Early Diagnosis Paper 3

The Early Diagnosis of Cancer of the Cervix

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In July, 1965, the Office of Health Economics held a colloquium on Surveillance and Early Diagnosis in General Practice at Magdalen College, Oxford. It was apparent from the discussion at this meeting that General Practitioners believed that if they were to act effectively in this field, they had to have clear cut information on current screening methods and the impact of early diagnosis of disease on the long term health of the patient. As a result of this view the Advisory Committee set up by the Office of Health Economics came to the conclusion that the best method of furthering this issue was to ask experts in a number of relevant clinical fields to write short papers specifically for General Practitioners. *The Early Diagnosis of Cancer of the Cervix* and *The Early Diagnosis of Depression* are the latest additions to the series. Other papers already published are *The Early Diagnosis of Raised Arterial Blood Pressure*, and *The Early Diagnosis of Visual Defects*.

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ALTHOUGH cervical cancer causes only 1 per cent of female deaths, it is responsible for almost one quarter of all deaths from cancer amongst women under the age of fifty.

For more than fifty years it has been believed that there are one or more stages of development before true invasive cancer appears; these early stages provide an opportunity to deal with the disease at an early and pre-cancerous stage. Moreover, effective techniques exist for making diagnosis at this stage. The technique most used is exfoliative cytology which provides accuracy levels of between 70 per cent and 95 per cent.

All established methods of screening are quick and entirely free from danger. Although a fair proportion of the public will attend for tests, those most at risk seem least willing to attend clinics. Assiduous long term follow-ups are essential, since the recall rates have so far been poor.

The cost of screening three-quarters of the women at risk over twenty-five years of age at five-yearly intervals would be little more than £3 million per annum. A successful screening campaign would double the immediate bed requirements if it were followed by adequate treatment of all early in-situ cases. Long term, the hospital bed usage for the disease should diminish by approximately two thirds due to early detection and treatment at this stage requiring shorter periods of hospitalisation.

Even should the general practitioner not wish to participate in the physical collection of smear material, his role in encouraging the initial and follow-up examinations amongst apparently healthy women is of vital importance.

THE PRESENT POSITION

Cancer of the Cervix is the one malignancy above all others that has had vast efforts brought to bear on its early diagnosis. This is largely because of the advent of exfoliative cytology, the accessibility of the cervix for smear collection and the existence of a pre-cancerous state which may be for ten or more years. Large population screening programmes have been carried out in various parts of the world, especially in the United States and are summarised in a review by Wilson[1].

Around 5000 cases of invasive cancer are diagnosed each year in England and Wales, in a population of 47 million (18·9 million women of cancer age), and just under 2500 women die of it. Carcinoma of the uterine body claims an additional thousand. These figures may not seem much compared with the 10,000 deaths from cancer of the breast, 3000 from ovarian cancer or 15,000 from carcinoma of the alimentary tract in women. Nevertheless although cervical cancer causes only 1 per cent of female deaths it is responsible for a quarter of cancer deaths in women before the age of 50.

A more detailed study of the 5000 invasive cases diagnosed each year reveals that about one third have a Wertheim hysterectomy, with its three week hospitalisation and an operative mortality rate of between 1 and 2 per cent, about two-thirds have radium therapy and about one quarter have both, or high voltage therapy pre or post operatively. Campbell[2] has shown that even so 54 per cent die within five years, and that the survival rate for this cancer in England and Wales is amongst the lowest of 14 countries possessing comparable Medical Services.

THE NATURAL HISTORY OF THE DISEASE

Most authorities[3,4,5] consider that there are one or two stages before true invasive cancer develops. This has been demonstrated in the individual case by serial biopsy, with observed passages from normal squamous epithelium, through dysplasia, to carcinoma-in-situ, then micro invasion leading to invasive squamous cancer[6].

The concept of carcinoma-in-situ has been recognised for over 60 years[7,8]. In 1933 Schiller first propounded what is now accepted as the orthodox American view that it should be regarded as cancer and handled as such[9].

The sequence of changes appears to be as follows. The normal maturation gradient of the stratified squamous epithelium of the cervix, from rounded basal cells to flattened superficial squames, is only partial in dysplasia and wholly absent in carcinoma-in-situ. In the latter the entire depth of the epithelium is composed of undifferentiated 'deep' cells. These cells, moreover, demonstrate changes characteristic of malignancy, again partial in dysplasia, but more complete in carcinoma-in-situ, with large irregular hyperchromatic nuclei, numerous and abnormal mitosis[10] and the abnormal chromosomal composition (polyploidy) on culture similar to that associated with invasive cancer[11].

Recently opinion has been hardening, that dysplasia may not always be a precursor but a well differentiated variant of carcinoma-in-situ[12,13] and that the latter may persist for many years, averaging from 10[14] to 15 years[15]. Later irregular downward protrusion of the basal layers of the epithelium appears. This is described as the micro invasive stage which may last up to four years; then follows the true invasive phase with the usual speed of progression we recognise in squamous cancer. The mean age incidence for patients at the various stages of development in the British Columbia Survey are given in Table A.

