

**Statement of  
Euphemia McGoogan MBChB FRCPath MIAC**

**Professional qualifications and experience**

1. I graduated MBChB from Aberdeen University Medical School in 1973. I trained in Pathology in the University of Edinburgh Department of Pathology and became a member of the Royal College of Pathologists in 1982. I have been a Senior Lecturer in the University of Edinburgh Department of Pathology with an honorary Consultant Pathologist contract since January 1983. My area of special expertise is cervical cytopathology.
2. I am currently Pathology Patient Services Director for the Lothian University Hospitals NHS Trust in Edinburgh and as such am responsible for the largest combined morbid anatomy, histopathology and cytopathology service in the UK.
3. In 1993 I was asked by the Secretary of State for Scotland to chair an Inquiry into Cervical Cytopathology at the Inverclyde Royal Hospital, Greenock. This was published as an HMSO Report (Schedule 3). In 1995 I was invited by the States of Jersey Health Authority to advise on the setting up of a population cervical screening programme for the States of Jersey. In 1996 I was asked by the Royal College of Pathologists to assist Kent and Canterbury NHS Hospital Trust in the early stages of their inquiry into standards in cervical cytopathology in the hospital. In 1997 I was a member of a three-man expert group invited to Sarajevo after the end of the conflict to advise on women's health development, including a cervical screening programme. Since 1998 I have been a member of the expert advisory group funded by the European Community Tempus Project looking at modernisation of laboratory services for breast and cervical screening in Hungary.
4. I am a member of Council of both the International Academy of Cytology and the British Society for Clinical Cytology (BSCC).

5. I have a wide experience in training and quality assurance. I set up the BSCC national Certificate of Competence in Cytology Screening examination (end of training examination for cytology screeners) in 1988 and ran it for three years. I was co-author of the National Health Service Cervical Screening Programme (NHSCSP) Training Logbook for cytology screeners and have been asked to design a logbook and training programme for trained cytology screeners wishing to gain competence in reading liquid based cytology cervical samples. I am the Director of the Scottish Cervical Screening Programme Training School and collaborate with the University Libre de Bruxelles, Belgium and the Cytology Training School in Dijon, France in a EC funded project (SOCRATES) to develop training materials for cytology screeners. I was a member of the European Community Training Project for Cervical Cancer Screening from 1992 to 1994 that published guidelines for training and aptitude testing in cervical cytopathology as well as translation tables for the various terminologies in use within Europe. From 1992 – 1998 I chaired the Department of Health National Co-ordinating Committee for EQA in Gynaecological Cytopathology with a remit to co-ordinate existing Regional EQA schemes and to design and implement a National Proficiency Testing Scheme for the Cervical Screening Programme.
6. I am a member of the National Advisory Group for the Scottish Cervical Screening Programme. I serve on a large number of the NHSCSP committees and I am a co-author of many of their publications.
7. I have been an inspector for Clinical Pathology Accreditation (UK) Ltd for five years.
8. My current research interests lie in the field of new developments in Cervical Screening, the role of HPV testing in Cervical Screening, and the use of telepathology for training and quality assurance.
9. In 1995 I was a guest lecturer at the Joint Australian and New Zealand Cytology Society's Annual Meeting where I delivered a lecture on the Role of Cytology in the Breast Screening Programme. Immediately afterwards I gave a guest lecture on Quality Assurance in Cervical Cytopathology to the Southern Hemisphere Medical Laboratory Technologists' Annual Meeting at the Gold Coast.

10. I attach my curriculum vitae and list of publications as Schedule 1

### **Introduction to evidence**

11. The purpose of this statement of evidence is to provide a wide-ranging review of Cervical Screening from the Cytopathologist's Perspective. I will cover the following topics:

- Cervical cancer, its epidemiology, aetiology and pathogenesis;
- Terminologies in use in cytopathology and histopathology;
- General principles of screening programmes;
- What do sensitivity and specificity mean?
- What is a cervical screening programme?
- The NHS Cervical Screening Programme;
- Factors limiting success of cervical screening programmes;
- The role of the cytopathology laboratory in the NHS cervical screening programme;
- What is a cervical smear test (Pap Test)?
- Assessing false negative and false positive smear results;
- The limiting factors in sensitivity and specificity of the cervical smear;
- How we can address the limiting factors in cervical smears;
- Setting standards and performance indicators in cervical cytopathology;
- Problems in assessing performance;
- Mass rescreening exercises involving large numbers of smears;
- NHSCSP Guidance on Managing Incidents in the Cervical Screening Programme

12. Thereafter I will discuss the findings and recommendations of two previous mass rescreening exercises in the UK namely the Inverclyde and Kent and Canterbury Inquiries.

## CERVICAL SCREENING - THE CYTOPATHOLOGIST'S PERSPECTIVE

### What is the uterine cervix?

13. The uterine cervix (neck of the womb) is the lower part of the uterus that protrudes into the upper part of the vagina. The outer part (ectocervix) has a flat surface and is covered by tough multilayered squamous epithelium (skin). The endocervical canal leading into the cavity of the womb is thrown into deep folds and is lined by a single layer of fragile columnar glandular epithelium. At puberty, the cervix changes shape and everts, exposing the lower part of the canal and its fragile endocervical epithelium onto the surface of the cervix protruding into the vagina. Since the vagina is a foreign, rather “hostile” environment, this area of glandular epithelium is gradually replaced by squamous epithelium by means of a normal physiological process called metaplasia. This area is called the transformation zone (TZ). Most cervical cancers arise at the transformation zone.

Diagram 1

### Sagittal section through female pelvis

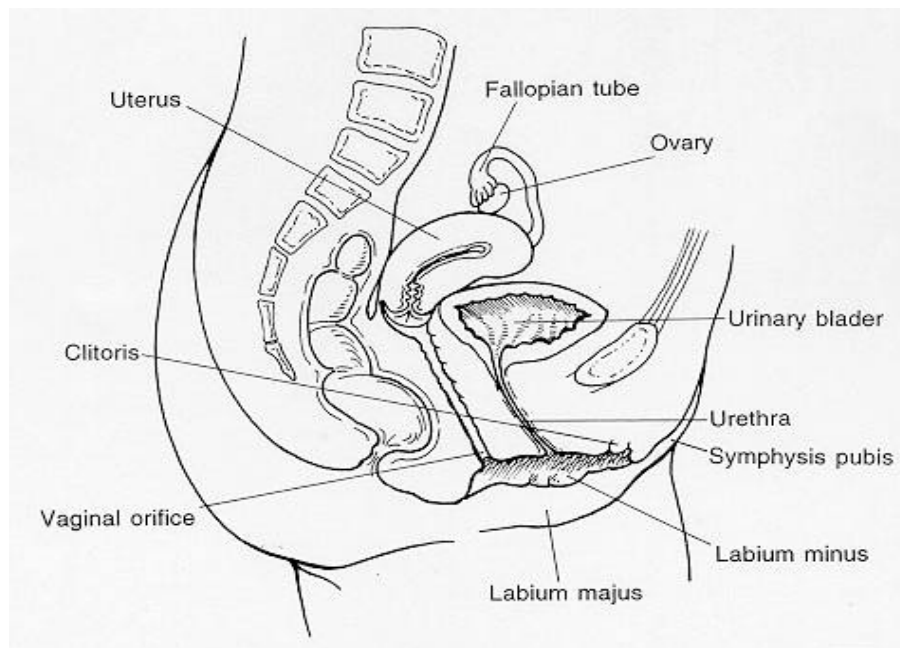


Diagram 2

**Diagram of female genital tract**

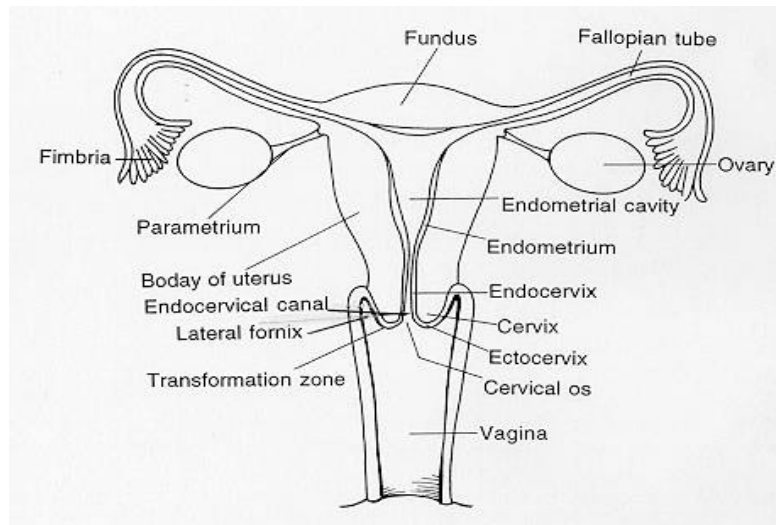
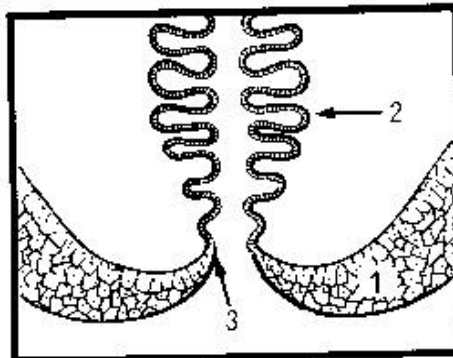


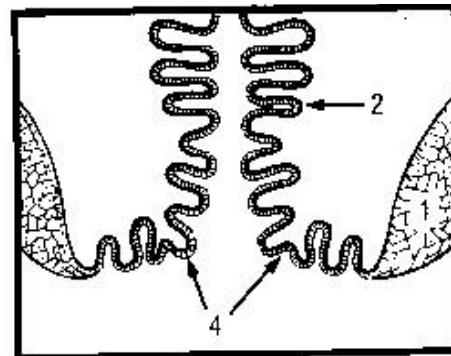
Diagram 3

**Development of transformation zone**

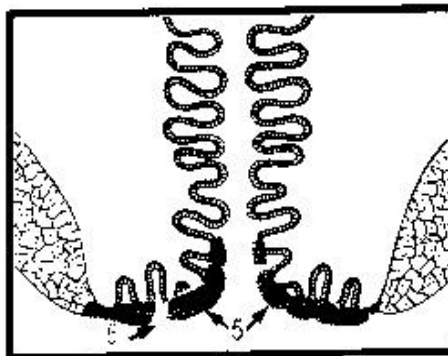
(Adapted from BSCC Booklet "Taking a Cervical Smear")



At puberty the junction of these two types of epithelium lies at the external os.



Hormonal changes at puberty and in pregnancy cause the cervix to change shape and the lower part of the endocervical canal becomes everted.

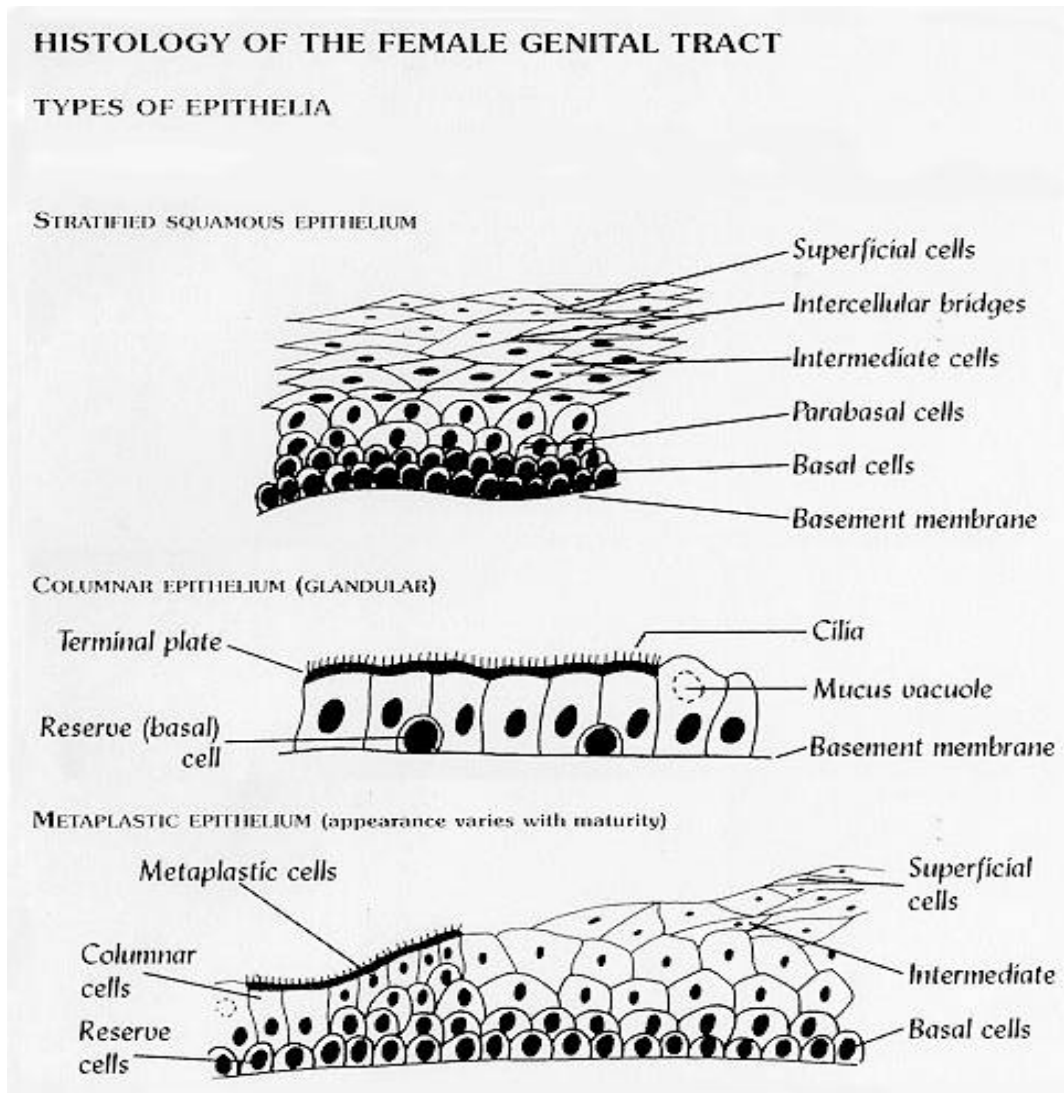


The surface of the everted columnar epithelium gradually changes to squamous epithelium. This altered area consisting of metaplastic squamous epithelium is known as the transformation zone.

