Papers and Originals

Cervical Cytology: Its Value and Limitations*

T. N. A. JEFFCOATE,† M.D., F.R.C.S.ED., F.R.C.O.G.

Brit. med. J., 1966, 2, 1091-1094

It is established beyond reasonable doubt that the routine examination of cervical smears can, if carried out efficiently, result in the discovery of invasive carcinoma before it is clinically evident, and also of changes in the epithelium which, if neglected, may at some future date develop into that condition. It cannot, however, be assumed that lesions such as carcinoma-in-situ and atypical epithelial activity, often called dysplasia, inevitably progress to cancer. Carcinoma-in-situ is found in four or five out of every 1,000 apparently normal women over the age of 25 years, which is more than expected for the known incidence of invasive cancer at a later age. Because its diagnosis depends on removal of the lesion for examination it is impossible to say how often carcinoma-in-situ progresses to invasive cancer, and estimates vary from 30 to 80% of cases (Kottmeier, 1953; Petersen, 1955; Boyes *et al.*, 1962). Whatever be the exact figure, carcinoma-in-situ is reversible in some cases, and this means that, in the hope of preventing invasive carcinoma, a certain number of women found to have this change in their cervix have to be treated unnecessarily. Even by doing this, and assuming that all women are screened routinely, it is unlikely that cervical cancer can be completely eliminated from any community, either because this disease arises without the epithelium going through the intermediate stages of abnormal activity or because the progression occurs too rapidly to offer an opportunity for these stages to be recognized in time.

Despite these limitations to the value of routine population screening, cervical cytology is of considerable help to the clinician. It was introduced into the practice of my unit 13 years ago. At first cervical smears were taken from all women aged 30 years and over who attended our gynaecological clinics. The age limit was soon dropped to 25 years and later removed. Routine cervical cytology was subsequently carried out in our postnatal clinics and more recently in the antenatal clinics. Now we also examine smears taken by doctors in charge of birth control and venereal disease clinics.

At all times only the Ayre scrape technique was used because it is more reliable than any other for the purpose of detecting cervical epithelial lesions. Examination of vaginal pool specimens, although making it more likely to pick up abnormal cells cast from malignant disease of the endometrium, is more difficult and time-consuming for the laboratory worker, and, in our experience, is not a worth-while routine test.

The comments which follow are based on the findings in the first 10,246 women examined, starting in 1954. These represent consecutive attenders (who had an accessible cervix) at gynaecological clinics, and only 175 (1.7%) were pregnant. Many patients had several cervical smears taken at intervals, either because this was prompted by the first report or because

of clinic reattendances during one to eight years after the original study. A total of 12,986 smears were examined, all by a pathologist,¹ who was able to scrutinize 20 to 25 slides in two hours.

The smears are always taken by an experienced gynaecologist, and this may explain why only 3 per 1,000 proved unsatisfactory for assessment. This compares with the findings of Osborn and Leyshon (1966), who reported that, of smears collected under all circumstances of medical practice, 10% have to be discarded by the cytologist, and that even when trained doctors take the specimens the incidence of unsatisfactory smears is as high as 2.4%.

Population Screening

If population screening by means of cervical cytology is to be reliable and free from risks it is not only necessary for the cytologist to be expert in this particular field of microscopy; he must be presented with smears containing cells which have been scraped from all aspects of the external os, and not collected blindly, possibly from the cervix, possibly from the upper vagina. So the person taking the smear has to be able to expose the cervix, and must have the necessary equipment. If working single-handed he or she requires a bivalve speculum and a good source of light. The sterilization of the speculum is also of great importance. Perfunctory cleaning and boiling do not kill monilia and trichomonas organisms, and these are readily transferred from one woman to another. The only safe procedure when groups of women are to be examined is to have all instruments serviced by a central supply department, or to use only disposable equipment which is discarded after a single use.

Although doctors without gynaecological training, nurses, and perhaps technicians can be taught to locate the cervix and to take smears efficiently, they cannot judge the state of the cervix clinically, let alone assess the health of other parts of the genital apparatus. This is a great disadvantage for the cytologist, whose accuracy is improved if he can be reliably told of the presence or absence of erosion, polyp, or other lesion on the cervix, of vaginitis, and of pregnancy. He should also have knowledge of the timing of the smear in relation to menstruation. Moreover, the taking of cervical smears by those not competent to pronounce authoritatively on the naked-eye characteristics of the cervix is dangerous for the woman. A negative smear is not infrequently returned in cases of clinically recognizable cancer.

