THE APPLICATION OF EXFOLIATIVE CYTOLOGY TO THE DETECTION OF UTERINE CANCER IN A HEALTHY POPULATION

by

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INTRODUCTION

Professor Sir Dugald Baird has been responsible for the overall supervision of this work and I am greatly indebted to him for his enthusiasm, encouragement and advice.

I am grateful to the Senior Gynaecological Registrar, Dr. Robert Yule, who took over the responsibility and management of the cases from the population survey after they had been detected cytologically.

Thanks are due to those general practitioners in Aberdeen who allowed access to their files and their patients and the use of their premises for the conduct of this pilot scheme.

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The entire clerical work in extracting the names of the women, sending out the routine letters, and in recording the replies and the smear results has been done by Miss Hazel Moore with meticulous care and great patience. She is also responsible for the typing of this thesis. I am greatly indebted to her for her patience and continued cheerfulness.

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Mr. W. Topp, of the Department of Photography was responsible for the photomicrographs and the photograph of the Ayre's spatula and glass slide.

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SECTION 1

The Development of Cytology

Biological behaviour is reflected in tissue patterns which in turn can be reflected in cell patterns. Walshe in 1851, observed fragments of malignant tissue in sputum and Dr. J. Bamforth working at St. Thomas' Hospital with Dudgeon and Patrick (1927) examined sputum, urine and other body secretions for malignant cells. About the same time, Papanicolaou (1928) working in the United States and Babes in Bucharest used a similar wet fixation technique for diagnosing cancer of the female genital tract. It was not until the 1940's, however, that Papanicolaou realised the full significance of this technique as a routine diagnostic test and in 1943 he published his now classic paper with Traut.

Cytology in Great Britain made slow progress, Saxton (1960) Pathologists were reluctant to accept cytological findings and it was left to the clinicians (or clinicopathologists) to widen the scope of cytology.

Gradually here, and in the United States where much pioneer work was done by Ruth Graham, (1950) cytology, particu-:larly cervical cytology, became established. This country, however, lags behind U.S.S.R. and U.S.A. where cytological examinations for uterine cancer have become routine procedures. Papers have been published from centres all over the world and

all have found the incidence of positive tests to be roughly the same and in particular, Anderson (1950), Wachtel and Plester (1952), Way (1953), Egerton (1957) and Yule and Cameron (1960) have made comparable observations. Boddington, Cowdell and Spriggs (1960) reported on cervical smears from 10,000 women in Oxford, and found 67 cases of carcinoma-in-situ and 11 cases of invasive cancer. The ability to detect early cancer has provided the greatest impetus to the development of cytology and has to some extent overshadowed its other potentialities such as in endocrinology (Wachtel and Plester, 1954), cyto-:genetics and sex determination.

This thesis is concerned with the use of cytological techniques to detect early cancer of the uterine cervix.

The accessibility of the uterine cervix, and the clinical simplicity with which each gynaecological specimen is obtained, makes the test readily available to all doctors. The inter-:pretation of the specimens requires long and meticulous microscopic examination and considerable specialised knowledge. For cytology to be successful, the clinician and cytologist must have a clear and accurate picture of each others problems and a diagnosis should be made only with the full knowledge of the patient's history, clinical signs and symptoms.

Technique

To obtain a cervical smear from a patient, a vaginal

speculum is inserted, the cervix exposed and a scrape of the squamo-columnar junction taken with an Ayre's spatula, (Fig. 1) which is so designed that at one end, prong A can be inserted into the os of the cervix and with a rotatory movement a scrape round all of the squamo-columnar junction of the epithelium is obtained. The other end of the Ayre's spatula, C, is designed to scoop up from the posterior fornix of the vagina, a sample of vaginal fluid which may contain exfoliative cells. Once the specimen is obtained it is smeared on a labelled glass slide, not allowed to dry, and fixed immediately in a solution of 50% Absolute Alcohol and 50% Methylated Ether for at least 15 minutes. The slides are then taken to the laboratory where they are stained, by Papanicolaou's Multichromatic stain, and examined microscopically.

The vaginal pool smear is excellent for evaluating the hormonal changes (Wachtel and Plester, 1954), radiation response (Graham, 1959) and fundal cancer detection, but it is less valuable than the cervical scraping for the early detection of cervical cancer, (Tolles, Horvath and Bostrum, 1961).

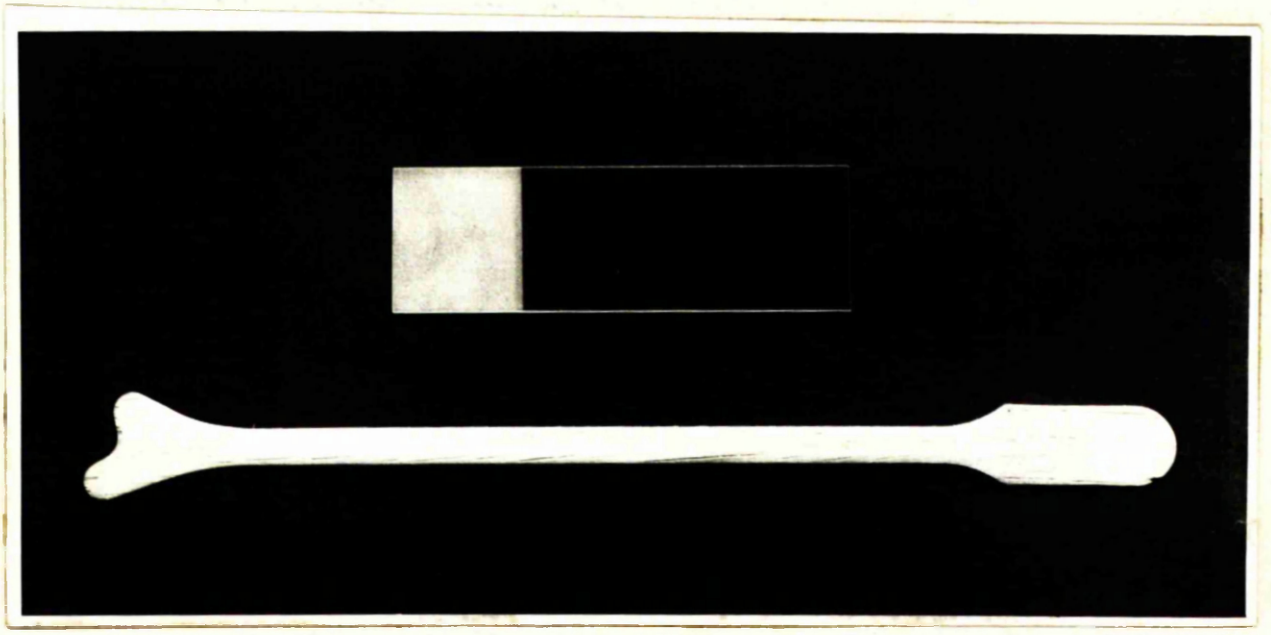

Fig. (1): Photograph of Ayre's Spatula showing the shaped end for insertion into the cervical os for taking a smear by rotary movement round the squamo-columnar junction. The spoon-shaped end is used to scoop up exfoliative material from the vagina. The glass slide is shown with ground glass at one end enabling it to be easily marked in pencil.

PART B

SECTION 2

Description of Cell Types found in Smears

A smear is composed of cells from the squamous epithelium.

(a) Basal cells These are cells lying in a single layer on the basement membrane which are germinal cells, and which are not normally exfoliated. These are seen usually, in a degenerate state when there is severe erosion or ulceration of the epithelium. Their staining is basophilic.

(b) Parabasal cells have thick, well rounded cytoplasm and a round or oval centrally placed nucleus with a delicate chromatin pattern. The nucleus takes up a considerable portion of the cytoplasm and the less mature the cell is the more 'rubbery' is the cytoplasm.

The less mature cell assumes a more spherical shape whereas the more mature cell spreads out on the glass slide and appears larger. The presence of these cells gives an indication of the absence of maturation factors such as oestrogens, progestogens etc. Their staining reaction is also basophilic.

Intermediate cells have thin wafer-like, spread-out cytoplasm and smaller round or oval vesicular nuclei. The intermediate cell appears larger than the parabasal cell because of the cytoplasmic attenuation but its actual volume is not increased. The chromatin pattern of the nucleus is regular and it stains

either basophilic or acidophilic.

(c) Superficial cells have thin wafer-like cytoplasm but the nucleus is pyknotic, not vesicular. The nucleus is the most reliable feature distinguishing intermediate cells from the superficial cells. In mature squamous epithelium this cell type lies on the surface above the intermediate cells. Occasionally anucleate superficial cells are found but usually only in abnormal conditions such as hyperkeratosis or leuko-:plakia.

Columnar cells are found in the female reproductive tract above the squamo-columnar junction of the cervix. The nucleus is vesicular and at one end of the cytoplasm, which appears to extend past the nucleus to form a wide blunt tail. There is great variation in the size of the nucleus but the chromatin pattern is uniform and evenly dispersed. There are three types of columnar cells; non-secretory with finely foamy cyto-:plasm but no gross secretory vacuoles; a secretory columnar cell which has multiple cytoplasmic vacuoles or one large vacuole, which may push the nucleus farther into the 'tail' of the cell and even compress the nucleus into a half-moon shape. This is found in inflammatory conditions such as cervicitis, and the large single vacuole is useful to denote secretion as opposed to degeneration or phagocytosis. The third columnar cell type is the ciliated cell which has delicate cilia across

the lumenal end of the cell. Should the cilia have disappeared this type is recognisable by the square-end of cytoplasm which remains.

(d) Endocervical cells These exfoliate in sheets and clumps with moulding of the cytoplasm but not of the nuclei. There is plenty of cytoplasm and endocervical cell nuclei can have bizarre shapes and great variation in size, but they usually are round or oval with uniform distribution of chromatin. Increase in the size of the nuclei usually occurs in inflammatory conditions.

(e) Endometrial cells also show moulding and are found in clumps. There is less cytoplasm than in endocervical cells, and they may show vacuolation. The nuclei are rounded, oval or indented and smaller than in endocervical cells. Nuclear size may also vary. As the menstrual cycle progresses these cells appear in more and more degenerate forms which may have alarming nuclear features and so may be confused with malignant cells from adenocarcinoma.

(f) Histiocytic cells: these cells usually appear singly. When they are clumped together, small spaces remain between the walls making it obvious that these cells did not grow together as in true tissue fragments. The outer border of the clump is rough and irregular, unlike the smooth epithelial border of a tissue fragment. The cytoplasm is very foamy and has multiple

vacuoles. The nucleus is eccentric usually touching the cell membrane and it is round or oval. When there is inflammation present the nucleus becomes kidney-bean shaped and the chromatin pattern uneven with prominent nucleoli. Mitoses may be seen.

The most common histiocyte is larger than a neutrophil leucocyte, but smaller than a parabasal cell. In response to inflammation or irritation it becomes larger and may even form a giant histiocyte, commonly found where there is a Trichomonas infection. These cells may be difficult to distinguish from malignant cells but there is a degree of uniformity which is not present in multinucleated malignant cells.

Description of Normal Smear patterns

The presence or absence of any of these cell types and the ratio of deep to superficial cells varies according to the time and place in the normal female life span. This can to some extent be measured by what is known as the Maturation Index (M.I.), obtained by a differential count of the three major cell types on any one smear, e.g. 5% parabasal cells, 70% intermediate cells and 25% superficial cells. This is expressed as 5/70/25. A release of less mature cells would indicate a shift to the left (40/50/10) while a shift to the right (5/40/55) indicates a greater degree of maturation before the cells are exfoliated.

This index is the basis of descriptions of various typical

smear patterns found and recognised in conditions, such as the pre-menstrual, menstrual, and post-menopausal states, pregnancy, and post-partum smears and in women with endocrinological upsets. e.g. A smear from a woman of 30 years of age would show changes according to the phase of menstruation.

(a) at ovulation - with an oestrogenic activity, cornified smear. M.I. swing to the right. (Fig. 2)

(b) at just pre-menstrual - progrestogen levels are high. M.I. shifts to mid-zone. (Fig. 3)

(c) During menstruation - both progestogen and oestrogen drop and oestrogen then rises alone with a return to the ovulatory pattern, about 14 days before onset of ovulation. The wide-spread use of oral contraceptives undoubtedly causes alteration of the normal smear pattern.

A smear from a post-menopausal woman of 60 years of age, lacks hormone activity and shows a swing to the left in the M.I., having a greater abundance of basal cells. (Fig. 4)

A smear from a pregnant patient shows the normal luteal phase proceeding much as in non-pregnant woman, with a gradual increase in intermediate epithelial cells. When the pattern reaches the menstrual phase it does not recede, but continues the increase of intermediate cells until it reaches the typical pattern for pregnancy. (e.g. M.I. 0/95/5) (Fig. 5)

Infection may cause a variation of this pattern with a

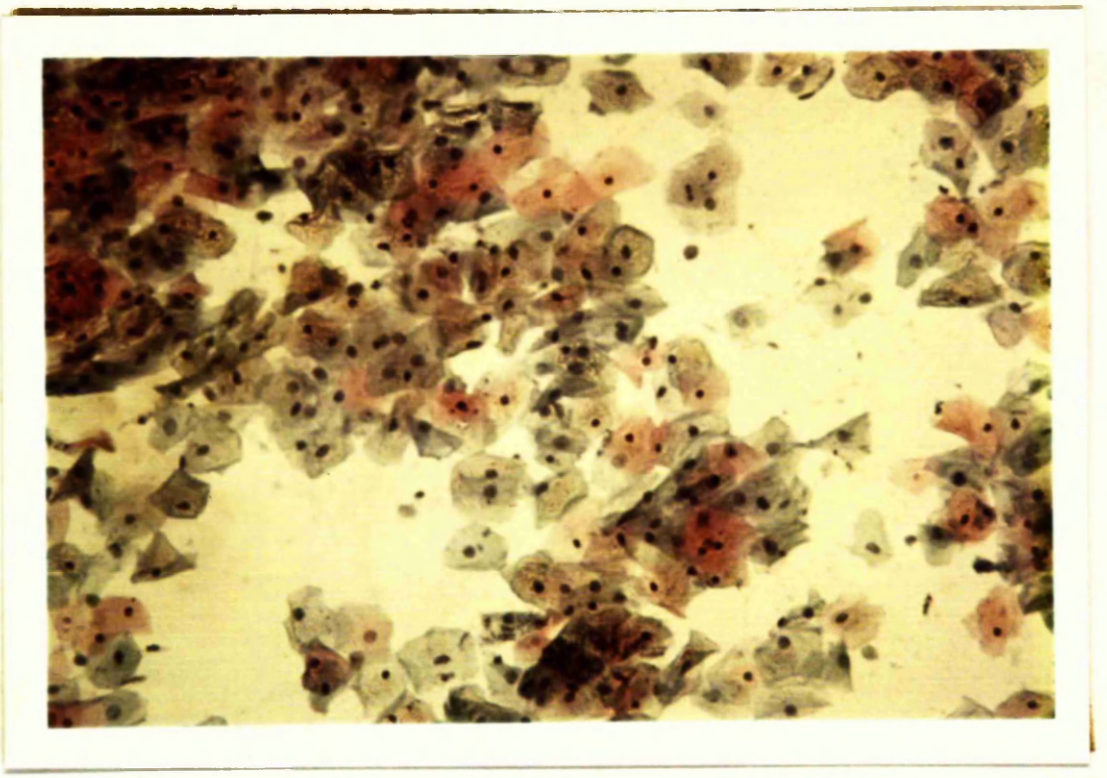

Fig. (2): Normal smear taken about ovulation (day 14) in a normal menstrual cycle, the cells lie singly and flat, the background is clean. The cells are well cornified and have small pyknotic nuclei. The M.I. was 0/40/60.