In postmenopausal women there is a reduction in size of the cervix. The squamocolumnar junction and part of the transformation zone come to lie in the endocervix.

- 1 Squamous epithelium
- 2 Columnar epithelium
- 3 Squamo-columnar junction
- 4 Everted columnar epithelium
- 5 Transformation zone
- 6 Gland openings in transformation zone

Diagram 4



#### What is cervical cancer?

14. Cervical cancer is the largest single cause of cancer related deaths among women in developing countries and worldwide is second only to lung cancer with an estimated half a million new cases worldwide each year.
15. Cervical cancer is the name given to a group of malignant diseases affecting the neck of the womb. These can be classified by histological type into squamous carcinoma, adenocarcinoma, adenosquamous carcinoma and a few rare types of cancer. Squamous carcinomas constitute the majority of cancers but in countries with organised screening

programmes where the incidence of squamous carcinoma has been significantly reduced, adenocarcinoma may constitute up to 20% of the cancers diagnosed.

16. Squamous carcinoma develops in squamous or metaplastic epithelium at the transformation zone. It usually shows keratin production. Adenocarcinoma arises from glandular epithelium at the transformation zone or within the endocervical canal. It shows glandular differentiation and is often recognised by its capacity to secrete mucus. The natural history of squamous carcinoma has been more extensively studied than that of adenocarcinoma. Mixed differentiation and mixed adenosquamous carcinomas exist but these tend to behave biologically in a similar manner to squamous carcinoma.
17. The majority of cervical cancers have a long pre-invasive stage lasting about 10 years. Invasive cervical cancer usually does not cause symptoms until a late stage.
18. Invasive cervical cancer can be divided into 4 stages: Stage 1 where the cancer is confined to the cervix; Stage 2 where the cancer extends beyond the cervix but has not reached either lateral pelvic wall and involvement of the vagina is limited to the upper two thirds; Stage 3 where invasive cancer extends to the lateral pelvic wall or lower third of vagina and Stage 4 where the bladder and/or rectum is involved or there is spread beyond the pelvis. Stage 1 can be further subdivided into 1a where there is microscopic invasion only (less than 5 mm deep and 7mm wide) and 1b where the lesion is greater than this in size. Stage 1a cancer is only rarely associated with metastases and thus has virtually the same prognosis as CIN3 which is sometimes described as Stage 0 (pre-invasive stage). Prognosis decreases with increasing stage.

### **What is the epidemiology of cervical cancer?**

19. Epidemiology is the study of the relationships of the factors that determine the distribution and determinants of a disease in a human community (i.e. who gets it and where)

20. By 1990 cervical cancer was the seventh most common cancer worldwide and the fifth most common cancer in developing countries. 80% of new cases of cervical cancer each year occur in developing countries and 250,000 women die each year from the disease. Although cervical cancer has declined in industrialised countries, it remains the most common cancer among women in the developing world where the increased risk of infection with HPV is compounded with the limited capacity for screening and treatment. Mortality from cervical cancer varies from < 4% in North America to >36.5% in parts of Asia, Africa and South America.
21. Since the 1960s the incidence of cervical cancer in England had been increasing steadily and by 1985 was 16.2 / 100,000 women. After the introduction of the computerised call and recall NHSCSP in 1988, the incidence in England began to fall and by 1996 had fallen to 8.9 / 100,000 women (about 3,000 new cancers/annum).
22. In the UK the incidence of cervical cancer among the poorer socio-economic groups is double that of the most affluent group. In the USA, black populations show a two fold increased incidence rate compared to whites. There are also variations in incidence throughout the UK with in general higher incidence rates in the north.
23. Women born since 1940 have an increased risk of developing cervical cancer and there is a corresponding peak incidence in registrations of cervical cancer in women aged 35 – 39 years age group. There is another peak in the 65 – 69 years age group. Five year survival in developed countries where most cancers are detected at Stage 1 or 2 is around 90% and the majority of deaths from cervical cancer occur in the >60 years age group.
24. WHO statistics in 1994 placed Scotland top of the league for deaths from cervical cancer among developed countries with a death rate of 5.8 / 100,000, England & Wales came third with a death rate of 5.2 / 100,000 and New Zealand fourth at 4.6 / 100,000. However, the introduction of the NHSCSP in 1987 is now showing its effect and deaths from cervical cancer in England are currently falling at a rate of 7% per annum (<1,300 deaths/ annum).

### What is the aetiology of cervical cancer?

25. Aetiology is the study of the causation or sum of knowledge regarding causes of any disease (i.e. what causes it)
26. Early studies of cervical neoplasia suggested a direct causal relationship with sexual activity, measured as early onset of sexual activity, early age of first pregnancy and multiple sexual partners.
27. Various causative agents have been considered over the past 20 years but each has been discarded as a likely cause of cervical cancer. These have included components of semen and several viruses such as Epstein Barr virus, cytomegalovirus (CMV), and herpes simplex II virus (HSV).
28. More recently human papillomaviruses (**HPV**) have emerged as prime suspects since they can be detected in over 95 % of CIN3 and almost all cervical cancers and they possess transforming viral oncogenes E6 and E7 (these are tumour producing genes). HPV are DNA viruses. They infect animals as well as humans and currently **over 100 human types** have been identified. They are ubiquitous, very hardy viruses and most commonly affect the skin causing warts on the hands or verrucas on the feet. There are worldwide geographic variations in the incidence of the various types of HPV.
29. HPV infection of the human genital tract most commonly occurs as an acute viral infection and follows the course of most such infections. There is a phase when the virus multiplies within the human cells but eventually the body mounts an immune response to the viral particles and completely clears the virus from the body (25). HPV infection of the human genital tract falls into 2 broad types: **low risk types** such as types 6 and 11 and **high risk types** such as types 16, 18, 31,33 and 45. Low risk (or non-oncogenic) types are the most commonly associated with exophytic papillary warts (condyloma acuminatum) or CIN1. High risk (oncogenic) types can usually be found in CIN2/3 and invasive squamous carcinoma although they can be also detected

in up to 30% of normal women who will not go on to develop cervical cancer. A high proportion of cervical glandular intraepithelial neoplasia (CGIN) and endocervical adenocarcinomas are HPV positive and, in the UK, HPV 18 has been implicated more in adenocarcinoma than squamous carcinoma.

30. Differences are also detected in the physical status of HPV in cervical neoplasia. Low risk types (6/11) in CIN1 lesions are maintained as extra-chromosomal circular DNA fragments while the genomes of HPV16/18 are found integrated into the human DNA strands in CIN3 lesions and cervical carcinomas. HPV integration into human DNA appears to be a critical event in the progression to cervical cancer as HPV oncogenes E6 and E7 are conserved intact and show evidence of persistent and increased expression in carcinomas. The main mechanism of action of E6 and E7 from HPV high risk types is rapid inactivation of the host cell's tumour suppressor proteins p53 and Rb. This inactivation does not happen with E7 from low risk HPV types.
31. Since HPV infection is so common among women, **HPV clearly does not act alone** in causing cervical cancer. Epidemiological studies have thrown up a range of putative **co-factors** needed for progression to invasive cancer. These include smoking (possibly via nitrosamines, constituents of tobacco smoke that can be detected in cervical mucus), immunosuppression (in particular HIV infection, AIDS), sex steroid hormones (based on association of cervical cancer with long term use of oral contraceptive pill and high parity) and HLA type. These co-factors appear to influence progression from latent HPV infection to CIN3 rather than CIN3 to invasive cancer.
32. Barrier contraceptives are useful but cannot fully protect against HPV infection which can be transmitted skin to skin. Even when barrier contraceptives are available, women cannot always insist on their use. Infection and transmission of HPV might most effectively be controlled if a vaccine were available. Prophylactic and therapeutic vaccines are under development but none are available at present and there is no current curative treatment for HPV infection.

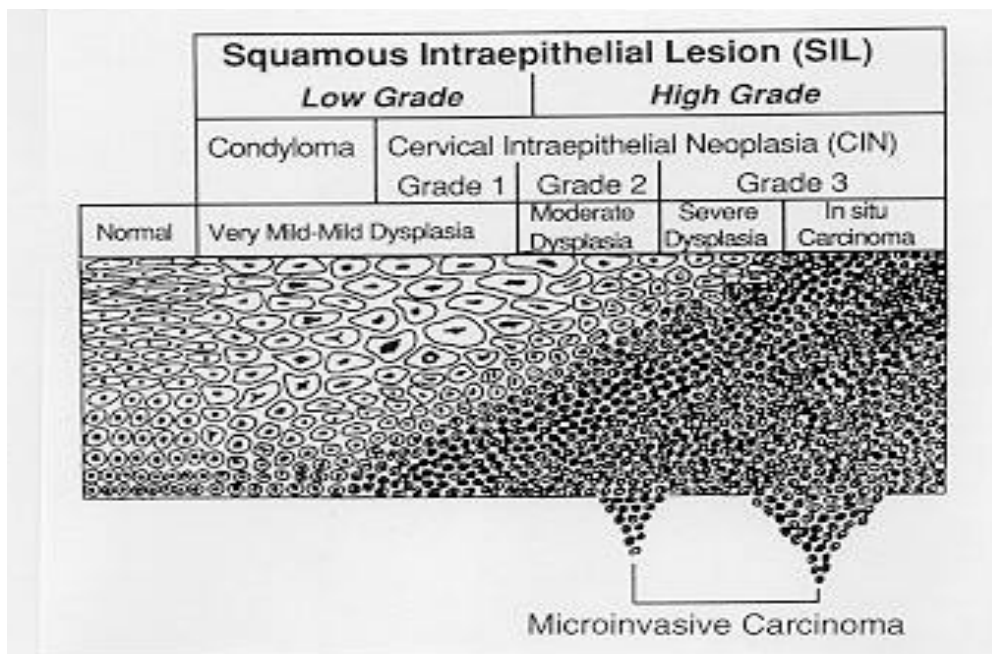
## What is the pathogenesis of cervical cancer?

33. Pathogenesis is the description of the stages in the development of a disease (i.e. how it develops).
34. Squamous carcinoma is a multistage disease which has a long precursor stage, known as cervical intraepithelial neoplasia (CIN), which represents a spectrum of changes limited to the squamous epithelium on the surface of the cervix. CIN can be categorised into arbitrary grades CIN1, CIN2 or CIN3 on the basis of whether abnormal cells comprise one third, two thirds or the entire thickness of the epithelium respectively. CIN is a neoplastic condition that, in some cases, can progress to invasive cancer. The relationship between CIN and The Bethesda System terminologies is dealt with later (see paragraph 42)

Diagram 5

### Cervical Intraepithelial Neoplasia

(Taken from Baustein's Pathology of the Female Genital Tract)



35. Most CIN1 lesions result from productive HPV infection and the current belief is that the majority of cases of CIN1 will return to normal over a period of 6 to 12 months if

left untreated. However, a proportion of CIN1 and increasingly higher proportions of CIN2 and CIN3 lesions will progress to invasive cancer over a period of many years. The exact timescale is unknown but evidence suggests it is in the region of 10 years. While the likelihood for regression decreases with increasing severity of CIN there is no way of predicting the clinical outcome of any individual lesion.

