Bronchoalveolar lavage
— Cytology

— Microbiology

— Virology (cytomegalovirus, cytopathic effect in cell culture. In some centres detection of α and β proteins (early proteins produced in cytomegalovirus replication 4-6 hours after cell infection)

Transbronchial biopsy
— Histology

— Microbiology (fungi, alcohol and acid fast bacilli, bacteria)

— Virology

Gallium scanning has been used extensively in the United States in patients with AIDS but less so in the United Kingdom. Gallium scans are frequently abnormal in *Pneumocystis carinii* pneumonia but also in the other respiratory manifestations of AIDS and are non-specific. We do not use this technique in our patients.

Open lung biopsy

This procedure may often be the only method to diagnose parenchymal Kaposi's sarcoma or lymphoid interstitial pneumonia.

Mechanical ventilation

Whatever the diagnosis or method used to achieve it, some patients will progress to respiratory failure, often rapidly, and the question of ventilation will arise. Experience with mechanical ventilation has shown universally poor results. In one large series no patient who had survived ventilation was alive at one year. Patients with *Pneumocystis carinii* pneumonia who do not respond to therapy and go into respiratory failure rarely improve through mechanical ventilation. There cannot be a uniform policy but mechanical ventilation seems appropriate as an exception rather than the rule.

Dr Ann Millar, MB, MRCP, is lecturer and honorary senior registrar in medicine, Middlesex Hospital Medical School, London.

I thank Professor S J G Semple for his advice on the preparation of this article and Miss Annette Skinner for her expert secretarial help.

Lesson of the Week

Complacency in diagnosis of cervical cancer

M J CAMPION, A SINGER, H S MITCHELL

Death from cervical cancer should be preventable. The pre-malignant stages of cervical neoplasia are well defined[1] and may be detected by a simple screening test[2] and treated by conservative measures with high rates of primary cure.[3] When invasive cancer occurs it is often associated early in its course with characteristic symptoms: vaginal discharge, postcoital bleeding, intermenstrual bleeding, and postmenopausal bleeding in older women. Many cases should therefore be diagnosed before the disease has spread, allowing radical treatment and a favourable outcome.

Despite at least a fourfold increase in the number of cervical smears taken in England and Wales over the past 20 years there has been only a small decrease in deaths from cervical cancer.[4] During this period there has been a dramatic increase in deaths from the disease among young women aged under 35,[5] with the attendant threat of future increases in deaths from cervical cancer at older ages.[6] This failure to reduce mortality from cervical cancer, particularly in younger women, is an indictment not only of government screening policies but also of doctors' failure to recognise fundamental aspects of the course of preinvasive cervical neoplasia and the clinical presentation of cervical malignancy.

All women in whom a cervical smear shows dyskaryotic cells should be referred for colposcopy. This applies equally to young women, in whom mortality from cervical cancer has increased appreciably

The failure of the screening programme for cervical cancer in England and Wales to produce the considerable decrease in mortality from cervical cancer that has occurred elsewhere, particularly in Scandinavia,[7] has been the subject of much controversy. Much attention has focused on the administrative failures in the cervical cytology screening programme: some workers have claimed that all the scientific facts needed to save most of the lost lives have been known for 20 years and the blocks to effective action are neither scientific nor technical but administrative.[8]

Although some administrative features of the screening programme for cervical cancer require review, failure to respond appropriately to abnormal cervical smears and a seemingly complacent attitude to symptoms and signs of cervical cancer are important factors. This is highlighted by the case histories of 14

Royal Northern Hospital, London N7
M J CAMPION, BSC, MB, research fellow
A SINGER, DPHIL, FRCOG, consultant gynaecologist
H S MITCHELL, MB, BS, research fellow

Correspondence to: Dr Campion.

young women with invasive cancer reported here. In all these cases measures could have been taken to avert the development of cervical cancer or at least to have prevented its spread.

