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Uncertainties of Cervical Cytology

Though the use of cervical cytology is familiar as a means of detecting cancer of the uterine cervix, the reasons for the controversy it continues to arouse are less well understood. The misunderstanding is not over its use in the diagnosis of invasive cervical cancer but over its value in the screening of healthy women. Nor is it simply the interpretation of the evidence that is debatable, for it is beset by some of the other problems which often surround the introduction of a new procedure. These problems, neither inevitable nor peculiar to cervical cytology, deserve attention.

To detect cancer in a preinvasive and curative stage is an appealing prospect, and, aided sometimes by public and political pressure, screening has become popular in many places. In England and Wales about 2 million smears are now examined yearly,[1] and in the United States 15 million women are estimated to have had at least one smear taken.[2] Such figures speak of the elaborate services which now exist to deal with such a volume of work. About 5 per 1,000 women are found to have carcinoma-in-situ, and most of them are then surgically treated. These measures its, advocates affirm, must save lives. Yet even after 20 years of effort there is a lack of convincing evidence that they have reduced mortality from cancer of the cervix anywhere in the world, though mortality has been declining even where there has been little or no screening.

Ways of reconciling this disappointing state of affairs with a continued belief in screening are not difficult to imagine, and they have been scrupulously discussed by successive reviewers. Firstly, it may still be too early for the benefits to appear, and, secondly, the wrong women may have been screened. As to the first explanation, it is true that we know little of either the rate of progression or the frequency of regression of carcinoma-in-situ. Both invasive cancer (irrespective of the presence of symptoms) and in-situ lesions may give positive smears. The distinction depends on a measure (histological examination of a surgical specimen) which is also curative of cervical carcinoma-in-situ. Thus we cannot know anything directly of its natural history in the absence of treatment.

As to the second explanation, that the wrong women are being tested, it is general experience that the women who offer themselves for cervical screening belong to a low-risk group of relatively high socio-economic class. Unfortunately it is not possible to estimate how low is the risk. Not only have social details seldom been noted at screening, but women self-selected from a given socio-economic class may be far from typical of the group as a whole. It is at least conceivable, therefore, that the low rates of clinical disease reported in screened women might not be very different in the absence of screening. And it is not difficult to see how even extensive screening might still miss most of those likely to develop a disease so uncommon that most general practitioners in Britain see a fatal case less often than once in five years.

The discovery that substantially more women have carcinoma of the cervix in-situ than would be expected to develop symptomatic invasive disease was an unexpected result of screening which even suggested to some that they might be separate diseases. Few would now subscribe to this view. Moreover, the recent report that positive smear rates are highly correlated with mortality rates from cervical cancer when both are distributed according to the occupation of the husband[3] adds further weight to the view that carcinoma-in-situ is closely related to the development of invasive cancer. The greater prevalence of carcinoma-in-situ can be at least partly explained by the tendency for screening to detect the more slowly growing and less fatal lesions (which is inherently likely) and regression of certain lesions (which has been reported at least of cervical dysplasias).[4]

In weighing the balance of evidence on cervical cytology and its implications for population screening on a country-wide basis other facts must be kept in mind. These include the wasted effort and misleading results of smears faultily taken, of false negative results, and of specimens collected too often or too seldom; the increasing tendency for total hysterectomy to replace cone-biopsies as therapy; the anaesthetic and operative complications; the needless surgery in those women, unrecognizable individually, who would never have developed clinical disease; the millions of man-hours at the microscope; the complexities of organizing the service itself, career structures, and training schemes for technicians. It has been argued that if screening programmes do nothing else, many women will be reassured by their negative smears, though some must owe their awareness of the disease to publicity about screening. It is also true that other women free of symptoms will be caused great anxiety by positive smears. Ultimately, reassurance is effective only when it has a firm basis.

Could the present uncertainty have been avoided? What may be admitted is that thorough studies should have been carried out earlier, and the one now under way in Cardiff[5] is to be welcomed. It is not a question of proving that screening has *no* value (this is always extremely difficult to show of any measure) but of deciding whether it has *sufficient* value to justify the risks and the efforts it entails. Society must decide what is sufficient, but in a context of competing demands on

limited resources firm evidence is required for an informed decision.

In the absence of better methods for evaluating cervical cytology other possible sources of evidence have been eagerly examined. Foremost among these is the extensive cytology service in British Columbia. This began sooner (in 1949) and quickly became more extensive than elsewhere in the world, so that 80% of women are now estimated to have been screened.[6] If screening is effective, it would be reasonable to expect mortality rates to be lower in that province than elsewhere in Canada. No such suggestion could be found when these rates were analysed up to 1965.[7] However, standardized mortality rates at ages 45-64 have recently been slightly lower there than in the rest of Canada.[8] Though the differences are not dramatic, they nevertheless provide the first suggestion of an effect of cervical screening on a population's mortality rates.

