

# THE LOCAL CERVICAL CYTOLOGY SCREENING SYSTEM

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## INTRODUCTION

Carcinoma of the cervix is the seventh most common cause of death from cancer in women and causes 2,000 deaths annually in England and Wales. In the Lancaster district six women died of the disease in 1988. Two of these patients were under the age of 45 years. In the same year, as part of the screening programme, 2,012 women had cervical smears and 41 of these cases were positive for cervical intraepithelial neoplasia. Thirty-three of these patients were less than 35 years of age. In 1988 we diagnosed, in the histology laboratory at Lancaster, 11 cases of invasive carcinoma of the cervix. From these figures we must conclude that cervical screening has not, as yet, succeeded in eradicating this serious disease of young women.

Papanicolaou in 1928 first reported that tumour cells could be identified in vaginal smears from women with cervical cancer. Biopsy of the cervix had been used at the end of the 19th century for pre-operative diagnosis of cervical cancer and from 1908 to 1925 the concept of carcinoma in situ of the cervix had been developed. Papanicolaou's method, therefore, appeared to provide an opportunity for detection of cervical cancer at an early stage. The first screening clinic was opened in Massachusetts in 1945.

The fundamental premise in cervical screening is that carcinoma in situ does, in fact, progress eventually into invasive squamous carcinoma. Let us reassure ourselves that the theory is correct! The pathologist can observe that the cells comprising carcinoma in situ are indistinguishable cytologically from those of invasive squamous carcinoma, i.e. they show cytological characteristics of malignancy. Specimens of cervix showing invasive squamous carcinoma almost always coexist with a zone of carcinoma in situ. What happens to carcinoma in situ if it is left untreated? Multiple retrospective and prospective studies, many from the older literature, reveal progression to invasive carcinoma in approximately 30% of patients over a period of 20 years. The epidemiological characteristics of carcinoma in situ are similar to those of invasive squamous carcinoma. This is an outline of the evidence by which we can be confident that the theory behind cervical screening is correct.

## CYTOLOGY

There is a continuous spectrum of changes in the cervical epithelium ranging from normal to carcinoma in situ. Since 1967 the term **cervical intraepithelial neoplasia (CIN)** has come to replace dysplasia and carcinoma in situ.

CIN I corresponds to mild dysplasia

CIN II corresponds to moderate dysplasia

CIN III corresponds to both severe dysplasia and carcinoma in situ.

On examination of cervical smears, the most common cells encountered (in women of reproductive years) are squamous cells of superficial type. These are quite similar to the cells found in buccal smears. There is a very large amount of cytoplasm and a small central nucleus (fig 1). The presence of superficial cells is a good indicator of oestrogenic activity and will give rise to a comment on the report form if identified in the post-menopausal patient.

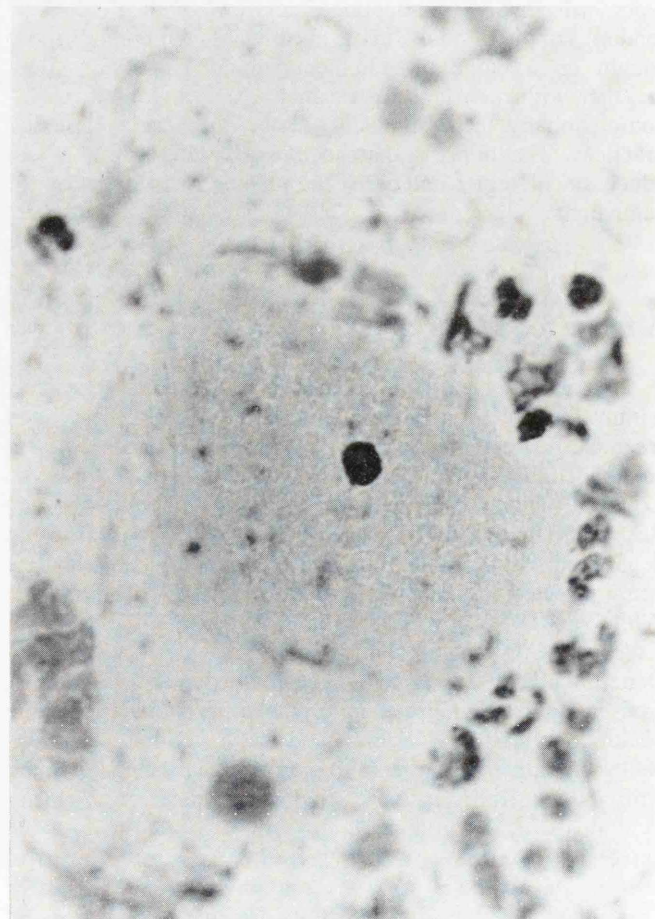


Figure 1 - In centre is a normal superficial epithelial cell.  
Pus cells at margins.