Table A
Mean Age of Patients at various phases in development of Squamous cell carcinoma of the Cervix

	Age	*No. of Patients*
Age at onset in cases with previously negative smear	37·7	49
In-Situ Cases	42·3	105
In-situ with microinvasive foci	50·4	53
Clinically invasive Cases	52·1	569

Reproduced from Bryans et al 1964. *Am. Journ. Obstet & Gynec.* 88, 898.

Although it has been shown that progression does occur and certain surveys suggest that only 30 per cent[16] to 60 per cent[5] of diagnosed carcinoma-in-situ turn invasive, there is considerable doubt as to the exact proportion. Further there is little evidence of the variability around the mean of the duration of the in-situ phase. Green[17], presenting his figures for Auckland, New Zealand, and comparing them with those of British Columbia, has claimed to show that, with 53 per cent to 60 per cent of the female population at risk included in the cytology programme, little or no reduction of the overall mortality rate from the disease has resulted. His chart, however, does not depict directly comparable curves for each series and is therefore not meaningful. Green also states that in a follow up of 267 cases (some for up to nine years), in which cone or ring biopsy incompletely removed the carcinoma-in-situ, no invasive growth had resulted. He concludes that either the pre-invasive phase is much longer than hitherto considered, i.e. over 20 years or a much smaller proportion of carcinoma-in-situ progress to invasion. In fact he believes with Graham[18] that possibly less than 10 per cent of carcinoma-in-situ may ultimately invade and Kirkland[19] has therefore advocated conservative therapy and careful follow up.

The latest figures received from British Columbia however do show a very small but distinct drop in mortality rate in Table B and the conclusion drawn by Boyes

Table B
Refined Mortality Rates for Squamous Carcinoma of the Cervix in the Province of British Columbia

Year	*Population in thousands over age 20*	*No. of deaths*	*Rate 1/100,000*
1958	473·0	54	11·4
1959	478·8	51	10·6
1960	486·4	48	9·9
1961	496·0	51	10·25
1962	503·0	65	12·9
1963	513·0	57	12·0
1964	526·8	56	10·6
1965	543·2	46	8·4
1966	565·4	44	7·8

and his colleagues[20] is that the survey may have been selecting the social class I and II groups with their relatively low risk rate while mortality of the higher risk groups in class III, IV and V was continuing largely unaltered.

It must be mentioned that Table B depicts a 'refined mortality rate' achieved by Dr Boyes who scrutinised all causes of death from carcinoma of the cervix in the British Columbia survey and excluded those whose deaths were not directly attributable to cervical cancer.

Doll, however, has analysed and compared figures for British Columbia, Ontario and other parts of Canada and finds no significant drop in the British Columbia death rate[21]. He believes that as only 24 per cent of women 20 years and over were examined at least once by the end of 1960, and 57 per cent by the end of 1964, and since 90 per cent of deaths from cancer of the cervix occurs within five years of the diagnosis, that some 20 per cent reduction in mortality rate should have occurred by 1965. Other factors such as self-selection, a trend towards greater accuracy in certification of cause of death, and already-present invasive cancer may tend to mitigate against such a reduction, and Dr Doll considers that if the cytology programme in British Columbia is to prove effective a significant reduction in mortality in British Columbia should be seen in the next few years.

Ashley[22] has gathered together data from various large surveys and considers that there are discrepancies between the morbidity rate curves of carcinoma-in-situ on the one hand and invasive cancer on the other, inferring from this that there may well be more than one form of progression; one group developing early in life and passing through a prolonged phase of carcinoma-in-situ with perhaps only a small

proportion progressing to invasive cancer, and a second group, probably much larger and of late onset with little or no recognisable pre-invasive phase, making detection by screening programmes difficult or impossible.

Knox[23], after reviewing previous reports, finds that all surveys to date have failed to produce accurately the rate of progression from in-situ to invasive cancer due largely to lack of age specific incidence data and adequate cohort control. He believes a large prospective survey of 100,000 women tested three times in five years would be required to provide adequate data.

POSSIBLE SCREENING PROCEDURES

Exfoliative cytology is the most extensively tried precancer and cancer detection test in the world and all other detection systems for cervical cancer are being compared to it. Its reliability as a test for cervical cancer has been claimed as up to 97 per cent[24], though others report levels of accuracy as low as 70 per cent[25] judging results against colpomicroscopy and repeat screening programmes. Collected and read well, the cervical scrape smear, however, may reach well over 90 per cent accuracy of detection. In contrast, the detection rate for carcinoma of the uterine body by cytology may be as low as 33–40 per cent[26], though again some workers obtain detection rates between 40 and 90 per cent[27, 25], probably at the expense of a relatively high false positive rate.

Smears can be collected in four ways. Firstly by the use of the Papanicolaou Pipette. By means of this angled glass pipette and rubber bulb the posterior fornix mucus with its contained exfoliated cells can be aspirated and smeared onto a glass slide. Secondly by the use of the Ayres Spatula Scrape method. By means of this specially designed knuckle-ended wooden spatula a circumferential scrape of the cervix is made to collect cells from the squamo-columnar junction, the commonest site of origin of carcinoma-in-situ. This requires more elaborate facilities with sterile or clean bivalve vaginal speculae but provides by far the best cellular sample. Here again smears are made on slides. Thirdly, again using vaginal speculae, endocervical and endometrial swabs and aspirate smears can be collected.