The problem of who should scrape the cervix cannot be resolved unless the object of community screening is established. The advertisement of cervical cytology to the lay public has

* Paper presented at a meeting of the Faculty of Radiologists (Radiotherapy Section) on 18 February 1966.

† Department of Obstetrics and Gynaecology, University of Liverpool.

¹ Now that the department is dealing with 10,000 smears annually the primary sifting is carried out by technicians, without so far any lowering of the accuracy of the reporting.

aroused a hysterical, and even political, reaction which is in danger of distorting the place and value of the technique. Carcinoma of the cervix is only one form of malignant disease that can be recognized early by routine examination, and it is not the most serious. In England and Wales in 1963 there were four times as many deaths from breast cancer as there were from cervical cancer. So on statistical grounds it can be argued that it is more important to examine a woman's breasts regularly than it is to examine cervical smears. Yet women attending clinics to "have a smear taken" have often been so falsely indoctrinated that they refuse to expose their breasts. There are even some who are under the impression that the cervical test can be performed without their submitting to a vaginal examination. They, and many in the profession, fail to recognize that cancer of the ovary, though not so common, is much more often fatal than is cancer of the cervix, and, with its quiet and insidious onset, is mostly incurable by the time it causes symptoms. To many women the finding of a negative cervical smear means that not only is the cervix free from cancer but also the uterus, tubes, and ovaries, and possibly all other organs too.

If population screening is to be really useful cervical cytology should be merely one part of a more thorough examination, or "check-up" as it would be called in North America. This means a careful assessment of at least the breasts, all the pelvic organs, and the rectum. The importance of this is well illustrated by the experience of a "well woman" clinic in Sydney. There, among 15,468 symptomless women subjected to repeated annual examinations totalling 50,008, 57 cases of cervical cancer were discovered, but the lesion showed invasive properties (and then early ones) in only 23. Meanwhile clinically diagnosed cancer was found in the breasts of 34 women, and in other sites in 18 women (Garrett, 1964).

Although not always appreciated, even by gynaecologists, cervical cytology is for the screening of women who are free from symptoms and signs which raise suspicions about the presence of cancer in the pelvic organs. When such are present, full investigation, including examination under anaesthesia, curettage, colposcopy, and cervical biopsy, is essential even though the cervical smear is negative. Indeed, there is a greater chance of false smears being obtained when there is clinical evidence of cancer in the cervix than when there is not. The more advanced the cancer the more likely are the superficial cells to be necrotic and unrepresentative, and the more likely is a smear to be reported negative.

Cervical Cytology in Cases of Clinically Diagnosed Cancer of the Cervix

In the series of 10,247 cases under review there were 167 women who were at the outset recognized by the clinician to be suffering from cervical cancer, but in only 139 were malignant cells found in scrapes from the growth. In nine cases the smear was so contaminated with inflammatory cells and debris that the cytologist refused to report; in two the appearances left him in doubt about the presence of cancer cells; and in 17 (10%) he returned a negative report, and this despite examining repeat smears in many instances. This only goes to emphasize that the person taking the cervical smear must be able to recognize cancer when he sees or feels it, and also that cervical cytology is not for the patient who has symptoms.

Cervical Cytology in Clinically Suspicious Cases

The above conclusions are borne out by analysis of the cytological findings in women in whom symptoms or signs led the gynaecologist to suspect the presence of cancer in the genital tract even though the results of his primary examination were inconclusive. There were 457 such cases, and in this group

seven of the smears were unsatisfactory from the standpoint of the cytologist, 39 were reported as positive, and 11 were classed as suspicious. Examination of repeat smears finally reduced these numbers to 38 positive and 6 suspicious, and cervical cancer or dysplasia (two cases) was subsequently proved present in all except one of the women concerned. In the exceptional case a repeatedly positive smear led to cone biopsy, but no evidence of malignant disease was found in the removed tissue. Subsequent smears remained negative.

In 400 cases the initial smear showed no evidence of malignant cells from the cervix but in some the cytologist correctly suggested that the presence of endometrial cells might indicate endometrial carcinoma. With this we are not concerned; more important is the fact that 5 of the 400 women with a negative smear suffered from significant lesions of the cervix. These were invasive cancer in three cases, carcinoma-in-situ in one, and dysplasia in one. In this group there were at least 1% false-negative returns, and the diagnosis in the cases concerned was made only because the gynaecologist properly proceeded to cervical biopsy on the clinical findings and disregarded the cytologist's report. In this respect it should be noted that in one case in which the cytologist reported a suspicious smear subsequent cervical biopsy failed to reveal cancer, yet an invasive lesion of the cervix was found in the hysterectomy specimen. Again, in one case in which the smear was repeatedly negative all the clinical investigations also failed to reveal a cancer which was sited deeply in the cervix and which was not diagnosed until two and a half years later, when laparotomy was carried out for a broad-ligament tumour.

