Occasional articles

Current views on cervical intraepithelial neoplasia

M C Anderson, C L Brown, C H Buckley, H Fox, D Jenkins, D G Lowe, B T B Manners, D H Melcher, A J Robertson, M Wells

Report of a Working Party convened by the British Society for Colposcopy and Cervical Pathology and sponsored by the National Health Service Cervical Screening Programme National Coordinating Network, 3 and 4 December 1990

Department of Histopathology, University of Nottingham Medical School
M C Anderson
D Jenkins

Department of Histopathology, The Royal London Hospital Medical College
C L Brown

Department of Histopathology, St Mary's Hospital, Manchester
C H Buckley

Department of Reproductive Pathology, University of Manchester
H Fox

Department of Pathology, St Bartholomew's Medical College, London
D G Lowe

Department of Histopathology, The Royal Surrey County Hospital, Guildford
B T B Manners

Department of Histopathology, The Royal Sussex County Hospital, Brighton
D H Melcher

Department of Histopathology, Perth Royal Infirmary
A J Robertson

Department of Histopathology, University of Leeds
M Wells

Correspondence to: Dr M C Anderson, Department of Histopathology, Queens Medical Centre, University of Nottingham NG7 2UM

Accepted 4 July 1991

Introduction

The system of nomenclature for cervical epithelial abnormalities, which uses the cervical intraepithelial neoplasia (CIN) terminology, has been widely adopted since its introduction.¹ The principal advantages over the previous dysplasia/carcinoma in situ system are that it recognises the unity of the disease process and is in keeping with current therapeutic approaches. When the CIN terminology was introduced, the intention was to emphasise that cervical abnormalities were a spectrum of one disease and that the concept was therefore, in theory, irreconcilable with subdivisions, but it has become customary to subdivide CIN into three grades. Recent publications have drawn attention to a worrying lack of diagnostic consistency among histopathologists at the less severe end of the disease spectrum.^{2,3} These studies have added weight to the concerns first expressed about the consistency of reporting using the dysplasia/carcinoma in situ terminology⁴ and, later, CIN terminology.⁵ As a result, it has been suggested that the current grading system for CIN should be modified and replaced by a two-tier system.^{2,3,6}

The Bethesda cytology system for reporting cervical and vaginal diseases⁷ has adopted a two-tier system for cervical epithelial abnormalities, and the originator of the CIN system has proposed that it should be abandoned in favour of a two-tier system.⁸ This led us to reappraise the diagnostic criteria for the diagnosis and grading of CIN and to consider whether the currently used and well established system of grading should be retained or replaced by some other system that might improve diagnostic consistency while maintaining relevance to treatment.

A histopathologist assessing a cervical biopsy specimen not only has the problem of placing an epithelial abnormality on a point within the spectrum of CIN but also, as the first event, of deciding whether the changes represent CIN. Indeed, some therapeutic approaches mean that deciding whether a lesion is CIN or not is of more practical importance than assessing the grade of CIN. For this reason, and because it has been shown that diagnostic consistency at the less severe end of the spectrum is appreciably worse than that at the severe end,^{2,3} we have specifically considered the most subtle his-

tological changes that allow a diagnosis of CIN to be made and have then addressed the difficult problem of how to assess epithelial changes that, although not quite amounting to CIN 1, are not normal.

This report represents the views of a working party convened jointly by the National Health Service Cervical Screening Programme National Coordinating Network and

Figure 1 CIN 1. The nuclear changes are mild, although some abnormality extends throughout the full thickness of the epithelium.

Figure 2 CIN 2.

the British Society for Colposcopy and Cervical Pathology.

Recommendations for terminology and grading

When considering a system of terminology for CIN it is important to recognise that the epithelial abnormalities form a continuous spectrum of disease: any form of grading system must not contradict or ignore this. We considered the three alternative possibilities of (a) using the term cervical intraepithelial neoplasia without division into grades, (b) division of CIN into two grades, and (c) division of CIN into three grades.

