Employees of ORHA—No charge for the course, but £10.00 is required to cover administration and hospitality costs. Others: £350. The FNA cytology component may be attended separately on 8–9 June. Fee: £100.

Course Organiser: Dr I D Buley, Consultant Pathologist, Histopathology & Cytology, John Radcliffe Hospital, Oxford OX3 9DU.

Further details from Miss Patsy King on 0865 220510.

**South Thames
West Regional Cytology
Training Centre
1995 Training Courses**

FNA Course for Pathologists:
9 May—Includes practical aspects and a microscopy session.

Non-Gynaecological Cytology Workshop for Pathologists:
11 May—Lectures and microscopy to include major organs.

Two day Pre-Certificate of Competence Course:
4 and 5 September—For MLSOs and cytoscreeners preparing for the Certificate of Competence exam.

Four week Introductory Gynaecological Course for MLSOs and Cytoscreeners:
2 to 27 October.

Gynaecological Update Cytology for Pathologists:
14th November.

One week Introductory Non-Gynaecological Cytology Course for MLSOs:
20 to 24 November.

One week Gynaecological Update Cytology Course for MLSOs:
27 November to 1 December.

Half day Breast Workshop (Regional EQA): 4 December—Lecture and microscopy.

Gynaecological Cytology Refresher Course for MLSOs: 7 December.

For further information, please contact: Dr Grace McKee or Mrs Jennifer Walker, Department of Cytopathology, Royal Surrey County Hospital, Egerton Road, Guildford, Surrey GU2 5XX. (tel: 01483 571122 ext. 4374/4373; fax: 01483 453615).

**Royal Brompton National
Heart and Lung Institute
presents the
Practical adult cardiovascular
pathology course
on**

Monday 16 October 1995

Course organisers: Professor M J Davies and Dr M N Sheppard.

This practical "hands on" course approaches in detail the problems that face the diagnostic pathologist when dealing with cardiovascular pathology. The approach to a cardiac necropsy and sudden death will be emphasised. Cardiac specimens will be made available for dissection and analysis and practical demonstrations as well as video demonstrations will be highlighted. A slide seminar with slides distributed to all participants is included. The course is aimed at trainees studying for the MRCPPath and also at senior pathologists who wish to update their knowledge.

Course fee: £75.00 (includes coffee, tea and lunch). There is a special fee of £50.00 for juniors in training.

For further information, please contact: National Heart and Lung Institute, Dovehouse Street, London SW3 6LY (tel: 0171 351 8172; fax: 0171 376 3422).

**Sheffield
Cytology Training School
Courses for Medical Staff 1995**

An Introduction to
Non-Gynaecological Cytology

17–19 May 1995

A three day course for junior medical staff providing both a practical and theoretical introduction to non-gynaecological cytology. Course tutors will include invited guest lecturers. Course fee (including refreshments): £250.

Cytopathology for Histopathologists

19–23 June 1995

An intensive five day course of lectures and practical instruction by local and visiting speakers suitable for the MRCPPath or Diploma in Cytopathology or for established consultants requiring an update. This course is timetabled to run consecutively with the Autopsy and Diagnostic Histopathology Courses organised by the Sheffield University Department of Pathology. Course fee (including refreshments): £350. This course has been approved for the Royal College of Pathologists CME Scheme and course participants in career grade posts will qualify for 5 CME points per day.

Accommodation is available on site at a modest additional charge.

For further information, please contact: Mrs EM Hewer, Manager, Sheffield Cytology Training School, Northern General Hospital, Herries Road, Sheffield S5 7AU (tel & fax: 0114 271 5500).