Case reports

During a 12 month period 14 young women (age range 26-37) with invasive cancer were referred to the colposcopy and oncology unit at this hospital. The table summarises details of 12 of the cases; the remaining two are reported below.

Case 1—A 26 year old woman had a routine cervical smear in July 1984, which was reported as showing "mild dyskaryosis." Clinical examination at that time showed a cervical "erosion," which was treated by electrodiathermy in September 1985. The procedure was complicated by prolonged bleeding. Examination and a biopsy directed colposcopically, performed in October 1985, showed stage Ib, moderately well differentiated squamous carcinoma of the cervix with lymphatic permeation. Wertheim's operation was performed in November 1985. Micrometastases were found in right obturator and internal iliac nodes, and the patient was referred for adjuvant radiotherapy.

Case 2—A 35 year old woman presented to her general practitioner with a vaginal discharge in May 1977. "Atypical squamous cells" were reported in a cervical smear. A follow up smear taken in May 1978 was reported as negative. She presented again in August 1982 with vaginal discharge. Cervical cytology was reported as showing "widespread dyskaryosis and trichomoniasis," and she was treated with metronidazole. She presented in January 1985 with intermenstrual bleeding and postcoital bleeding and was referred to a gynaecologist. Clinical examination showed a cervical erosion, which was treated with electrodiathermy. A massive secondary haemorrhage required admission to hospital and blood transfusion. She returned again with intermenstrual and postcoital bleeding in June. Cervical cytology was reported as showing "severe dyskaryosis and bizarre keratinised squamous cells," and she was referred for a cone biopsy. She was unaware that the previous smears had been abnormal. She refused cone biopsy and requested referral for colposcopy. Examination and a biopsy directed colposcopically showed stage Ib, poorly differentiated squamous carcinoma. Wertheim's operation was performed in September 1985. Extensive spread to the pelvic nodes was found, and she was referred for adjuvant chemotherapy and radiotherapy.

Discussion

Cervical cancer kills 2000 women each year in England and Wales, most of whom have not had previous cervical smears.[9] A considerable and increasing minority of women presenting with and dying from cervical cancer have, however, had recent cervical smears but have still developed disease.[10] Many of these women are young and considered to be at low risk of cervical cancer. Similar findings have recently been reported from North America.[11] Our case histories suggest complacency and a lack of awareness of the importance of abnormal cervical smears and clinical symptoms of invasive disease, particularly in younger women, in the diagnosis of cervical neoplasia.

Women who present with symptoms of cervical cancer, such as abnormal vaginal discharge or bleeding, should be carefully assessed to exclude disease regardless of age. A satisfactory cervical smear is mandatory, and if symptoms persist referral for definitive diagnosis is indicated. In the presence of such symptoms any cytological abnormality, including inflammatory atypia and mild dyskaryosis, must be regarded with great suspicion and the patient should be referred for colposcopic assessment. The current practice of relying on cytological surveillance is inadequate. A patient's refusal to undergo investigative examination may not absolve the clinician from responsibility unless adequate measures are taken to

Details of 12 women who developed cervical cancer, with indications for referral and clinical findings