NO SUBDIVISION OF CIN BY GRADE

For

- The removal of subdivisions from CIN supports the concept of unity of the dis-

Figure 3 CIN 3. The nuclei are considerably enlarged, with a greatly increased nuclear:cytoplasmic ratio compared with normal. Hyperchromasia and pleomorphism are also pronounced. Severe changes extend almost to the surface and a mitotic figure is present in the superficial third of the epithelium.

ease process and so reinforces the original proposal of CIN.

- The diagnosis is unitary and attention is therefore, concentrated on deciding whether CIN is present or absent.
- Diagnostic inconsistency as a result of disagreement in allocating grades of CIN would be eliminated (though inconsistencies in distinguishing CIN from a minor non-CIN lesion would not be affected).
- It would be in keeping with the therapeutic approach which suggests that the extent of the lesion is of greater importance than the degree of abnormality.⁹

Against

- A system that does not include grading would be unhelpful to clinicians who use a therapeutic approach that depends on the grade of CIN.
- It would not allow detailed cytological correlations to be made.
- It ignores the fact that a histological diagnosis of CIN 3 is largely reproducible³ and has an established clinical importance.
- Failure to recognise CIN could lead to totally inappropriate management.
- Removing the need to allocate a histological grade to CIN would be likely to blunt diagnostic acumen if a resumption of grading became necessary.

DIVISION OF CIN INTO TWO GRADES

Four different terminologies have been proposed for the two-tier system for CIN:

- Division into "borderline CIN" (presently CIN 1 and human papillomavirus (HPV) associated changes) and "CIN" (presently CIN 2 and CIN 3).²
- Division into "low grade CIN" (presently CIN 1 and CIN 2) and "high grade CIN" (presently CIN 3).³
- Division into "low grade intraepithelial squamous lesions" (presently CIN 1 and flat condyloma) and "high grade intraepithelial squamous lesions" (presently CIN 2 and CIN 3).⁷
- Division into "low grade CIN with HPV related changes" (presently CIN 1 and flat condyloma) and "high grade CIN" (presently CIN 2 and CIN 3).⁸

These suggestions can be considered together:

For

- This is the most relevant system for patient management.
- Many clinicians already group CIN 2 and CIN 3 together for treatment.

Against

- Adopting a two-tier grading system might encourage the misguided belief that there is a two stage process in the natural history of CIN.
- There is disagreement over where the split between "low grade" and "high grade" lesions should lie, and whether HPV related features should be included with CIN in the "low grade" category (see below).

A

B

Figure 4 CIN 1. A and B. In both these examples the degree of nuclear abnormality in the basal layers is very mild but is just sufficient for a diagnosis of CIN to be made.

- Diagnostic errors could have a more important impact on patient management than with a three-grade system.
- The use of a two-grade system will neither eliminate nor reduce errors, though it will have the apparent but illusory effect of increasing the diagnostic consistency of the two categories that have been grouped as one (such as CIN 2 and CIN 3, or CIN 1 and CIN 2).

These two effects of reducing the number of grades from three to two will depend on where the divisions are made and on their reproducibility.

DIVISION OF CIN INTO THREE GRADES

For

- A three-grade system underlines the concept of continuity of CIN more than a two-grade system.
- The system is well established.
- Retention of the present system will continue to allow retrospective comparative studies to be done.
- Comparison with the cytological findings is established.

Against

- Inconsistencies of diagnosis have been shown,²⁻⁵ though it is accepted that CIN 3 is a robust and reproducible diagnosis.
- The choice of three subdivisions is quite arbitrary.

In view of the above arguments and in the absence of compelling reasons to change from the well established current terminology, we have agreed that the currently used three-grade system for CIN should be retained for the present, though we recognise that there are some arguments in favour of a two-grade system. We would emphasise that this decision does not preclude a future review in the light of new information that becomes available.