36. Ostor (1) in his classic study showed regression in 57% of CIN 1 cases, 32% persisted, progression to CIN 3 was established in 11% and progression to invasive cancer estimated in 1% of cases. The corresponding figures for CIN 2 were 43%, 35%, 22% and 5% respectively. The association of HPV with CIN has further complicated the natural history studies on these lesions. However, results from the early perspective follow-up studies are remarkably consistent. Progressing from HPV negative CIN (koilocytosis without CIN) to CIN 1 or greater was found in 8 - 13% of women. The natural history data of cervical pre-cancer lesions should have important implications in the treatment practice of these lesions, whether to treat or follow-up. CIN 1 and even CIN 2 lesions can be safely followed-up, provided that patient compliance can be ensured. It is essential to realise, however, that CIN3 lesions represent the immediate cancer precursor lesions, advocating prompt ablative treatment with biopsy confirmation of the free margins. Unfortunately, while these data apply neatly to a large series of women, they are of little help in predicting disease outcome for the individual women.
37. CIN is not cancer. It represents a pre-cancerous stage that if left untreated might progress to cancer. All grades of CIN are limited to the skin of the cervix by its basement membrane and at this stage the disease does not threaten the life of the woman. Invasive squamous carcinoma develops from CIN when neoplastic cells breach the basement membrane and invade the underlying deep tissues. Here the malignant cells may spread and grow locally or break through the walls of lymphatic and blood vessels and thus circulate round the body, becoming trapped and growing at distant sites as tumour metastases (see diagram 5).
38. Despite the existence of a spectrum of change, the development of invasive carcinoma may not necessarily involve sequential progression through stable CIN1, CIN2 and

CIN3 stages. Possible pathways may involve progression to invasive cancer from normal epithelium via a CIN3 stage only. Furthermore, some cases of CIN3 do not progress in the lifetime of the woman, some persist and others regress.

39. The natural history of adenocarcinoma is less well understood. Cervical glandular intraepithelial neoplasia (CGIN encompassing adenocarcinoma-in-situ, cervical glandular dysplasia and cervical glandular atypia) has been proposed as a precursor lesion on the basis of its morphological features. However, there has been no direct proof that CGIN will progress to invasive adenocarcinoma.
40. CIN is present in association with CGIN in over 50% of cases.

### **Terminologies in cervical cytopathology and histopathology**

41. A multiplicity of classifications and terminologies for both histological (biopsy) and cytological cervical precancerous changes are in use worldwide. These tend to use different criteria for classification and thus, unless one has intimate knowledge of both classifications, it is difficult to translate precisely from one to another. Furthermore within any published classification, there may be local or individual variations in the criteria applied or sub-classifications invented.
42. The Bethesda System (TBS) terminology used in the United States utilises a “squamous intraepithelial lesion” (SIL) classification rather than “cervical intraepithelial neoplasia” and classifies into two grades: low grade squamous epithelial lesion (LSIL) and high grade squamous intraepithelial lesion (HSIL). LSIL corresponds closely to CIN1 but includes smears and biopsies showing evidence of HPV infection without definite CIN. Both CIN2 and CIN3 are combined within the HSIL category. Within TBS there is a category for those smears with cellular changes that are insufficient to classify as SIL but which are not entirely normal. This category is called ASCUS (atypical cells of undetermined significance). Similarly there is a category for glandular cells changes short of adenocarcinoma – AGUS (atypical glandular cells of undetermined significance). In recent years in the US, due to fears

of litigation, there has been an increasing tendency to classify smears as ASCUS / AGUS which had formerly been assessed as within normal limits or benign cellular changes associated with inflammation and repair. **ASCUS is not a clinical condition of the woman. It is merely an inability of the pathologist to classify the smear as either normal or abnormal.**

43. The UK has used the dyskaryosis classification for 15 years. Cellular changes are classified by the degree of nuclear abnormality into mild, moderate or severe dyskaryosis of squamous cells. Dyskaryosis of glandular cells is classified as glandular abnormality. Where the nuclear changes do not amount to definite dyskaryosis, particularly in the presence of productive HPV infection, smears are classified as borderline nuclear changes.

#### **General Principles of Screening Programmes.**

44. Wilson and Junger in their WHO Report in 1968 (2) described the basic principles required for a screening programme as follows:
- the disease should pose an important health problem for the individual and the community;
  - its natural history should be well understood with a recognisable early stage;
  - treatment at an early stage should be advantageous;
  - an appropriate and acceptable screening test should be available and offered at suitable intervals;
  - there should be adequate facilities for the diagnosis and treatment of abnormalities identified;
  - the chance of physical or psychological harm must be less than the chance of benefit;
  - the costs of the screening programme should be balanced against the benefits it provides.
45. The aim of a screening programme is to sort out those who **probably** have the disease from those who **probably** do not.

46. The aim of a **screening test** is fundamentally different from that of a **diagnostic test**. A screening test aims to identify asymptomatic disease in women (not patients); the consultation is initiated by the doctor who recommends the screening test to the woman because it will benefit her. On the other hand, a diagnostic test aims to investigate symptomatic disease and deals with patients who themselves initiate the consultation because they have a problem. The doctor recommends appropriate tests to investigate the symptoms and make the diagnosis. Those responsible for the programme, therefore, have an ethical obligation to ensure that the benefits outweigh the adverse effects.
47. In order to obtain sufficient resources a screening programme must be well organised and monitored. It must be able to demonstrate value for money and that it does more good than harm. In order to do this, quality standards for each component of a screening programme must be set.

### **What do sensitivity and specificity mean?**

48. **Sensitivity** is the proportion of truly diseased persons in the screened population who are identified by a “positive” screening test. It is a mathematical expression of the ability of the programme or test to detect disease in a diseased population. (i.e. 1 minus the false negative proportion expressed as a percentage)
49. **Specificity** is the proportion of truly non-diseased persons who are identified by a “negative” screening test. It is a mathematical expression of the ability of the programme or test to refrain from falsely diagnosing disease in a non-diseased (i.e. normal) population. (i.e. 1 minus the false positive proportion expressed as a percentage)
50. With most screening tests there is to some extent a “trade off” between sensitivity and specificity. If the threshold of the test is set to give higher sensitivity then this will be at the expense of reduced specificity and large numbers of normal people will be made

unnecessarily anxious by the screening programme due to “false positive” results suggesting a condition they do not have; similarly increasing the specificity will tend to reduce the sensitivity and thus the effectiveness of the screening programme will be reduced. As with other screening methods, the relationship between sensitivity and specificity in cervical screening can be formally assessed.

51. All screening programmes have false negatives and false positives. It is impossible to run a screening programme without false negatives and false positives. Therefore the false negative and false positive rates can never be zero (i.e. sensitivity and specificity cannot be 100%). Thus most false positive and false negative results are phenomena of the screening test rather than incompetence or negligence. In most cases the word “error” should be avoided. The challenge for those managing screening programmes and their quality assurance is to strike a good balance between the false positive rate and the false negative rate.
52. It is worth noting that a poor quality cytopathology service may have both a high false negative rate and a high false positive rate. In this situation, most true high grade lesions would be missed and reported as negative. At the same time the laboratory would report many cases as high grade lesions which are actually within normal limits or only low grade. Thus the reporting profile and laboratory statistics may appear to be within the normal range but the laboratory has both a low sensitivity and a low specificity.
53. Moreover, the “truth” or at least something approximating to the truth must be known in order to calculate sensitivity and specificity in a meaningful way. This is not possible and thus a surrogate “reference diagnosis” must be defined for positive and negative results. However, in cervical screening no consistently used reference diagnosis exists. Ideally one would compare against biopsy diagnosis but biopsy reporting also has a sensitivity and specificity less than 100%. Furthermore it would be unethical to carry out an invasive procedure on potentially normal women with negative cytology simply to prove they are normal. This might possibly be justified in women in high-risk groups, but this would give a biased assessment of the sensitivity of the test in the general population.

54. Finally, and most importantly, the sensitivity of the whole screening programme rather than of individual screening tests within it must be considered. The sensitivity of any one test does not fully represent the sensitivity of the programme as a whole. One false negative test may be of no significance if the abnormality is picked up before the development of invasive or symptomatic disease when the woman is next screened. Thus, the programme sensitivity will be a function of the screening interval and it may, for example, be a better policy to reduce the screening interval and/or ensure women do not miss a screening round than improve on the sensitivity of individual tests.
55. A wide range of performance has been reported by Fahey for sensitivity and specificity with current cervical smear tests (3). In part this is due to differences between studies in respect of what is considered a “positive” result (i.e. whether ASCUS / AGUS is included or not). As a broad approximation, Fahey’s review concluded that the sensitivity for conventional smears was on average about 55-65% and the specificity 65-70%. However, they caution that, as the reference test itself may not be perfect, it is likely that the sensitivity and specificity are prevalence dependent and that the sensitivity may be underestimated.
56. False positive and false negative rates are only partial expressions of a broader concept of diagnostic accuracy. Positive predictive value (PPV) is the probability of disease being present in those individuals with a “positive” test result and is another expression of diagnostic accuracy. Likewise negative predictive value (NPV) measures the probability that those individuals with a negative test result are disease free.
57. The challenge for any screening programme is that the false positive rate and the false negative rate are universally related and measures to reduce one may increase the other. It also has to be accepted that there will be inter-observer and intra-observer variability in any screening programme that depends upon an individual perception of abnormality (22). Thus, when reviewing smears a proportion of negative smears will always be reclassified as positive even if reviewed by the same individual who read the smear on the first occasion. Steps need to be taken to agree the degree of inter and intra observer variability which is acceptable.

### What is a cervical screening programme?

58. Although the effectiveness of screening has never been properly demonstrated in randomised controlled trials, firm evidence to confirm effectiveness comes from British Columbia in Canada and from the Nordic countries where the implementation of widely different approaches to cervical screening policies resulted in sharply contrasting trends in incidence and mortality. Thus the effectiveness of cervical screening programmes based on cervical smear tests at regular intervals in reducing mortality from carcinoma of the cervix and the incidence of invasive disease is well established. (4) The protection from a single smear remains relatively high for three years but falls off rapidly after five years.
59. Nick Day in the International Agency for Research on Cancer (IARC) publication in 1986 estimated the reduction in risk for women who participate in a cervical screening programme with varying screening intervals in the age range 35 – 64 years. The number of smears in a lifetime is a surrogate for the cost of the programme. Starting screening at age 20 years markedly increased the number of smears without a great effect in reduction in risk. Regular screening, however, is necessary to overcome the low sensitivity of a single cervical smear. In addition, some screening programmes have recommended repeating the first ever smear in one year especially when screening starts at 35 years and the screening interval is 5 yearly.

Table 2 (Adapted from IARC Publication No 76 1986)

Screening schedule Age range 35 -64	% reduction in cumulative rate	No of smears in lifetime (= cost)
Every 10 years	64.0	3
Every 5 years	83.0	6
Every 3 years	91.2	10
Every 2 years	93.3	15
Every 1 year	93.3	30

Note: these estimates presume that all women 35 – 64 are screened regularly.

60. Cervical screening programmes meet many but not all of the Wilson and Junger criteria. In developing countries cervical cancer is a major health problem but in developed countries it is relatively uncommon and its natural course is not well understood. The natural history of CIN and in particular CGIN is still not fully determined. The cervical smear is not a very reliable or repeatable screening test and a single smear has a low sensitivity. Microscopic evaluation of cervical smears is very skilled and labour intensive and there is a shortage of trained laboratory staff to carry out the test.
61. It has been estimated that the NHS Cervical Screening programme prevents up to 3,900 cases of cervical cancer each year. The Programme between 1988 and 1997 saved over 8,000 lives. Currently approximately 1,300 lives are saved each year, 800 for women less than 55 years of age.
62. It is important to recognise that cervical screening programmes are designed to reduce the population mortality from squamous carcinoma but not adenocarcinoma. Although CGIN and adenocarcinoma may be identified in a cervical smear, the smear test is only designed to detect CIN.
63. For screening to be effective, it is especially important that the programme be organised according to an agreed policy, the essential elements of such a policy are:
- the target population has been identified;
  - individual women are identifiable;
  - measures are available to guarantee high coverage and attendance (such as a personal letter of invitation, good health education programmes);
  - there are adequate field facilities for taking smears
  - there are adequate laboratory facilities to examine smears;
  - adequate colposcopy facilities exist for diagnosis;
  - adequate facilities exist for appropriate treatment of confirmed neoplastic lesions;
  - adequate resources exist for the follow-up of treated women;

- there is an organised programme for quality control of all components of the programme with data collection;
- a system is in place to monitor and evaluate the data collected;
- there must be a carefully designed and agreed referral system, an agreed link between the women, the laboratory and the clinical facility for the diagnosis following an abnormal screening test, management of any abnormality found, providing information about normal screening tests and failsafe follow up of women who default.
- the programme must also educate and inform women and health professional about the benefits and limitations of screening.

Thus cervical screening involves a large number of health professionals who must work together as a team.