## Severe Dyskaryosis (CIN II-III)

Cells derived from areas of CIN show cytological abnormalities described as dysplasia or dyskaryosis. These terms are synonymous; dyskaryosis is the term favoured in the proposed new national report form and will therefore be used in this paper. Severe dyskaryosis is quite easy to identify in a cervical smear. The cells have much larger nucleo-cytoplasmic ratios than superficial cells.

The enlarged nuclei are of irregular shape. The chromatin pattern is heavy for the size of the nucleus and shows irregular granular staining (fig 2). We assume that such severely dyskaryotic cells are derived from an area of CIN III. Less severe abnormalities can be classified as moderate or mild dyskaryosis. All cases of severe dyskaryosis or moderate dyskaryosis are recommended for colposcopy.

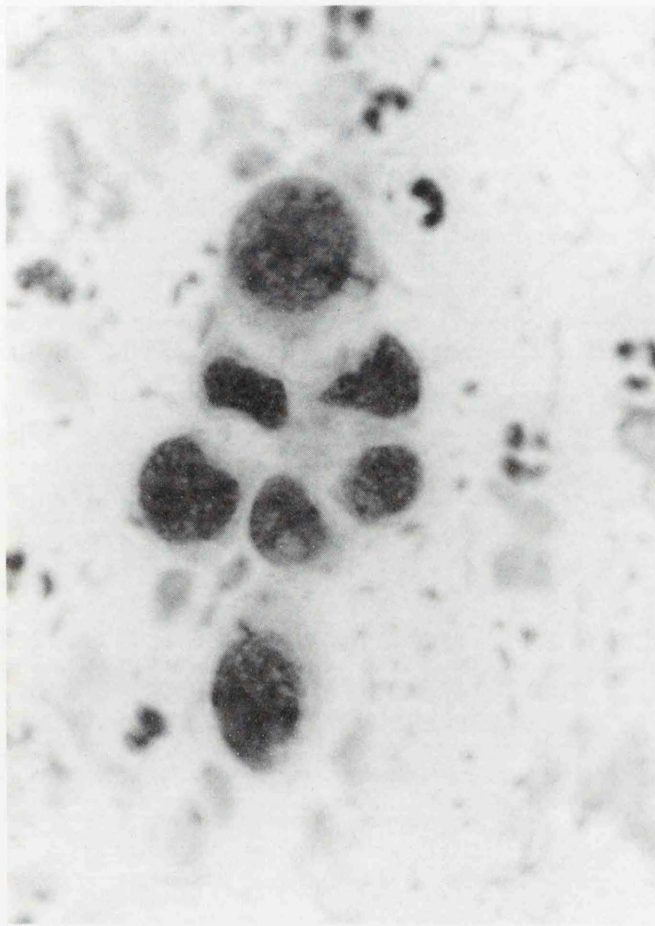


Figure 2 - Severely dyskaryotic epithelial cells. Note large nuclei and high nucleocytoplasmic ratio.

#### **Invasive Malignancy**

Some severely dyskaryotic cells may assume an elongated shape, the so-called 'fibre-cell'. These cells suggest the presence of invasive malignancy, and colposcopy will be recommended.

#### **Glandular Neoplasia**

Dyskaryotic cells may possess open nuclei with prominent nuclei and there may be vacuolated cytoplasm; these features suggest glandular neoplasia. Suspicion of glandular neoplasia will prompt a recommendation for colposcopy.

#### **Mild Dyskaryosis (CIN I)**

Compared with severe dyskaryosis, mild cellular changes are more difficult to classify and more frequently encountered. Mild dyskaryosis corresponds with CIN I and some, but by no means all, of these lesions progress to more severe epithelial abnormality. More important is the finding that 30% of cases diagnosed on cervical smear to have mild dyskaryosis have been found on subsequent investigation to have areas of CIN III. This finding probably reflects incompleteness of cervical sampling in the smear technique. The plan for mild dyskaryosis is to repeat the smear after 3 months and refer for colposcopy if the repeat is positive. If the repeat is negative the advice is to repeat the smear 3-monthly until three consecutive negative smears are obtained, and then to return to normal screening.