All smears are immediately fixed in alcohol or ether/alcohol mixtures (wet fixation) or sprayed or flooded with carbowax/alcohol or polyethylene glycol solution and allowed to dry. The slide can then be sent by post to the laboratory for screening. The fourth method involves use of an irrigation pipette. This 'do-it-herself' plastic pipette was first described by Dr Hugh Davis of Baltimore[29]. With this method the patient is given or sent the pipette which is filled with a preservative solution of 20 per cent alcohol in normal saline, recently modified and improved, with instructions to use it at or near the midcycle. By selecting this time the cytological smear is cleanest and easiest to read. She inserts the pipette into the vagina, squeezes some irrigation fluid out by compressing the bulb and retrieves it admixed with cells by releasing

the bulb. The used pipette is then placed in a tube and posted back to the laboratory where it is centrifuged, and the cell deposit smeared on slides. Using this method Davis claims results comparable to scrape smears and Bredahl et al[31] and Finn Koch[32] also speak highly of this technique, though many workers in this country and the United States do not achieve such good results.[33,34,35,36].

Whichever technique is employed patients reported as having a positive smear are advised to have a diagnostic punch or diagnostic or curative cone biopsy or uterine curettage and ultimately may be advised to have a hysterectomy if that is thought to be necessary.

There are a number of other possible cancer screening tests but most of these are still in the experimental stage. Perhaps the most tried of these are the estimation of enzymes in vaginal secretions. Of these the Beta Glucoronidase and Alpha Mannosidase enzymes initially showed promise[37]; more recently the 6 phosphogluconate dehydrogenase (6 PGD) has produced some interesting correlations[38,39,40]. Most of the enzyme series have shown high false positive rates—around 20-30 per cent, which would just be acceptable if cytology were also to be performed on this group. This would be an elimination of 80 per cent of normal cases. Though there appears to be almost 100 per cent detection of invasive cancer with the 6 P G D enzyme, in some hands only 50 per cent of the carcinoma-in-situ cases yielded raised enzyme levels, i.e. positive results[40]. It was thought initially that this failure may reflect a possible non-progressive lesion but further investigations have not supported this idea. Moukhter and Higgins[41] claimed much higher detection rate of carcinoma-in-situ using the 6 PGD enzyme, and in consequence some centres are now giving this enzyme a trial as a pre-screening technique.

Another approach has been the use of a cell counter with a size distribution plotter. Ladinsky[42] measured the number of cells of differing size in the vaginal secretions and was able to demonstrate a secondary peak of concentration of cells of larger volume in patients with malignant disease. However, workers in this country (using this method) have observed a high incidence of both false positive and negative tests making it impractical to apply the technique at present[43].

Automated and computerised scanners of cells with the use of visible or ultra violet light, laser beams or phosphors are being developed, exploring the field of pattern recognition, but as yet no reliable apparatus for routine use has emerged [44,45,46,47,48].

THE ACCEPTABILITY OF THE TESTS

Cytology, and all sampling methods requiring the collection of vaginal or cervical secretions, are quick, free from danger, and apart from the self collecting cytopipette, equally convenient, though some enzyme tests at present require estimation within a few hours, or freeze drying to avoid loss of titre. Nevertheless, if women will not

accept them they are of little value. The degree of co-operation depends very largely upon how the procedures involved in the test are presented.

Most surveys requiring clinic attendance vary in response from 40 per cent using mass radio and television advertisement[49] to 60 per cent using personal letter[50].

By contrast Davis demonstrated both in Copenhagen and Baltimore that self collection by cytopipette can achieve over an 80 per cent acceptance[29].

Leyshon,[30] employs the district nurse to approach the lower socio-economic groups by entering their homes to collect scrape smears, since experience shows that this group are less likely to present themselves at a clinic. Furthermore, they form the majority of the high risk groups, i.e. in social classes IV and V.

Leyshon[51] claimed that in this personal domiciliary service the cost of finding a positive was nearly half that in the Clinic series. Of course this advantage must be offset against the failure to obtain a proper clinical examination, lack of which Jeffcoate[52] considers one of the dangers of a cytological screening service by itself. It is well known that a scrape smear alone may fail to detect a well advanced cancer with its sloughing, almost acellular, surface.

There is little difference in acceptability of the different procedures of collection once the patient is at the clinic. The aspiration (Papanicolaou) pipette demands little in the way of preparation compared with the spatula and takes half the time (about 3–5 minutes), but if the patient is told that the spatula produces the more reliable smear she usually happily accepts it.

In a series comparing the spatula scrape test with the irrigation pipette 68 per cent preferred the latter as being more convenient while the commonest reason for the 20 per cent preferring the scrape test was that they were unsure of the reliability of something done by themselves[53]. Most surveys show that mention of the cytology test by the general practitioner is a potent stimulant to the patient to have a test[54].