64. The false negative cervical smear may not be the biggest problem in cervical screening today. The false positive cervical smear is far more prevalent and results in additional economic costs to the health service and emotional stress to the woman. In an attempt to lower the false negative rate, laboratories have been increasing their false positive and inadequate rates with resulting additional economic and emotional costs associated with increased referral for repeat smear or further investigation. It is worthy of note that ASCUS reporting rates are much higher in countries where litigation is common. Specificity is particularly important in screening programmes because false positives cause morbidity. Indeed some “true positives” are also a problem if they identify and lead to treatment of conditions which would not have progressed to significant disease and become apparent. The majority of low grade lesions identified on cervical smears and referred for colposcopic treatment would regress spontaneously.
65. Cervical screening must be run as a system with objectives, criteria to measure progress towards those objectives and standards and targets. Clinical and programme audit is integral to an effective cervical screening programme. Such an audit should include monitoring of
- the population coverage

- the quality of smear taking - especially inadequate rates by individual smear taker,
- the rates of reporting for the various grades of cytological reports per laboratory,
- turnaround times for smear result to woman,
- colposcopy referrals,
- smear correlation with biopsy and outcome,
- within normal limits biopsy rate
- recurrence rates following treatment,
- failsafe follow up,
- investigation of the smear history of women who develop invasive cervical cancer.

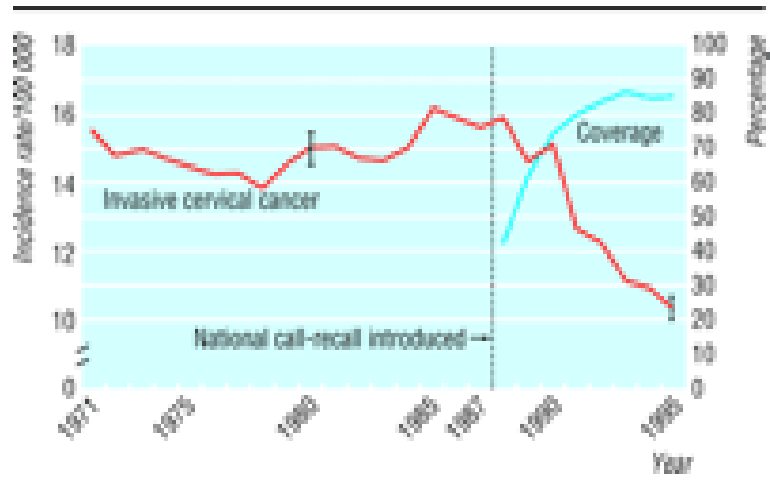
66. The success of a cervical screening programme depends on the effectiveness of each of its component parts. Evaluation and monitoring of the total programme is organised in terms of incidence and mortality rates at the level of the total target population among those attending, and among those not attending. Quality control of these epidemiological data should be established. At a national level, changes in cancer incidence and mortality are valid measures of effectiveness. However, for the population served by health authorities or individual laboratories, population numbers are too small for statistical significance and incidence and mortality data are less valid. Here other measures of the cervical screening process may have to be used. e.g. the percentage of women who have had a smear test, the false positive rate.
67. To measure and improve the quality of a service, it is necessary to have explicit standards, an information system that allows the necessary data to be collected and a quality assurance system that allows action to be taken should any part of the programme fail to meet those standards. A common data set for programme evaluation should be agreed and steps must be taken to improve the validity of the data collected. Each national and regional programme should have a Programme Co-ordinator whose job description, line of accountability and responsibilities are clearly documented. Each health authority should produce an annual report on the cervical screening programme for its population and the national programme should publish a national programme annual report.

68. It is important to emphasise the need for a high degree of training for all staff involved in smear preparation, laboratory evaluation and colposcopic assessment as well as a comprehensive quality assurance programme.

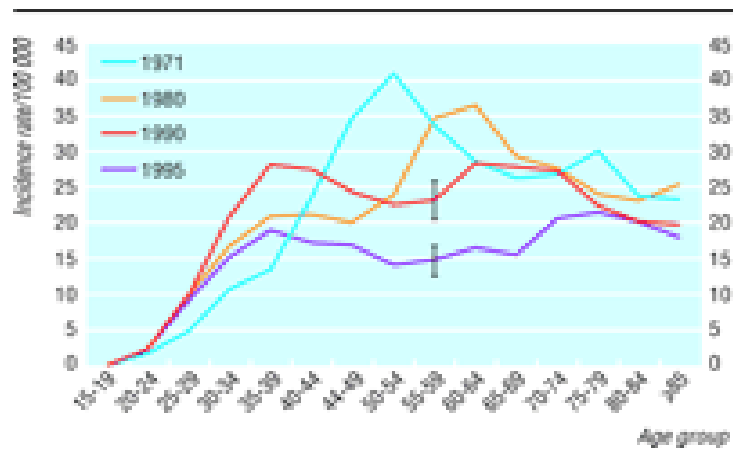
### **The history of the NHS Cervical Screening Programme (NHSCSP)**

69. Cervical cytopathology was introduced in the UK in the late 1940s and grew in a haphazard fashion in the 1960s, 1970s and 1980s led mainly by enthusiastic gynaecologists. Cervical smear tests identified many women with precancerous changes in their cervix who received treatment and never developed invasive cancer. Successive White Papers set out policies for cervical screening, determining the age group and the recommended intervals. However, since only a small proportion of the population were presenting themselves for regular cervical smear tests, there was little impact on the population incidence and mortality from cervical cancer. We must recognize that, at that time, the UK was dealing with a national **cervical screening policy** and not an **organised cervical screening programme**.
70. In the late 1980s a national call and recall cervical screening programme was introduced in the UK and tremendous efforts were made by public health and primary care physicians to encourage full population participation in this re-organised cervical screening programme. A population coverage of over 80% of the target age group 20 – 64 years was achieved and by the mid 1990s, this had resulted in major reductions in the incidence from cervical cancer in the populations screened (Tables 1, 2). The mortality is now dropping at a rate of 7% per annum (Table 3). Thus the NHS cervical screening programme was established and proving successful.
71. The implementation of quality assurance in the NHSCSP has included the development and implementation of standards for all aspects of the programme. Regional Quality Assurance Teams have been set up by the National Co-ordinating Team to monitor and review performance against the standards, and national co-ordinating committees are being set up to further the development of quality assurance.

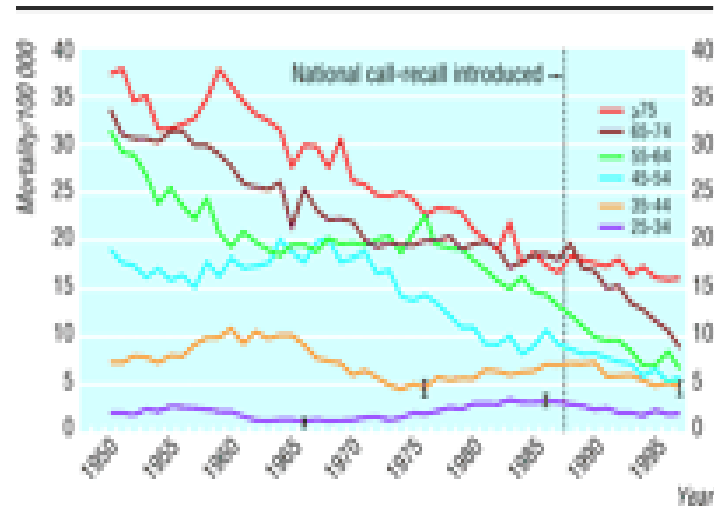
**Table 1** (taken from Quinn et al BMJ 1999)



**Table 2** (taken from Quinn et al BMJ 1999)



**Table 3** (taken from Quinn et al BMJ 1999)



72. The NHSCSP has published guidelines for good practice and quality standards not only for laboratories but also for each component of the screening programme. Thus there are publications covering: Standards and Quality in Colposcopy; Quality Assurance Guidelines for the Screening Programme; Guidance Notes on the Safe Use of Diathermy Loop Excision for the Treatment of CIN; Improving the quality of the written information sent to women about cervical screening; A Practical Guide for Health Authorities; Guidelines for Clinical Practice and Programme Management; Resource Pack for Training Smear Takers; Histopathology Reporting in Cervical Screening; Qualifications and Training for Non-medical Laboratory Staff in the UK Cervical Screening Programmes and Guidelines for Managing Incidents in Cervical Screening. In addition the NHSCSP has commissioned several other works such as the Medical Devices Agency report “Guidance on the application of minimum ergonomic working standards for personnel engaged in the preparation, scanning and reporting of cervical screening slides” and the joint report from the National Coordinating Network, the BSCC and the Royal College of Pathologists on “Borderline nuclear changes in cervical smears: guidelines on their recognition and management”. It is interesting to note that only two of the eleven NHSCSP publications address standards for laboratories.
73. The priority for the first five years of the NHSCSP was to improve coverage and fail-safe systems (back up reminders). The priorities for the second five years were to improve the quality of smear taking, to reduce inter-observer variability by defining

the borderline nuclear changes category, to develop a much more scientific approach to the analysis and management of variations in performance. The current priorities are to support the work of the Regional Quality Assurance Teams, commission pilots for the introduction of new technologies such as liquid based cytology and HPV testing, and maintaining and developing the workforce since recruitment and retention of staff is a problem across all laboratory medicine specialties in the UK at present.

74. The challenge facing the NHSCSP in the millenium is to further improve the rate of reduction in the incidence of cervical cancer. The situation faced today by the NHSCSP is very different to that it faced in 1987 when the organised call and recall programme was launched. At that time, the biggest gains were to be achieved by screening a larger percentage of the population at risk since most cancers occurred in unscreened women. Population coverage is now maintained at over 80% and to continue to achieve further reductions in the incidence of cervical cancer, the sensitivity of the Programme to detect abnormalities in women participating in the Programme must be addressed. This might be achieved by reducing the screening interval to two or one year but the cost would be prohibitive. The most important cause of false negative results is the quality of the sample sent to the laboratory for assessment and this is where attention must be given if the sensitivity of the NHSCSP is to be increased further.

**Table 4** History of major events in NHSCSP

Year	Event
1948	Cervical cytology laboratories began to function.
1967	Opportunistic Cervical Screening Policy published (women over 35 every 5 years)
1986	Terminology in Gynaecological Cytopathology: Report of the Working Party of the BSCC (published in J Clin Pathol)
1986	Recommended Code of Practice for Laboratories providing a Cytopathology service (BSCC publication)
1987	Cytology Screener grade introduced. Certificate of Competence examination set up to mark completion of training and confirm competence
1988	NHS Cervical Screening Programme launched with population call and recall for women aged 20-64 every 3-5 years
1988	National Co-ordinating Network established
1988	EQA - Proficiency Testing Scheme introduced (Department of Health) - Regional schemes implemented
1989	National Certificate of Competence examination introduced
1990	GP Target Payments for cervical smears (incentive payments) for primary care introduced.

1992	“Health of the Nation” White Paper –target to reduce incidence of cervical cancer to less than 12 per 100,000 women by the year 2000
1993	First round of the NHSCSP completed
1993	National Audit Report criticizing NHSCSP for lack of clearly defined standards and targets.
1993	Report of Inquiry into Cervical Cytopathology at Inverclyde Royal Hospital Greenock
1994	National Co-ordinator and National Co-ordination Team appointed
1995	Cervical Cytopathology Training Log (NHSCSP) (second edition 1998)
1995	Scottish Office Report of the Working Party on Internal Quality Control for Cervical Cytopathology Laboratories.
1995	First NHSCSP publication – “ABC” for laboratories
1996	NHSCSP document Quality Assurance Guidelines for the Cervical Screening Programme
1996	Kent and Canterbury Hospital Inquiry
1998	Second round of the NHSCSP completed
1998	Laboratory accreditation mandatory

### Factors limiting the success of cervical screening programmes

75. Health professionals in the UK have done an extraordinary and commendable job of educating the public about the benefits of cervical screening. We have been less successful and conscientious about explaining and defining the limitations of a single cervical smear test. Cases are judged on an individual basis without significant consideration of the general performance of the cervical smear in laboratories operating in compliance with recommendations for good practice and with documented and comprehensive quality control practices in place. It is no wonder then that the public has come to expect unattainable levels of detector proficiency, diagnostic accuracy and clinical management guidance from a test that was originally designed to screen for, rather than to specifically diagnose, cervical cancer and its precursors.
76. The aggregate effect of all the publicity surrounding individual case litigation has all but eclipsed the extraordinary success of cervical screening programmes in reducing deaths from cervical cancer in the last half century. **Many more women have benefited from a cervical smear test than have failed to benefit from one.** Even in the poorest quality laboratory some women with CIN3 will have been identified, referred for colposcopy and treated so they have not developed invasive cancer.

77. The benefits and limitations of the cervical screening programme need to be explained clearly to professionals, to the public and the press. Information should be made clearly available to women being offered screening so that they understand the potential and limitations of the screening test.
78. Both sensitivity and specificity for cervical screening are significantly less than 100%. The cervical smear is not a highly sensitive test and the benefit to women comes from repeated tests at regular intervals. Failure to regularly screen all women in the “at risk” age group and deficiencies of the quality the sample sent to the laboratory have been identified as the major limitations of the sensitivity of cervical screening programmes. In addition, the success of the programme may be limited by a reluctance among women to present themselves for **regular** tests, the length of the agreed screening interval which may miss rapidly growing cancers, deficiencies in following up and managing women with identified abnormalities in their smears, a failure to cure all women treated for pre-invasive disease and the inability of the test to detect all women with those particular high grade CIN lesions which will progress to invasive cancer if left untreated.