Great interest is bound to be directed over the next few years towards Canada to see if these inter-province differences in mortality become more pronounced, and also towards the outcome of current studies. It is to be hoped that support will be given to the appeal by A. I. Spriggs[4] for details of cases of positive smears in women who then refuse surgical intervention. The opportunities for contacting during pregnancy or the puerperium those women at high risk who tend to elude the screeners deserve further exploration.

As with B.C.G. vaccination, anticoagulant therapy, and coronary care units, experience of screening by cervical cytology has underlined the necessity of looking ahead to the best ways of evaluating a new therapy. Otherwise, as E. G. Knox[9] stated in 1966, equivocation will be encouraged by uncertainty about whether a given enterprise which diverts skilled manpower from other worthwhile work is adequately justified or whether there is a failure to carry out a measure which should be more widely applied. In either event the consequence is to be costed in terms of lives.

[1] Department of Health and Social Security, *Annual Reports of Chief Medical Officer of Health*, London, H.M.S.O.
[2] Schneider, J., and Twiggs, L. B., *Obstetrics and Gynaecology*, 1972, **40**, 851.
[3] Wakefield, J., Yule, R., Smith, A., and Adelstein, A. M., *British Medical Journal*, 1973, **2**, 142.
[4] Spriggs, A. I., *Lancet*, 1971, **2**, 599.
[5] Taylor, N. R. W., and Wynne Griffith, G., in *Portfolio for Health*, 2, ed. G. McLachlan. London, Nuffield Provincial Hospitals Trust, O.U.P., 1973.
[6] Boyes, D. A., in *Symposium of British Society for Clinical Cytology*, 26 September 1972.
[7] Ahluwalia, H. S., and Doll, R., *British Journal of Preventive and Social Medicine*, 1968, **22**, 161.
[8] Kinlen, L. J., and Doll, R., *British Journal of Preventive and Social Medicine*, 1973, **27**, 146.
[9] Knox, E. G., in *Problems and Progress in Medical Care*, 2nd series, ed. G. McLachlan. London, Nuffield Provincial Hospitals Trust, O.U.P., 1966.

Guardians of Ethics

Two years ago the Chief Medical Officer wrote to the then president of the Royal College of Physicians of London and put some questions to him about the supervision of the ethics of clinical research in hospitals and other institutions. The college set up a committee to consider the matter, and its report is published this week.[1] It discusses the composition of ethical committees, the kind of investigations that should be referred to them, and some of the ethical questions that may arise.

For some years variously composed local committees have existed to advise clinicians on the ethical propriety of investigations they wish to carry out on patients. Hospital boards have a duty to see that unethical practices do not occur, and the public has a right to be satisfied likewise. The medical profession too must be vigilant in guarding its reputation from the harm that could come to it if unethical conduct went unchecked. But, though the overwhelming majority of doctors who do clinical research are entirely scrupulous in the treatment of their patients, they know that difficult questions of ethics can legitimately arise. For ethical conduct is not controlled by regulations set out in a lawyer's convoluted if unambiguous phraseology. It is much more aptly summed up in the words from the World Medical Association's Declaration of Geneva, "The health of my patient will be my first consideration," and no physician with any concern for his professional standards would ever depart from that injunction. Consequently the first object of any ethical committee should be to act not as a policeman but as an adviser. According to the college's report its members should be "experienced clinicians with a knowledge of clinical research investigation and in addition there should be a lay member," and this proposed composition may be endorsed. The lay member could bring a refreshing outside view to the committee's discussions and would need to be a man—or woman—of some personality to stand up to the doctors.

In being able to bring his proposals to an informed and experienced committee a clinical investigator should be able to feel that his project is examined with the idea of improving rather than blocking it. But there must also be occasions when such committees are nothing less than guardians of public health or safety. Work which in the view of at least some editors fails to conform to acceptable ethical standards does get carried out and written up. A recent editorial in the *Archives of Disease in Childhood*,[2] for instance, states "we have occasionally asked an author to excise the unethical component of a piece of work." Whether, if that is done, the result should be published is a matter of opinion. Again, the *B.M.J.* cannot be alone in rejecting—though rarely—a paper on ethical grounds. The mere existence of the lapses from what individual editors and their advisers believe to be proper standards indicates that both control and education must be part of the work that ethical committees carry out.

It is important too that these committees should not work in isolation, for judgements on ethical matters have a large subjective component just as they do on some clinical matters, such as termination of pregnancy. Free discussion of the problems they must face is particularly desirable if only to ensure that wildly different standards do not prevail in different hospital areas.

The report is right to advocate that all clinical research, including trials of drugs approved under the Medicines Act and teaching demonstrations on students, should be submitted for approval to the ethical committee. The only exception is to be the treatment of an individual patient outside the research context. Therefore some thought should be given to the setting up of these committees in areas or for hospitals at present lacking them. Possibly a joint committee of the colleges could survey the situation and give some advice on where and how they might be appointed, for the best way of selecting their members is not self-evident.

[1] Royal College of Physicians of London, Committee on the Supervision of the Ethics of Clinical Research Investigations in Institutions, *Report*, July 1973 (published 30 November 1973).
[2] *Archives of Disease in Childhood*, 1973, **48**, 751.