PRIORITY FOR HIGH RISK GROUPS

Assuming that progression of carcinoma-in-situ to invasive cancer takes place in a large enough proportion of cases to warrant attention (the estimated percentages vary from 60[5] to 10[17]), there is the necessary incentive and obligation to eliminate the condition, certainly in the high risk groups.

In the age groups 25 to 65 there is an average *prevalence rate* of 3 to 7 per 1000 cytologically 'positive' cases on first screening a population (invasive and carcinoma in-situ cases) and this may reduce to an *incidence rate* of 0·3 or 0·2 per 1000 on re-screening the next year[20] and even lower when screening is repeated yearly as shown in Table C.

Dunn has shown by comparison of the age specific prevalence and incidence rates as illustrated in Figure 1 that the initial screening yields a high prevalence rate in the 35 to 40 age group, (5 to 11 per thousand). On rescreening the population a

Table C
Incidence of clinically invasive cervical cancer in women over 20 years of age in British Columbia.

	SCREENED			UNSCREENED		
	Women screened to previous year (in thousands)	*Clinically invasive cancer cases*	*Rate per 100,000*	*Women screened to previous year (in thousands)*	*Clinically invasive cancer cases*	*Rates per 100,000*
1961	146·8	5	3·4	339·6	110	32·3
1962	201·6	7	3·5	294·0	71	24·1
1963	214·9	10	4·65	298·4	88	29·52
1964	260·0	12	4·6	266·8	74	27·8
1965	310·0	13	4·2	233·2	67	28·8
1966	357·0	17	4·6	208·0	60	28·6

different rate of detection is obtained with an overall lower incidence rate, but with a small increase in the 25 to 30 age group. This may indicate the need to commence screening at the age of 25[55]. Wilson [56] has shown also that 30 per cent of 'positive' cases occur before the age of 35 and that commencing screening at 25 would detect 90 per cent of potentially invasive lesions.

Screening can usefully be carried out in older women. The majority of in-situ lesions occur before 65[55] but at any age there is a chance of detecting an early phase of invasive cancer.

Haenzel & Hillhouse[57] have demonstrated a high rate in negro and Puerto Rican women and a low rate in Jewish women. The disease is virtually unknown in nuns[58,59] and much commoner in married than single women[60]. Wynder[61] has demonstrated that early marriage with frequent intercourse doubles the incidence of carcinoma-in-situ; further, a woman married twice or more had two to four times the risk of a woman married once only. These findings are confirmed by Boyd & Doll[62] who also demonstrated a slightly reduced incidence of carcinoma of cervix in those using obstructive methods of contraception.

Wynder[61] and Khanolka[63] demonstrated that the cervical cancer rate was lower in circumcised Muslims than in the uncircumcised Hindus, while Khanolka[63] showed further that the uncircumcised Parsees had a lower rate than the Muslims. He pointed out that Parsees practise a very high degree of hygiene and cleanliness and this has suggested that there may be a possible carcinogen in smegma. This is only partially confirmed experimentally[64,65] but it does suggest that hygiene may be the governing

Figure 1

Age Specific prevalence and incidence rates for Carcinoma-in-situ; British Columbia, San Diego County and Memphis-Shelby County.