#### **Minimal Abnormalities**

Very minor degrees of nuclear change are much more frequent and present considerably greater diagnostic difficulty than cases of definite dyskaryosis. An otherwise normal smear might contain a few slightly enlarged nuclei with a regular shape and normal chromatin pattern. These are likely to be described on the report as "A few slightly enlarged bland nuclei." The repeat time recommended on the report form will be six months. For rather more marked changes difficult to distinguish from mild dyskaryosis, the term "Borderline" is used instead of "Negative", and there will be a request for a repeat smear in three months' time. If the minor abnormality persists in two smears, then the patient should be referred for colposcopy. If two repeat smears are negative, then the patient can return to normal screening. Simply to ignore minor nuclear changes is not acceptable, because in some cases of persisting minor nuclear change, a more serious abnormality is in due course detected.

#### **Inflammation**

Almost every cervical smear contains some inflammatory cells. This is normal. The presence of an unusually large number of pus cells will prompt a diagnosis of inflammation on the report form. In a few of these cases, *Candida* or *Trichomonas* may be identified and the presence of perinuclear vacuolation of the cell cytoplasm is one feature to suggest viral infection. By themselves and in the absence of any nuclear abnormalities, these changes do not require a repeat smear and the patient can continue as part of the normal screening programme. An occasional exception is when there are so many pus cells that the smear cannot be interpreted and is therefore inadequate (see below). Whether investigation or treatment of cervical inflammation should be carried out is a matter for the general practitioner, and the main criterion is whether the inflammation is symptomatic, e.g. producing discharge.

In inflammatory smears there may be minor nuclear abnormalities including nuclear enlargement and some abnormality in chromatin pattern. Whilst these changes are in many cases reactive, it is not always possible to be confident of their true nature. These smears are likely to be reported as negative, with a comment 'Inflammatory nuclear changes' or 'Minor nuclear enlargement associated with inflammation' and a request made for repeat.

#### **Inadequate Smears**

Smears may be inadequate for diagnosis for the following reasons:

- (a) the smear is too thin, i.e. there are too few cells present;
- (b) epithelial cells may be obscured by excessive haemorrhage or pus cells;
- (c) there is a problem in slide preparation, e.g. poor fixation.

In case (b) repeat should be carried out mid-cycle or after treatment, as appropriate.

### **TAKING A CERVICAL SMEAR**

It is self evident that in order to obtain a good cytological result the initial smear needs to be properly taken. The smear should be taken from the area adjacent to the squamo-columnar junction. It is possible for the cytologist to assess how likely it is that this area has been sampled by looking for endocervical cells. If endocervical cells are seen it is likely to be a good cervical smear.

Unfortunately, the squamo-columnar junction does retreat up the cervical canal with age. This means that in older women it may be extremely difficult to take a smear from this area and, if so, it is unlikely that endo-cervical cells will be obtained. It is not practicable to repeat cervical smears in patients in whom endocervical cells have not been obtained and indeed in some women it may be quite impossible to obtain such cells.

The cervix should be demonstrated with a bi-valve speculum and under good direct illumination a smear taken from the area of the external cervical os. It is usual at the moment to use an Ayres spatula although there are others on the market (all, of course, slightly more expensive) which do allow better sampling of the endocervical canal. Unfortunately, they have disadvantages such as increased haemorrhage and there is no clear recommendation at the moment as to which to use.

It is important when the cytological specimen is placed on the slide that the smear should be of just the right thickness. Smears that are too thick or too thin will provide problems of interpretation. The fixative should be applied immediately. The smear is then placed in its airtight container.

Finally, it is necessary to emphasize the importance of accurate labelling of cytology slides and request forms. This may seem obvious, but we often receive cases in which there is some discrepancy between slide and request form in surname, Christian name or unit number. Often these discrepancies are substantial, for example the surname may be different on slide and report form. Recently in a batch of five smears discrepancies were found in four of them. We have also received a batch of two different cases with the same surname, but the smears only bore the common surname! We only accept smears when we are happy about the identification. Commonsense is used here, but if in doubt, forms and smears are returned to the sender. Unfortunately, this happens several times per week. As an absolute minimum we require surname and Christian name on both slide and form, and preferably also the date, and unit number (if applicable). Labelling of slides and forms should not be delegated to inexperienced personnel.