### **The role of the cytopathology laboratory in the NHSCSP**

79. In the UK, the role of the laboratory is the same whether it is a health service laboratory or a private laboratory. It should provide a consultative and advisory service - not simply a “results only” service. Health service laboratories should be cost effective. A service of acceptable quality as specified in the standards for the local and national cervical screening programmes must be delivered. Performance in external quality assurance must be satisfactory. The laboratory should attain and maintain full accreditation with CPA (UK) Ltd (see below).
80. The laboratory should use the nationally agreed terminology for cervical cytopathology and follow the recommended management for abnormalities detected. Results should be kept in a computerized database to facilitate statistical data collection and audit of the service. Appropriate information should be forwarded to the local health authority

as agreed to assist in auditing and managing the cervical screening programme. In particular, laboratories have a responsibility to co-operate with primary care teams to help provide a back up reminder (failsafe follow up) of women with abnormal smears who default from follow up.

81. Laboratory responsibility has changed very little since the publication of the BSCC Code of Practice for Cytopathology Laboratories in 1987 and current standards can be summarized under the following headings
  - Laboratory and individual workloads
  - Staffing
  - Laboratory practice
  - Performance standards and quality assurance
  
82. NHSCSP recommended minimum laboratory cervical cytopathology workload is set at 15,000 cervical smears / annum. There is also need to ensure that there is a full range of diagnostic material coming through the laboratory, the work output for each cytotechnologist and each pathologist is sufficient for them to maintain their skills, the availability of previous smears in same laboratory and the availability of colposcopic biopsies for correlation with previous smears
  
83. The laboratory workload of 15,000 smears / annum was chosen as the minimum since this would require at least two cytology screeners and would generate about 1,500 smears / annum referred for a pathologist's opinion (~10%). In every laboratory there should always be at least two pathologists competent in cytopathology to cover for periods of sickness and annual leave so the minimum each would see per annum would be 750 cases (plus review of all previous smears for high grade lesions). This minimum workload figure is supported by the published data from the 1992 College of American Pathologists PAP Error Rates which showed a watershed in performance between laboratories at 15,000 smears / annum. The performance in the EQA scheme was significantly poorer for laboratories with workloads less than 15,000 than for laboratories with workloads greater than 15,000.

84. The BSCC Guidelines published in 1987 recommended staffing levels as follows:
- 1.5 whole time equivalent Pathologists / 25,000 smears (plus other general cytology) / year
  - 1 Primary screener / 7,000 smears / year
  - 1 Senior technical supervisor / 3 primary screeners
  - 1 Clerical staff / 3 primary screeners
85. The cervical cytopathology service should be professionally led by a named consultant cytopathologist who is responsible for delivering the agreed laboratory specification of service. He/she must liaise with local NHSCSP programme co-ordinator and other personnel and routinely be available in the laboratory every working day.
86. The laboratory must be staffed with appropriate numbers and grades of medical and technical staff. Medical staff should be Members of the Royal College of Pathologists. (A major component of the current MRCPATH examination is competence in breast and cervical cytopathology). Technical staff should be appropriately trained and hold the NHSCSP Certificate in Cytology Screening or previous equivalent (prior to 1996 the BSCC and Institute of Biomedical Sciences held separate cytology examinations). All staff should have their continuing competence tested at regular intervals through the Proficiency Testing Scheme. Laboratories should provide facilities for continuing education for all their staff.
87. The laboratory should adhere to good practice guidelines as set out in the NHSCSP publications. Screeners should not perform primary microscopic screening for more than 4 hours per day. Individual medical and technical staff should record the number of cases screened and ensure that they meet the minimum annual numbers to ensure continuing competence. In the UK technical staff should primary screen between 3000 and 7500 slides per annum, medical staff should report at least 750 cervical cases (including review of previous smears) per annum. All smears which show ASCUS / AGUS (borderline) or a more severe abnormality must be referred to and reported by a pathologist. Smears should be retained in a secure archive for at least 10 years.

88. Laboratory operation and practice is accredited by CPA (UK) Ltd, an independent company formed by the Royal College and Professional Bodies in 1992 to provide a peer review based accreditation system for laboratories in all disciplines and in both the public and private sector. (There are only a handful of private laboratories in the UK). Standards of good laboratory practice are agreed with the professional bodies and published. These are reviewed and revised at regular intervals. There are standards for organisation and administration, staffing and direction, facilities and equipment, policies and procedures, staff development and education and evaluation. The CPA process is simple. Laboratories assess themselves against the standards and complete a questionnaire to indicate compliance with the standards. The relevant Specialist Advisory Committee considers the application and, if accepted, then a team of inspectors visits the laboratory to confirm compliance with the standards. Inspectors are drawn from consultant pathologists, clinical scientists and senior biomedical scientists nominated by the professional organizations. In the UK laboratory accreditation is still voluntary except for those laboratories which report cervical smears. It became mandatory for cervical cytopathology laboratories in April 1998.
89. External quality assurance of cervical cytopathology laboratories has relied heavily on the UK Proficiency Testing Scheme which was established according to a Department of Health protocol issued in 1988. By 1995 every region had a scheme: 235 laboratories, 2000 technical staff and 500 medical staff were participating annually. The scheme involves a Facilitator taking selected slide sets of 10 slides to the laboratory and every individual who issues results on cervical smears must screen a set in a 2 hour period. However, monitoring laboratory statistics (published annually) was also seen as an important quality assurance measure.

90. Formal performance standards for laboratories providing a service for the NHSCSP were published in 1995 in the Achievable Standards, Benchmarks for Reporting and Criteria for Evaluating Cervical Cytopathology (“ABC”) document (6). This states that it is the responsibility of the smear taker to ensure that the whole of the transformation zone has been sampled and that an adequate sample is sent to the laboratory. The laboratory can only assess whether the smear is satisfactory for microscopic assessment.
91. The document includes several quality standards such as achievable standards for the laboratory reporting profile (see table below), the sensitivity of primary screening as assessed by rapid review of all negative and inadequate smears, and the positive predictive value for a high grade smear when compared against subsequent biopsy. In 1995, the achievable range for sensitivity for primary screening (for detecting moderate and severe dyskaryosis) was set at 85 - 95%. The achievable standard range for Positive Predictive Value (smear reported as moderate dyskaryosis or worse and biopsy showing CIN 2 or higher ) was set at 65 - 85%. The ABC document was a first attempt to establish standard ranges for laboratory performance, and experience and continued evaluation of new data will result in adjustment of the ranges in due course. A revised edition of the ABC document is about to be published.

<b>Laboratory profile Smear result</b>	<b>Achievable standard</b>
Moderate + severe dyskaryosis	1.6 (+/- 0.4%)
Borderline + mild dyskaryosis	5.5 (+/- 1.5%)
Inadequate	7.0 (+/- 2.0%)

92. The document also emphasizes the need for a wide range of other quality assurance and, in particular, internal quality control; external quality assurance; clinical audit and programme audit; appropriate training of all staff; and continuing education and professional development.
93. Appropriate internal quality control should be in place in every laboratory and be fully documented. The original BSCC Code of practice recommended full double screening

of slides from “high risk” women (i.e. with symptoms suspicious of disease or previous abnormal smears) together with a targeted or random selection of a further proportion of smears. It also recommended reviewing all previous smears from women when the current smear shows a high grade lesion or invasive carcinoma. The current internal quality control recommended is that set out in the Scottish Office Recommendations for Internal Quality Control in Cervical Cytopathology Laboratories (7) published in 1995 in response to the Inverclyde Inquiry recommendation. This covered all quality aspects of cervical cytopathology laboratory practice. In the UK rapid review of all negative and inadequate smears is carried out before the report is issued. Results for sensitivity and specificity of individuals and the laboratory as a whole are calculated according to a nationally agreed mathematical formula and anonymised laboratory statistics are published. Cervical smears are correlated with subsequent cervical biopsies and the positive predictive value of smears with moderate and severe dyskaryosis (HSIL) is calculated. The reporting profile of each member of staff and the laboratory as a whole are recorded.

94. Recommended laboratory responsibility for clinical and programme audit includes: assisting other health professionals and programme co-ordinators to monitor the quality of smear taking; inadequate rates per smear taker; percentage of smears from women under 50 years with transformation zone material present; biopsy - smear correlation; colposcopy referrals, recurrence rates; failsafe follow up; screening history and review of previous smears for women who develop invasive cervical cancer.

### **What is a cervical smear test (Pap Test)?**

95. While frankly invasive squamous carcinoma can be seen on inspection of the cervix, all grades of CIN are completely indistinguishable from normal epithelium by naked eye examination alone. However, epithelial cells scraped from such lesions show morphological changes which can be identified when these cells are spread on a glass slide, “fixed” (i.e. preserved, usually with an alcoholic fluid, so that the cells do not decompose), stained with dyes and examined down the microscope.

96. The cervical smear test was designed as a screening test and has remained essentially unchanged in 50 years. The cervical smear is taken by first clearly visualizing the cervix using a vaginal speculum. Then cells are scraped from the full circumference of the cervix (360°) at the transformation zone (junction between the squamous epithelium of the ectocervix and the glandular epithelium of the endocervix) using a sampler, usually a wooded spatula. After taking the sample, the method in current use is to “smear” the cellular material onto a glass slide that is then rapidly sprayed with or immersed in a fixative solution to preserve the cells.
  
97. This slide is sent to the laboratory where it is stained, covered with a glass coverslip to protect the cells and then examined under a microscope by a cytologist. The microscopic examination of one cervical smear slide takes around 4 - 10 minutes since an average smear contains over 500,000 cells. The cytologist attempts to evaluate all the cellular material on the slide by systematically scanning the slide from one edge to the other, overlapping each field of view so that no area of cellular material is missed. This is a subjective assessment by highly trained individuals. The microscopic examination is often repeated by a second cytologist according to laboratory protocols which take into account previous smear results, any current symptoms or appearance of cervix or because the first cytologist is uncertain that the smear is within normal limits. Smears with ASCUS / AGUS (borderline changes) or a definite abnormality are passed to a consultant pathologist for reporting. However, most negative and inadequate smear results are issued by technical staff.
  
98. The smear report should not only describe any abnormality present but also make a recommendation for optimal management of the woman following nationally agreed protocols. This requires that the results of previous smears are known to the laboratory and may require review of previous smears. Women with negative smears and no signs of abnormality will be recommended for re-testing at the regular screening interval (currently between 3 and no more than 5 years in the UK). Those whose smears are unsatisfactory for evaluation are recalled for a repeat test immediately. Those in whom abnormalities are detected are managed according to the degree of cellular abnormality detected. This can range from a repeat smear in a reduced period of time to referral for

colposcopic assessment and biopsy. Treatment is then in accordance with the result of this more definitive, diagnostic examination. Women with moderate and severe dyskaryosis are referred for colposcopy. Women with a mild dyskaryosis smear are managed by repeat smear in 3-6 months. Women with a borderline smear are managed by repeat smears at 6-12 months. Women are referred for colposcopic assessment on the second mild dyskaryosis and third borderline result. It is worthy of note that where the smear taker has any suspicion of invasive carcinoma, the woman should be referred for colposcopy regardless of the smear result. It is recognised that the smear test is designed for pre-invasive disease and is not a diagnostic or even reliable test for invasive carcinoma.

99. One of the key factors in determining the effectiveness of a cervical screening programme is the quality of smear taking. An appropriate sampling device should be used and an appropriate sample (from 360° of the TZ) sent to the laboratory. Extended tip samplers have been shown to give superior samples to the original wooden Ayre's spatula. Cotton swabs or tongue depressors are not suitable sampling devices.
100. In the UK up to 10% of smears may be reported as inadequate (unsatisfactory) for microscopic assessment depending on the incidence of infection in the population being screened and the criteria used for evaluating adequacy of samples. The inadequate rate varies from country to country and according to which classification is used. Smears may be found to be inadequate due to a variety of factors, most of which are not related to the skill of the smear taker. Excess inflammatory exudate or blood may obscure the epithelial cells on the slide. There may be too few intact squamous cells present, a particular problem in smears taken in pregnancy or in the second half of the menstrual cycle due to cytolysis or from post menopausal women due to atrophy (thinning) of the squamous epithelium. On the other hand the sample may be contaminated by lubricant, poorly spread, inadequately fixed or the slide inadequately labeled by the smear taker. Since the sample must be taken from the full 360° circumference of the TZ then a sample collected when the cervix has not been fully visualized, is by definition an inadequate sample.

101. There are many reasons for failing to obtain a satisfactory smear test. These include: woman tense since not adequately reassured; cervix could not be visualized properly; cervix not scraped firmly enough; transformation zone not completely sampled; cellular material inadequately transferred to the slide; sample poorly spread on the slide (too thick, too thin, cell distortion due to excess pressure, or some of the cellular material spread onto the frosted end of slide); smear allowed to partially dry before fixation; insufficient fixative or an inappropriate fixative used; cervix covered in inflammatory exudate, contact bleeding on taking the smear, contamination with lubricant, spermicide or vaginal cream; smear taken during menstrual period with excess endometrial debris and blood; incorrect or inadequate labeling of glass slide; incorrect or inadequate information on request form.

