CORRESPONDENCE

Current views on CIN

The authors of the recent article on cervical intraepithelial neoplasia have, in the past, made major contributions to gynaecological pathology.¹ It is therefore deeply disappointing to find them clinging to outdated dogma while producing no original evidence in support of their views. They recommend, despite detailed evidence demonstrating gross inconsistencies in the grading of CIN,²⁻⁴ that the current terminology be retained with the addition of a fourth category termed "basal abnormalities of uncertain significance".

The authors emphasise that the lesions which have been collectively termed CIN form a morphological spectrum. However, the lower end of this spectrum extends to encompass gradations of inflammatory atypia and immature squamous metaplasia. Clearly, these morphological findings do not necessarily represent a single—that is neoplastic—disease process. Indeed, it is likely that the minor morphological abnormalities of cervical squamous epithelium which we and others have shown to be associated with the greatest diagnostic inconsistency²⁻⁴ are caused by a variety of different pathological processes. The authors tacitly admit this possibility when they recommend that, in the presence of severe inflammation, ungradable CIN and CIN1 be included in their proposed category of basal abnormalities of uncertain significance.

Morphological classification of disease has two main purposes: to guide treatment and prognosis; and to provide a basis for epidemiological studies and health statistics. Neither of these aims are furthered by creating spuriously accurate subdivisions which are based on non-specific morphological criteria. Where morphological changes are non-specific it may be necessary to adopt a pragmatic classification to guide treatment until more specific diagnostic techniques become available. On the basis of our work on observer variation we have recently suggested a two tier nomenclature for cervical squamous epithelial lesions which would not only improve diagnostic consistency but would also have clear management implications.^{2,3} The authors of your leading article reject our suggestion on the insufficient grounds that there is disagreement among different investigators as to the precise location of the divide, and that adoption of such a nomenclature would "encourage the misguided belief that there is a two stage process in the natural history of CIN". Pathologists who are interested in mechanisms of disease are aware that carcinogenesis in the cervix, as elsewhere, is a multistage process which is not necessarily accompanied by stepwise morphological changes. The question of the location of the division point, for the purpose of clinical management, may be settled by a study of risk assessment which is currently in progress.⁵ The preliminary analyses from this work support our suggestion that the division point should be located between CIN 1 and 2 (Wilkinson C, personal communication).

At present, one of the major practical problems in gynaecology and surgical pathology is the large number of cervical resection specimens which show no clinically important pathological abnormality. The reported figures vary from 27% of loop diathermy resections carried out for abnormal smears⁶ to 64% of cone biopsies performed for mild dyskaryosis.⁷ The problems thus largely stem

from vigorous treatment of lesions at the lower end of the so-called CIN spectrum. Some may consider that the risk of resecting normal cervixes with transient minor morphological abnormalities is outweighed by the benefit from removing, albeit in a minority of patients, the earliest stages of cervical neoplasia. The evidence, however, suggests that cervical resection is not free of morbidity,^{8,9} that only a small proportion of patients with mild and moderate dyskaryosis progress to invasive carcinoma¹⁰ (Jenkins MLF, Bradfield JWB, Mackenzie EFD. Abstract presented at the British Society for Clinical Cytology. 1990 29th annual meeting), and that surveillance is an entirely satisfactory way of managing these patients. The psychological impact on the patient of a diagnosis of neoplasia should also be borne in mind.

It is no longer possible for pathologists to hide behind their microscopes and deny all responsibility for the practices of their clinical colleagues. The delusion, perpetuated by some pathologists, that it is possible to detect cervical neoplasia at its earliest stages by the presence of minor morphological changes, the surgical treatment of which can abort progression of the disease, has resulted in overtreatment of a great many women. This cannot be justified on economic, ethical, or scientific grounds. The subject requires rational debate based on critical evaluation of existing evidence, preferably followed by a study which evaluates the applicability of any suggested new nomenclature.

SM ISMAIL

Department of Pathology,
University of Wales,
College of Medicine,
Heath Park,
Cardiff CF4 4XN