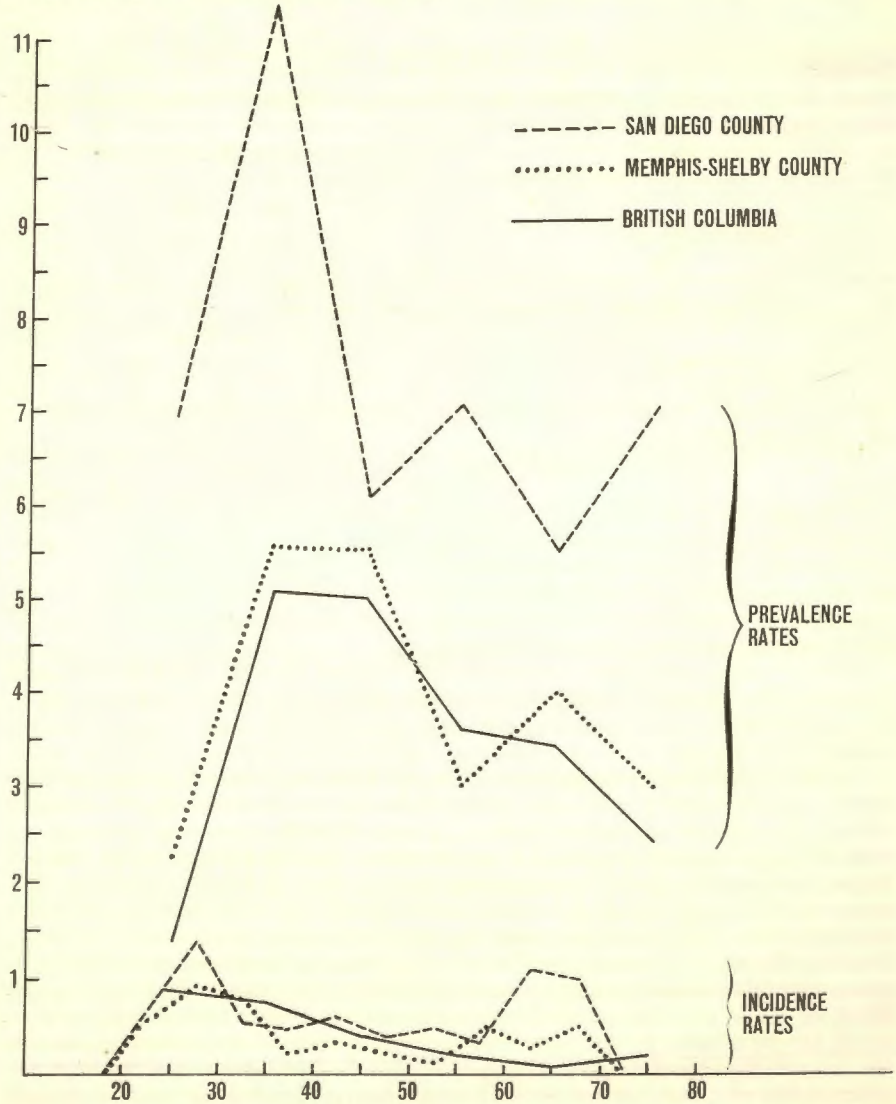

Table D

Social factors involved in mortality from carcinoma of Cervix. Standardised mortality rates. England & Wales (GRO 1958).

A. *Social Class of Husband (Married women aged 24-64 only).*

		Social Class				
All Married Women		*I*	*II*	*III*	*IV*	*V*
SMR	100	64	75	98	105	134

B. *Social Class of Woman (Single women aged 20-64 only).*

		Social Class				
All Single Women		*I*	*II*	*III*	*IV*	*V*
SMR	100	40	61	87	121	115

C. *Marital States*

	All Women	*Single*	*Married*	*Widowed & Divorced*
SMR	100	30	101	127

factor in the differing rates just mentioned. The low rate found in Jews has been attributed to circumcision. Aitkin Swan & Baird[66] however did not find a higher rate of carcinoma in uncircumcised consorts.

Wilson[56] has shown from Reports of the General Registry office occupational mortality figures that the lower socio-economic classes (IV, V) have more than double the mortality rate from cervical cancer compared with the upper classes I and II Table D.

There is a real need for long-term follow-up. With high rates of internal and external migration this presents problems which have so far not been satisfactorily solved. The recently introduced National Request/Record form is in quadruplicate with one copy intended for use in a central record department such as the General Registry Office. This could be used as the basis for a possible recall, at present in five years in this country. A national recall system would be ideal but may be a little too cumbersome to manage, and a system on a large Public Health Authority grouping or Regional Board Area size may well be more practicable. A system similar to that in practice by West Sussex County Council could well become the model for the future. Here, by use of the Electoral Roll, the initial call and further control, and eventual recall, can be effected by computer.[67] If a limited number of such centres—based on the (intended) reduced number of (larger) local authorities—were to serve the population in this way, with a linked system between centres to permit up-dating of records

due to migration of population, an integrated national programme could be worked. Test results should be collected and stored on computer tape, and linked records would then provide the necessary interchange and up-dating of data that would result from population movement.

Short-term recall must be the responsibility of the appropriate clinic or general practitioner. Ideally, all recalls over a year, or even six months, should be initiated by the Central Records Department, but the larger the centre, the more difficult will this be.

With various authorities collecting smears (Local Health and Family Planning) there appears to be the need for that authority to send a special note to the general practitioner in addition to his own copy of the cytology report to define responsibility for the next step.

THE IMPLICATIONS OF SCREENING IN TERMS OF COST AND RESOURCES PUBLIC HEALTH, GENERAL PRACTITIONER AND HOSPITAL

In the USA the test is commonly repeated every year. McGregor and Baird[69] consider that screening every five years should suffice as the discovery of 'positive' cases will remain low (0·2 to 1 per 1000) between these times. This is the frequency of repeat adopted by the Ministry of Health. In the absence of more precise knowledge of the natural history of carcinoma-in-situ, the decision of a five year interval is necessarily largely empirical, and to a considerable extent based on economic considerations.

Ignoring for the moment the issue of preferential screening of high risk groups and assuming a service directed at women over 25 with a repeat examination every five years, we have the basis on which to build an assessment. The population of England and Wales is around 47 million (1961) census, with a total female population of 24 million. Of these, 9,326,000 are between 35 and 65; 15,220,000 between 25 and 65: and 18·9 million between 20 and 70 years.

If all women between 25 and 65 were screened at five yearly intervals, just over three million smears would need to be examined each year. This is assuming a steady rate of presentation for examination. Most surveys achieve only a 50 per cent or 60 per cent acceptance rate, but since there is need to repeat at least 3 per cent of doubtful and 5 per cent to 10 per cent of unsatisfactory smears, and as approximately 5 per cent will be duplications (from GP/Clinics and then hospitals) the more realistic figure to be aimed at is 75 per cent of the population at risk, or 2,287,000 smears per year.

Costs can best be divided into (1) Smear Test Collection, and (2) Smear Test Examination.