### **Assessing false negative and false positive cervical smear results**

102. Screening and interpretation of cervical smears is fraught with considerable opportunity for misinterpretation (8) There is a clear acceptance that in every laboratory some abnormal smears will pass through the laboratory without being detected. A literature review by the NHSCSP in 1994 indicated that the overall sensitivity of primary screening (for all reports leaving a laboratory) was usually in excess of 85% and that sensitivities of greater than 95% were unlikely to be achieved. More recently, following an informal national survey in the UK, it would appear that many laboratories and individuals are achieving primary screening sensitivities as measured by rapid review in excess of 90% for all abnormalities, and more than 95% for high grade abnormalities. The estimated false negative proportion of Kreiger and Naryshkin (9) was based on random rescreening of the laboratory's current workload by its current staff and was generally at least 5% even in good laboratories.
103. Large volume rescreening exercises usually detect a false negative rate of 20% or higher. In a Centre for Disease Control (CDC) study in the US, 10,000 slides were exchanged between two laboratories including >800 slides originally called precancerous or cancer. Almost 30% previously called abnormal were called negative when reviewed by the other laboratory and another 30% called benign cellular

changes. The false negative rate in some categories approached 60-70%. If one selects previous smears from women with a histological diagnosis of CIN3 or invasive cancer then the false negative rate may be as high as ~68% (10). These variations can be largely explained on the basis of the different definitions of false negative used.

104. Calculation of the false negative rate is dependent on several variables including the method of detecting errors, the definition of “disease”, and the threshold for “error”. If the error rate is calculated as the number of wrongly reported smears in the entire population of slides screened then the percentage is miniscule (e.g. 50 missed abnormal out of 100,000 slides = 0.05%) If it is calculated as a percentage of all high grade smear results then it becomes more substantial e.g. 50 missed abnormal smears out of 500 later detected abnormal smears = 10%). However, the number of errors should be recorded and taken into account, not just the percentage. Missing one out of a possible two high grade smears in a batch of several hundreds of otherwise correctly reported cervical smears gives a false negative rate of 50% but the observer only missed one case!
105. There is no easily measurable and reproducible “gold standard” or “truth” against which to measure false positive and false negative smear results. Colposcopic assessment and the histological assessment of cervical biopsies both have a sensitivity and specificity less than 100%. The biopsy taken may not be representative of the most abnormal area in the cervix and the histopathology report is subject to observer variation by the histopathologist. Agreement between pathologists is high for CIN3 but poor for CIN1 (12). The true outcome of a negative smear may not be apparent for several years. There is biological progression and regression of all grades of CIN with time. Even a delay of one month between a smear being taken and colposcopic assessment of the woman’s cervix could result in a CIN1 lesion completely regressing or appearing de novo during that time.
106. A commonly used surrogate for a gold standard to test the accuracy of cervical smear reporting is review of the slide or slides by another experienced cytologist or by a panel of cytologists. **Here there is enormous potential for bias.** The interpretation of cervical smears is a subjective assessment based on minor variations of cell colour,

shape, size and density in which some diversity of opinion is inevitable. The information available at the time of primary screening is important as is the frequency of abnormal smears in the laboratory workload, the expectation that the next smear will be negative, the workload a screener is expected to deliver each day and the condition of the original slide. The knowledge that a patient later developed cancer will naturally influence the degree of confidence of the reviewer in assessing any minor degree of abnormality or equivocal changes present in a previous cervical smear. It is acknowledged that while the inter-observer and intra-observer variation for high grade lesions show fairly good correlation, those for ASCUS and low grade lesions show extremely poor correlation.

107. The nature of the abnormality that might be present in the previous smear will depend on the interval since that smear and the diagnosis of invasive cancer. If one reviews previous smears of women with current HSIL then one frequently finds missed cases even in the best of laboratories. If a population with current invasive cancer is selected then the probability of an abnormality in a previous smear is extremely high. Koss says in his definitive textbook “Adequate cervical smears obtained several years prior to invasive cancer nearly always contain at least a few abnormal cells that were either missed on screening or misinterpreted.” (13)

**The limiting factors in sensitivity and specificity of the cervical smear.**

108. The cervical smear or Pap test has remained essentially unchanged in over 50 years. It is not a highly sensitive test and the cervical screening benefit to the population comes from repeated tests at regular intervals and high coverage. The sensitivity of a single cervical smear is variably assessed in the literature at between 6% and 55%. Hakama et al in the Report of the IARC Working Group on Cervical Cancer Screening (4) calculated an inherent false negative rate of between 40% and less than 10%. The potential deficiencies in the conventional cervical smear are wide ranging and are highlighted by women who develop invasive cancer despite having had regular negative smears. Public attention has focused on the laboratory as the main cause of false negative test results but this is probably not the case (8, 14).

109. False negative smear results can arise in a variety of ways: when there are no abnormal cells on the slide because of failure in collecting cells from lesions or transferring such cells to the slide; when the disease is rapidly progressing and the lesion itself was not present at the time of sampling (this situation is considered to be quite uncommon) or when there are abnormal cells present in the sample that were not detected or have been misinterpreted in the laboratory.
110. The sensitivity of the conventional cervical smear is limited by many factors. These include inadequate sampling of appropriate cells from the cervix, poor transfer of the cellular material on to the glass slide, a non-random transfer of cells resulting in a sample which is not representative of the population of cells removed from the cervix, sub-optimal preparation and fixation by the smear taker and, only to a lesser extent, microscopic assessment in the laboratory which in itself is affected by all of the above.
111. It is well recognised that since cervical smears are prepared on site by clinicians and not by skilled laboratory staff, they are subject to great variations in quality, cellular distribution is uneven, squamous cells may be obscured by blood or inflammatory exudate and fixation is variable resulting in sub-optimal staining. Poor preparation and fixation limit microscopic assessment and this is compounded by the repetitive nature of the task. The laboratory assessment is subject to limitations of the continuing expertise of the cytotechnologist and the skill of the cytopathologist in interpreting any unusual or doubtful cells identified.
112. Sampling and preparation together are said to be responsible for 53 - 90% of all false negative tests (8). Possibly up to two thirds of sampling error is due to a failure of smear takers to harvest representative diagnostic cells from the cervix. Depending on the sampler used up to 90% of the cellular material scraped from the cervix may be discarded with the sampler. The amount of material transferred successfully to the glass slide ranged from 6.5% at worst to 62.5% at best (8). Furthermore, since some spatulas have a well recognised "trapping effect" and the distribution of the abnormal cells on the sampling device is not uniform, only a selected, non random proportion of the cells are placed on the glass slide. Thus the material on the slide may not contain

the most diagnostic cells removed from the cervix (8). Preparation and fixation of smears in the doctor's clinic setting give little control of the critical parameters required for accurate microscopic assessment: cellular morphology, clarity, density and uniformity. Smears are frequently unevenly spread and poorly fixed and many are rendered inadequate for accurate assessment. Improvements in diagnostic accuracy of the cervical smear test need to begin in the doctor's clinic with better quality smear taking, preparation and fixation (14).

113. Sampling problems are not only associated with the actual taking of the smear but are influenced by the size and site of the lesion within the cervix and its histological type. Very small lesions and lesions located deep within endocervical crypts or high in the canal are more difficult to sample with routine spatulas. The particularly poor sensitivity of the cervical smear test to detect precursors of endocervical adenocarcinoma is well-recognised (15).
114. Within the laboratory, training and continuing education of technical and medical staff have been addressed in recent years as has the screening environment and equipment. It is now well accepted that quality assurance procedures are necessary to confirm the continuing competence of staff. Habituation and fatigue problems are contained by limiting the numbers of hours spent on primary screening per day and the number of slides screened each year. On the other hand, problems may arise from lack of regular experience resulting from seeing too few slides or too few abnormal cases. Detection and interpretation problems are well documented. Detection is currently limited by the resolution of the light microscope and the human eye. Poor fixation and preparation, particularly in the presence of inflammatory or menstrual exudate or blood make detection of abnormal cells difficult. This is particularly true when there are very few abnormal cells present or where the abnormal cell nuclei are small in size or palely stained (hypochromatic).
115. The presence of inflammatory or menstrual exudate makes not only detection but also the interpretation of abnormal cells difficult. Endometrial cells, tuboendometrial metaplasia, macrophages and follicular cervicitis are cytological "lookalikes" of high-grade cells and may be a source of both false positive or false negative reports.

116. Human factors are also important. Laming (16, 17) describes the cytotechnologist's task as the inspection of a series of rather similar slides with no immediate feedback. He constructed an experiment where subjects were asked to detect similar flashing lights and he compared the effects of immediate feedback with lack of feedback. Performance improved with immediate feedback and decreased with lack of feedback. He also noted the effect of imposing penalties for "false positives". This also resulted in poorer performance. In a second experiment, he studied the interaction between successive judgements and showed that response assimilation led to accumulation of errors and judgement "runaway". He postulated this as one reason why some pathologists identified in some major screening scandals had failed to recognise as abnormal, many of the abnormal smears referred to them by technical staff or screened by themselves. This emphasised the need for biopsy smear correlation and review of previous smears when high-grade abnormalities are found. In addition, participation in external quality assurance is necessary to ensure morphological cell changes are being interpreted in a standard way.
117. In an attempt to discover why some smears were not recognised by laboratory staff as abnormal, Mitchell and Medley (18) carried out a case control study of CIN3 where false negative smears were compared with true positive smears. The false negative smear profile showed that the correct diagnosis was unlikely to be made where few abnormal cells were present in the smear (i.e. less than 50), the cells were present as single cells rather than as a combination of groups and dispersed cells, where the cell size was small and where the nuclear chromatin pattern was very similar to that of normal cells (normochromic with a fine chromatin pattern). Bosch et al (19) showed similar findings in their study of smears preceding invasive cancers but also noted that false negatives were repeatedly missed in the routine screening situation while often detected when cytotechnologists know they are being tested. However a doubling in the screening time and a threefold increase in the false positive rate accompanied this! Robertson and Woodend (20) confirmed that false negative smears preceding invasive cancer often had very few abnormal cells present, but noted that the abnormal cells were often present only as fragments rather than single cells. This was particularly common with adenocarcinoma (50% of cases).

118. Robertson and Woodend suggested that smears lacking an endocervical component (i.e. suggesting a poor quality sample) were a common occurrence in negative smears preceding cervical cancer. However, Mitchell and Medley showed the incidence of CIN was not significantly different between women whose first smear lacked endocervical cells and those which included endocervical cells. Thus the common theme in false negative reports is one of poor quality samples either in the cellular content or presentation for microscopic assessment.
119. The histological type of the invasive cancer is also important. An increasingly higher proportion of cervical cancers is diagnosed at a microinvasive stage or stage 1B where curative treatment is expected. In Sasieni's study (21) 26% of invasive squamous cancers were microinvasive and a further 53% were stage 1B. (Is it reasonable to look on these as failures when almost all of these women can be cured by the routine treatment for CIN3 or simple hysterectomy?) Some invasive cervical cancers are mixed adenosquamous in type and it is unclear whether the natural history for these histological types is different. Some publications have suggested a rare rapidly progressive form of cervical cancer with a poor prognosis particularly the small cell neuro-endocrine carcinomas. The incidence of endocervical adenocarcinoma has more than doubled in women less than 35 years in the last three decades. Endocervical adenocarcinoma now constitutes about 20% of cervical cancers in areas with well organised screening programmes. However, one must remember that cervical screening programmes are designed to detect squamous intraepithelial lesions and not endocervical neoplasia or adenocarcinomas. Among invasive cancers occurring in screened women, a higher proportion are adenocarcinoma or adenosquamous carcinoma possibly confirming other evidence that cervical screening based on the Pap smear has a lower sensitivity for the detection of these histological types. It may, therefore, be important to allocate these histological types into separate categories when presenting audits of cervical screening programmes.
120. The NHSCSP ABC document (6) for laboratories includes sections on pitfalls in reporting cervical smears. Potential false negatives may result from small cell severe dyskaryosis, pale dyskaryosis, CIN3 "microbiopsies" and CIN2 or CIN3 involving

endocervical crypts, small keratinised dyskaryotic cells particularly in atrophic inflammatory smears, sparse dyskaryotic cells and moderate dyskaryosis which may be difficult to distinguish from immature metaplasia. Potential false positives may result from normal endometrial cells, endometriosis or tuboendometrial metaplasia, lower uterine segment endometrium, histiocytes, and follicular lymphocytic cervicitis.