Case No	Age (years)	Total No of smears	No of abnormal smears	Details of first abnormal smear	Details of last abnormal smear	Indication for colposcopy	Final diagnosis	Metastatic disease	Treatment
1	29	4	3	Feb 1982: mild dyskaryosis	July 1985: malignant cells	Smear report	Stage Ib poorly differentiated SCC	Internal iliac nodes	RHND+adjuvant radiotherapy
2	29	6	4	April 1979: mild dyskaryosis, inflammatory changes	March 1986: severe nuclear atypia, inflammatory changes	Postcoital and intermenstrual bleeding; patient requested it	Stage II poorly differentiated SCC	Internal iliac and obturator nodes	RHND+adjuvant chemotherapy
3	33	5	4	March 1975: mild dyskaryosis, severe inflammatory changes	July 1985: malignant cells	Smear report; patient unaware of previous abnormal smears	Stage Ib poorly differentiated SCC	Internal iliac nodes	RHND+adjuvant radiotherapy
4	33	7	3	Dec 1978: inflammatory changes, nuclear atypia	Jan 1986: moderate dyskaryosis	Persistent vaginal discharge; patient requested it	Stage Ib poorly differentiated SCC	Internal iliac nodes	RHND
5	33	3	3	March 1984: mild dyskaryosis (antenatal smear)	Aug 1985: atypical squamous metaplasia	Intermenstrual bleeding; patient requested it, unaware of result of antenatal smear	Stage Ib poorly differentiated SCC	External iliac nodes	RHND+adjuvant radiotherapy
6	34	4	3	Jan 1981: inflammatory nuclear atypia	May 1986: malignant cells	Postcoital and intermenstrual bleeding for 9 months; smear report	Stage Ib poorly differentiated SCC	Internal and external iliac nodes	RHND+adjuvant chemotherapy
7	35	3	2	Nov 1984: mild dyskaryosis	May 1985: mild dyskaryosis	Patient requested it	Occult stage Ib poorly differentiated SCC	Lymphatic channels affected but not nodes	RHND+adjuvant chemotherapy
8	35	1	1	Patient refused smears in Jan 1983 and June 1984 when presenting with heavy postcoital bleeding	June 1985: severe dyskaryosis	Smear report and postcoital bleeding	Stage Ib poorly differentiated SCC	None	RHND
9	35	6	6	Feb 1980: abnormal glandular epithelial cells	May 1985: large syncytial sheets of cells with large atypical nuclei	Recurrent abnormal smears	Stage Ib poorly differentiated adenocarcinoma of cervix	None	RHND
10	36	5	3	Aug 1979: inflammatory atypia	Aug 1986: severe dyskaryosis	Smear report; patient requested it	Stage Ib poorly differentiated SCC	Internal and external iliac nodes	RHND+adjuvant chemotherapy
11	37	2	1	June 1983: postcoital bleeding, negative smear	Jan 1985: mild dyskaryosis	Referred for diathermy of cervical "erosion" causing postcoital bleeding	Stage II poorly differentiated adenocarcinoma of cervix	Extensive pelvic node disease on computed tomography	Radiotherapy and chemotherapy
12	37	4	3	April 1984: atypical endocervical cells	Nov 1985: suspicious endocervical cells	Smear report; patient unaware of earlier abnormal smears	Stage Ib poorly differentiated adenocarcinoma of cervix	None	RHND

SCC=Squamous carcinoma of cervix. RHND=Radical hysterectomy and lymph node dissection.

inform her of the possible grave consequences of her refusal. Women in whom follow up smears show mild abnormalities, including mild dyskaryosis and inflammatory atypia without dyskaryosis, represent a group at high risk of appreciable degrees of cervical neoplasia, including cancer. The 14 young women presented here had a total of 56 cervical smears, 43 of which were abnormal (often reported as showing mild atypia), but all still developed invasive cervical cancer.

In recent studies from this unit about 30% of women with mild dyskaryosis in a cervical smear were shown to have histologically proved cervical intraepithelial neoplasia grade III or invasive cancer at the time of referral.[11 12] Others have reported similar findings, of 49%[13] and 39%.[14] This information has been available for 15 years but has not been acted on.[15 16] The considerable malignant potential of untreated cervical intraepithelial neoplasia grade III has been shown recently.[19]

Our case reports also show the risk of cervical cancer in women whose repeat smears are reported as "class 2" inflammatory atypia without dyskaryosis. This risk seems to be especially high in women whose follow up smears show severe inflammatory changes in cervical epithelial cells or "borderline" changes with dyskaryosis, suggesting cervical intraepithelial neoplasia. Recent studies have shown cervical intraepithelial neoplasia grade II-III in at least 30% of women in whom a single smear showed severe non-specific inflammatory atypia, particularly in those aged 20-30.[13 14 18 19] This figure increases to 70% if such atypia is detected in repeated smears.[17]

Resources are not available to offer colposcopy to all women whose smear is reported as showing severe inflammatory atypia. An endocervical swab should be cultured and any lower genital tract infection, particularly chlamydial cervicitis, should be treated. The smear should be repeated within six months, and any further atypia should be investigated by colposcopy. If the repeat smear is negative regular smears should be offered and future atypia taken as an indication for colposcopy.