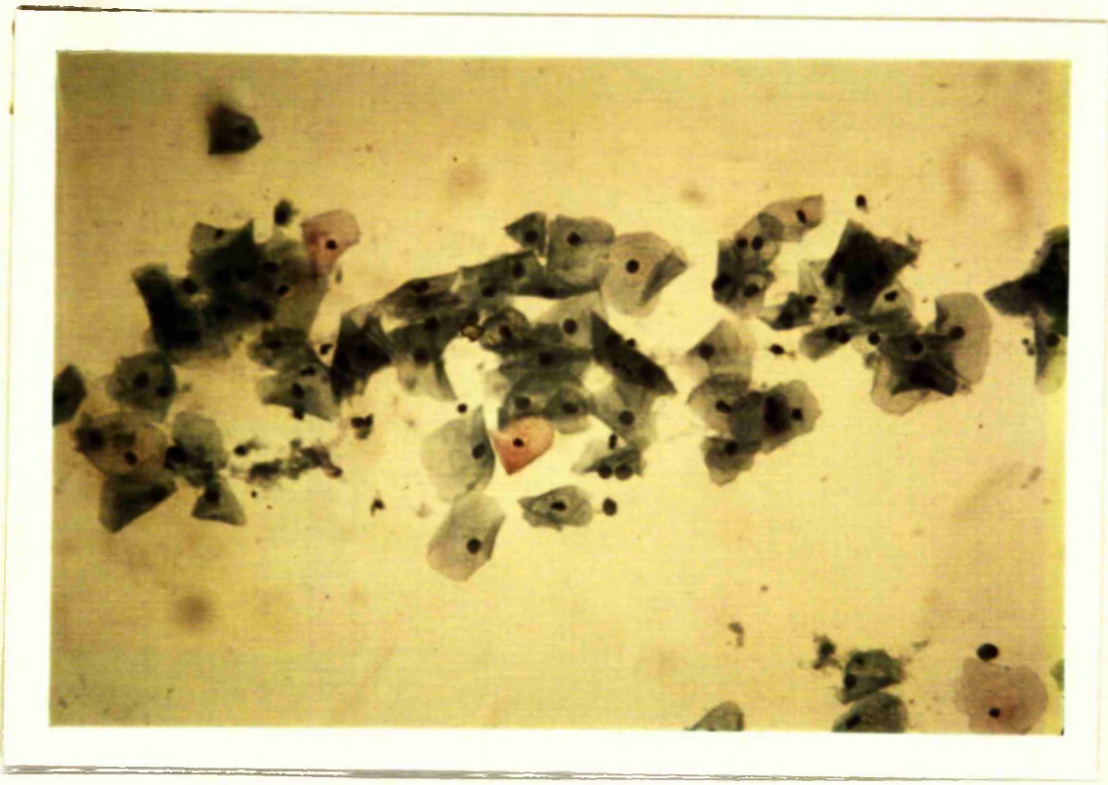

Fig. (3): Normal smear taken before menstruation shows the cells with a tendency to clump and the background is dirty. There is a predominance of intermediate squamous epithelial cells with vesicular nuclei. The M.I. was 0/70/30.

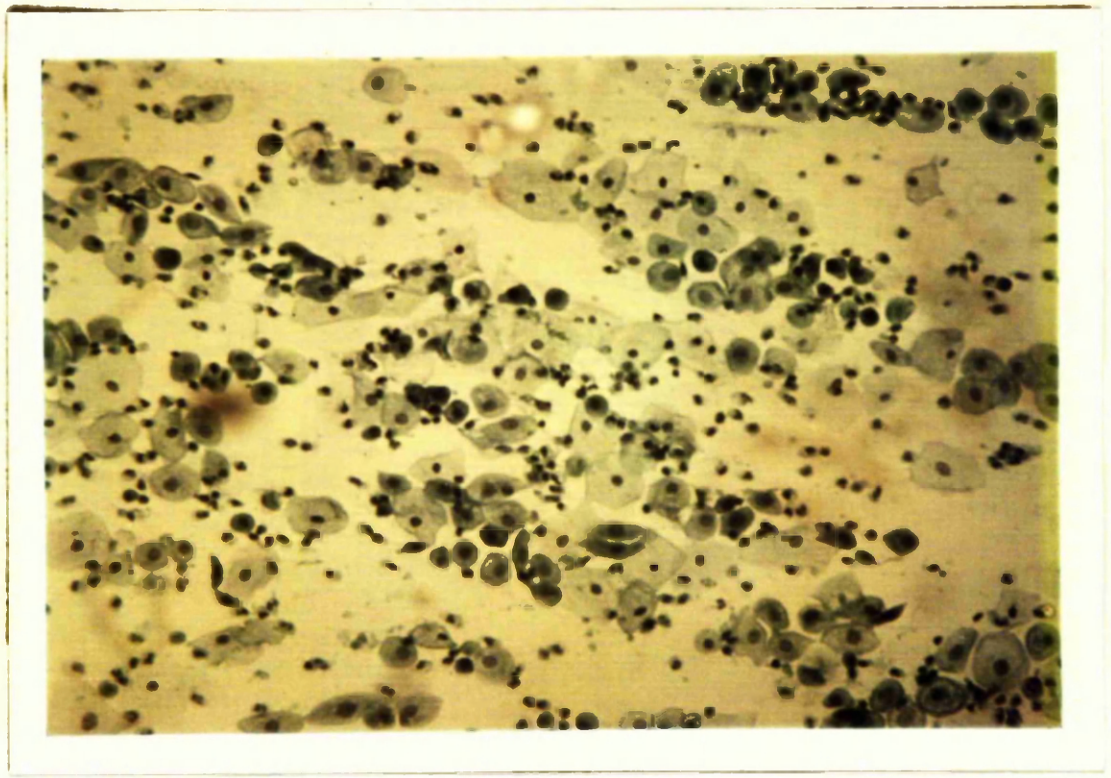

Fig. (4): Post-menopausal smear shows lack of maturing factors and this causes a predominance of parabasal cells in the exfoliative material. The M.I. was 90/10/0.

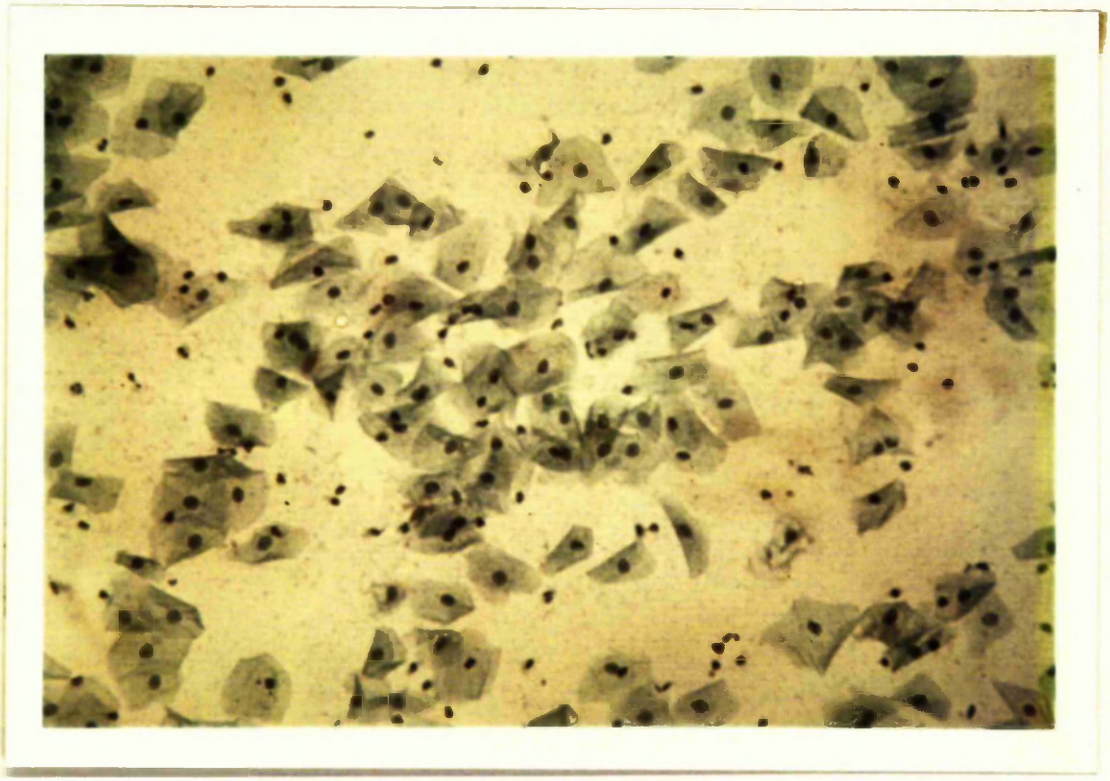

Fig. (5): Pregnancy smear taken during the fourth month of a normal pregnancy and shows the typical M.I. of 0/95/5, a dominance of intermediate squamous epithelium. Doderlein's bacilli and Monilial infection are often seen in pregnancy smears but are not obvious in this photomicrograph.

shift of the M.I. towards the left, but as the levels of oestrogens, progestogens and steroids are so massive in normal pregnancy even small therapeutic doses of hormones do not alter this characteristic pregnancy pattern.

Appreciable variation in the pregnancy pattern (in the absence of inflammation) is significant and indicates gross alteration of hormone levels. Alteration in either direction of the M.I. during pregnancy may indicate impending abortion and should foetal death occur the M.I. shift will be, as in the post-partum period, to the left.

A post-partum smear shows a swing of the M.I. to the left for some weeks after delivery and stays there for a variable period depending largely on whether the woman breast-feeds the baby. It then gradually returns to the normal menstrual pattern. (Fig. 6)

Description of Abnormal Smear Patterns

Once the normal cell patterns are known it becomes possible to distinguish abnormal patterns and cells.

(a) Inflammatory Changes

These abnormal patterns and cells may be caused by infections such as trichomonas and candida albicans which can be recognised and specific therapy advised. In general, any virus, fungal, bacterial or protozoal infection will produce an inflammatory reaction in the epithelial cells. (Fig. 7)

Inflammatory response is also brought about by irritation,

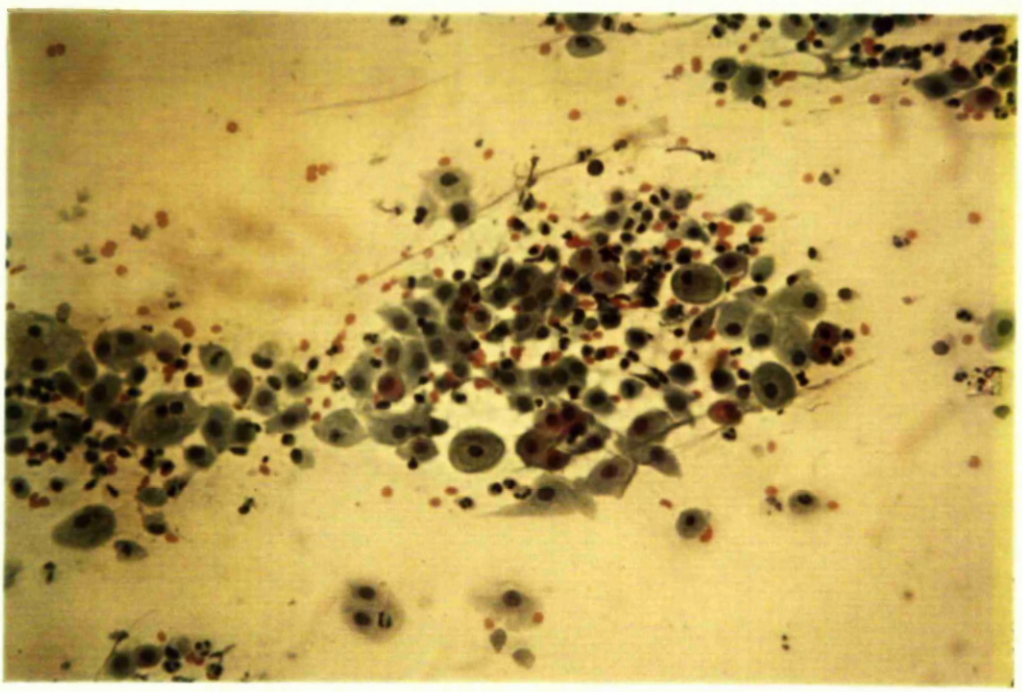

Fig. (6): Post-Partum smear taken six weeks after delivery and shows a picture similar to that of the post-menopausal smear. There is lack of maturing factors causing the bulk of the cells to exfoliate while still in basal cell form. The M.I. was 80/20/0.

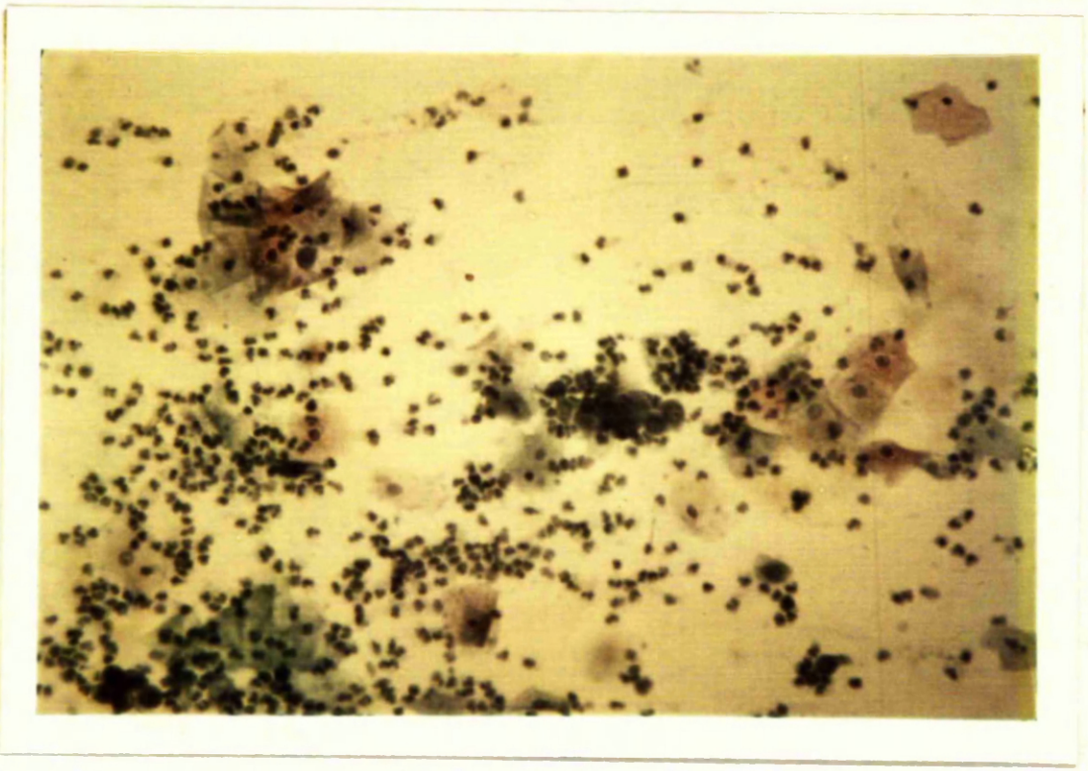

Fig. (7): Inflammatory smear taken from a woman with a vaginal infection. This shows the neutrophil lymphocytes, mucus and degenerate cell forms. Endocervical cells are seen with little or no cytoplasm. A cervical erosion was present. This type of smear can be unsatisfactory and difficult to interpret. The M.I. in inflammatory smears frequently show a spread to include all cell types, M.I. 33/34/33.

e.g. chronic irritation in cases of prolapse or prolonged use of a pessary. In these cases, superficial cells appear without a nucleus.