We appreciate, however, that there are some instances of basal changes that are not clearly CIN 1 but, equally, cannot be unequivocally allocated to a non-neoplastic category. We therefore propose that such cases should be placed in a new category, for which the term *basal abnormalities of uncertain significance* is recommended. The histological features of this category are described below.

Diagnostic criteria for cervical intraepithelial neoplasia

The diagnostic features of cervical intraepithelial neoplasia have been fully described¹⁰⁻¹² and are well-known: it is not necessary to repeat them here. Figures 1, 2, and 3 are examples that we think fall at the mid-points of CIN 1, CIN 2, and CIN 3, respectively. Confident diagnosis and grading of CIN is hampered if the tissue is not adequately fixed, processed, or stained; many diagnoses may be uncertain because of less than optimal handling of the material. Furthermore, because of the variation in the degree of abnormality that may be present, even in a small area of epithelium, it is essential that the biopsy specimen is adequately sampled by sectioning at several levels. A biopsy specimen often contains epithelium with more than one grade of CIN and in these instances all grades present should be recorded in the report. Studies of diagnostic consistency have shown that the diagnosis of CIN 3 is much more robust and reproducible than that of CIN 1.^{2,3}

MINIMUM CRITERIA FOR THE DIAGNOSIS OF CIN 1

Figure 1 is an example of what we considered to be the mid-point of the CIN 1 grade, but fig 4 shows the minimum features which would be acceptable as CIN 1. The minimum histological changes that justify a diagnosis of CIN 1 are:

Figure 5A CIN 1. Subtle abnormalities of mitotic figures (dispersed metaphase).

Figure 5B CIN 1 with an obvious quadripolar mitotic figure.

Figure 6 HPV associated features: no basal cell hyperplasia or CIN present.

- Some degree of nuclear abnormality that extends throughout the full thickness of the epithelium although being most apparent in the cells of the basal layers. In this report, the term “basal layers” refers to the basal and parabasal layers of cells. These nuclear abnormalities are:

A mild degree of nuclear pleomorphism.

An increase in the nuclear:cytoplasmic ratio.

Some degree of enlargement of nuclei.

Mild hyperchromasia, which is often minimal in CIN 1 and has a finely stippled chromatin pattern.

- The presence of normal mitotic figures is not helpful but the presence of abnormal mitotic figures supports a diagnosis of CIN 1. Abnormal mitotic figures occur in about 30% of cases of CIN 1 but the changes are often subtle^{13 14} (fig 5A) and focal, necessitating the examination of an adequate number of sections.

The features of CIN 1 can be found in mature, immature, or atrophic squamous epithelium and also in epithelium showing the features of human papillomavirus (HPV) infection. As with the more severe grades of CIN the

Figure 7 HPV associated features with basal cell hyperplasia.

Table 1 Histological features of human papillomavirus infection

Koilocytosis
Multinucleation (frequently binucleation)
Individual cell keratinisation
Acanthosis
Parakeratosis
Papillomatosis

mation: under these circumstances basal abnormalities of uncertain significance should be diagnosed. Features of severe epithelial inflammation include spongiosis and intra-cellular oedema, as well as inflammatory cells obscuring the basal layers.

HPV ASSOCIATED FEATURES
The histological features suggesting infection of cervical epithelium by HPV have been well documented^{15 16}; they are listed in table 1 and illustrated in figs 6 and 7. The presence of koilocytosis is essential for the diagnosis of HPV infection in cervical epithelium, but it is important that koilocytosis is not overdiagnosed. To merit diagnosis as a koilocyte, the nucleus of the cell should have a wrinkled nuclear outline and be enlarged and hyperchromatic, and there should be cavitation of the cytoplasm (fig 8). Koilocytes are rarely present in the basal layers of the epithelium, and then only if they are present more superficially. The changes are often focal. In the absence of superimposed CIN the basal layers of an epithelium infected by HPV do not show nuclear pleomorphism. Numerous mitotic figures may be present at all levels of the epithelium but these are not abnormal in configuration. Uniform nuclear enlargement may be present in the basal layers as a manifestation of basal cell hyperplasia.