The management of women who have a minor grade of cervical epithelial disease (human papillomavirus infection I or cervical intraepithelial neoplasia grade I) presents a dilemma. Three recent cytological and colposcopic studies showed the potential of such disease to progress to severe neoplasia, including microinvasive cancer, within three years.[12 20 21] The risk of cervical intraepithelial neoplasia grade III or invasive cancer in women who have evidence of human papillomavirus infection I alone without dyskaryosis in a cervical smear is increased by a factor of 15.[22] Two recent studies showed aneuploidy in cervical human papillomavirus infection I alone, suggesting that such disease may be the earliest stage of cervical intraepithelial neoplasia.[23 24]

Often the women seen are young with small cervical lesions that may regress, especially after biopsy. A recent study from this unit showed considerable adverse psychosexual sequelae associated with conservative treatment of preinvasive cervical disease, but not colposcopic examination, in young women.[25] A period of rigorous cytological and colposcopic follow up of these women is therefore justified, and the high risk of developing cervical intraepithelial neoplasia grade III, or worse, must be remembered even when the disease seems to regress.

The incidence of cervical adenocarcinoma in situ and invasive adenocarcinoma seems to have increased recently. Cervical adenocarcinoma represents a particular problem for cytodiagnosis because of difficulties in obtaining a representative sample of endocervical cells and because cytological distinction between hyperplasia and neoplasia of endocervical cells is poorly defined.[2] Cytological evidence of atypical endocervical cells should be investigated further, and referral is mandatory when there is clinical suspicion of malignancy, regardless of the cytological findings or the patient's age.

Our cases suggest that preinvasive cervical disease may progress rapidly to cancer, particularly in younger women. This questions the protective value of screening at five year intervals and underlines the necessity for prompt management of abnormal cervical smears. The rate of primary cure for most conservative treatments for cervical intraepithelial neoplasia is over 90%.[3 13] The five year survival for young women with stage Ib cervical cancer is less than 50%,[15 26] with survival rates as low as 10% when lymphatic spread is present.

Eleven of our 14 patients were aged 35 or less at the time of diagnosis, and none had more than two children. They were therefore considered to be at low risk of developing the disease and not officially entitled to a smear by their general practitioners. Because regular screening is not being offered to younger women doctors must avail themselves of any opportunity to take a smear from them and so diagnose treatable preinvasive cervical neoplasia. Women who have atypical cervical smears must be informed of the abnormality and its implications. If this cannot be done the woman's medical records should be "flagged" in an easily recognisable way to alert the doctor should she present at a later date.

We believe that the pattern of cervical neoplasia is changing, with a more rapid progression of preinvasive cervical neoplasia to cancer. Cervical cancer in younger women is often a poorly differentiated tumour with potential for rapid spread to the lymphatic vasculature and distant spread, which has a much worse prognosis. A greater awareness of this is needed if deaths from cervical cancer are to be prevented.

MJC is funded by the Cancer Research Campaign. HM is the British Petroleum research fellow in gynaecological oncology.