1 SMEAR TEST COLLECTION

(*a*) *Public Health Service*

Local Authorities, by special approval of the Ministry of Health, have been given powers under section 28 of the National Health Services Act (1946) to establish specific well women clinics to collect cervical smears. The usual practice in these clinics includes the taking of a medical history, and a clinical examination of breasts, ovaries, uterus and cervix is carried out. This is done by a team of a doctor and nurse, and with a clerk to one or more such teams. The costing is therefore not just for smear collection but for a fairly elaborate clinical check. Most clinic doctors say they cannot see more than 10 to 15 cases per half-day session.

In more detail, the cost of running such a clinic for say 12 patients per session to include the services of doctor (£2000), nurse (£800), part-time clerk (£300) for approximately 230 half-day clinics a year (a five day week with allowance for holidays) would cost 25s. per patient attendance. Add to this the cost of running a clinic with its sterile apparatus, heat, light, and water, and cytology kits, and it is unlikely that each case can be dealt with much under 30s. Quotations by various local authorities for unit cost of running local health authority clinics (Maternity and Child Welfare) and Geriatric) range from 20s. to 40s. Leyshon in Derby has made returns indicating an average cost of 22s. per smear collection[51].

Postage or transport adds further to the cost, and such items as local advertising and communication would be included in these costs, all borne by the local rates.

To obtain more than 2·25 million smears per year would require about 400 such doctor/nurse teams working whole time. It must be remembered that a variable proportion of these smears will be collected by general practitioners and in hospital gynaecological and ante and post natal clinics so that allowance would need to be made for these services.

(*b*) *General Practitioner Service*

At present the general practitioner in the National Health Service receives 7s. 6d. per smear. This fee is very shortly to be increased to 15s. This payment is for the collection of smears alone, and this accounts for only part of the costs referred to above. Materials for preparing the smears are available free from National Health Service sources.

(c) *Hospital Services*

The cost of smear collection within hospitals is not negligible because additional doctors' and nurses' time is needed, but this should not cost more than 5s. per test, including materials.

Assuming one third of the smears are collected by each branch of the Service, i.e.

Local Authority Clinics, Hospitals and General Practitioners, which is apparent from laboratory returns, the average cost per smear collection would be just under 20s. (including the cost of kits) and this would amount to £2,200,000 per year for England and Wales.

2 SMEAR TEST EXAMINATION

Under the NHS the reading of smears is based on the National Hospital Laboratory Services which employ specially trained laboratory technicians as screeners, supervised by more experienced technicians and pathologists. The career structure of the non-technical screener in the team is not yet decided, due to the lack of suitable career grades, examinations and pay structure.

The Ministry has established five main Cytology Training Schools[68], two in London and one each in Birmingham, Manchester and Newcastle, and these have a combined capacity for training 200 pathologists and technicians each year in courses from six to twelve weeks' duration. These return to their parent laboratory to train further members of their staff.

Wilson[56] has calculated that a population of a quarter of a million served by a Hospital Management Committee would include 83,000 women at risk (over 35 years) requiring 17,000 smears per year. The Ministry of Health has advised that 7000 smears per screener per year is a possible work load. The average output in the United States is 5000 smears per year[69]; this is a much more realistic aim with the existing partially trained staff now available in this country. Assuming 75 per cent smear submission, two to three screeners if fully qualified and in full-time employment could cover the suggested load. With such a small team the absence of one member on account of illness, training or resignation almost halves the output of the unit. A larger centralised unit employing ten to fifteen screeners, a chief technician and deputy, with adequate clerical staff, two part-time pathologists in control would cope more effectively with 50,000 to 100,000 smears per year without recurrent crises. The possible disadvantages of remoteness and lack of controlled follow up under such a scheme could be overcome by a good communication system and the siting of the unit adjacent to one of the major laboratory centres in a region.

A possible compromise would be for the hospital laboratories to examine all smears from within their hospital group and also provide a general practitioner service, leaving the larger centres to deal with the clinics, and some general practitioner references.

Calculated on the larger centre of ten cytoscreeners (each at £1000) a chief technician (£1700) and deputy (£1500), junior technician (£750), secretary (£850), clerk (£700), and part-time pathologists (£4000) dealing with 50,000 to 70,000 smears per year, the total salary cost would be £19,500 or 6s. 0d. per smear. Add to this the cost of 1s. 9d. for processing materials, stains, filing, storage 9d. for main-

tenance of premises and a 1s. 0d. postage for sending out up to 3 copies of reports the total cost for the examination of the smear would be 9s. 6d., or for 2,287,000 smears per year would be £1,086,000.

Therefore the grand total cost of screening 75 per cent of the women at risk over the age of 25 at five yearly intervals collected by all three authorities, GPs, Clinics and Hospitals, would amount to £3,286,000. Because of simpler facilities required and greater speed of collection the Papanicolaou aspirate pipette smear technique would amount to about one-tenth cheaper per test and lead to an overall cost of £2·9 million and the cytopipette if solely used should cost approximately £1,180,000.

If automated methods were used, such as the 6 phosphogluconate dehydrogenase enzyme test, the cost would be similar to the aspirate pipette method and this would then do away with much of the cytoscreener problem though it is likely that all so called 'positives' which may amount to ten or twenty per cent of the total would still have to be checked cytologically.