Radiation, trauma and endocrine upsets can also produce inflammatory reactions.

The inflammatory reaction of the cell, if sufficiently gross, may result in such distortion and degeneration that it is difficult to distinguish these changes from those associated with malignancy.

(b) Non-inflammatory changes

The presence of cervical polypi can produce cells of widely varied character and bizarre shapes. Endometrial cells are frequently found and may have characteristics similar to those found in adenocarcinoma. The cells may be very large with vacuolated cytoplasm and distended nucleus. The nucleo/cyto-plasmic ratio may be upset or the cytoplasm may be degenerate or completely absent. The nuclei of these cells do not as a rule have increased chromatin content nor angularity of the nuclear membrane. (Fig. 8)

The epithelial changes in pregnancy were at one time thought to give smear patterns which were confusing and liable to misinterpretation. It is now recognised (Dean, Ishbell and Woodward (1962) and Kantor, Roman, Leonard, Leib and Van Burkleso (1961)) that any malignant change which first appears during pregnancy will persist afterwards.

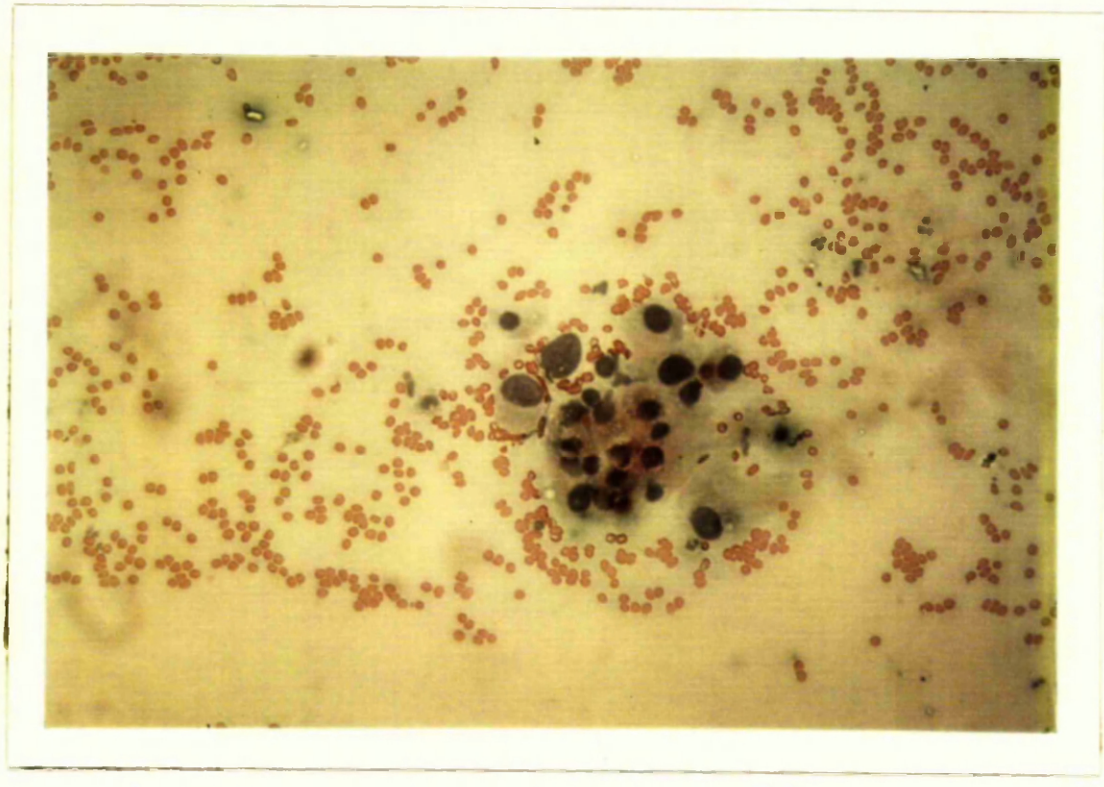

Fig. (8): **Polyp smear** taken from a woman with a large cervical polyp and shows red blood cells due to the vascularity of the polyp. The epithelium is identical with the point of origin of the polyp, here the endocervical mucosa. The great variation in size and shape of the endocervical nuclei is shown and they can readily be confused with malignant nuclei. The nuclei shown here are atrophic and degenerate.

Malignant Smears

General Criteria

There are certain general criteria which can be applied to any malignant cell. It is important however, never to diagnose malignancy in a degenerate cell. The cell under examination must be in a good state of preservation.

(a) The Nucleus

(1) There is usually an increase in the size of the nucleus which also becomes irregular and angular.

(2) The chromatin pattern shows hyperchromasia in well pre-:served cells, with chromatin clumping and abnormally clear areas.

(3) The nuclear membrane shows angularity.

(4) The nucleoli becomes angular.

(5) Multinucleation is helpful only if the nuclei produced vary in chromatin content and pattern.

(b) The Cytoplasm

(1) Cytoplasm must be present.

(2) The cytoplasm tends to decrease in amount in proportion to the size of the nucleus. Thus the nucleo/cytoplasmic ratio (N/C) is greater than normal.

Specific Criteria

1) Squamous Cell Carcinoma

This can be divided into two groups: the undifferentiated

and the differentiated malignant cells.

(a) Differentiated cell types

(1) Fibre-cells these usually occur in groups and have the nucleus with a sharp border and an increase in the chromatin content which may become dense. They are elongated in shape but their length and width may vary. They occasionally produce pearl formations.

The cytoplasm of fibre-cells extends from both ends of the nucleus and is slender and fibre-like. (Fig. 9)

(2) 'Tadpole' cells these usually occur singly.

The nucleus has a sharp border, is abnormally large, is situated in the head of the cell and has clumping of the chromatin with abnormally clear spaces.

The cytoplasm is 'tadpole' shaped and has clear borders (Fig. 10)

(3) 'Third-type' cells described as such by Graham (1950), are immature dyskaryotic cells. The nucleus has sharp but uneven borders and may be indented, the chromatin is dark and uneven, and it is large for the amount of cytoplasm present. The cytoplasm is well outlined, decreased in amount and usually surrounds the nucleus.

(b) Undifferentiated cell types

These are the most common tumour cells. They usually occur singly and then the general criteria for malignancy must

Fig. (9): Fibre cells are shown in a smear from a woman with early invasive squamous carcinoma. These differentiated malignant cells show the elongated, angular, hyper-:chromatic nuclei of varying width and length, centrally situated with cytoplasm projecting on either side.

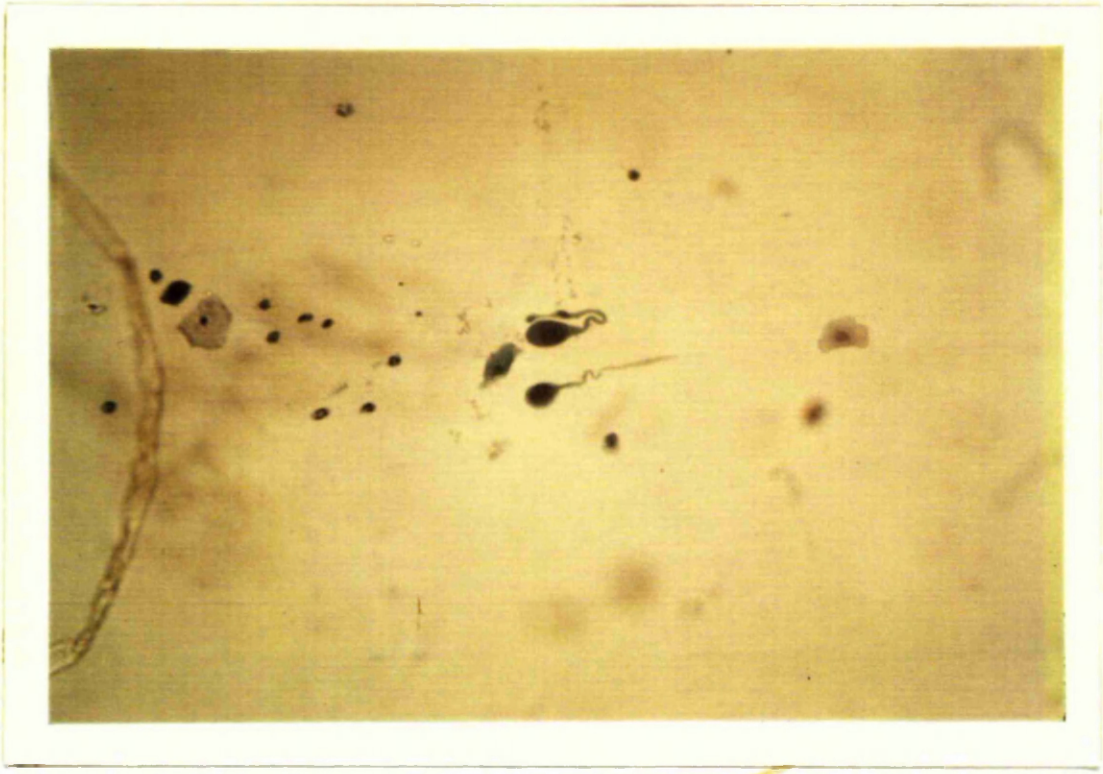

Fig. (10): Tadpole cells have a characteristic shape and show nuclei with chromatin clumping and abnormally clear vesicular spaces. The nucleus is at one end of the cytoplasm, which forms a characteristic tail.

be applied. If they do occur in groups, it is then possible to compare nuclear size and shape for variation between cells. (Fig. 11)

2) Adenocarcinoma

The malignant cells here do not show the great variation evident in squamous carcinoma and therefore are not so easy to interpret cytologically.

Malignant cells from adenocarcinoma can be classified into two groups: differentiated and undifferentiated cells, basing the classification on the presence of cell borders.

The differentiated cells have an apparent cell border although this may not be sharp. The nuclei are round or oval, large and eccentric. They have the usual characteristics of malignant nuclei. The nucleo/cytoplasmic ratio is abnormal. The cytoplasm has marked vacuolation. (Fig. 12)

(This cell differs from the third-type squamous carcinoma cell by the eccentric nucleus and the vacuolation).

The undifferentiated cell of adenocarcinoma usually occurs in groups with a tendency to piling up. The cell borders are absent. The nucleus has the characteristic features of malignancy and varies more in size than in shape but the increase in size is never gross. Any shadow of cytoplasm which may be present is vacuolated.

The structure of the nucleus identifies the cell as

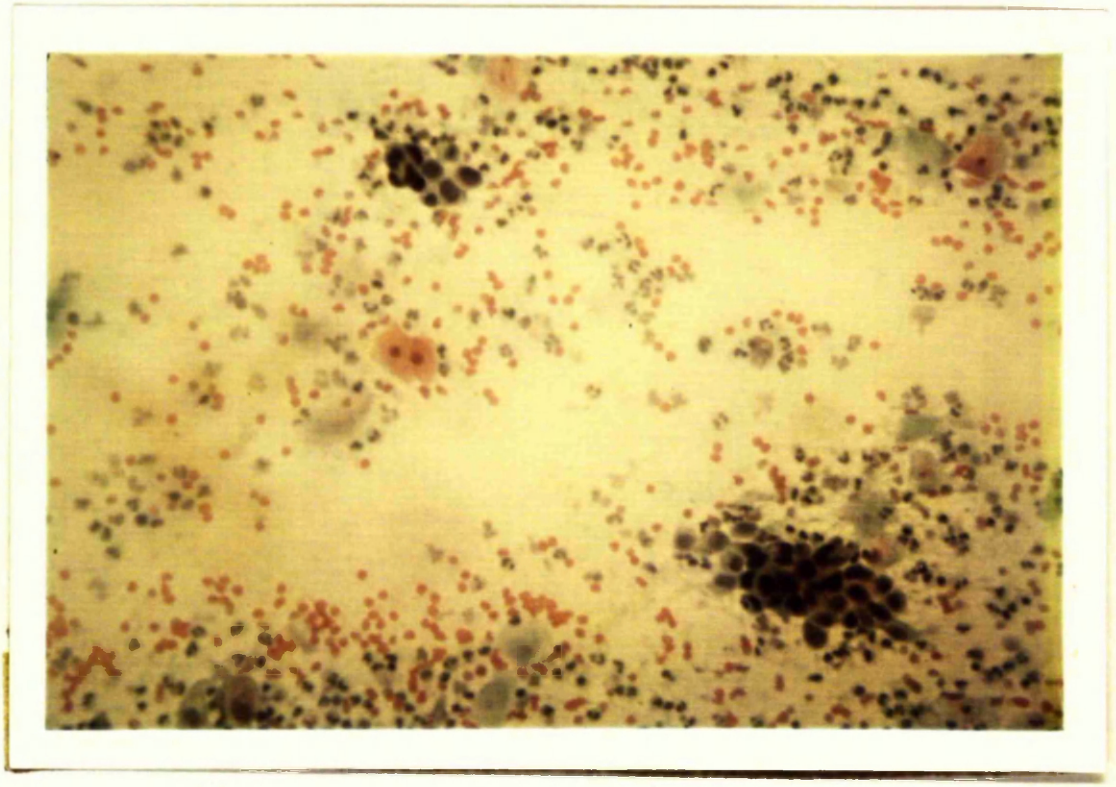

Fig. (11): Undifferentiated cancer cells from a woman with a preinvasive squamous carcinoma show the alteration in the nucleo/cytoplasmic ratio. The increase in chromatin content of the nuclei and irregular angular nuclear membrane can be seen.