## COLPOSCOPY

Colposcopy has developed to complement cervical cytology. It allows extra information about the cervix to be obtained so that a more accurate diagnosis can be made. This allows treatment to be tailored to the requirements of each patient.

The technique was first developed by Hinselmann in Germany in 1925. It has only become widely adopted in this country over the last two decades. It is now applied almost exclusively to patients with abnormal cytology although this was not the case when it was first developed.

### Which patients should be referred for colposcopy

In general it is those patients with abnormal cervical smears, showing CIN II or CIN III, who should be investigated further by colposcopy.

Cervical smears showing only CIN I can be repeated and referred if the abnormality persists (*see above: 'Minimal Abnormalities'*). The same applies to inflammatory smears with which the cytologist is not totally happy.

### What is Colposcopy?

The technique involves examining the cervix with a microscope. The magnification is usually times 10 to 16 but it can be varied outside these limits. After an initial examination of the cervix a 5% solution of acetic acid is applied. This has very little effect on the normal epithelium but makes the abnormal epithelium (CIN) appear white. This is usually described as aceto-white epithelium and the whiteness of its appearance will denote, to some measure, the degree of abnormality. CIN III is also characterized by the appearance of an abnormal vascular pattern within the area of the aceto-white epithelium.

The photograph (fig 3) shows aceto-white epithelium with mosaic vascular markings characteristic of CIN III.

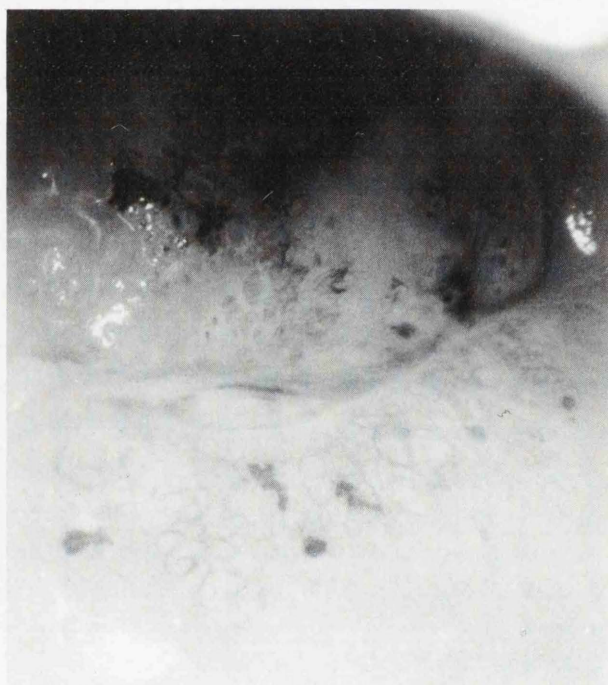


Figure 3 - Cervix viewed by colposcope showing CIN III

Once these areas are identified biopsies are taken from the most severely affected areas for subsequent histology. A note is made of the extent of the lesion and also whether it extends on to the vagina or into the cervical canal. In younger women it is usually possible to identify the whole of the lesion right up to the squamo-columnar junction. As a woman becomes older the squamo-columnar junction tends to retreat into the cervical canal, so that in older women it is often not possible thoroughly to examine the whole of the aceto-white area. If the whole of the area can be identified and the abnormality present in the epithelium is not more severe than CIN III, a 'conservative' approach to treatment can be adopted. If there is any doubt that the lesion extends into the cervical canal or amounts to more than CIN III, i.e., micro-invasion or frank invasion, a cone biopsy is required.

## CONE BIOPSY

Previously all patients with abnormal smears were treated by cone biopsy. This technique has the disadvantage that a large amount of cervical tissue is removed. Haemorrhage is common during the first 10 days following the procedure.

The bleeding can be severe. Long-term problems, mainly those of cervical stenosis but also cervical incompetence occur as well. The patient needs to spend, on average, two days in hospital and to have a general anaesthetic. Indeed, it may take the patient several weeks to get over the procedure. The advantage of cone biopsy, however, is that the specimen removed can be examined histologically and any occult invasive disease readily diagnosed.