- 1 Anderson MC, Brown CL, Buckley CH, *et al*. Current views on cervical intraepithelial neoplasia. *J Clin Pathol* 1991;44:969-78.
- 2 Ismail SM, Colclough AB, Dinnen JS, *et al*. Observer variation in histopathological diagnosis and grading of cervical intraepithelial neoplasia. *Br Med J* 1989;298:707-10.
- 3 Ismail SM, Colclough AB, Dinnen JS, *et al*. Reporting cervical intra-epithelial neoplasia (CIN): intra- and inter-pathologist variation and factors associated with disagreement. *Histopathology* 1990;16:371-6.
- 4 Robertson AJ, Anderson JM, Swanson Beck J, *et al*. Observer variability in histopathological reporting of cervical biopsy specimens. *J Clin Pathol* 1989;42:231-8.
- 5 Wilkinson C, Peters T, Harvey I, Stott NCH. Risk assessment in cervical cytology screening: a new look at an old problem. *Br J Gen Pract* (in press).
- 6 Luesley DM, Cullimore J, Redman CWE, *et al*. Loop diathermy excision of the cervical transformation zone in patients with abnormal cervical smears. *Br Med J* 1990;300:1690-3.
- 7 Lopes A, Pearson SE, Mor-Yosef S, *et al*. Is it time for reconsideration of the criteria for cone biopsy? *Br J Obstet Gynecol* 1989;96:1345-7.
- 8 Jones JM, Sweetnam PM. The Cardiff cervical cytology study. Morbidity from and effectiveness of cone biopsy of the cervix. In: Anderson MC, ed. *Proceedings of Fourth World Congress*. London: International Federation for Cervical Pathology and Colposcopy, 1982; 99:102.
- 9 Ismail SM. Cone biopsy causes cervical endometriosis and tubo-endometrioid metaplasia. *Histopathology* 1991;18:107-14.
- 10 Robertson JH, Woodend BE, Crozier EH, Hutchinson J. Risk of cervical cancer associated with mild dyskaryosis. *Br Med J* 1988;297:18-21.

erbB2 expression in breast and other human tumours

Having been involved during recent years in

the study of *erbB2* expression in breast and other human tumours,^{1,2} we were interested to see the report from Fox and colleagues³ regarding the apparent absence of *erbB2* protein overexpression in male breast carcinoma. Shortly after this report was published, a 71 year old man was referred to the Department of Surgery at the Royal Victoria Infirmary with a six week history of a mass beneath the right nipple. The appearances of a fine needle aspirate were consistent with ductal carcinoma, and histological examination of the subsequent mastectomy specimen showed an invasive ductal carcinoma (Bloom's grade 2) (fig 1) with a comedo in situ component. Assessment of *erbB2* protein expression (performed routinely in all breast carcinomas) using NCL CB11 at a dilution of 1 in 20 and an indirect immunoperoxidase method showed membrane staining throughout the tumour, indicative of overexpression (fig 2). A section of a known *erbB2* positive breast carcinoma and omission of primary antibody were used as positive and negative controls, respectively.

This observation indicates that *erbB2* overexpression (and therefore possibly amplification) is a feature of a proportion of male breast carcinomas. Since Fox and colleagues were unable to demonstrate overexpression in any of their 21 cases it

Figure 1 Invasive ductal carcinoma of male breast.

Figure 2 Male breast carcinoma showing membrane staining with NCL-CB11 antibody, indicative of *erbB2* overexpression.

would appear that this proportion is not large, but clearly larger numbers need to be examined before an accurate estimate can be made.

C WRIGHT
K PRASAD
TJW LENNARD
University of Newcastle upon Tyne
School of Pathological Sciences,
Division of Pathology,
Royal Victoria Infirmary,
Newcastle upon Tyne NE1 4LP

- 1 Wright C, Angus B, Nicholson S, *et al.* Expression of c-erbB2 oncoprotein: a prognostic indicator in human breast cancer. *Cancer Res* 1989;49:2087-90.
- 2 Wright C, Mellon K, Johnston P, *et al.* Expression of mutant p53, c-erbB2 and the epidermal growth factor in transitional cell carcinoma of the human urinary bladder. *Br J Cancer* 1991; 63:967-70.
- 3 Fox SB, Day CA, Rogers S. Lack of c-erbB2 oncoprotein expression in male breast carcinoma. *J Clin Pathol* 1991;44:960-1.

False positive reactions with rotavirus latex agglutination test

Bendall and Gray describe a false positive reaction with a rotavirus latex agglutination test ("RotaScreen", Mercia Diagnostics Ltd, Surrey) on a stool sample from a child with haemorrhagic colitis and haemolytic uraemic syndrome.¹ We describe a further two patients in which potential false positive reactions were obtained with this test.

Case 1

This 1200 g baby girl was the first of twins born at 29 weeks' gestation by caesarian section. She received artificial ventilation for two weeks for hyaline membrane disease and pulmonary interstitial emphysema. At 27 days of age she passed a loose stool which was sent for virological examination. The RotaScreen latex agglutination test was performed according to the manufacturer's instructions and found to be positive. The stool was not tested for blood but on the following day there was a small amount of blood present in the nasogastric aspirate.

Case 2

This 560 g baby was born at 24 weeks' gestation and had a difficult neonatal course including a prolonged ventilatory requirement and sepsis. He was eventually weaned on to low flow oxygen and full nasogastric feeds. At 85 days of age he developed the signs and symptoms of bowel obstruction with constipation, abdominal distension, and hyperactive bowel sounds, bile stained vomit, and splinting of the diaphragm with increased oxygen requirements. The following day he passed a large blood-stained loose stool which was sent for virological examination. This was found to be rotavirus positive using the latex test.

When examined by negative staining electron microscopy no viruses were detected in either stool specimen.