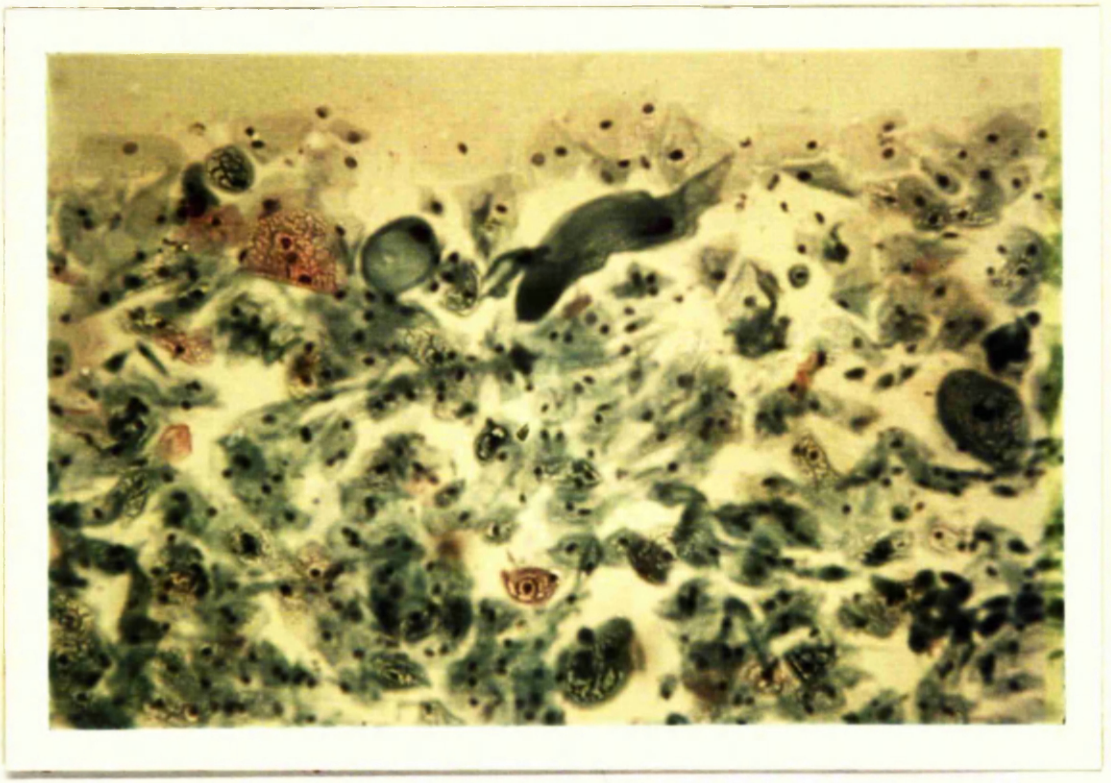

Fig. (12): Adenocarcinoma cells from a woman with adeno-:carcinoma of the cervix. This shows the gross and bizarre changes that can occur. The vacuolated cytoplasm pushes the nucleus to one side and it may be difficult, as here, to asses the malignancy of the nucleus.

Fig. (13): Undifferentiated cancer cells from the same patient as Fig. 12, with adenocarcinoma. These show the increase in chromatin content and irregularity of outline of the nucleus and dyskaryosis typical of malignant cells.

malignant and the vacuolation classifies the cell as adeno-
:carcinoma. (Fig. 13)

SECTION 3

Histological Picture

The evidence provided by cytological techniques indicates changes that may have taken place in the tissue. Consequently a cytological smear which shows malignant cells cannot, alone, be taken as proof of the presence of malignant changes in the tissue. Every 'positive' cytological smear should be followed by a biopsy to obtain, if possible, histological confirmation of the changes suspected because of the exfoliative cytological appearances.

The responsibility for proper and adequate biopsy belongs to the clinician. The pathologist cannot be expected to find a lesion if the tissue submitted is insufficient. Punch biopsies, while less traumatising to the patient than a cone biopsy, are seldom satisfactory even when Schiller's iodine test has been used to indicate the most suspect area. Punch biopsies are used widely in the U.S.A.

The suspect area is the squamo-columnar junction and a good cone biopsy of the cervix is the most satisfactory procedure. Histological sections at many levels can then be examined either, to find a lesion, or to definitely exclude all possibility of one being present. The lesion may be present in one part of the biopsy tissue but lacking in another (Foote and

Stewart 1948).

The cone biopsy itself may result in cure, but this can never be assumed. In more than a few cases, intraepithelial cancer has been found well up in the canal. This makes any surgical procedure short of hysterectomy inadequate.

There are two types of cervical carcinoma, squamous cell, or epidermoid carcinoma and adenocarcinoma. Adenocarcinoma is far less common than epidermoid cancer. Carcinoma of the cervix is predominately epidermoid in nature, with a frequency about 25 times greater than adenocarcinoma. On the other hand, uterine body cancer is predominately adenocarcinoma.

Squamous cell carcinoma of the cervix can be divided into firstly the preinvasive, also known as the intraepithelial, or carcinoma-in-situ, type, and secondly the invasive type. It may arise within the cervical canal but it more usually occurs near the external os, at the squamo-columnar junction.

Preinvasive squamous cell carcinoma, intraepithelial cancer or carcinoma-in-situ are names given to changes in the cervical squamous epithelium which are now known to precede cancer. On microscopic examination there is loss of the regular mosaic pattern of stratification due to replacement by atypical forms of basal epithelium. In the pre-cancerous atypical epithelium there is a complete loss of stratification of the cervical epithelium and an almost total replacement by abnormal

cells; these are hyperactive and may show mitoses (Fig. 14). In the diagnosis of 'atypical' cervical epithelium some strati-:fication will still be present although the area near the basement membrane may be composed of irregularaly arranged dark staining active basal cells, changes which may be due to inflammation and irritation. The basement membrane is intact in both cases. Extension to the glands may occur and is not necessarily associated with invasive changes.

Invasive squamous cell carcinoma on microscopic examination shows all the features described above but in this case the basement membrane is broken and a down-rush of malignant cells into the stroma can be seen. Strands and sheets of malignant cells may be present and nests of cancer cells may be found in the stroma far beneath the surface. Glandular involvement may be present (Fig. 15).

Adenocarcinoma usually arises within the cervical canal but may start in the region of the external os. When adeno-:carcinoma in the cervical biopsy is examined microscopically it may be difficult to be certain as to its primary origin, and it may even be a downward extension from the more common endo-:metrial lesion.

This type of carcinoma produces malignant changes in the lining epithelium of the glands which may become thick. The cells lose their high columnar appearance and become lower and

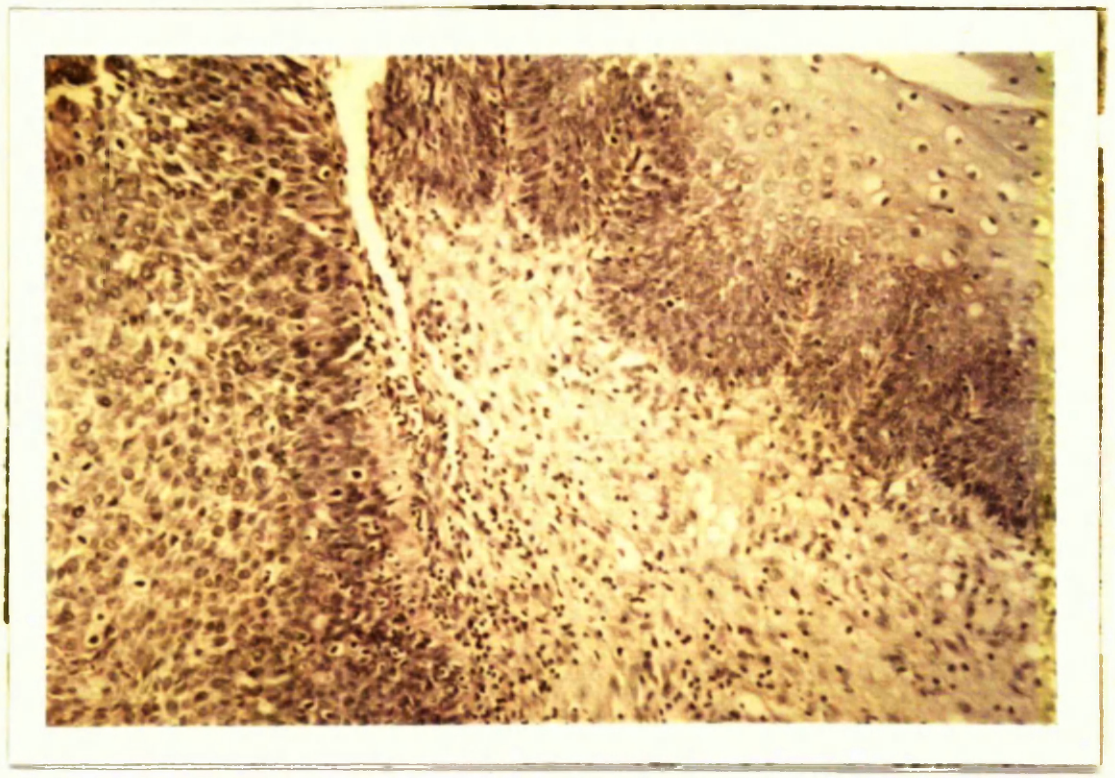

Fig. (14): Histological section of cervical epithelium from a woman with a preinvasive squamous carcinoma showing the complete loss of the normal mosaic pattern and the replacement of the stratification by abnormal basal cells with some mitotic figures. The basement membrane is intact.

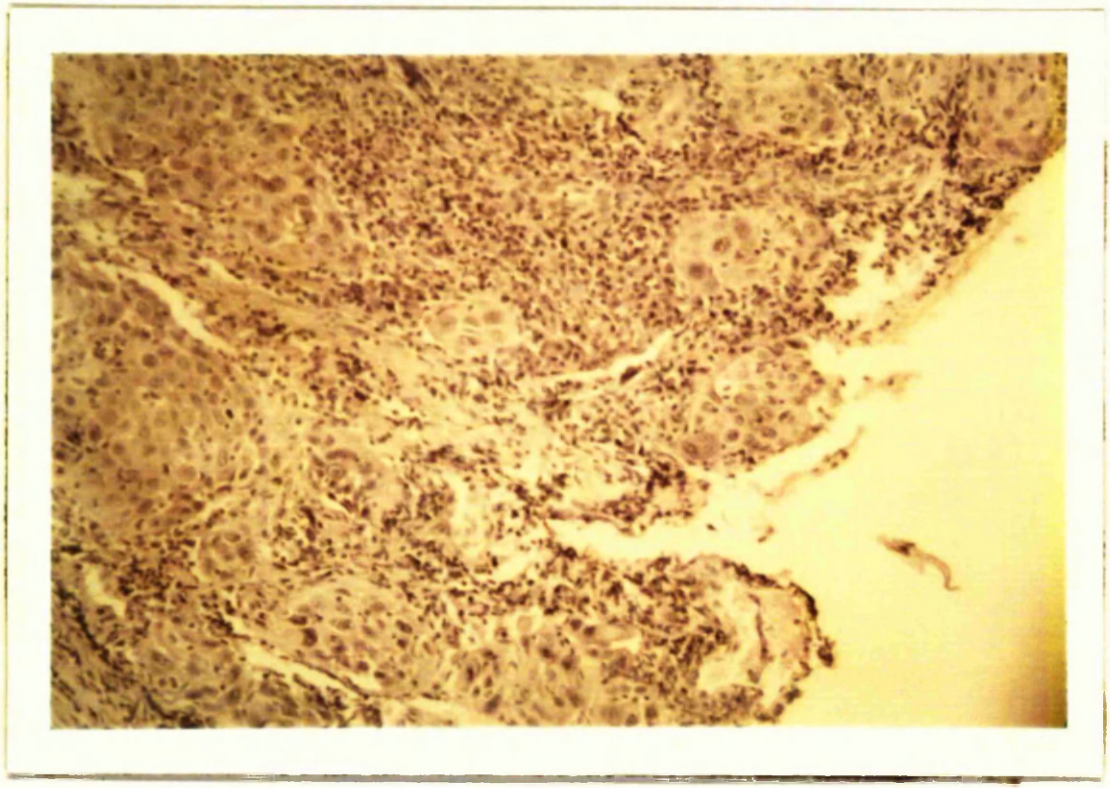

Fig. (15): Histological section of cervix from a woman with invasive squamous cell carcinoma showing the loss of stratification in the epithelium, breaking of the basement membrane, and invasion of the stroma by abnormal basal cells.

more rounded and the nuclei become large and darkly stained. Mitoses are seen and there is an inflammatory reaction in the stroma.

Cytological techniques can distinguish between cells derived from squamous cell carcinoma and those from adenocarcinoma, but it is not possible by such techniques to predict whether a squamous cell carcinoma is in the preinvasive or invasive stage, Boddington, Cowdell and Spriggs (1960).

SECTION 4

Background to the development of the Survey

The ease with which a smear can be obtained from the cervix encouraged the adoption of this technique and it is easy to define the criteria which can, with experience, be applied to establish a diagnosis of malignancy. Results of studies in various centres were consistent with each other, and it became apparent that the procedure was suitable to apply to members of the general population, provided that the necessary staff and finance could be obtained.

Such a programme has been advocated by a number of workers, including Lawson (1957) and the Central Health Services Council (1961) who recommended that 'consideration should be given to the provision of more widespread facilities with commensurate training arrangements'.

In the U.S.A. large scale population screening projects have been conducted in various centres and in Tennessee, Dunn (1958) studied a group of 53,585 women by taking vaginal smears. It was intended to re-screen this group but poor records and the difficulty in tracing many of them has made this an almost impossible task. In Britain, Boddington, Cowdell and Spriggs (1960) reported their findings on 10,000 hospital patients who had smears taken in Oxford. The opportunity to have a cervical smear taken has not yet been offered to the general population

in Britain, although facilities are provided at St. Bartholomew's Hospital, London by the Cancer Diagnosis Clinic. This service is brought to the notice of women over 35 years of age, working in the City of London, by means of notices displayed in the staff common rooms of large city firms, Medical News (1962). In the first two years 678 patients have been screened. Only two patients had suspicious smears and of those, one was con-:firmed by histological examination to be carcinoma-in-situ. This low detection rate may be explained because the women most likely to respond in such a campaign would be of higher intel-:ligence from the middle socio-economic group. This group is, in our experience, least likely to contract the disease.