Figure 8 Koilocytes: the nuclei of affected cells are enlarged and hyperchromatic with a wrinkled outline, surrounded by cavitation of the cytoplasm.

Figure 9 HPV associated features with CIN: nuclear pleomorphism and enlargement are present in the basal layers, together with an abnormal mitotic figure. Striking koilocytosis is seen in the superficial layers.

HPV ASSOCIATED FEATURES WITH CIN

If the features of CIN and HPV infection are present at the same site the changes described above for both of these are superimposed (fig 9), resulting in nuclear pleomorphism of the basal layers with koilocytosis in the superficial layers. The nuclear changes often appear exaggerated, and the tendency to attribute too high a grade of CIN should be resisted. It should also be remembered that the features of HPV infection can be seen in all grades of CIN.

We do not agree with the view that all examples of CIN 1 are simply an expression of HPV infection, and we maintain that it is possible and indeed desirable to distinguish between CIN 1 with HPV infection and CIN 1 without HPV infection. For this reason and also because of the therapeutic implications, we rejected the systems of terminology that group epithelia with HPV associated changes alone with epithelia showing CIN 1.^{2,8}

BASAL ABNORMALITIES OF UNCERTAIN SIGNIFICANCE

The histological features of this entity are:

- A minimal degree of nuclear pleomorphism

limited to the basal layers in the *absence* of severe inflammation (fig 10).

- The features of CIN 1 in the *presence* of severe inflammation involving and/or immediately beneath the epithelium (fig 11).
- A thin epithelium in which a diagnosis of CIN (grade not specified) would have been appropriate, but in the *presence* of severe inflammation (fig 12).

In all these instances, the changes may be associated with the features of HPV infection. In any of the above circumstances the finding of abnormal mitotic figures should result in a diagnosis of CIN. A diagnosis of basal abnormalities of uncertain significance in a colposcopic biopsy specimen is an indication for subsequent colposcopic review.

Areas of diagnostic difficulty

BASAL CELL HYPERPLASIA

Basal cell hyperplasia is characterised by regular replication of basal layers and nuclear enlargement; nuclear pleomorphism and hyperchromasia are absent (fig 13).

SQUAMOUS METAPLASIA

Squamous metaplasia is a physiological process characterised by reserve cell hyperplasia, early squamous differentiation, variable polarity and nuclear enlargement; nuclear pleomorphism and hyperchromasia are absent (figs 14 and 15). Similar changes can be seen in an epithelium healing after treatment. There may or may not be columnar cells on the surface of the epithelium. If there is nuclear pleomorphism CIN should be diagnosed (fig 16), even if columnar cells are present on the surface (fig 17). Grading of this, in terms of the proportion of the epithelium occupied by undifferentiated cells, may be difficult or impossible and attempts at grading in these circumstances should be based on the degree of nuclear abnormality. If this is also impossible, a diagnosis of CIN (grade not specified) is acceptable. HPV associated features are not usually seen in immature metaplastic squamous epithelium.

LOW OESTROGEN STATES

In low oestrogen states—for example after the menopause and in women taking low oestrogen oral contraceptives—the cervical squamous epithelium may be composed entirely of cells of parabasal type and is usually thin (fig 18). A mild degree of nuclear hyperchromasia is often a feature of such an epithelium, but in the absence of pleomorphism CIN should not be diagnosed. If nuclear pleomorphism is present CIN should be diagnosed; grading, in terms of the proportion of the epithelium occupied by undifferentiated cells, may be difficult or impossible and attempts at grading should be based entirely on the degree of nuclear abnormalities (fig 19). When this is impossible CIN (grade not specified) should be diagnosed.

THIN EPITHELIUM

In an epithelium that has only a few layers of cells it may not be possible to grade CIN confidently (fig 20). In the absence of severe

Figure 10 Basal abnormalities of uncertain significance (A) and (B). In both these examples, the degree of nuclear abnormality is less than that required for a diagnosis of CIN. No inflammation is present.