In both these patients the initial rotavirus positive result caused considerable concern and influenced patient management. With case 1, transfer back to the referring hospital was delayed. With case 2, a diagnosis of necrotising enterocolitis had been made and metronidazole was started. The rotavirus latex result caused some uncertainty about the appropriate further management of the child. In addition, the possibility of cross-infection in the nursery was considered as these patients had been in the same room and gloving and gowning was instituted for routine care of both babies.

The signs and symptoms of infection in neonates are often non-specific, requiring laboratory tests to provide a definite diagnosis. The availability of tests for rotavirus

such as the latex agglutination test has permitted more widespread testing for this virus than when electron microscopy was the only available method. Our observations indicate that the results obtained with the latex test were probably false positive results. This supports the finding of Bendall and Gray, who describe a false positive reaction with a rotavirus latex agglutination test in a child with bloody diarrhoea. In our cases the sample from case 2 was clearly bloody. The stool from case 1 was not tested for blood but a nasogastric aspirate taken the following day contained a small amount of blood.

In view of these findings we feel that the results of latex tests for rotavirus should be interpreted with caution, especially if there is evidence of blood in the stool. It is our policy to use the latex test as an initial rapid screening test but to examine all stools electron microscopically as well. This permits the detection of both false negative as well as false positive latex agglutination results. Other viruses associated with diarrhoeal disease may also be detected.

N BRINK
S RICE
C PICKERING
Division of Virology,
University College and Middlesex School of Medicine,
Riding House Street,
London W1P 7PN
S THURLBECK
Neonatal Unit,
University College Hospital

- 1 Bendall RP, Gray JJ. Haemorrhagic colitis and haemolytic-uraemic syndrome: False positive reaction with a rotavirus latex agglutination test. *J Clin Pathol* 1991;44:609-10.

Drs Bendall and Gray comment:

Brink *et al.*'s description of false positive reactions with the RotaScreen latex test when testing bloody stools agrees with our own findings. Since our original report we have tested further stools with this kit and found a false positive rate of 28% with bloody stools. There were no false positive results in non-bloody stools. We hope to publish the details of our study shortly.

We agree that the "RotaScreen" test is a sensitive test and well suited to screening for rotavirus infection, but the high incidence of false positive results mean that some other means should be used to confirm the diagnosis.

NOTICES

Preliminary announcement

British Lymphoma Pathology Group Tutorial

9-11 September 1992
Chilworth Manor Residential
Conference Centre, Chilworth,
Southampton

Topics will include: T cell lymphomas; New techniques in lymphoma diagnosis; the borderline between Hodgkin's and non-Hodgkin's lymphoma; MALT lymphomas; monocytoid B cell lymphomas; diagnostic pitfalls in lymphoma pathology

Course Fee £250.00

For further information please contact:
Dr A D Ramsay, BLPG Secretary,
Department of Histopathology,
Southampton General Hospital,
Tremona Road, Southampton SO9 4XY.
Tel: 0703-796447 Fax: 0703-705580

Postgraduate training programme in pathology (IAP, Austria)

The Austrian division of the International Academy of Pathology (IAP) in collaboration with the Royal College of Pathologists (London), offers postgraduate courses in English in anatomical pathology and its subspecialties. The courses are designed to supplement the training in the home country and may be tailored to the special needs of the individual physician. The courses are recognised for the Part I MRCPPath examination of the Royal College (Diploma in Pathology). The main thrust of the programme is directed towards hands-on experience in necropsy pathology in preparation for the Part I examinations. Preference will be given to physicians-in-training with considerable experience in surgical pathology from countries with limited access to autopsies.

A limited number of places for a complete specialty training programme in anatomical pathology and cytology for physicians with knowledge of English and German is available, leading to the Part I MRCPPath (Diploma) examination.

Training programmes in advanced techniques in diagnostic pathology, ultrastructure, and cell biology may be arranged on request for pathologists and their laboratory staff.

Direct enquiries to: AKH-Klinische Pathologie, W Dutz MD, FRCPath, FCAP Course Director, IAP Austria AKH, Währinger Gürtel 18-20 A-1090 Wien, Austria Fax: 0043-1-424302

Association of Clinical Pathologists

Junior Membership

Junior membership of the Association is available to medical practitioners who have been engaged in the practice of pathology for a period of less than four years. Junior members are able to remain in this category for a maximum of six years or on the attainment of consultant status. The annual subscription is £34 for those resident in the United Kingdom and £65 for those overseas. The annual subscription may be claimed against tax.

Junior members receive the *Journal of Clinical Pathology* each month. Other benefits are reduced registration fees to attend ACP scientific meetings, all the documents regularly sent to full members of the Association including *ACP News*, which has a regular column for juniors, and the twice yearly summary of pathology courses included in the ACP programme of postgraduate education. Junior members have their own representative body, the Junior Members' Group, which has a direct input to Council.

For Junior Membership apply to: The Honorary Secretary, Association of Clinical Pathologists, 221 Preston Road, Brighton BN1 6SA. (0273) 561188.