The cytology service in Aberdeen has gradually expanded since 1958 (Table I) for all women attending the Department of Obstetrics and Gynaecology. The total number of smears taken and the detection rate (from April, 1958 - Decem, 1961) is shown in Table II. Each case of cancer detected by cytology was in a woman who had no previous clinical signs or symptoms of cervical cancer but who on subsequent cone biopsy and histo-:logical examination showed evidence of early invasive cancer or varying degrees of histological abnormalities of the cervical epithelium of a type now known as carcinoma-in-situ, or pre-:invasive cancer. The result (Yule and Cameron 1960) Table III show that of 1,342 post-natal patients examined, 9 cases of

TABLE I

Expansion of Cytology Service - December, 1961

	No. of patients screened	No. of positive smears
1958	1,081	22
1959	3,178	28
1960	4,132	46
1961	8,000	59
Total	16,391	157
1962	8,676	

TABLE II

Cervical Cytology (1st April, 1958 - 31st Decem, 1961)

Total number of patients screened	:	16391
Unsuspected positive smears	:	157
Detection Rate	:	0.96%

Histology

(i)	Invasive squamous carcinoma	:	42
(ii)	Intraepithelial carcinoma	:	115
	Total	:	157

TABLE III

Age Group	30 years	30-39 years	40-49 years	50-59 years	60+ years	Total
Post-natal Patients						
No. of patients	658	648	36	-	-	1,342
Positive cases	2	7	-	-	-	9
Detection rate	0.3%	1.08%	-	-	-	0.6%
Gynaecological Patients						
No. of patients	501	1127	955	580	314	3,477
Positive cases	1	16	19	3	2	41
Detection rate	0.2%	1.4%	1.9%	0.52%	0.63%	1.2%

unsuspected cancer were detected. In 3,477 gynaecological patients examined, 41 cases of unsuspected cancer were found. From the total, (4,819 cases) 50 positive smears which were confirmed by histological examination were detected overall, a detection rate of 1.04%. These detected cases contained 34 cases of carcinoma-in-situ and 16 cases of early invasive squamous carcinoma.

This detection rate of 1%, is similar to that found by other workers, Anderson (1959), Marjury (1961), Scott (1960), and justified a more widespread screening of the population. (Table IV)

Women at Risk

Carcinoma of the uterine cervix has been shown, Wynder (1954), to be a disease of married parous women, although the risk does not appear to be directly proportional to the number of pregnancies, (Lawson 1957), (Gagnon, 1950).

It is also shown to be a disease of the lower income groups, Kaiser and Gilbain (1958).

Terris and Oalmann (1960) did a large survey of patients with cervical cancer with special reference to the significance of age, race, parity, use of contraceptives, marital history, sex relationship, douching, education and circumcision. They found that there seemed to be some significant association between cervical cancer and early marriage, extramarital

TABLE IV

Centre	Detection Rate %
Edinburgh	1.0
Newcastle	1.2
Mayo Clinic	0.9
Aberdeen	1.04

relations, multiple marriages, early coitus and non-use of contraceptives. Stocks (1957) found that the number of con-:finements was not a factor in women who married late in life, but if they married under 25 years of age, multiple pregnancies predisposed towards cervical cancer. Likewise, Wynder (1954), Jones, et al (1958) and Lombard and Potter (1946) found the risk of developing carcinoma of the cervix was greater in women who married before 20 years of age.

An analysis of the age distribution of patients between 25 - 59 years with clinical carcinoma of the cervix in the City and County of Aberdeen is given in Table V, and an analysis of the age groups of the women in Aberdeen who had early carcinoma detected by cytology gives an indication of the age of the women most at risk (Table III) (Yule and Cameron 1960). This shows the highest incidence (1.9%) in the 40 - 49 age group with a sharp falling off in those over 50 years and under 30 years. The detection rate is highest in the group of women between 30 - 50 years of age.

It seems reasonable therefore to screen parous women between the ages of 25 and 60 years and thus hope to detect most cases before they present clinically.

TABLE V

Age Distribution of Patients aged 25-59 with Clinical Carcinoma Cervix. City (1942-61) and County (1950-60)

	City	County
25 - 29	3	3
30 - 34	15	9
35 - 39	37	13
40 - 44	52	10
45 - 49	51	19
50 - 54	70	16
55 - 59	65	10
	293	80
Median	48.3 years	45.8 years

SECTION 5

Methods of Approach

Previous experience in cytology justified a more widespread screening programme but two practical difficulties had to be faced: firstly, some women view a vaginal examination with distaste and, secondly, contemplation of the word 'cancer' sometimes engenders fear in patients.

Hospital Survey

It was decided to start by examining women who were already actually in hospital undergoing medical examination, as this would be administratively easy. Permission was therefore obtained from surgeons and physicians in the Aberdeen Royal Infirmary to take cervical smears from the patients under their care, especially from married women between the ages of 25-60 years. With the co-operation of the sisters-in-charge, a visit was paid to each ward once a week, and smears taken from suitable patients admitted during the previous week.

The approach was made by a married woman doctor (author), a brief obstetric history taken, and a pelvic examination suggested. The word 'cancer' was not used. The examination suggested was 'a routine check-up'. In almost all cases it was accepted eagerly and many expressed fears and symptoms they felt could only be confided to another woman. There were only half-a-dozen refusals in over 1,200 cases.

Some of the more thoughtful patients asked if cancer could be detected by this examination and on having the test fully explained to them, expressed the wish that their relations and friends might have the same opportunity for examination. No cases of cancerphobia are known to have been produced; on the contrary many patients were greatly relieved, particularly those who had previously defaulted from a post-natal examination.

This screening of suitable in-patients in Aberdeen Royal Infirmary has now become an established procedure and has been expanded to include patients in the associated Woodend Hospital. In 1961, there were seven positive smears out of 1,207 smears taken. Subsequent histological examination of the cervix showed that there was invasive cancer in three cases and that the remaining four cases showed the features characteristic of carcinoma-in-situ (Table VI).

General Population Screening

Having found that this test was acceptable to women in hospital, it was decided to extend the service, if possible, to the general population. This had been felt by many workers (Lawson (1957), Boyes, Fidler and Locke (1962)) to be highly desirable but fraught with practical difficulties.

About 95% of the women in the City of Aberdeen are registered with general practitioners. The use of the general practitioners' lists, with occasional help from the lists

TABLE VI

From General Medical & Surgical Wards, 1961

Total smears	1207	
Total cases of cancer	7	
Histology		
Preinvasive	4	
Invasive	3	
	7	(0.6%)

maintained by the Executive Council to avoid duplication, was thought to give the most convenient and systematic method of identifying the women at risk in the City.

Place of Examination

It was decided that the initial approach to the patient should be through the family doctor and the doctors in the first general practice selected were found to be most helpful and co-operative. A very carefully phrased letter (Fig.) was composed by the staff of the Department of Obstetrics and Gynaecology and the family doctor. This was signed by the family doctor and sent to each patient, inviting her to attend at his consulting room for examination. This was considered to be more personal and probably more acceptable than a visit to a hospital out-patient department or a Public Health Clinic. Furthermore, the examination was to be conducted by a woman doctor, and many patients subsequently expressed satisfaction at this. There was some apprehension in the waiting room in the early stage of the experiment but subsequently, as information about what actually happened became fairly widespread, fear was dispelled.

Method

From the practitioners' lists a typist extracted the names and addresses of all married women between 25-60 years and sent the letter signed by the family doctor. A second letter was sent to most of the patients who did not respond to the first

FIGURE 16

Doctor's consulting room

Dear

You will recall the Mass X-Ray Campaign against Pulmonary Tuberculosis which took place in Aberdeen three years ago. You possibly were X-Rayed then and, while you did not think you had tuberculosis, you were glad to know that your chest was clear.

This was an example of preventive medicine and I am writing you to tell you of another campaign of preventive medicine and asking you to co-operate.

Research has shown that in certain parts of the body it is possible to detect cells which if untreated would in years to come turn to cancer. One such part of the body is the cervix or neck of the womb. Arrangements are being made to examine married women between 25 and 60 years of age. Dr. Elizabeth Macgregor of the University Department of Midwifery and Gynae-:cology will assist in this work. The test is simple and pain-:less and the disease when detected early can be completely cured. I trust you will take advantage of this service.

You should attend at

Yours sincerely,

- - - - - - - - - - - -

Doctor's consulting room

Dear

You received a letter inviting you to have a quick, pain-:less test. The time stated was probably not convenient for you, so we will be pleased to see you if you will come to

Yours sincerely,

but for a variety of reasons this was not sent to all defaulters.

Technique

Sessions were held in the general practitioners' surgeries at times convenient to them and distinct from the routine surgery hours. The women were given appointments and about twenty smears were taken in a session of less than two hours. No woman was kept waiting more than 15 minutes.

A vaginal speculum was inserted, the cervix exposed and a scrape of the squamo-columnar junction taken with an Ayre's spatula. Material was not taken from the posterior fornix since it has been shown, (McLaren and Attwood (1961), Tolles, Hovarth and Bostrum (1961)) that a cervical scrape is more effective for the detection of cancer. Smears were made on glass slides, which had ground glass at one end and could be marked in pencil with the patient's name and immediately fixed, and taken to the laboratory and stained.

The smears were all taken by the author. It was feasible to take twenty smears in a morning and then to interpret the twenty smears taken the previous day. All abnormal smears were examined by more than one cytologist and the final responsibility for arranging for the supervision of the patient and cone biopsy rested with the Senior Gynaecological Registrar in charge of cytology.

Response

In the course of the survey, 2683 smears were taken in three general practices, and 18 unsuspected cases of cervical carcinoma, consisting of five cases of early invasive cancer and thirteen cases of carcinoma-in-situ, were discovered. In addition, one case of clinical carcinoma was detected. (Table VII)

The results in the three practices are compared in Table VIII.

A 'reply' is defined as the acquisition of information about the patient irrespective of whether a smear was subsequently taken or not. The 'response rate' is calculated from the number of patients who actually received the letter. The number of wrong addresses varied in each practice from 1% in one practice to 19% in another. The reasons for not taking a smear from all those who 'replied' varied but included ill-health, previous hysterectomy and the fact that smears had been taken less than one year previously. Sometimes patients sent a letter stating they did not, for various reasons, wish the examination. In this survey, smears were not taken from pregnant women as they are routinely taken at all post-natal examinations in the area.

In the first practice, Practice A, there was active co-operation from the doctors, who in the course of their day to

TABLE VII

Results of General Practice Survey

Total women invited	5340
Total smears taken	2683
Total Abnormal smears	24

Analysis of Abnormal smears

Clinical case	1
Preinvasive carcinoma	13
Invasive carcinoma	5
Chronic cervicitis	5
	24

Detection rate of 0.67%

TABLE VIII

Comparable Reply Rate in Three Practices

Practice	No. invited	No trace at address	No. replied	No. smears taken	Cases Detected
A	1483	19	1159 (79%)	1022 (69%)	4 (0.4%)
B	3156	339	1459 (51%)	1295 (41%)	11 (0.9%)
C	701	86	448 (71%)	366 (52%)	3 (0.9%)

day practice did all they could to encourage their women patients to attend for the test. This practice was selected initially as being a good, well documented and well run practice in a 'good' area of the city. There were three principles in the practice of 7,200 patients, all of whom took an active interest in the survey and personal interest in all of the cases (4) detected. They mentioned the test to women attending their regular surgeries and in the course of their visits to any family, would ask the women at risk to come when they received the letter. This co-operation resulted in a reply rate of 79%. The number of letters returned as 'address unknown' was in the region of 1% in this practice.

This response was so encouraging that it was decided to attempt a similar technique of approach in one of the city's largest practices in a part of the city of lower social class. This practice, Practice B, had four principles, and two assistants and 12,769 patients. The doctors, while tolerating the investigation, were frankly sceptical and less enthusiastic about its value. This practice had a reply rate of 47% and the 'address unknown' letters were as high as 19% of the total.

The discrepancy in the reply rate in the two practices was thought to be due largely to the influence of the family doctor, and not to the social class of the women concerned. In an attempt to measure the influence of the family doctor on the

reply rate, the doctors in the next practice, Practice C, were asked to take no active part in the investigation.

Practice C was composed of two principles with 3,939 patients and was the smallest practice. By asking the doctors here to take no active part, this practice was very comparable to Practice B. The reply rate was 50%, very comparable to Practice B and the 'address unknown' figure was only 7%.

It will be noticed (Table VIII) that in Practice B and C, although the percentage of smears actually taken was lower than in Practice A, the percentage found to be positive was higher. The explanation of this is probably due to the social content of the practices. The social content of Practice A was highest resulting in the highest reply rate, e.g. more women had and did use the telephone to explain reasons for not having a smear taken. They were probably more intelligent and therefore understood the benefits of the test and came forward more readily for examination. But the very fact that they were of a middle social class meant that they were less vulnerable to this disease and consequently the detection rate (0.4%) was low.

The percentage of smears taken in Practices B and C is remarkably similar (47%) and (50%). The social content of these practices is similar and consequently the detection rate is also similar, .9% and .9%. The apparent contradiction in Practice C between the high reply rate and the low percentage

of smears taken is due to the home visits paid in this practice after the women had not attended in response to the first letter and will be discussed later. The home visits paid in this practice by the health visitors invariably elicited some reply even if it was only a definite refusal to attend and of the 231 women visited, 54 definitely refused for various reasons to attend for examination.

Response to Screening techniques

While much was known about the women who attended and replied, very little was known about those who stayed away and did not communicate at all. A second letter was sent to all those who did not respond to the first letter in Practices A and B. In Practice C however, the group who did not reply to the first letter were divided into three sections. One group received the routine second letter for comparative purposes, a second group was visited by Health visitors, in uniform, who often knew the women, and a third group was visited by women unconnected with the medical profession, (W.V.S. members). It was expected that the Health visitors would be the most successful in causing these women to attend.

In fact, Table IX shows that the reply rate on the second letter was poor in all these practices, and in Practice B it was as low as 17%. However, of the eighteen cases of early cancer detected in the course of the survey, six attended in

TABLE IX

Reply Rate

	Practice A			Practice B			Practice C			
	Sent	Replied	%	Sent	Replied	%	Sent	Replied	%	Attend
First letter	1483	1038	70	3156	1186	38	701	317	45	294(4
Second letter	306	121	40	1596	273	17	99	33	33	28(2
Visited by H.V.	-	-	-	-	-	-	114	55	48	28(2
Visited by lay visitor	-	-	-	-	-	-	117	43	37	16(1
Total replies	1159			1459			448			

(H.V. = District Health Visitor)

response to a second invitation. This high proportion bears out the theory that no matter what the incidence of the disease is amongst those who respond, it is probably twice as high amongst those who stay away.

In practice C, the Health visitors visited 114 women and 55 of those (48%) said they were willing to attend. In the event only 28 attended and had a smear taken when given a further appointment (24%). The non-medical visitors were even less successful. They visited 117 and could only elicit definite replies from 43 (37%) of those, and only 16 (14%) actually attended and had smears taken. The reply rate to second letters sent in this practice was 33%, less than in Practice A (40%) but more than in Practice B (17%). This reply did in fact usually take the form of a visit to the surgery to have a smear taken, giving an attendance rate of 28% in response to the second letter.

From these responses in Practice C, we concluded that it was more effective to send out a second letter, thus putting the onus for action on to the women concerned. This was more effective than sending someone to the house, where a promise to attend was readily given but not adhered to.

The return was greater and the expenditure of time and effort much less when a second letter was sent, than when house to house visits were paid.