Figure 11 Basal abnormalities of uncertain significance with inflammation. (A) Inflammation affects the stroma immediately beneath the epithelium. (B) Inflammatory cells also infiltrate the epithelium.

Figure 12 Basal abnormalities of uncertain significance: a thin epithelium in which a diagnosis of CIN (grade not specified) would have been appropriate, but severe inflammation is present.

inflammation CIN (grade not specified) should be diagnosed, but if severe inflammation is present basal abnormalities of uncertain significance should be diagnosed (fig 12).

Histological diagnosis and patient management

Although the histological diagnosis of a colposcopic biopsy specimen plays an important part in determining the subsequent management of the patient it must be remembered that other factors, including the cytological diagnosis, the colposcopic appearances, and the clinical features of the case will also have a great impact on management.

The biological behaviour of an epithelial abnormality cannot be predicted accurately from the histological appearances, neither are there any special techniques at the moment that allow this to be done. Static ploidy studies indicate that aneuploidy is related to disease progression,¹⁷ but the ploidy state cannot reliably be predicted on haematoxylin and eosin

Figure 13 Basal cell hyperplasia: regular replication of the basal layers and nuclear enlargement are present but there is no nuclear pleomorphism or hyperchromasia.

Figure 14 Reserve cell hyperplasia.

stained sections. In routine practice it is not useful to identify the specific type of human papillomavirus, and even when these are known they should not influence patient management. Similarly, immunohistochemical and receptor studies have not as yet been found useful.

Relation between histological and cytological diagnoses

The recommended histological terminology seems to parallel the cytological classification recommended by the British Society for Clinical Cytology, but a direct correlation of grades from one system to the other should not be expected. Diagnosis of the higher grades is

Table 2 Classification of cervical intraepithelial abnormalities

Basal abnormalities of uncertain significance
Cervical intraepithelial neoplasia grade 1
Cervical intraepithelial neoplasia grade 2
Cervical intraepithelial neoplasia grade 3
Cervical intraepithelial neoplasia (grade not specified)

generally more robust, both cytologically and histologically, and so a better correlation is likely for the more severe abnormalities.

Cytology and biopsy are different sampling processes. A large biopsy specimen, in most cases, will accurately show all CIN changes present. Frequently these are of more than one grade, with the higher grade tending to be more centripetal and located towards the endocervical edge of the transformation zone.^{18,19} A small colposcopic biopsy specimen does not always accurately identify the highest grade of CIN present. The relation between cytological grade and underlying disease depends not only on the grade of CIN but on the size of the lesion,²⁰ the shape of the cervix, and the type of spatula used, as well as operator and observer variation. Similar factors also affect the occurrence of false negative cytology.²¹

Conclusion

The Working Party recommend the continuation of the present grading system for CIN and

Figure 15 Squamous metaplasia: although nuclear enlargement is present, there is no pleomorphism or hyperchromasia.

Figure 16 Squamous metaplasia with nuclear pleomorphism and hyperchromasia. A diagnosis of CIN should be made in these circumstances; this example has the features of CIN 1.

Figure 17 Reserve cell hyperplasia with nuclear pleomorphism and hyperchromasia. A diagnosis of CIN should be made, even though columnar cells are present on the surface. Grading of this example is not possible and a diagnosis of CIN (grade not specified) is acceptable.

Figure 18 Atrophic squamous epithelium, composed entirely of cells of parabasal type. Although there is mild hyperchromasia, no nuclear pleomorphism is present.

Figure 19 CIN 2 occurring in an atrophic squamous epithelium. Grading is based on the degree of the nuclear abnormalities.

Figure 20 CIN (grade not specified): the epithelium is only a few cells thick and, although the presence of nuclear abnormalities is unequivocal, confident grading is not possible.

the introduction of a new category of epithelial abnormality to encompass those lesions in which a diagnosis of CIN cannot be made with certainty (table 2).