References

1 Buckley CH, Butler EB, Fox H. Cervical intra-epithelial neoplasia. *J Clin Pathol* 1982;35:1-13.
2 Hudson E. The prevention of cervical cancer: the place of the cytological smear. In: Singer A, ed. *Cancer of the cervix: diagnosis and treatment*. London: W B Saunders, 1985:33-51.
3 Singer A, Campion MJ. Modern treatment of cervical precancer. *Journal of Obstetrics and Gynaecology* 1985;5:564-9.
4 Elwood JM, Cotton RE, Johnson J, Jones GM, Curnow J, Beaver MW. Are patients with abnormal smears adequately managed? *Br Med J* 1984;289:891-3.
5 Ward BG, Shepherd JH, Monaghan JM. Occult advanced cervical cancer. *Br Med J* 1984;290:1301.
6 Beral V, Booth M. Prediction of cervical cancer incidence and mortality in England and Wales. *Lancet* 1986;i:495.
7 Day NG. Effect of cervical cancer screening in Scandinavia. *Obstet Gynecol* 1984;63:714-6.
8 Anonymous. Cancer of the cervix: death by incompetence [Editorial]. *Lancet* 1985;ii;363-4.
9 Draper DJ, Cook GA. Changing patterns of cervical cancer rates. *Br Med J* 1983;287:510-2.
10 Chamberlain J. Failures of the cervical cytology screening programme. *Br Med J* 1984;289:853-4.
11 Singer A, Walker PJ, Tay SK, Dyson J. Impact of introduction of colposcopy to a district general hospital. *Br Med J* 1984;289:1049-51.
12 Campion MJ, McCance DJ, Cuzick J, Singer A. Progressive potential of mild cervical atypia: prospective cytological, colposcopic and virological study. *Lancet* 1986;ii:237-40.
13 Soutter WP, Wisdom S, Broughs AK, Monaghan JM. Should patients with mild atypia in a cervical smear be referred for colposcopy? *Br J Obstet Gynaecol* 1986;93:70-4.
14 Walker EM, Dodgson J, Duncan ID. Does mild atypia on a cervical smear warrant further investigation? *Lancet* 1986;ii:672-3.
15 Nyirjesy I. Atypical or suspicious smears: an aggressive diagnostic approach. *JAMA* 1972;222:691-3.
16 Davis RM, Cooke JK, Kirk RI. Cervical conisation: an experience with 400 patients. *Obstet Gynecol* 1972;40:23-7.
17 McIndoe WA, McLean MR, Jones RN, Mullins PR. The invasive potential of carcinoma-in-situ of the cervix. *Obstet Gynecol* 1984;64:451-3.
18 Tay SK, Jenkins D, Singer A. Management of squamous atypia (borderline nuclear abnormalities): repeat cytology or colposcopy. *Aust NZ J Obstet Gynaecol* (in press).
19 Reiter RC. Management of initial atypical cervical cytology: a randomized, prospective study. *Obstet Gynecol* 1986;68:237-40.
20 Evans AS, Monaghan JM. Spontaneous resolution of cervical warty dysplasia: the relevance of clinical and nuclear DNA features: a prospective study. *Br J Obstet Gynaecol* 1985;92:165-9.
21 Nash JD, Burke TW, Hoskins WJ. Biologic course of cervical human papillomavirus infection. *Obstet Gynecol* 1987;69:160-2.
22 Mitchell H, Drake M, Medley G. Prospective evaluation of risk of cervical cancer after cytological evidence of human papillomavirus infection. *Lancet* 1986;i:573-5.
23 Hughes RG, Neill WA, Norval M. Nuclear DNA analysis of koilocytic and premalignant lesions of the uterine cervix. *Br Med J* 1987;294:267-9.
24 Watts KC, Campion MJ, Butler EB, Jenkins D, Singer A, Hussain OAN. Quantitative DNA analysis of patients with mild cervical atypia:a potentially malignant lesion? *Obstet Gynecol* (in press).
25 Campion MJ, Brown JR, McCance DJ, Atia W, Cuzick J, Singer A. Psychosexual trauma of an abnormal cervical smear. *Br J Obstet Gynaecol* (in press).
26 Hall SW, Monaghan JM. Invasive carcinoma of the cervix in the younger woman. *Lancet* 1983;ii:731-2.