The use of self collection systems such as the cytopipette for such automated enzymatic tests might well cut the costs to that of the cytopipette level given above.

Wilson[56], assessing the cost of treatment against that of the screening programme, has pointed out that there are about 10,500 discharges from hospital per year for cervical cancer with a total bed occupancy of 220,000 days. The total hospitalisation time of a woman with invasive cervical cancer is approximately fifty days compared with a stay of seven days for a cone biopsy. Estimating that probably twice the number of women would have cone biopsies as would develop cervical cancer, he estimates that if the screening programme were near 100 per cent successful it would *ultimately* cut down the hospital bed usage by a factor of three or four. However, in the early days of a screening programme with both the old invasive and early in-situ carcinoma cases being dealt with together, it would nearly double the bed requirement for the disease, that is an extra two beds per quarter of a million population.

It is apparent, therefore, that screening for a potentially dangerous condition is not without cost. It is obvious that this cost mounts up the more the programme sets out to detect, though multiple testing clinics can be made economic, as Dr R. J. Donaldson has shown from his Rotherham Open Door Clinic[70]. The cost rises considerably the moment a medical interview and clinical examination is included.

The compromise must be that fine balance between a cheap screening technique and a more general examination, and also on the ability of a publicity programme which effectively brings in the high risk group to be tested. Here the general practitioner has an important and vital part to play.

1 WILSON, J. M. G. (1961). *Mon. Bull. Minist. Hlth.*, **20**, 214.
2 CAMPBELL, H. (1966). *J. Obstet. Gyneac. Brit. Cwlth.*, **73**, 27.
3 DUNN, J. E. (1953). *Cancer*, **6**, 873.
4 WHEELER, J. D. and HERTIG, A. T. (1955). *Amer. J. Clin. Pathl.*, **25**, 345.
5 BOYES, D. A., FIDLER, H. K., LOCK, D. R. (1962). *Brit. Med. Journ.*, **1**, 203.
6 FRIEDAL, G. H., HERTIG, A. T., YOUNGE, P. A. (1960). *Carcinoma-in-situ of the Uterine Cervix*. Charles C. Thomas, Springfield, Illinois.
7 CULLEN, T. S. *Cancer of the Uterus*, New York, D. Appleton & Co. 1900.
8 BRODERS, A. C. (1932). *JAMA*, **99**, 1670.
9 SCHILLER, W. (1933). *Surg. Gynaec. & Obst.*, **56**, 210.
10 KIRKLAND, J. A. (1963). *J. Obstet. & Gynaec. Brit. Cwlth.*, **70**, 232.
11 BODDINGTON, M. M., SPRIGGS, A. I., WOLFENDALE, M. R. (1965). *Brit. Med. Journ.*, **1**, 154.
12 GOVAN, A. D. T., HAINES, R. M., LANGLEY, F. A., TAYLOR, C. W. and WOODCOCK, A. S. (1966). *Journ. Obstet. Gynaec. Brit. Cwlth.*, **73**, 883.
13 GRUBB, C. and JANOTA, I. (1967). *Journ. Clin. Path.*, **20**, 7.
14 DUNN, J. E. (1966). *Proc. Roy. Soc. Med.*, **59**, 1198.
15 BRYANS, F. E., BOYES, D. A., FIDLER, H. K. (1964). *Am. Journ. Obstet. Gynaec.*, **88**, 898.
16 PETERSEN, O. and WEEKLUND, E. (1959). *Acta Radiol (Stockh)*, **188**, 210.
17 GREEN, G. H. (1966). *Am. Journ. Obstet. & Gynaec.*, **94**, 1009.
18 GRAHAM, J. B., SOTTO, L. S. and PALOVCEK, F. P. (1964). *Carcinoma of the Cervix*, Philadelphia, 1964, W. B. Saunders Co.
19 KIRKLAND, J. A. (1963). *J. Clin. Path.*, **16**, 150.
20 BOYES, D. A. (1967). Personal Communication.
21 ARLOWALIA, H. S. and DOLL, R. (to be published).
22 ASHLEY, D. J. B. (1966). *J. Obstet. Gynaec. Brit. Cwlth.*, **73**, 373.
23 KNOX, E. G. (1966). *Problems and Progress in Medical Care*, Nuffield Provincial Hospitals Trust, Oxford University Press. 277.
24 GRAHAM, R. M. (1963). *The Cytologic Diagnosis of Cancer, 2nd. Ed.*, London, Saunders.
25 GARRATT, L. J. (1964). *J. Obstet. Gynaec. Brit. Cwlth.*, **71**, 517.
26 MCGOWAN, G. (1964). *Acta Cytol.*, **8**, 434.
27 GRAHAM, R. M. (1958). *Cytologica*, **2**, 579.

28 Fidler, H. K., Boyes, D. A., Auersperg, N., and Lock, D. R. *Canad. Med. Ass. J.*, **86**, 779 & 883.

29 Davis, H. J. and Kurz, L. (1962). *Dan. Med. Bull.*, **9**, 12.
Davis, H. J. (1964). *Maryland Dept. Health Mon. Bull.*, 36.