Reasons for Non-attendance

In an attempt to determine why some women did not attend, the Health visitor, specifically attached to Practice A, was asked to visit some of these women about whom nothing was known except their name and address. This was done after the survey in Practice A had been completed. The reasons given, in their own words are shown in Table X . There is no evidence that fear of cancer was a major factor. The largest group, one-third of the total, gave the reason 'can't be bothered'. It would be interesting to know if these women adopt a similar attitude to life's problems generally, and to other preventive health measures such as immunisation and vaccination.

In Practice C the reasonsfor non-response were determined by various Health visitors in the districts in which the women lived. There was less personal contact with the practice and it can be seen that more women in this practice firmly refused to come but would give no definite reason for this. This may have been because they were not personally known to the Health visitors but is also consistent with the fact that this practice contained a higher percentage of women in the lower socio-economic group, a group that is usually least articulate.

Education

It was obvious that fear of cancer is not an important reason for non-attendance. Many of those who attended knew of

TABLE X

Reasons for Non-co-operation elicited by Health Visitors

Practice A (34 cases)			
Family ties	3	Afraid of cancer	7
Afraid of hospital	1	Might attend later	7
Too busy at work	2	'Can't be bothered'	12
Previous serious illness	1	Away from home	1
Practice C (36 cases)			
Definite refusals	13	Done before	2
Working	2	Hysterectomy	3
'Coming' and did not	7	Dislikes hospital	2
Don't want to know	5	Wanted own doctor	2

the existence of cancer in members of their family and were afraid they too might develop it. Fear is as likely to cause a person to attend as to stay away. As far as can be ascertained, no case of cancerphobia resulted from the investigation.

There is a widespread belief that cancer in any form is incurable. Many who thought cancer incurable became eager for the test as a result of hearing about someone who had been successfully treated. Relatives of those with positive smears who had been successfully operated upon were enthusiastic advocates of screening. After the scheme had been running for eighteen months it was found that 50% of a group of about 100 parous women who were interviewed for an entirely different research programme knew of 'the new test for cancer' in Aberdeen.

Comparison of the Structure of the Practices

Age

The ages of general practice patients attending for screening are compared with those from other sources in Table XI It can be seen that in the practices and in the hospital wards, the age distribution and the incidence of positive smears is the same (.6%). This detection rate is lower than the gynaecological patients (1.2%) but the number of women in the over 50 years age group is greater in the practices and general wards than at the out-patient Gynaecological clinics.

TABLE XI

Comparison of the Age Composition of the various groups of women examined Cytologically

Total patients		Detection Rate	20-29 years	30-39 years	40-49 years	50-59 years	60+ years
2683	Practices	.66%	13%	28.8%	27.6%	28.2%	4.2%
1513	Wards	.6 %	7.7%	21.4%	32.3%	33.3%	5.1%
1342	Post-natal	.6 %	49.0%	48.2%	2.7%	-	-
3477	Gynae.Clinic	1.2 %	14.4%	32.4%	27.5%	16.4%	9.0%
	Average Population		19.8%	25.1%	24.9%	17.5%	12.7%

The most vulnerable group, those with the highest detection rate, have been shown (Yule and Cameron, 1960) to be those between 30-50 years and this accounts for the relatively high detection rate (.6%) at post-natal clinics where the bulk of the patients are in this age group, although relatively they are younger than in the practices and wards.

The age distribution is remarkably similar in all three practices (Table XII). Each ten year age group between 30 years and 60 years contained between 25 and 30 percent of the total, the rest being in either the over 60 or under 30 age group in equal proportions.

Parity

There was a small difference in the parity distribution of the patients in the practices (Table XIII). In Practice B, which had the highest detection rate, the average parity rate was highest, 2.6. The rates in Practices A and C were 2.3 and 2.4 respectively.

Social Class

The occupation of the woman's husband was noted when the woman attended for examination and the social class of Practice A was somewhat higher than that of B and C which were predominately from social classes IIIa, III, IV and V.

Analysis of the 18 cases detected

Eighteen cases found to have malignant cytological smears

TABLE XII

Age Comparison

	Total patients	20-29	30-39	40-49	50-59	60+
A	934	112 (12.5%)	255 (26.5%)	271 (28%)	275 (28.5%)	21 (2.5%)
B	1313	176 (12.5%)	327 (24%)	346 (26%)	379 (28%)	85 (6%)
C	394	55 (13.9%)	127 (32.2%)	115 (29.1%)	91 (23%)	6 (1.5%)
Total	2641	343 (13%)	709 (26.8%)	732 (27.6%)	745 (28.2%)	112 (4.2)

TABLE XIII

Parity Comparison

	0	1	2	3	4	5	6	7	8	9	10+	Total
A	83	197	323	165	88	45	11	9	6	3	4	934
B	112	269	362	245	159	73	37	23	11	12	13	1313
C	40	64	112	75	49	28	15	6	1	2	2	394

Average Parity A 2.3

" " B 2.6

" " C 2.4

in the course of the survey were admitted to hospital and had a cone biopsy performed. In 5 cases histological evidence of early invasive squamous carcinoma, and in 13 cases the changes of carcinoma-in-situ were found. There were, in addition, 5 women who had apparently positive cytological changes but on careful histological examination of the cervical cone biopsy no change in the tissue pattern was found other than gross inflammatory changes which were consistent with chronic cervicitis. None of these women had any clinical signs or symptoms of cancer. Such patients are classified as having 'false positive' smears.

Case reports of three typical positive cases detected in the course of the survey are described:

A.M. aged 34 years. Parity 3.

This woman attended at her doctor's surgery. She had no gynaecological complaints. The cervix was found to be eroded and a cervical smear taken on 9.6.61, this was found to contain cells suspected to have malignant changes. She was brought into hospital three weeks later for cone biopsy and the smear taken on admission to hospital also showed malignant cells. A cone biopsy of the junctional epithelium was performed and histological examination showed alterations in the epithelium which were consistent with carcinoma-in-situ. She was allowed home and three months later at follow-up the cervical smear was negative. A hysterectomy was done and histological examination

revealed no evidence of residual malignancy. Follow-up smears in this woman, up to fifteen months, after her hysterectomy have been negative.

J.C. Aged 50 years and with twelve children was the wife of a labourer and attended in Practice B in response to the second invitation. She had no complaints. On examination she was found to have a vaginitis and the epithelium of the cervix was intact. The cervical smear taken showed cells which were conclusive of malignancy. She was given several dates for admission to hospital to have a cone biopsy but although she expressed willingness to have this investigation, she always found some excuse for postponing admission. She was admitted to hospital six months after her initial smear and the smear taken on admission also showed cells conclusive of malignancy. Histological examination of the cervical cone biopsy showed an invasive squamous cell carcinoma and she was treated by radium therapy. Three months later the cervical smear showed cells changes which were not malignant but due to the radiation. The follow-up three months later showed no evidence of malignancy and the radiation changes had cleared.

A.M. Aged 61 and parity 16 had been separated from her husband for over 10 years and she was employed as a fish filleter. She attended, in Practice B, in response to the first letter. She expressed thankfulness at receiving the letter because she

had had vaginal bleeding on and off for some months, but was so occupied in earning a wage and bringing up the last of her sixteen children she had put off consulting her doctor. She was relieved to find an appointment made for her to attend.

On examination she was found to have a foul-smelling, blood-stained vaginal discharge. It was impossible to visualise the cervix without removing the debris and when exposed, it was found to be badly 'eroded'. The cervical smear was difficult to read because of the blood, pus and debris but cells which were highly suspicious of malignancy were found.

This woman was admitted to hospital immediately and the smear taken on admission showed changes conclusive of malignancy. She was found to have a Stage II carcinoma of the cervix and was treated by radium.

This case had clinical cervical carcinoma but would not have been detected for definitive treatment if the cervical smear survey had not been carried out.

Table XIV shows the social class, age distribution and the parity of the eighteen cases detected. This was then compared (Table XV) to the cases detected from other sources such as Gynaecological clinics, Post-natal clinics and Family planning clinics etc., over the past four years. There were 178 cases detected from these sources and the age incidence (Table XV) relatively high parity (Table XVI) and low socio-economic group

TABLE XIV

Social Class of 18 Cases detected in Survey

Social Class	I	II	IIIa	III	IV	V	Total
No. of Cases	-	-	2	11	4	1	18

Age Groups of 18 Cases detected in Survey

Years	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60+	Total
No. of Cases	-	1	5	2	4	3	1	2	-	18

Parity of 18 Cases detected in Survey

Parity	0	1	2	3	4	5	6	7	8	9	10+	Total
No. of Cases	1	2	6	2	2	2	1	-	-	-	2	18

TABLE XV

Comparison of Cases Detected in Survey with those from Other Sources

AGE Groups	No. of cases	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60+
G.P. Survey	18									
Preinvasive	13	-	1	5	1	4	-	1	1	-
Invasive	5	-	-	-	1	-	-	2	-	2
Other Sources	178									
Preinvasive	130	2	14	34	20	21	23	9	4	3
Invasive	48	-	-	10	11	5	9	8	2	3

TABLE XVI

Comparison of Cases Detected in Survey with those from other Sources

PARITY	No. of cases	0	1	2	3	4	5	6	7	8	9	10+	Average Parity
G.P. Survey	18										Average parity in Britain 2.2		
Preinvasive	13	-	1	6	2	2	2	-	-	-	-	-	2.9
Invasive	5	1	1	-	-	-	-	1	-	-	-	2	5.4
Other Sources	178												
Preinvasive	130	1	14	24	33	22	17	12	3	3	1	-	3.5
Invasive	48	2	5	8	13	8	3	2	3	2	1	1	3.6

TABLE XVII

Comparison of Cases Detected in Survey with those from other Sources

SOCIAL CLASS	No. of cases	I	II	IIIa	III	IV	V
G.P. Survey	18						
Preinvasive	13	-	-	2	9	2	-
Invasive	5	-	-	-	2	1	2
Other Sources	96						
Preinvasive	72	-	5	8	25	21	13
Invasive	24	-	1	-	7	9	7

(TableXVII) of these is similar to those 18 from the survey. The socio-economic class of the detected cases in the survey, i.e. III, IV, and V, mostly manual workers, may not be signi-:ficant as the numbers are so small and these social groups do form the bulk of a general population but nevertheless it is significant that there were no cases detected in the survey in social class II and few in this social class detected from the other sources. (It was only possible to ascertain the social class of 96 of the 178 cases detected from other sources.)

Our results lend weight to the belief that this is a disease of parous women of lower social class and the most vulnerable age group for early detection is between 30-50 years of age.

PART C

SECTION 6

Atypical Smears

Not all cervical smears can be classified into a positive or negative category, and many have to be interpreted as 'atypical'. To ascertain the eventual development of an atypical smear a review of all atypical smears that had occurred between March 1958 - March 1961 was conducted (Table XVIII). Of 6400 smears examined 256 (4%) were found to have abnormal but not definitely malignant cells. These women have had repeat smears taken over periods varying from 3 months to 2 years and it can be seen that in 176 (68%) of cases the repeat smear was normal.

Thirteen cases re-examined showed the presence of cells typical of preinvasive or invasive cancer and this was subsequently confirmed histologically by cone biopsy. This may have been due to rapid progression of the lesion in this relatively short time of 3 - 24 months or to the unsatisfactory nature of the original smear. Review of the original smear did not in any case suggest that malignant changes were present at that time.

In eight clinical cases, with atypical smears initially, repeat smears suggested that the lesion was malignant and histological examination confirmed this. Smears from clinically

TABLE XVIII

Analysis of Atypical Cervical Smears

Atypical Smears	256 (4% of all smears)
Clinically diagnosed cases	8 (3% of all atypical smears)
Advanced to Invasive	5)
Advanced to Preinvasive	8) (5% of all atypical smears)
Returned to Normal	176 (68% of all atypical smears)
Still Atypical	59 (23% of all atypical smears)

diagnosable cancer of the cervix can be unsatisfactory and difficult to interpret (Novak and Woodruff, 1960). Cells are often scanty and difficult to see because of the presence of leucocytes red blood cells, mucus and necrotic debris. Sometimes a better smear may be obtained if particular care is taken to remove much of this before scraping the cervix. The danger of such cases being missed or not receiving adequate treatment is negligible as in such cases a biopsy of the cervix would obviously be indicated on clinical grounds alone and there should therefore be little or no risk that a cancer would be missed by reliance on cytology alone.

Unsatisfactory Smears

These present a real problem. In reviewing several thousand smears it was found that 1.0% of them were classed as 'unsatisfactory'.

The presence of pus, Trichomonas infection, blood, mucus and debris can make interpretation of a smear difficult. If the cervix and/or vagina is dry, then there may be only scanty cells present.

No reliance can be put on a report that no cancer cells were found if at the same time the smear itself is not satis-:factory. It is possible for many of these unsatisfactory smears to be repeated, e.g. when the patient is first seen at the out-patient department and a smear is taken or when the

patient is subsequently admitted to hospital for some minor gynaecological treatment. In many cases however, where further treatment is not required, the smear is not routinely repeated.

False negative and false positive rates

False Positive

It is relatively easy to asses the false positive rate because any smear which is cytologically positive but is not associated with histological changes of malignancy after care-:ful examination of an adequate cone biopsy, must be regarded as 'false positive'.

On the other hand some cases with positive smear cytology and subsequent negative histology of a cone biopsy continue to have positive smear cytology. In such cases further biopsy and histological examination is required. It is essential that the gynaecologist takes an adequate biopsy and that the path-:ologist looks at sufficient sections of the cervical biopsy.

Cytology can in many cases give conclusive evidence of malignancy and the time may come when definitive treatment will be undertaken on the cytological findings alone. Meanwhile, however, it is still possible for apparently misleading con-:clusions to be drawn from the interpretation of some smears.

Out of approximately 20,000 smears, there have been in addition to about 200 detected cases, 8 cases in whom suspici-:ously malignant cytology was associated with negative histology,

Subsequent cytology smears after the biopsy remained negative and this may have been because there never was a lesion, or, any lesion present was completely removed by the cone biopsy but not detected histologically. This is unlikely. The longest follow-up so far has been three years. This gives an incidence of false positive satisfactory smears of 4%.

Occasionally, however, negative findings on cone biopsy can be shown to be unhelpful in reaching a true diagnosis. For example, persistently positive smears may indicate the necessity for radical treatment even after a negative biopsy.

J.G. aged 60 years and parity 6, was the wife of a fish porter and attended in response to a second invitation in Practice C. The cervical smear taken showed changes conclusive of malignancy.

She was admitted to hospital two weeks later for cone biopsy. The smear taken on admission confirmed the original findings there being, conclusively malignant cells present. The histological examination of the biopsy did not reveal a malignant lesion despite full examination of the biopsy material available.

On follow-up two months later this woman's cervical smear still contained abnormal cells which were deemed atypical and a further smear was taken one month later. This showed cells with malignant changes and arrangements were made for this woman

to be admitted for hysterectomy. The smear taken on admission showed cells with classical signs of malignancy.

The histological examination of the whole uterus and the cervix showed an invasive lesion present in her cervix.