### LASER TREATMENT

A thorough colposcopic assessment of the cervix does allow, in the majority of cases, the cervix to be treated by methods other than cone biopsy. Laser ablation of the abnormal epithelium is now a common procedure<sup>1</sup>. The laser apparatus generates a very narrow beam of laser light. An infra-red laser is used to treat the cervix; the abnormal area is vaporized. Smoke is produced and has to be removed through a special filter apparatus. The procedure is carried out as an out-patient under local anaesthetic. It takes about 15 minutes.

The cervix heals very readily after this form of treatment and there is high patient acceptability. There are no problems with cervical stenosis or incompetence. Indeed very little scarring of the cervix is produced. Immediate complications of the procedure are minimal. A few days' discharge or slight bleeding is all that the patient usually notices.

The disadvantage of this form of treatment is that the abnormal tissue is vaporized and, therefore, there is no histological record of the tissue removed.

### LOOP DIATHERMY EXCISION

Another technique is to remove the abnormal epithelium with a diathermy loop<sup>2</sup>. This procedure can again be done as an out-patient under a local anaesthetic and is not at all uncomfortable for the patient. The advantage of this treatment is that it does provide a specimen for subsequent histological analysis. The treatment is newer than laser ablation and, therefore, the long term effects of this treatment have not been so clearly evaluated. It would appear, however, to have a very low complication rate and to produce very acceptable results.

### FOLLOW UP OF PATIENTS AFTER TREATMENT

Whatever the form of treatment which has been applied to the cervix, the patients require close follow up. This quite clearly applies to both cone biopsy and the newer more conservative treatments. All the methods of treatment are roughly comparable in that 5% of patients will again develop abnormal cytology and require further treatment. Most of the relapses will occur in the first year following treatment and usually represent inadequate treatment, i.e. the whole of the abnormal area has not been removed. Inevitably, a small percentage of patients will develop invasive carcinoma. Following laser vaporization this percentage is a little difficult to determine exactly but has been put at 0.2%<sup>3</sup>.

The number of patients requiring treatment means that there is pressure to reduce the frequency of follow-up examinations and to restrict these to cytology only. At the moment we recommend a colposcopic and cytological follow up at 3 and 6 months, after which we revert to cytological follow up only. This we carry out 3-monthly in the first year, 6-monthly in the second year and then yearly until the 5th anniversary of the treatment when we feel it is quite safe for the patient to revert to the normal screening interval, that is 3-yearly.

### CONCLUSION

The vast majority of patients with CIN can now be treated as out-patients. At present we are treating conservatively about 120 patients per year. This represents about 80% of the patients who would formerly have needed cone biopsy. The majority of these patients have been treated by laser vaporization but an increasing number are now being treated by loop diathermy excision. There is no doubt that the demand for colposcopy is increasing. The recent computerisation of cytological records allows proper screening of the women in the district and gives us an opportunity to bring about the reduction in the incidence of invasive carcinoma of the cervix that we should all so much like to see.

### FUTURE CYTOLOGY ORGANISATION

At the present time most of the routine cervical smears originating in the Lancaster district are reported at Christie Hospital. Routine cervical smears taken in South Cumbria are processed and reported in the pathology laboratory at Barrow. The laboratory at Lancaster processes and reports 3,500 cervical smears per year, a high proportion of which are derived from hospital gynaecology clinics. From time to time we are asked by general practitioners to take on the reporting of more routine cervical smears, but without appropriate funding we are unable to expand the service. For reasons of statistics and quality control the present system is undesirable, but full responsibility for cervical cytology services is likely, in the future, to be transferred to district hospitals in the North-Western region, and Lancaster has already expressed a willingness to take on all the cervical cytology originating in the Lancaster district.

### References

1. Anderson MC. Treatment of cervical intraepithelial neoplasia with the carbon dioxide laser: report of 543 patients. *Obstet. Gynaecol* 1982; 59: 720-725
2. Prendiville W, Cullimore W, Norman S. Large loop excision of the transformation zone (LLETZ). A new method of management for women with cervical intraepithelial neoplasia. *Br J Obs and Gynae* 1989; 96: 1054-1060.
3. Anderson MC. *Gynaecological Laser Surgery*. Perinatology Press, New York. 1985 137-143.

### GENERAL READING FOR CYTOLOGY

Report of the Intercollegiate Working Party on Cervical Cytology Screening 1987  
obtainable from  
The Royal College of Obstetricians and Gynaecologists  
27 Sussex Place  
Regents Park  
London NW1 4RG

#### Answer to Quiz on page 37

1. Myxomatous degeneration of the mitral valve
2. Ventricular tachyarrhythmia