30 Osborn, G. R. and Leyshon, V. N. (1966). *Lancet*, **1**, 256, and personal communication.

31 Bredahl, E., Kock, F. and Stakeman, G. (1965). *Acta. Cytol.* **9**, 189.

32 Finn Koch (1966). *The population screening for cervical carcinoma in the Borough of Frederiksberg 1962–63, Munksgaard*, Copenhagen, 1966.

33 MacGregor, J. E., Frazer, M. E. and Mann, E. M. F. (1966). *Lancet*, **1**, 252.

34 Anderson, A. F. and Clark, F. R. (1966). *Lancet*, **1**, 479.

35 Muskett, J. M., Carter, A. K., Dodge, O. G. (1966). *Brit. Med. Journ.*, **II**, 341.

36 Anderson, W. A. D. and Gunn, S. A. (1966). *Acta Cytologica*, **10**, 149.

37 Lawson, J. G. (1957). *J. Obstet. Gynaec. Brit. Cwlth.*, **64**, 198.

38 Bonham, D. G. and Gibbs, D. F. (1962). *Brit. Med. Journ.*, **2**, 823.

39 Lawson, J. G. and Watkins, D. K. (1965). *J. Obstet. Gynaec. Brit. Cwlth.*, **72**, 1.

40 Cameron, C. B. and Husain, O. A. N. (1965). *Brit. Med. Journ.*, **1**, 1529.

41 Moukhter, M. and Higgins, G. (1965). *J. Obstet. Gynaec. Brit. Cwlth.*, **72**, 677.

42 Ladinsky, J. L., Sarto, G. E., Peckham, B. M. (1964). *J. Lab. Clin. Med.*, **64**, 970.

43 Husain, O. A. N., and Cameron, C. B. (1966). *Proc. Roy. Soc. Med.*, **59**, 982.

44 Mendleson, M. L., Kolman, W. A., Bostrom, R. C. (1964). *Am. N.Y. Acad. Sci.*, **115**, 998.

45 Kamentsky, L. A., Melamed, M. R. and Derman, H. (1965). *Science*, **150**, 630.

46 Ward, A., McMaster, G. W. (1965). *Nature*, **208**, 428.

47 Boddington, M. M., Diamond, R. A., Spriggs, A. I. (1967). *Brit. Med. Journ.* **II**. 160.

48 McMaster, G. W. (1968). *Acta Cytolog.*, **12**, 9.

49 Kaiser, R. F., Erickson, C. C., Everett, B. E., Gilliam, A. G., Graves, L. M., Walton, M., and Sprunt, D. H. (1960). *J. Nat. Canc. Instit.*, **25**, 863.

50 MacGregor, J. E. and Baird, D. (1963). *Brit. Med. Journ.*, **1**, 1631.

51 Leyshon, V. N. (1965). Personal Communication.
Osborn, G. R. and Leyshon, V. N. (1966). *Lancet*, **I**, 256.

52 Jeffcoate, T. N. A. (1966). *Brit. Med. Journ.*, XX, **II**, 1091.

53 Husain, O. A. N. (1968). In press.

54 WAKEFIELD, J. (1964). Personal Communication.
55 DUNN, J. E. (1966). *Proc. Roy. Soc. Med.*, **59,** 1198.
56 WILSON, J. M. G. (1965). *Mon. Bull. Minist. Hlth.*, **24,** 72.
57 HAENSEL, W. and HILLHOUSE, M. (1959). *J. Nat. Cancer Inst.*, **22,** 749.
58 GAGNON, F. (1950). *Amer. J. Obstet. Gynaec.*, **60,** 516.
59 TOWNE, J. E. (1955). *Amer. J. Obstet. Gynaec.*, **69,** 606.
60 LOGAN, W. P. D. (1953). *Lancet*, **II,** 1199.
61 WYNDER, E. L., CORNFIELD, J., SCHREFF, F. D., DORESWARMI, K. B. (1954). *Amer. J. Obstet. Gynaec.*, **68,** 1016.
62 BOYD, J. T. and DOLL, R. (1964). *Brit. Journ. of Cancer*, **18,** 419.
63 KHANOLKA, V. R. (1958). in *Cancer*, edited by R. W. Raven, Vol. III, 272, London.
64 PLAUT, A. and KOHN-SPEYER, A. C. (1947). *Science*, **105,** 391.
65 HEINS, H. C., DENNIS, E. J., PRATT THOMAS, H. R. (1958). *Amer. J. Obst. Gynaec.*, **76,** 726.
66 AITKIN SWAN, J., and BAIRD, D. (1965). *Brit. Journ. of Cancer*, **19,** 217.
67 SAUNDERS, J. and SNAITH, A. H. (1967). *The Medical Officer*, 117, 299.
68 HEALTH & WELFARE SERVICES (1964). *Cmnd.* 2389, London, HMSO.
69 HORN, D. and SIEGAL, A. (1961). *Cancer, N.Y.*, **II,** 97.
70 DONALDSON, R. J. and HOWELL, J. M. (1965). *Brit. Med. Journ.*, **II,** 1034.

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