False negatives

'False negative' smears are more difficult to detect and it is not known how many of the 20,000 smears examined and reported as negative may in fact have had an early cancerous lesion which has not as yet given any clinical signs and symptoms

Cases of overt clinical cervical cancer can give negative smears. Smears, which because of debris, pus and blood are difficult to read. It is difficult to obtain a good smear from a clinically malignant cervix and any suspicious looking cervix must be biopsied without reliance on cytology.

Among the 20,000 smears and 200 detected cases there were 7 cases that were known previously to have had technically satisfactory but negative smears. On review of these smears there was only one case which could, in retrospect perhaps have been interpreted as suggestive of malignancy. This gives a 'false negative' rate of about 3.5%.

Boddington, Cowdell and Spriggs (1960) while examining 10,000 smears, found 67 cases of carcinoma-in-situ and 11 cases of invasive carcinoma. During this time they had fifteen 'false positive' smears and nine 'false negative' ones.

The actual incidence of false positive and false negative smears depends on many factors, not least of which is the satisfactory nature of the initial smear. It is not possible to calculate a definite incidence rate but it must be appreciated that inevitably such cases may occasionally occur.

Variation in Histology

For every cervical smear showing cells suspected of malignant changes a cone biopsy must be performed on the suspect cervix and the resulting histological sections examined carefully at various levels. If the histological sections show obvious signs of malignant changes the final diagnosis is certain, but where there are no signs of malignant changes in the first sections examined the whole of the available material must be meticulously examined before malignancy can be definitely excluded.

The changes associated with invasive carcinoma can be defined with accuracy by competent pathologists, but the changes in the epithelium representing carcinoma-in-situ are much more difficult to assess.

There is no doubt that there is a degree of observer variation among pathologists as to the accepted criteria of carcinoma-in-situ, and histological reporting should preferably be 'blind' in the sense that the pathologist should be unaware of the cytology of the cervical smears. Nevertheless, there

must always be a reasonable assumption that previous smears have been positive if a biopsy sample has been submitted for examination.

SECTION 7

Estimated detection rate in City of Aberdeen

While working in the Department of Obstetrics and Gynaecology in Aberdeen, Lawson (1957) calculated that the annual incidence of clinical cases of cervical carcinoma should have an associated incidence of positive smears of about 0.5% of the population at risk if the latent pre-clinical period was 10 years

The Census data of 1951 made it possible to estimate that in the year 1950 there were about 20,000 married women between the ages of 35 and 64 in the City of Aberdeen, who between 1950 and 1959 might be expected to produce 99 clinical cases of cancer. If 10 years is accepted as the minimum latent period - and assuming that all lesions could be discovered - then 99 latent cancers should have been found, a detection rate of 1 in 200 (0.5%).

If examination of all or any random sample of the 20,000 women had given a higher detection rate than 0.5%, this would mean either: (1) that the sample was not representative of the group as a whole (2) that some of the lesions discovered were not destined to become invasive or (3) that some cancers evolve over a longer period than 10 years. A lower detection rate would indicate that either the diagnostic technique was not always successful or that only some cervical neoplasms are pre-

:ceded by a protracted pre-invasive phase.

The detection rate of 0.67% for the three General Practices is in line with these calculations, taking into consideration that it is now known that all cases do not necessarily progress to clinical cancer. It is also consistent with the view that the length of the preinvasive stage is about 10 years (Boyes, Fidler and Locke, 1962). Even here selection factors operate, as can be seen from the differing rates of detection between Practice A and Practices B and C due probably to variations in social composition of the practices.

SECTION 8

Estimated length of the Preinvasive stage

The frequency with which invasion supervenes upon a pre-:invasive lesion and the time taken to do so is not know precisely.

A retrospective study (Galvin, Jones and Te Linde, 1952) showed that of 13 patients known to have developed clinical carcinoma of the cervix and on whom biopsy had been carried out one to seventeen years previously, 11 had lesions in the histo-:logical sections of the cone biopsy which would today be classified as carcinoma-in-situ.

Prospective studies present a more difficult problem. It would be unjustifiable not to treat a woman with malignant cytological changes and the histological picture of carcinoma-in-situ.

Prospective studies by Younge, Hertig and Armstrong (1949) and Gusberg and Moore (1953) have, however, shown progression from carcinoma-in-situ to invasive carcinoma in such untreated cases over many years. This progression did not occur in every case and the 'regression' in some of the cases could be explained by the removal of the lesion at the time of biopsy.

Petersen (1955) working in Copenhagen, studied the proportion of 127 cases which, if left untreated, progressed to invasive carcinoma. He concluded that about 35% of such cases diagnosed

by himself, as carcinoma-in-situ would eventually develop carcinoma of the cervix. He found that regression usually occured in the first year and that 50% of the lesions persisting beyond this time developed carcinoma within 10 years.

Kottemeir (1955) noticed that lesions known as carcinoma-in-situ were often to be found at the edge of invasive lesions and 23 out of 74 of his patients with carcinoma-in-situ did in fact progress to invasive carcinoma.

In Vancouver, Boyes, Fidler and Locke (1962) suggested that as many as 60% of cases of carcinoma-in-situ progress to invasive cancer. This calculation was based on statistical evidence. The age-specific incidence rates for clinically invasive carcinoma of the cervix in British Columba for 1955-60 were collected. A large scale population screening programme was launched and, if carcinoma-in-situ was really a precessor of invasive cancer, a detectable fall in the subsequent incidence of clinical cases would be expected. Over a 12 year period there was a reduction of the incidence of clinically invasive cancer from 28.4 cases per 100,000 in 1955 to 19.7 cases per 100,000 in 1960. Even allowing for social factors and a possible change in the age structure of the population this still was a significant drop in incidence.

The mean ages at which the lesions presented in Vancouver, were 35.7 years for carcinoma-in-situ, 46.5 years for early

invasive and 52.8 years for clinically invasive carcinoma. This shows a progression over a period of 17 years.

This progression is supported by the evidence, in Table XIX derived from the cases detected in Aberdeen. This shows that amongst women between the ages of 25 and 60 the mean age of those with a preinvasive lesion was 39.6 years, which is 4 years less than that of women with clinically unsuspected invasive cancers, and 9 years less than that of women with clinically diagnosed cancer.

Almost 65% of women have their first baby before the age of 25 and the incidence of positive smears is known to be very low in women under 30 years, but reaches into maximum in the 40-50 age group. If, as many believe, the process of carcinoma is initiated after the first birth, there must be a long gap until the first appearance of exfoliative malignant cells, and, on average, a further 9 years before the appearances of clinical signs and symptoms. If all clinical cancer of the cervix, irrespective of age when detected are included, the average age becomes 52.7 years. This would imply an average interval from the appearance of the positive cervical smear until the development of clinical carcinoma, of 13 years.

It may, therefore, be concluded that re-screening procedures at intervals of 5 years should detect most cases of cancer before they present clinically. This seems to be a more realistic

TABLE XIX

Mean age of patients between 25 - 60 years with positive cervical smears and clinical cancer of the cervix

Stage	Mean Age (years)	No. of cases
Preinvasive	39.6	130
Invasive	43.6	48
Clinical cancer	48.3	273

approach than to attempt to examine every patient at intervals of 6-12 months, as has been attempted by some groups, Boyes, Fidler and Locke, 1962.

SECTION 9

Treatment of cases diagnosed by cytology

The normal treatment in Aberdeen since 1958 of pre-clinical invasive carcinoma, diagnosed on the basis of a positive cervical smear and subsequent histological examination of the cervical biopsy, has been the application of radium to the cervix, using the Sheffield technique.

Where alterations in the epithelium thought to be typical of preinvasive 'cancer' were found, total hysterectomy has been performed in most cases. This policy has been adopted only after much care, and detailed consideration of the problem of the optimal treatment for this potentially highly dangerous, but at present very small lesion. The mortality from hyster-:ectomy is now so low, and the general ovarian activity so well preserved, that there is much to commend it. Most of the women had finished childbearing, were over 30 years of age, and had become aware that suspicious cells had been discovered in the smear and biopsy. They were usually anxious to have a hyster-:ectomy.

In many cases, also, associated gynaecological symptoms existed likely to be relieved by hysterectomy.

This policy is also supported by other considerations: one quarter of those patients with positive smears are found to have

invasive cancer and at least one-third of the remainder will progress to invasive cancer. In some cases a satisfactory ring biopsy may result in the lesion being completely removed, making hysterectomy less necessary. However, if hysterectomy is not performed the patient must be re-examined at intervals and re-investigation in hospital undertaken as soon as positive cells reappear. This policy has obvious disadvantages, as it entails frequent out-patient attendances, and has a bad effect upon the patients' morale.

Alternatively, if women do not wish to have the uterus removed, no pressure is brought to bear upon them, particularly if they are young and desire more children.

Re-examination at suitable intervals is arranged and, in these circumstances, is acceptable to the patient.

J.M. Aged 27 years and parity 2 was twice invited to attend, in Practice A, but did not reply in any way. At this time she attended the family planning clinic, where routine cervical smears are taken, and was found to have an eroded cervix. The cervical smear taken there showed signs conclusive of malignancy.

She was admitted to hospital three weeks later and on admission the smear still showed malignant changes. She had a cervical cone biopsy which on histological examination showed an intraepithelial lesion diagnosed as carcinoma-in-situ. This

woman did not wish hysterectomy as she wanted another child.

The follow-up by cytology three months later showed no malignant cells and it was hoped the lesion had been completely removed by the cone biopsy.

Nine months later this woman had a baby delivered by Caesarian section and the smear taken before she left hospital had very active cells and cell changes suspected of malignancy. In view of the post-partum nature of this smear a further smear was taken two months later and the cells continued to show malignant changes.

This patient agreed to have a hysterectomy.

SECTION 10

Survival Rates

The 5 year survival rate of clinical cases of cervical carcinoma treated in Aberdeen during the years 1948-53 is shown in Table XX (Lawson, 1962) and is 41.8%. The standard treatment was local application of radium followed in Stage II and III cases by deep X-Ray therapy to the lymphatic glands. In some women with Stage I and Stage II lesions considered to be good operative risks, a Wertheim's hysterectomy was performed 6-8 weeks after local radium treatment of the cervix.

Our experience of the cytological diagnosis of cancer is too short to give any estimate of survival rates. Out of 157 women found to have a positive smear and abnormal histology in the years 1958-61, 42 had invasive cancer diagnosed histologically and all are alive and free from recurrence to date. Since the survival rate of Stage I clinically diagnosed cases is 70% there seems every likelihood that very few of these pre-clinical cases of cancer should die.

All the 115 cases with lesions known as carcinoma-in-situ are alive to date. The majority were treated by hysterectomy and in view of the very low mortality from this operation the policy seems justifiable until some more precise method is available to differentiate those patients in whom the lesion will progress to invasive cancer.

TABLE XX

5 Year Survival Rate in Clinically Diagnosed cancer of the Cervix (Aberdeen)
(Percentage figures in parenthesis)

	1942 - 47				1948 - 53			
Stage	Total	Dead	Unknown	Survivors	Total	Dead	Unknown	Survivors
I	42	15	4	23 (54.8)	86	24	2	60 (69.8)
II	112	74	5	33 (29.5)	111	60	1	50 (45.0)
III	71	57	2	12 (16.9)	78	63	0	15 (19.2)
IV	28	28	0	0 (0.0)	24	24	0	0 (0.0)
Total	253	174	11	68 (26.9)	299	171	3	125 (41.8)

PART C

SECTION 11

The Practical problem of Screening

According to the census of 1951 (Table XXI) the population of Aberdeen city at that time was 182,729 and of these about one-fifth are married women between 25 and 60 years of age, that is 36,000 women in all. It would seem reasonable to attempt to screen these women every 5 years and expect to detect all cases of cervical carcinoma before they presented clinically. This would necessitate the examination of 7,500 women every year, a load within the capacity of the present staff.

However, the women most likely to develop cancer of the cervix, those of lower social class, relatively high parity between the ages of 30-50 years, are on the whole, the least likely to attend for examination, because of domestic commitments and indifference towards their own health.

The most effective method of overcoming their difficulties is to enlist the active co-operation of the family doctor.

From our limited experience, it would seem that many doctors are either too busy to help or are ignorant of the advantages of this technique.

It is necessary to explain the procedure clearly and enthusiastically. The greater the number of women examined the more quickly the benefits of early diagnosis and treatment

TABLE XXI

The population enumerated in the City of Aberdeen in 1951 Census

Males	83,636
Females	99,093
	182,729

Female population of City of Aberdeen by marital state and age group

	Total females	Ever Married	Single	Not Stated
25 - 29	7,290	5,290	1,994	6
30 - 34	6,406	5,280	1,119	7
35 - 39	7,101	5,856	1,238	7
40 - 44	7,298	5,959	1,333	6
45 - 49	7,158	5,711	1,439	8
50 - 54	6,446	5,122	1,315	9
55 - 59	5,513	4,327	1,173	13
	47,212	37,545	9,611	56

will spread, and this should lead to greater co-operation from the public. The facts are now sufficiently well established to make a wide appeal justified.

Systematic control of initial screening and of re-screening must be maintained. Re-screening is proving difficult in U.S.A. because of rapid and widespread movements of population, random selection of patients to be screened and the difficulty of a continuous and unified recording system. In the U.S.A. many women are screened too frequently, often not even by the same doctor. A more static and easily defined population and the facilities of the National Health Service are a great advantage.

It is planned to re-screen patients at intervals of five years. If the calculations are correct, nearly all cases of cervical carcinoma should thus be detected in the preclinical phase. If rapid progression should prove to be exceptional, positive smears found on re-examination after a five year interval should be coming from a pre-invasive lesion, or, less often, from an early invasive, but <u>not</u> clinically diagnosable cancer. Firm knowledge on this point is required before the possible success of such a detection campaign can be assessed. Generally speaking, the more frequently examinations have to be done to be effective, the less likely is such a scheme to succeed.

Who is to Screen and Re-screen?

No source of data provides the necessary information about age, marital state and parity except the general practitioners' lists. This information is not available in census data or street directories, and can only be obtained from the family doctor.

The women most at risk, parous women between the ages 25-60 years are less likely to come for periodic examination if they are of lower social class than are the women from the upper socio-economic groups who are much less likely to develop the disease. The problem therefore of obtaining the co-operation of the women most concerned is not easy, and yet it is they who must be identified. The family doctor is in the best position to do this. Any interested general practitioner can take a cervical smear but many have neither the facilities, the time, nor inclination to do so.

Smears cannot be taken during routine consulting hours, except in a random fashion, and no systematic cover of all patients at risk would be possible. Special arrangements require to be made and the necessary time set aside. This could be arranged in a well organised and equipped group practice.

An increase in hospital diagnostic facilities for exfoliative cytology would be necessary before any comprehensive service could be operated successfully.

SECTION 12

Slide Screening Procedures

The main obstacle to the extension of facilities for cervical cytology to the women at risk in the general population is the difficulty, time and effort required to interpret the prepared and stained smears.