Cervical Cytology in Cases in which Genital Cancer was not Suspected

There were 9,623 women aged 25 years and over who did not have any symptoms or signs which made the gynaecologist suspect cancer in the pelvic organs. Because they had some reason to attend a hospital clinic, these cannot be regarded as representative of the healthy women in the community. Nevertheless, the majority had nothing seriously wrong and complained only of sterility, backache, urinary symptoms, menstrual tension, and dysmenorrhoea, or came merely for advice on family limitation. Among this group cervical cytology led to the discovery of 52 unsuspected cases of cervical carcinoma; in 11 of these the lesion was invasive, in 41 intra-epithelial. A further 10 cases of dysplasia were also brought to light. This "unexpected pick-up rate" of five cancers (one invasive) per 1,000 cases tallies with that of most workers dealing with women drawn from a similar population. Only one woman in this group was exposed to unnecessary cervical biopsy, in the sense that smears repeatedly reported as suspicious were obtained from a cervix in which no significant abnormality was found on section.

Out of 9,510 cases in which the smear was reported normal there were five in which subsequent investigation revealed lesions of the cervical epithelium. These amounted to invasive cancer in one case, carcinoma-in-situ in one and dysplasia in three.

So far as is known only two cases of cancer were missed by cytological studies carried out on symptom-free women with clinically innocent cervixes, but it should be emphasized that in the majority of cases in which smears from well women are reported as negative there is no means of testing the accuracy of the findings. It is known that in our series 1,020 patients maintained a negative smear during the next one to eight years. Moreover, a further 600 came to surgery for conditions such as prolapse or uterine fibroids and their cervixes were examined histologically. So the five cases in which abnormality of the cervix was later proved should be set against the 1,620 in which there was some sort of check on the findings and not against the total number of women with negative smears. This means

a known false-negative rate of approximately 1 in 300. Had all the women in whom cancer was clinically unsuspected been investigated further over the subsequent years it seems likely that the results would have shown that a total of 15 or 16 cases of cancer or incipient cancer were missed at the time of the negative cytological study. Even so, our experience is considerably better than that reported by Friedell *et al.* (1960), who said that up to 12% of women with negative smears subsequently show positive ones. Moreover, Garrett (1964) reached the conclusion that, if positive findings one to two years after a negative report mean that the original assessment was erroneous or misleading, for every 40 cases of cervical cancer discovered in a well woman clinic 10 are missed on the first smear. Garrett also quotes other writers to substantiate the generally high false-negative rate for cervical cytodiagnosis.

Significance of Cytodiagnosis to the Patient and the Gynaecologist

The percentage of false-positive and false-negative smears returned for women without clinical evidence of cervical carcinoma inevitably depends on the accuracy with which the cervix is scraped and the experience and skill of the cytologist.

It might be argued that, from the standpoint of population screening, false-negative reports are of little consequence and that the discovery of a proportion of the women with early or incipient invasive cancer is better than allowing all to be overlooked. For the individual, however, whose early cancer is missed, the matter may be serious, for, reassured by the satisfactory report, she may neglect symptoms when they appear. The issuing of false-positive or suspicious reports may also seem to the cytologist to be of such little consequence that he regularly "plays for safety." In fact, for the patient and her attendant such reports are a serious matter. For whenever a second smear is also reported as suspicious or positive the gynaecologist has little option but to proceed to cervical biopsy. And no matter what may be the result, the patient, having once had her fears raised, is likely to lack confidence in her cervix thereafter.

Except when naked eye or colposcopic examination indicates the site of the lesion, adequate cervical biopsy means a cone excision of the external os and endocervix, and this is not a simple minor procedure. It can be extremely difficult, and is often complicated by haemorrhage during or several days after operation. It leaves permanent injury to the cervix, which, for the young woman, may prejudice future child-bearing.

The ability of a cytologist is to be judged not by the number of cancers which he overlooks but by the number of false-positive or doubtful reports which he issues; that is, by the number of women whom he unnecessarily exposes to worry and cervical biopsy. In the whole series of cases reported here only two women were subjected to this operation without the tissues removed showing abnormal epithelial activity, and one of these had suspicious clinical features which justified investigation irrespective of the smear report.