### **Can we address the limiting factors in cervical smears?**

121. The limiting factors of cervical smears can be summarised as the quality of the sample, the presentation for microscopic assessment and the accuracy of observer.
122. We can improve the quality of the sample by addressing the training, education and monitoring of smear takers, looking at sampler design, and considering sending all the cellular material to the laboratory as well preserved cell suspensions (liquid based cytology) rather than smears on glass slides. Skilled laboratory staff can take a representative sample of the cellular material and prepare it in an optimal way for microscopic assessment having first removed much of the blood and inflammatory exudate (14).
123. We can improve the cellular presentation for microscopic assessment by limiting or removing blood, pus, and debris, ensuring standard good quality fixation so that standard good quality staining is obtained, by preparing a thin, even distribution of cells and by reducing the area (and thus number of cells) to be scanned. Again liquid based cytology would facilitate this (14).
124. We can improve accuracy of the observer by addressing the training and education of all laboratory staff - medical and technical; by monitoring individual and laboratory performance; by providing a quality environment and equipment for laboratory staff screening smears and by using high quality preparations (again liquid based cytology would facilitate this). Computers attached to conventional microscopes might help the cytotechnologists monitor their own performance. HPV testing or automated scanning devices might help identify samples requiring particular scrutiny or identify which women with an ASCUS smear result need early recall.

**Setting standards and performance indicators in cervical screening.**

125. There are three types of standards: excellent, minimum acceptable and achievable standards. The excellent standard is achieved by the best service but this is of limited value for most services since such services are usually excellent because their population is particularly suitable to achieve excellence or because a chance collection of skilled individuals happened to come together to provide teamwork at one site that cannot be duplicated in other parts of the country. The minimum acceptable standard is that below which no service should fall. However, the minimum standard is no guarantee of quality and thus it is better for programmes to set target achievable standards as useful standards for quality improvement. These achievable standards lie somewhere between the minimum acceptable and the excellent and assist in the continual pursuit of excellence.
126. The latest guidance from the NHSCSP for laboratories due to be published shortly will use performance indicators for reporting cervical cytopathology rather than the achievable standards used in the existing guidance. These will be based on the 10<sup>th</sup> and 90<sup>th</sup> centiles of figures achieved by laboratories in the previous year's statistic returns from all laboratories. Laboratories whose performance falls outside the indicated range should investigate and be able to provide evidence to support the explanation, which might not necessarily be related to reporting practice. Should adjustment to reporting practice be required, this should be undertaken immediately. Performance outside the indicated range might be due to inadequate or inaccurate statistical information and this too should be examined and corrected where necessary.
127. Internal quality control is an essential component of laboratory quality assurance. With respect to primary screening, the NHSCSP guidance recommends that the rapid review of all negative and inadequate smears is currently the most cost effective method. This can provide a quantitative measure of performance in primary screening for both individuals and the laboratory as a whole. Sensitivity of primary screening for abnormal smears following rapid review should be calculated for the laboratory as a

whole and for individual screeners (26). It must be recognised that quality control by rapid review, although primarily a method of monitoring primary screening, also depends on the reporting accuracy of both cytopathologists and supervisors. Rapid review is also not an exact science and it cannot detect every false negative. False negative cases will still be detected years later when previous slides are reviewed from women with abnormalities found on their next smear.

### **Problems in assessing performance**

128. Assessing the competency of a laboratory or individual requires much more than the simplistic approach of the calculation of a false negative rate by whatever definition. No single methodology can be expected to identify all problems or errors or to assess competence.
129. Frequently medico-legal review of smears which might be false negatives is undertaken by the “best screeners” who rescreen the slide intensely taking as much time as they need and often with multiple rescreens. This is not a fair comparison with the quality of the original primary screener’s assessment in the routine situation.
130. Vooijs (22) states that cervical smear interpretation is one of the most difficult tasks in medicine. Diagnostic reproducibility in cervical smears particularly those showing low grade abnormalities is poor. Experts very often fail to agree and may differ significantly one to another when viewing and assessing slides.
131. Inter observer variability does not indicate negligence. Intra observer variation does not indicate that an individual who classified a smear as negative on one occasion and abnormal on another is necessarily negligent or incompetent (22).

### **Mass retrospective rescreening of cervical smears**

132. The intensive nature of the quality assurance programme for the NHSCSP results in frequent situations where standards have not been met for a variety of, often very

good, reasons and local investigation is required. However, inconsistencies in the reporting of cervical smears result in a major problem for the NHSCSP. The critical factor is determining at what point any suspected error rate falls outside acceptable limits. At this point the screening process could be considered to have failed and some action may be required.

133. Historically, the remedial action taken when such a situation exists has been to undertake a mass re-screening of smears to re-examine slides in order to identify those which have previously been misdiagnosed as a result of a problem in the laboratory. The ScHARR report (23) has shown this incurs considerable cost to the NHS. Furthermore, depending on the scale of the problem and the size of the error, the costs of identifying a single additional abnormal case can be very variable. The major issue then is to find some way of determining at what point the costs of undertaking a major re-screening exercise are justified in terms of the likely detection of an additional abnormal case.
134. This is further complicated by the degree of abnormality detected. Patient consequences are likely to be significantly different if a screening problem is failing to detect severe abnormalities rather than mild abnormalities that have a high chance of spontaneous regression. A mass rescreening exercise because of the latter problem could in fact result in some women being investigated and possibly treated for abnormalities that might have disappeared by their next routine screen. Conversely severe abnormalities that remain undetected for a long period of time, present the risk of development of invasive cancer that, if treated early, could have been prevented.
135. The decision about whether or not to rescreen slides where a reporting problem has been identified is not an easy one to make. There is no single combination of factors that can be identified which will determine at which point a rescreen should take place and no study has provided a definitive answer to this question. The ScHARR report considered the rescreening process in isolation. However, if a mass rescreening exercise does take place there are longer term consequences for the screening service that also need to be considered. One service that has conducted a mass rescreening

exercise has identified post rescreen effects that result from loss of confidence and low moral which include:

experienced cytology screeners leaving the service

increased caution in the screening process resulting in an increase in the number of suspect smears being passed to the checking and pathologist stages with

“defensive” reporting and increased rates of borderline abnormality (ASCUS).

decreased efficiency as new cytology screeners are recruited and trained – a process that can take up to three years

136. All these factors will have an effect on both costs and efficiency. Thus, it is important that the following factors be taken into account when assessing the need for a major rescreening exercise. The need to establish the significance of a potential error before any re-screen cannot be over-emphasised. The critical factor here is whether or not an error detected is sufficiently greater than that which is within acceptable limits to be of concern. Where the error rate detected is at the margin, and therefore small, the costs of detecting each additional false negative smear will be very high.
137. Consideration should also be given to the degree of error, i.e. whether it is mild or severe abnormalities that are being missed. It is severe abnormalities that present the most risk to patients and this should be the primary focus of any decision about the need for a rescreening exercise. If mild abnormalities are the problem it may be more cost effective to recall women for a routine examination at a shorter interval.
138. Once the significance of an error has been identified, the model provided by SchARR can be used to provide estimates of the likely consequences in terms of both costs and outcomes. The major driver is the unit cost of a screen. Previous rescreening exercises have reported wide variation in the costs quoted for the rescreening of slides. The SchARR model allows an estimation of the likely financial impact of different costs before any decision about whether to rescreen is made.
139. Cervical cytology is a process that requires the application of personal judgement by screeners and pathologists and, as such, is therefore always open to error. In recent years a number of quality control mechanisms and standards for reporting have been

introduced into cytology laboratories to try and minimize the risk of errors in cervical smear examination and reporting. The consequences of unacceptably high error rates are serious. Firstly, for a small number of women, there are significant affects on their clinical management, leading to recall for colposcopy and possibly treatment. At worst, there is the knowledge that they could have been treated at an earlier stage. Secondly, for a much larger number of women, there is little or no effect on their clinical management, but the rescreening exercise, particularly if this is a public exercise, subjects them to a period of anxiety until their personal outcome is known. Such events undermine public confidence in the cervical screening programme and the rescreening process is costly to the health service. It is therefore important to have some understanding of the cost-effectiveness of this mass reexamination of cervical smears to inform future policy in the management of these incidents.

140. It is also important to note that there is an exponential relationship between the size of the error and the cost per additional high-grade smear result detected. At present using UK costs, this ranges between a cost per case of more than £12,000 for a 0.05% error, to £332 for an error rate of 2%. If the rescreening is a public exercise, cost can increase by almost 25%.

**NHSCSP Guidelines on Managing Incident in the Cervical Screening Programme  
November 1999 (Schedule 2)**

141. The Guidelines for Managing Incidents in the Cervical Screening Programme outline the means by which a suspected problem may be identified. The stages of the investigation of a suspected problem and diagnosis of its cause from an initial investigation and then, if required, a formal investigation are described. It recommends the sequence of steps to be taken by the “Incident Team” if a problem is confirmed which has consequences for the clinical management of women (i. e. there is an “incident”). The factors to be taken into account when considering mass rescreening of smears or recalling women for additional investigation or treatment are set out and guidance is provided for closure of an incident.

142. Arrangements for quality assurance for the NHSCSP are being developed within the framework of clinical governance. Regional quality assurance teams have been set up by the National Co-ordinating Team to monitor and review performance against the standards. The introduction of quality assurance means that potential problems are identified, investigated and remedied at an early stage as part of the normal routine of quality assurance, and thus they should not become incidents.
143. The document states that laboratory performance outside the standard target ranges should primarily be considered as a quality assurance issue and is not necessarily an indicator of substandard performance. The importance of individual indicators must be judged in the context of the overall performance of the laboratory.
144. Unless a problem is very obvious (such as occurred in previous major incidents), statistical analysis of screening performance is likely to prove the best indicator of substandard performance. If the analysis leads to the suspicion of an underlying problem in a laboratory, then further investigation is warranted. This will normally take the form of a review of a sample of smears selected from those reported by a particular individual, or from a particular period of time. A review of a consecutive sample of 500 to 1000 smears is usually sufficient to reveal a problem if one exists. Such a review may form part of a formal investigation of a suspected problem.
145. Other factors that need to be taken into account are the size of the problem (how many women are likely to have been adversely affected, the timing of the problem – over what period of time and how long ago it was, the costs of mass rescreening and the availability of resources to undertake such action. The benefits and disadvantages of mass rescreening exercises are detailed.
146. The document also provides guidance for the Health Authority, the National Co-ordination Team, and the Department of Health when an “incident” is confirmed. Common to these is guidance on issuing press statements and the recommendation to provide a spokesperson to deal with queries from the public, worried women, the media or other health professionals.

147. The appendices to the guidelines include guidance on incidents affecting other components of the NHSCSP such as smear taking, colposcopy and Call and Recall as well as key messages about managing an incident, dealing with the media, and telephone helplines.

**The Inquiry into Cervical Cytopathology at Inverclyde Royal Infirmary requested by the Secretary of State in 1993** (Schedule 3)

148. The Inverclyde Hospital review exercise was initiated by concerns voiced by a new pathologist taking up a post in the laboratory when the first pathologist retired. It involved a mass rescreening of 20,000 negative smears: 2,000 smears were found to be non-negative, 109 were re-graded as moderate or severe dyskaryosis or invasive cancer. However, most of these women had already been referred for colposcopy due to frequent early repeat smears. No new cases of squamous carcinoma were identified in the mass rescreening exercise but 2 cases of endometrial adenocarcinoma were found.
149. The Inverclyde Hospital Pathology Laboratory was staffed by a single handed pathologist assisted by a part time medical assistant. Over 15 years the cervical cytology workload increased from under 3000 to over 7000 smears per annum with no increase in consultant staffing. In addition the histopathology workload increased to about 5000 specimens with over 200 autopsies and 1000 semen samples. Despite this huge workload, turnaround times were maintained. This was achieved at the expense of internal quality control, external quality assurance and continuing professional development, none of which took place. External monitoring was in place but was inadequate and there had been no complaints from gynaecologists or General practitioners.

**Inverclyde Inquiry - Summary of findings**

150. The sensitivity to detect abnormalities in respect of cervical smears reported at Inverclyde Royal Hospital between 1987 and 1992 was lower than that to be expected from a laboratory with good practice. The sensitivity to detect borderline and all

grades of dyskaryosis was in the order of 30%, i.e. a false negative rate of 70%; and the sensitivity to detect severe dyskaryosis alone was in the order of 50%. The full data to enable a determination of the rate prior to May 1987 was not available but the information available indicated that the level of reporting of abnormal smears was not previously higher.

151. Of the women whose smears were under-reported, many did in fact receive treatment in due course. This was because:

a substantial number of smears were reported as negative but early repeat in 3-6 months was recommended because of "inflammatory changes"

all women whose smear showed any grade of dyskaryosis were routinely referred for colposcopy

abnormalities were detected on a subsequent routine smear.

152. As a result, notwithstanding the high false negative rate, the incidence and mortality of invasive squamous carcinoma of the cervix in the Inverclyde Royal Hospital catchment area was not obviously greater than that which might be expected in an area with a similar socio-economic profile. No women with invasive cancer of the cervix were detected by the rescreening exercise.

### **The high false negative rate**

153. The high false negative rate was not the responsibility of one individual alone but was attributed to deficiencies in :-

- the approach of the Argyll and Clyde Health Board to cervical screening
- the staffing and operation of the laboratory

154. The Argyll and Clyde Health Board did not ensure that there was a well-defined programme with appropriate targets for cervical screening. Nor did they put in place a management structure that would be effective in introducing and operating such a programme.