- 1 Richart RM. Natural history of cervical intraepithelial neoplasia. *Clin Obstet Gynecol* 1967;10:748-84.
- 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 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.
- 4 Cocker J, Fox H, Langley FA. Consistency in the histological diagnosis of epithelial abnormalities of the cervix uteri. *J Clin Pathol* 1968;21:67-70.
- 5 Bellina JH, Dunlop WP, Riopelle MA. Reliability of histopathologic diagnosis of cervical intraepithelial neoplasia. *South Med J* 1982;75:6-8.
- 6 Robertson AJ. Histopathological grading of cervical intraepithelial neoplasia (CIN)—is there need for a change? *J Pathol* 1989;159:273-5.
- 7 Solomon D. The 1988 Bethesda system for reporting cervical/vaginal cytological diagnoses. *Acta Cytol* 1989;33:567-74.
- 8 Richart RM. A modified terminology for cervical intraepithelial neoplasia. *Obstet Gynecol* 1990;75:131-3.
- 9 Richart RM, Townsend DE. Outpatient therapy of cervical intraepithelial neoplasia with cryotherapy or CO₂ laser. In:

- Osofsky HJ, ed. *Advances in clinical obstetrics & gynecology*. Vol 1. Baltimore: Williams & Wilkins, 1982: 235.
- 10 Buckley CH, Butler EB, Fox H. Cervical intraepithelial neoplasia. *J Clin Pathol* 1982;35:1-13.
 - 11 Anderson MC. Premalignant and malignant disease of the cervix. In: Fox H, edn. *Haines and Taylor: Obstetrical and gynaecological pathology*. Vol 1. 3 edn. Edinburgh: Churchill Livingstone, 1987:255-301.
 - 12 Anderson MC. Cervical Precancer. In: Anderson MC, ed. *Female reproductive system*. In: Symmers WStC, ed. *Systemic pathology*. Vol 6. 3 edn. Edinburgh: Churchill Livingstone, 1991:92-7.
 - 13 Winkler B, Crum CP, Fujii T, et al. Koilocytotic lesions of the cervix: the relationship of mitotic abnormalities to the presence of papillomavirus antigens and nuclear DNA content. *Cancer* 1984;53:1081-7.
 - 14 Jenkins D, Tay SK, Campion MJ, Clarkson PK, Singer A. Histological and immunocytochemical study of cervical intraepithelial neoplasia associated with HPV 6 and HPV 16 infections. *J Clin Pathol* 1986;39:1177-80.
 - 15 Koss LG, Durfee DR. Unusual patterns of squamous epithelium of the uterine cervix: cytologic-pathologic study of koilocytotic atypia. *Ann NY Acad Sci* 1956; 61:1235-61.
 - 16 Meisels A, Morin C, Casas-Cordero M. Human papilloma virus infection of the uterine cervix. *Int J Gynecol Pathol* 1982;1:75-94.
 - 17 Bibbo M, Dytch SB, Alenghat E, Bartels PH, Weid GL. DNA ploidy as prognostic indicators in CIN lesions. *Am J Clin Pathol* 1989;92:261-5.
 - 18 Burghardt E. Premalignant conditions of the cervix. *Clin Obstet Gynaecol* 1976;3:257-94.
 - 19 Jenkins D. The pathology of lower genital tract premalignancy. In: Singer A, ed. *Clinical practice of gynaecology*. New York: Elsevier Science Publishing Co. Inc, 1991.
 - 20 Jarmulowicz MR, Jenkins D, Barton SE, Goodall AL, Hollingworth A, Singer A. Cytological status and lesion size: a further dimension in cervical intraepithelial neoplasia. *Br J Obstet Gynaecol* 1989;96:1061-6.
 - 21 Giles JA, Hudson E, Crow J, Williams D, Walker P. Colposcopic assessment of the accuracy of cervical cytology screening. *Br Med J* 1988;296:1099-102.