One of the problems inherent to the screening of the general community as distinct from a hospital clinic population is that, under most circumstances, the cytologist concerned has little control over the subsequent clinical management of the cases on which he has reported; he may not even learn their outcome. When reports from a centralized cytodiagnostic laboratory are issued to general practitioners, or to doctors in charge of local health authority clinics, the recipients can then only refer women with positive or suspicious smears to a gynaecologist for further action. Gynaecologists still vary in their management of such patients. Some may proceed to immediate hysterectomy without realizing that a positive smear from an apparently healthy cervix may mean invasive rather than carcinoma-in-situ, or may be misleading. Some may take no action. Most gynaecologists undertake cervical biopsy as the

next step, but the biopsy may be inadequate in its type and extent. In any case, the biopsy material is then submitted to the pathologist of the particular hospital to which the patient is admitted. Pathologists differ in their handling of such specimens, and many hesitate, perhaps because of pressure of other work, to prepare and examine 12 to 16 blocks of each cone. Even if this is done the criteria adopted for the diagnosis of carcinoma-in-situ vary considerably from laboratory to laboratory, and are far from reliable. So a pathologist may decide that a cervix is free from cancer when the cytologist is reasonably certain that it is not, and unless the closest co-operation is established the cytologist in a centralized unit may never learn the results of biopsy or have an opportunity of studying the microscopical sections.

For community screening to be efficient it seems essential that the cytologist and the histologist should be the same individual. The person issuing a positive smear report should always receive the biopsy material to handle as he thinks best. Only by constantly comparing smears, negative as well as positive, with microscopical sections of normal as well as abnormal cervixes can the cytologist raise and maintain his standards of reporting. The ideal is that the cytologist should also work regularly with the same gynaecologists, so that co-operation between them is personal and close, each case in which the smear is not normal being the subject of consultation. Only in this way does the patient receive the maximum benefit from cervical cytology.

It follows that, although some centralization of cytodiagnosis may be necessary in certain areas to provide for the needs of doctors working outside hospitals, and possibly for the purpose of training technicians, each hospital of reasonable size should have its own cytological service as an integral part of its histological laboratory. Moreover, this should aim to serve not only the hospital population but the community from which the hospital naturally draws its patients.

Access to the Community

A difficulty now well known is that, no matter where facilities for the taking and the examination of cervical smears are provided, only a proportion of the women at risk make use of them. The ones that do are those in the higher social grades, among whom the chances of cancer and of a positive smear are least likely (Stocks, 1955; Lawson, 1957; Macgregor and Baird, 1963; Boyd and Doll, 1964). It is the women who are careless of health and of hygiene and lacking in education, and who have consorts of similar character, who are most prone to carcinoma of the cervix; and these are the ones who, even if repeatedly requested, refuse to be examined so long as they feel well. The same type of woman is also the one who fails to report for postnatal examination. To surmount this difficulty some local authorities are arranging for nurses or health visitors to visit and take cervical smears from women in their own homes (Osborn and Leyshon, 1966). Even if this uneconomic arrangement were practicable on a large scale the taking of smears under these conditions makes for inefficiency, and many women would still refuse the test.

The way in which to provide for a reasonable coverage of the women at risk is to introduce cervical cytology as a routine procedure for all patients attending venereal disease, infertility, gynaecological, birth-control, and antenatal clinics (including those conducted by general practitioners in their surgeries). Only a proportion of the unmarried women, in whom cervical cancer is rare, would then escape the net.

With this arrangement the majority of cervical smears would come from pregnant women. Their interpretation in these circumstances requires the maximum skill and experience on the part of the cytologist. Even though the epithelial reaction to pregnancy should not confuse the expert, our experience of routine cytology in antenatal clinics during the past two years

leads us to conclude that a number of women develop dysplasia, if not carcinoma-in-situ, during pregnancy which disappears after lactation is complete. Although it is said that women whose smears are positive in pregnancy generally have a positive smear subsequently, there are clearly some whose cellular picture returns to normal after delivery. This, as well as other considerations, leads to the conclusion that, unless a patient has symptoms or signs suggesting carcinoma of the cervix, the finding of a positive smear during pregnancy should not prompt immediate biopsy. On all counts it is better to wait until after delivery, and then confirm the cytological findings, before taking active steps to establish the diagnosis.

Frequency of Cervical Cytology

The taking of cervical smears routinely during each pregnancy also has the advantage that in most cases the test is repeated automatically every two or three years. In the screening of non-pregnant symptom-free women, how often should cervical cytology be practised? Although on average it takes 10 years for carcinoma-in-situ to become invasive cancer, there are wide individual variations, and the answer to the question, at present at least, is determined by economics as much as by scientific knowledge. It depends on how frequently the patient or the State can afford to have smears examined, and whether there are enough cytologists to screen a particular population every one, three, or five years.