155. The Department of Public Health Medicine had a piecemeal approach to the implementation of the Scottish Office Report on Cervical Cytology Services in 1978

and following that, the Strong Report in 1987. They introduced a Call and Recall system without developing a strategy for the adoption of other recommendations of the Report relating to cervical cytopathology laboratories.

156. The Department of Public Health Medicine did not put in place effective monitoring and evaluation procedures which would have identified the deficiencies in laboratory practice and could have led to early remedial action.
157. The Argyll and Clyde Health Board Cervical Cancer Group was established with a broad remit and set itself specific objectives but failed to direct its attention to suitable means of achieving those objectives or to take effective action.
158. The Argyll and Clyde Health Board failed to anticipate the staff resources required for the expected increases in workload following the adoption of a policy of 3 yearly routine recall in 1988 and the introduction of the new General Practitioner contract in 1990.
159. The consultant pathologist in charge of the laboratory did not routinely report cervical smears and therefore became increasingly unable to provide the level of supervision which such work demanded. He failed to assimilate new developments in the field of cervical cytopathology and to introduce them to the laboratory.
160. The consultant pathologist in charge of the laboratory did not accord sufficient priority to internal quality control and external quality assessment in cervical cytopathology. He did not take sufficient steps to ensure that the laboratory was adequately and appropriately staffed. He failed to ensure that cervical smears and reports were stored for an adequate period of time.
161. A part-time consultant pathologist appointed in 1989 had the requisite skills in cervical cytopathology to recognize and address the deficiencies in laboratory practice but those skills were not properly utilized in Inverclyde Royal Hospital Pathology Department.

162. The Associate Specialist who did most of the screening, consistently under-reported during the period concerned. Her initial training had been satisfactory but she failed to maintain and develop her skills in cervical cytopathology. She was not therefore in a position adequately to supervise primary screening by technical staff. She allowed herself to work long hours without recognizing that the quality of her work might thus be jeopardized.

### **The Argyll and Clyde Health Board's rescreening exercise**

163. The rescreening exercise initiated by the Argyll and Clyde Health Board was an inadequate and inappropriate response to the situation. No priority was given to assessing the degree of extra risk to which the women of Inverclyde District might have been subjected. The Press Release was therefore precipitate with no clear information available at that time on the scale of the problem leading to unnecessary anxiety being generated in the public.

### **Summary of recommendations**

164. The Scottish Office Home and Health Department (SOHHD) set the standards for a systematic cervical screening programme in the 1978 and Strong Reports (1987). In order to facilitate compliance with these standards at Health Board level, the Department was invited to consider:

introducing a structured organisation with well defined objectives and targets and clearly identified funding;

establishing a working party to formulate a policy for implementation of internal quality control in all laboratories carrying out cervical cytopathology;

acknowledging the importance of external quality assessment in cervical cytopathology by continuing to fund it;

adopting a policy that all cervical cytopathology laboratories should be under the supervision of a consultant cytopathologist personally responsible for the reporting of all abnormal smears; that MLSOs (laboratory technical staff) who undertake cervical screening should be encouraged to acquire a Certificate of Competence which is mandatory for progression from Trainee Cytology Screener to Cytology

Screener; that provision is made for continuing education for technical and medical staff in non training grades;  
 promoting a national health education programme to improve awareness of the benefits of regular screening;  
 draw up guidelines for investigation of perceived reporting discrepancies by laboratories or individuals  
 encouraging Health Boards to rationalise the use of small laboratories with a workload below or close to the recommended minimum.

165. To ensure the satisfactory provision of a cervical screening programme within the Health Board area, we recommend the Argyll and Clyde Health Board:-

set appropriate short term and long term targets for the programme in respect of matters such as coverage, turnaround time for reporting, acceptable technical standards for smear takers and laboratory staff, efficiency of follow up and failsafe procedures, recurrence rate after treatment, distribution of invasive cancer and incidence and mortality rates;

appoint a programme manager with managerial and budgetary authority to co-ordinate, evaluate and monitor all aspects of the programme;

ensure that monitoring and evaluation includes comparison of statistical returns and audit of screening history of all new cases of squamous carcinoma of the cervix;

consider rationalising the cervical cytopathology service for the Health Board area on one site in order to provide cost effective use of resources and the optimal environment for the maintenance of staff skills, training and continuing education;

ensure that all aspects of Quality Assurance are exercised within the laboratory and funded accordingly; participation in the Scottish Proficiency Testing Scheme or equivalent recognised EQA scheme<sup>4</sup> should be mandatory for all staff who at any time report cervical smears;

make provision for continuing education for technical and medical staff in non-training grades and a person in each hospital should ascertain that all staff make use of this;

computerise the cytopathology laboratory and provide for electronic transfer from the laboratory computer system to the health authority Call and Recall database;

set a target date by which each laboratory must apply for accreditation with CPA UK;

ensure that medical staff are consultant histopathologists with appropriate experience in cytopathology.

as purchasers ensure that laboratories from whom the service is purchased in the future have documented evidence of good practice.

166. In order to restore public confidence in the cervical cytopathology service provided by the Argyll and Clyde Health Board area, laboratories providing that service should:-
- review their staffing requirements for cervical cytopathology in relation to the workload and the operation of recommended quality control measures and ensure that the service is supervised by an appropriately experienced consultant cytopathologist;
  - review the training, skills and qualifications of all staff and encourage all technical staff to obtain a Certificate of Competence in Cervical Cytology Screening;
  - undertake and document clinical audit including routine correlation of cervical smears with subsequent biopsies, screening history of women who develop invasive cancer and advice to smear takers about the quality of cervical smears;
  - make comparisons of cytopathology results with results from other centres and national statistics
  - ensure that adequate internal quality control procedures are in place and documented, that all staff who report smears at any time participate regularly in a recognised EQA scheme, such as the Scottish Proficiency Testing scheme<sup>4</sup>, and that the laboratory obtains CPA UK accreditation as soon as possible.
167. In summary a cervical screening programme should have a structured organisation with defined objectives, standards and funding. Internal quality control and external quality assurance must be in place again with defined standards. The staffing, training and continuing education of all staff must be addressed. A public health education promotion about cervical screening benefits and limitations was required as were guidelines for investigating perceived reporting discrepancies for laboratories or individuals.

### **Audit Commission Report: (1993) (24)**

168. It is interesting to note that the Audit Commission Report published soon after the Inverclyde Report also recommended that “Amalgamation of small departments serving an area should be considered in order to make the best use of the resources available. The pattern of continuing to fund many small laboratories with workloads far below the minimum recommended for good practice, is an inefficient use of the resources available.”

### **Kent and Canterbury Inquiry (1996)**

169. This incident resulted in a series of investigations and reports including a Royal College of Pathologists nominated team report which was never published, an Internal Report, a Formal Inquiry Report, a National Audit Office Report and a Public Accounts Committee Report.
170. The inquiry team found that the reasons for the failures at Kent and Canterbury were complex and interrelated but the four main ones were:
- Poor and confused management at the Trust and in the cytology laboratory
  - The repeated warnings of understaffing, poor training, low morale and breakdown in relations between primary screeners and senior technical staff, senior technical staff and consultants, and consultants and management went unheeded over many years
  - Consultants’ remoteness and apparent lack of interest in the cytology screening programme
  - Lack of a clear line of accountability on both management and quality assurance for the national programme through the NHS Executive and health authority to the Trust.

171. The rescreening exercise at Kent and Canterbury Trust involved full review of >91,000 smears and the recall of 5,566 women for further investigation. 331 women were found to have HSIL, 21 women required hysterectomy for carcinoma and 8 deaths from invasive cancer were recorded during the period under investigation.
172. Although the Kent and Canterbury Trust accepted full responsibility for the failures in cervical screening and apologised to the women affected, the report did include recommendations for the NHSCSP that were taken on board to enable lessons to be learned both locally and nationally.
173. These recommendations included:
- The need to overhaul the lines of accountability for the national programme
  - Revision of the scope and content of the quality assurance programme
  - New national guidelines for inquiries and major re-screening exercises including communications and help lines
  - Specific improvements to the East Kent cervical screening programme for which the laboratory work is currently being carried out satisfactorily at another laboratory.
174. Kent and Canterbury Report included other recommendations as follows:
- It identified an urgent need for public health education about screening
  - Clearer lines of accountability for the national programme
  - Guidance for clear specifications for laboratory contracts
  - The appointment of a programme manager for each Health Authority
  - A Working Group to develop incident handling guidelines
  - Guidance on rights and responsibilities of staff to raise concerns
  - Revision of the scope and content of quality assurance programme
  - Better feedback mechanisms for poor performance
  - Improved monitoring of laboratory performance

## **Conclusions and caveats for mass rescreening and review of individual cases**

175. The basic principle of doing more good than harm must be paramount in any considerations dealing with perceived problems with any aspect of a screening programme. This includes psychological harm as well as physical harm and also public confidence in the cervical screening programme. The greater good must be considered since a screening programme cannot offer 100% accuracy in identifying women with an abnormality in the first place.
  
176. Review of smears has a real risk of applying unreasonably high standards to the routine primary screening process. In particular there is a high chance of overcalling ASCUS / AGUS (borderline changes) and higher grading of detected abnormalities . One must remember that single errors or small numbers of errors are inevitable in screening and that virtually all women who have participated in a screening programme and who go on to develop invasive cancer are likely to have had a false negative test (with correct laboratory interpretation of the smear due to a sampling problem) or a false negative smear report (due to failure of the laboratory staff to detect and correctly interpret abnormal cells present in the smear). The original false positive rate of the reporting laboratory and the rescreening false positive rate of the reviewing laboratory should also be taken into account when considering false negative rates in rescreening exercises. One must to compare like with like. Standards of care must be assessed within the cost constraints and accepted practice of the situation under consideration. In particular the knowledge base and standard practice in place at the time of originally reporting the smears must be considered, not those in place in the review laboratory and time of the rescreening exercise.
  
177. A potential problem situation may be brought to attention by new medical or technical staff joining the laboratory or colposcopy service who immediately recognise that something is wrong. Or it may be suggested by identified individual poor performance in internal quality control or external quality assessment, laboratory statistics outside the expected range, complaints or anecdote or the local incidence and mortality from cervical cancer.

178. The first step must be to determine whether there is really a problem. One must review the evidence and establish the facts. Until then it is not an “incident” and no public statements should be made which might cause unnecessary public concern. A critical factor is the size of the sample used to estimate the scale of the problem before a mass re-screening is made. If the sample size is too small or is a selected sample (e.g. previous smears from women with known abnormalities), there is extreme variability around the central estimate of the number of additional false negative smears that may be detected and the size of the problem.
179. These risks are not easy to define. Comparison of the local background incidence and mortality of cervical cancer with that of another similar population can be helpful in identifying if the population is at substantial risk.
180. A major incident is usually subjectively obvious unlike minor incidents, which require detailed statistical analysis to confirm or refute. Often a major incident is “discovered” by a new member of staff in the laboratory and it is immediately obvious during routine duties in the laboratory. They frequently result in mass rescreening of slides with recall of large number of patients for colposcopy.
181. There have been several other large rescreening exercises in the UK since 1996 with over 150,000 smears reviewed. The cost of this has been enormous not only in financial terms but also in loss of confidence both of the public and laboratory staff. Here we must question whether they did more harm than good.
182. The need for guidance in handling incidents was identified in the Inverclyde Inquiry Report and again in the Kent and Canterbury Inquiry Report. The NHSCSP have now published Guidelines for Managing Incidents in Cervical Screening in November 1999 (Schedule 2) together with the SchARR Final Report to the Cervical Screening Programme on the costs and outcomes of cervical rescreening (23). The Institute of Biomedical Sciences previously published guidelines for technical staff in 1997. Laboratories and Health Authorities need to know: when is a look back exercise

necessary? What needs to be done? How much needs to be done? Who does it? Who do you tell before? Who do you tell after? Must you go public?

183. Review exercises are often undertaken on the principle that all women must receive the same standard of care. If that were the case then all laboratories should be as good as the very best, all smear takers should be as good as the very best, all regions should have the same coverage and screening interval as the very best and all colposcopy should have the same outcomes. This is patently not achievable and unrealistic.
184. I strongly believe that instead of rescreening archived slides many of which are poor quality, many years old and do not reflect continuing or new disease which may currently be present in the woman, we should be rescreening women. Why “look back” if you can “look forward”? If we identify a population who has received a screening service of questionable quality in the past, a further high quality smear test should be offered as soon as possible and a high quality screening programme established for the future.
185. A more common word in our day to day vocabulary for mass rescreening or look back is “re-search” (research, look back, look again). We must try to ensure that every rescreening exercise, however big or small, or review of individual cases, increases our understanding of risk assessment, improves our knowledge of the aetiology and pathogenesis of cervical cancer and develops our effectiveness in delivering cervical screening.

### **List of schedules**

- Schedule 1 Curriculum vitae
- Schedule 2 NHSCSP Guidelines for Managing Incidents in Cervical Screening Programmes NHSCSP Publication number 11 November 1999
- Schedule 3 Report of the Inquiry into Cervical Cytopathology at Inverclyde Royal Hospital, Greenock. HMSO 1993 ISBN 0 11 4951810

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