The woman with a positive or suspicious smear must of necessity be retested at frequent intervals as dictated by the circumstances of her particular case. Even if she has carcinoma-in-situ treated by total hysterectomy regular follow-up is still important. This is because this disease is often merely one manifestation of a widespread field-change and its elimination in one site does not preclude its later appearance elsewhere—in the vagina, for example.

In the case of the woman whose initial smear is negative our practice is to take a second smear in not less than one year if she presents again. This is to cover the possibility that cancer was overlooked on the first occasion. If, however, the second smear is negative further tests are carried out at three-yearly intervals. Many workers, such as Garrett (1964), report that it is not uncommon to find smears changing from negative to positive during the years. Our experience is different, and among the series of cases reported here there was only one woman whose cervical scrapes were found to contain abnormal cells, having previously been repeatedly clear. This patient was under regular supervision because of a clinical diagnosis of leucoplakia of the cervix. After two and a half years of study the smear became suspicious and cervical biopsy then showed dyskeratosis.

Conclusion

For the handling of women who have reason to consult him, cervical cytology is of the greatest value to the gynaecologist. It is more often the negative rather than the positive finding which helps. Cytodiagnosis, however, is valuable only when its standards are of the highest. If the cytologist reports a large percentage of smears as doubtful or suspicious, the gynaecologist and patient are better off without his services. For the

cytologist to maintain and improve his work and retain his interest it is essential that he should be responsible for the examination of any biopsy material which becomes available; indeed, a histopathologist should supervise all cytology. Moreover, if the patient is to receive the best care, close and personal cooperation between the cytopathologist and the clinician is also necessary.

For the screening of well women, as part of preventive medicine, it is even more important that cytology is accurate and precise. Otherwise more women may be killed or harmed from unnecessary surgery than would have died from cancer. Finally, it has to be recognized by those whose enthusiasm may put cytology in a wrong perspective that the discovery of early cancer by the routine regular examination of apparently normal women will still not prevent deaths from the disease. Garrett (1964) reported that among 107 symptomless women discovered to be suffering from carcinoma when they attended a well-woman clinic 18 died from the disease within the ensuing years. These included 4 out of the 23 in whom cervical cytology revealed unsuspected and very early invasive carcinoma of the cervix.

I am grateful to Dr. A. S. Woodcock, who not only initiated the cytological work in my department but during the years has maintained a remarkable degree of accuracy in his reports. His contribution to the care of the women whose cases are reported here is inestimable.

Addendum

Since this paper was prepared one patient in the series of cases in which cancer was not suspected has developed an invasive growth in the cervix. She was aged 37 years when she first attended hospital complaining only of backache. Examination revealed vaginitis, which was proved to be caused by trichomonas infection, and it was assumed that this accounted for the fact that the cervix bled a little when scraped. The cervical smear was reported negative, and cytology was not repeated until four years later, when the patient returned, having had postcoital bleeding for three months. Early invasive cervical carcinoma (shown to be squamous type on section) was then clinically evident, and the smear contained malignant cells.

Re-examination of the original smear confirmed the absence of any abnormal squamous cells, suggesting, but by no means proving, that this woman developed invasive cancer within four years of not having any unusual activity in the cervical epithelium.

REFERENCES

- Boyd, J. T., and Doll, R. (1964). *Brit. J. Cancer*, 18, 419.
- Boyes, D. A., Fidler, H. K., and Lock, D. R. (1962). *Brit. med. J.*, 1, 203.
- Friedell, G. H., Hertig, A. T., and Younge, P. A. (1960). *Carcinoma in Situ of the Uterine Cervix*. Thomas, Springfield, Illinois.
- Garrett, W. J. (1964). *J. Obstet. Gynaec. Brit. Cwlth*, 71, 517.
- Kottmeier, H. L. (1953). *Carcinoma of the Female Genitalia*. Williams and Williams, Baltimore.
- Lawson, J. G. (1957). *J. Obstet. Gynaec. Brit. Emp.*, 64, 488.
- Macgregor, J. E., and Baird, D. (1963). *Brit. med. J.*, 1, 1631.
- Osborn, G. R., and Leyshon, V. N. (1966). *Lancet*, 1, 256.
- Petersen, O. (1955). *Acta radiol. (Stockh.)*, Suppl. No. 127.
- Stocks, P. (1955). *Brit. J. Cancer*, 9, 487.