The Aberdeen laboratory uses an Elliot's tissue processor especially adapted for the Papanicolaou staining technique and this is capable of staining twenty slides in one batch. The staining process takes, from start to finish, thirty minutes. The slides are then mounted and are then ready for microscopic examination by a trained cytologist.

It is not possible to say exactly how long is required to read a given slide. A few minutes may be all that is required for a normal smear whereas a doubtful, inflammatory or infected smear may take twenty minutes to interpret and still require to be reviewed later.

The training of a technician to become competent to assess and interpret smears independently, requires at least six months, and even then no ultimate responsibility should be taken, for doubtful smears require to be seen by a cytologist of several years standing. The present shortage of technicians in many laboratories makes this time consuming procedure unpopular.

Fluorescent Microscopy has been advocated by many workers including Von Bertalanffy, Masin and Masin (1958); Sussman (1959); Umiker, Pickle and Waite (1959); Hunter, De Witt and Brown (1961) and Grubb and Crabbe (1961). They have claimed it to be easier, quicker and as accurate as the Papanicolaou technique.

Other workers (Harrison, Kornfield and Werder, 1960) agreed that fluorescent microscopy was useful, but found that the Papanicolaou technique had to be applied to any smear which appeared suspicious under the fluorescent microscope before a final diagnosis could be reached.

For the fluorescent technique, smears are stained by Acridine Orange (A.O) and then viewed, while still wet, under a fluorescent microscope. Staining by Acridine Orange is simple and requires about half the time taken by Papanicolaou's multichromatic stain. Slides thus stained by A.O require to be read before they dry, almost immediately after staining, and consequently they are not permanent and cannot be retained for reference. It is possible to wash out the A.O stain and re-stain any suspect slide by Papanicolaou's method.

The A.O technique is based on the role of the nucleic acids in carcinogenesis. The changes of cytoplasmic RNA (ribonucleic acid) appear to precede morphological changes of the nucleus - upon which conventional methods of cytological cancer diagnosis

are based. The DNA (desoxyribonucleic acid) of the nucleus appears with a green-yellow fluorescent while the RNA of the cytoplasm has increasing concentrations from brown, reddish brown, orange and then bright red fluorescence. Malignant cells have a high RNA content, because they are proliferating and are engaged in active protein synthesis. They consequently present a bright red cytoplasmic fluorescence which, in theory, is easy to distinguish. (Fig. 17)

Elevitch and Brunson (1961) found that of 641 smears screened by an untrained observor, 70% were correctly inter-:preted but that this fluorescent technique was of no value for post-radiation smears.

Bertalanffy (1961) claimed that fluorescent microscopy was 100% accurate for cervical and vaginal (gynaecological) cancer but not for sputum analysis nor gastric washings,

The detection of pathogenic vaginal flora is facilitated by this technique (Van Niekerk, 1962) and infections such as Trichomonas, Candida albicans and Leptothrix can easily and rapidly be identified and then receive specific treatment.

It was felt in Aberdeen that the use of the Acridine Orange method might facilitate the screening of the gynaecological smears by providing quicker staining and screening techniques, and the use of a less highly trained individual for initial screening. Furthermore, more time might become available for

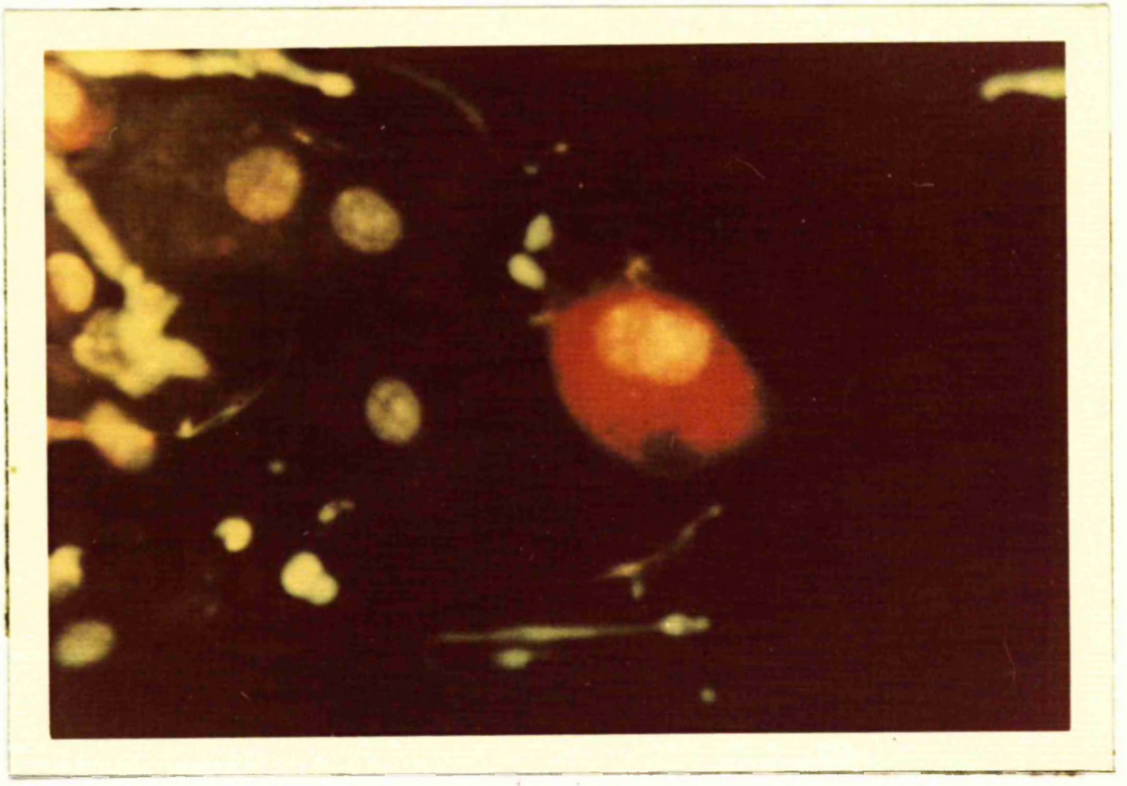

Fig. (17): Malignant smear stained by Acridine Orange and viewed under fluorescent microscope. The malignant cell shows bright red fluorescence of the cytoplasm with a yellow irregular nucleus. Free nuclei are seen greenish-yellow in colour and a dense yellow leucocyte is present.

the review of doubtful slides after they had been re-stained by the Papanicolaou stain.

In order to test the technique, duplicate smears were taken from 100 of the women in the general population survey. One set of smears was stained and read by the orthodox Papanicolaou method. The other set was stained by A.O and studied under the fluorescent microscope. Any doubtful smears were washed and re-stained by Papanicolaou. This re-staining was found to be entirely satisfactory and the previous A.O staining did not effect the Papanicolaou stain.

The presence of pathogenic vaginal flora and leucocytes was much more obvious than in slides stained by Papanicolaou's stain.

The cytoplasmic colour changes were found as described, but the bright red fluorescence expected of malignant cells was found also in regenerating cells. Smears which had a pre-:dominance of proliferating cells, i.e. those smears which are also difficult to interpret by Papanicolaou's stains, were equally doubtful by A.O. The morphology of the nucleus could be distinguished but it was not clear until stained by the Papanicolaou technique.

This masking of the diagnosis was studied by Masin and Masin (1960) who attempted to show a difference in the dye retention in proliferating atypical cells and malignant cells in cervical

smears, by washing out the dye by immersion in buffer solution. They found this took longer in cases of invasive cancer than in proliferating tissue smears, e.g. 6 minutes for atypical proliferating cells, 12 minutes for carcinoma-in-situ lesions and 18 minutes for invasive type cancer. Thus it took three times as long to wash the dye from malignant cells as from the cells of normal proliferating epithelium.

The disadvantages of the A.O dye and the fluourescent microscope technique became obvious. While there is still doubt as to the length of the preinvasive stage, reference to slides taken previously is of utmost importance, and A.O stained slides cannot be kept for future reference. Furthermore, training for this technique, although perhaps less extensive than that for the Papanicolaou technique, would still be necessary. Finally, many slides would come into the doubtful category and would require to be re-stained by the Papanicolaou method in any case.

If some practicable form of automation by fluourescent microscopy could be evolved, such as by the photoelectric recording of the degree of fluorescence present in a numbered and identifiable slide, the procedure might become practicable as an initial screening step.

Cytoanalyser

A study of the quantitative characteristics of exfoliative cells was undertaken by Tolles, Horvath and Bostrum (1961) who

used the measurements to develop an instrument called a 'cyto-:analyser'. Subsequently, Bostrum, Tolles and Spencer (1962) reported that slides could be automatically fed to the machine and measurements recorded of the nuclear density and nucleo-cytoplasmic ratio, thus establishing the presence or absence of malignant cells. The apparatus is large, costly and cumbersome.

Enzyme Techniques

Lawson (1959) suggested that the B-glucuronidase content of vaginal fluid might be used as an index of the presence of cervical carcinoma. Another technique for the detection of gynaecological cancer by the use of the enzyme 6-phosphogluconate has been described by Bonham and Gibbs (1962). This technique may be practicable but it is difficult to see how it will be possible to distinguish the enzyme content of malignant cells from that of normal regenerating cells.

In Aberdeen the results with this enzyme technique are being compared with those obtained by Papanicolaou's staining technique.

It is concluded that Papanicolaou's technique is meanwhile the simplest and most effective screening method in spite of the lengthy and meticulous training required for technician or cytologist.

SECTION 13

Costs of Population Screening

The cost of inviting 5,340 women in general practice to attend for examination and of taking and examing 2,683 smears from them is shown in Table XXI.

The cost for consumable laboratory and clerical materials is under one shilling per smear taken. The biggest item was the part-time salary of the doctor taking and reading the smears. 19 cases of cancer, invasive and preinvasive, were detected and the cost per case detected amounts to £59. The Medical Officer of Health of the City of Aberdeen, Dr. I. A. G. MacQueen, has estimated that the cost of detecting each case of tuberculosis in a Mass Radiography Campaign was approximately £60.

The costs of biopsy of the cervix and subsequent histo-:logical examination are not included. At least half of these patients would eventually arrive in hospital in any case and would cost the hospital service much more than they do when admitted for diagnosis and treatment in an early stage of the disease.

TABLE XXI

Cost of General Practice Survey

	£
Smears taken, 2700 @ 1/- per smear	135
Half salary of typist for clerical work	200
Half salary of junior technician for staining	200
Salary of doctor taking and reading smears	600
	£1135

Detected 19 cases of cancer = £59 per case detected.

PART D

SECTION 14

Conclusions

If the death rate from cancer of the cervix is to be reduced substantially in the foreseeable future, women in all sections of society must be induced to undergo a cytological test at suitable intervals.

In view of the limited resources, skill and money avail-:able, the service must be carefully planned. Otherwise some women will be examined at unnecessarily frequent intervals and others too infrequently or not at all. There is much to be said for concentrating attention on parous women aged 25-60 years since few smears are positive before the age of 25. If the test is negative at the age of 60 the patient has a very good chance of escaping the disease altogether, or of having its onset delayed till she is over 70.

The test should be done on all parous women attending a gynaecological out-patient clinic irrespective of age. When the back log of women not previously examined has been accom-:plished it should be possible to concentrate on the cohorts of younger women entering the high risk group.

It has been calculated that if all parous women between the ages of 25 and 60 years are to be examined at 5 yearly intervals (that is, eight times in all) the number of smears to

be examined in a City of 200,000 persons would be almost 8,500 per year. The evidence points to the fact that this would result in a great reduction in the number of cases not diagnosed until clinical signs and symptoms develop.

The greatest difficulty to be encountered in any extension of exfoliative cytology is probably the lack of available trained personnel to interpret the slides.

Different methods of screening slides are consistently under review and in time some form of automation may become possible. In the meanwhile Papanicolaou's technique is simple and has advantages over alternative techniques.

There is no insuperable difficulty in the use of this test to reduce the incidence of cervical carcinoma, and until definitive cure of established clinical cancer is possible, early diagnosis and appropriate treatment offers the best prognosis.

SUMMARY

1) The development of exfoliative cytology in Britain and U.S.A. has been described with special reference to cervical cancer.

2) The technique of taking smears has been described. The interpretation of vaginal and cervical smears has been discussed and the technique used to screen a section of healthy population outlined in detail.

3) After reviewing surveys conducted in Britain and U.S.A. and results of the cytology service in Aberdeen between 1958-61, it was found that the women most at risk in a general population were married women between the ages of 25 and 60 years.

4) It was decided to develop an intensive cervical carcinoma detection drive in a section of a healthy general population.

5) Several methods of approach to these women were explored initially in the general medical and surgical wards of the Royal Infirmary, Aberdeen. The test was found to be acceptable to almost all the women approached. In 1,207 cases examined 3 cases of invasive cancer, and 4 cases of carcinoma-in-situ were found.

6) Methods of obtaining access to the women at risk in the general population have been discussed. It was decided that the lists of general practitioners provided the most systematic and comprehensive coverage as they are the only source of

information on marital state, age and parity.

7) The Papanicolaou technique for cervical cytology has been applied systematically to the parous women between the ages of 25 and 60 years in three general practices in Aberdeen. 5,340 women were invited to attend and ultimately smears were taken from 2,683 patients. Eighteen cases of clinically unsuspected preinvasive or early invasive carcinoma were detected a rate of 0.67%, which is consistent with the occurrence of clinical cervical carcinoma in Aberdeen.

8) The reply rate was highest (79%) and the detection rate was lowest (0.4%) in the practice where there was the greatest degree of co-operation from the family practitioners, and where the social class of the practice was possibly higher than average. The detection rate was high (0.9%) in practices which had the lowest percentage of smears taken (41% and 52%) and a lower than average social class content.

9) There was no evidence to suggest that the survey increased the incidence of cancerphobia and on the contrary it stimulated interest in the problem and a sense of relief that a cure was possible.

10) In Aberdeen women between the ages of 25 and 60 years, the mean age of 130 women with preinvasive 'cancer' of the cervix detected by cytology was 39.6 years. In 48 patients with a histologically diagnosed invasive cancer the average age was

43.6 years. The mean age of women, aged 25-59 years, with clinically diagnosed cancer of the cervix was 48.3 years. This suggests that there may be a steady progression over nine years from preinvasive to clinical carcinoma. If women over 60 years of age with cancer of the cervix are included the mean age of clinically diagnosed cancer is raised to 52.7 years.

11) The cases of cervical carcinoma detected by the cytological technique are predominately women of higher parity and from the lower social classes (III - V). Experience shows that they are least likely to volunteer for this examination. Particular attention must therefore be given to the problem of eliciting their co-operation in detection drives.

12) Systematic screening of the whole population most at risk (parous women between 25 and 60 years) would be practicable if one-fifth of the group was screened annually, and re-screened at 5 year intervals.

13) The occurrence of atypical and unsatisfactory smears and the difficulty of histological interpretation has been noted, and the problems presented by the occasional 'false positive' smear for which no histological justification can be found, are discussed. The true incidence of 'false negative' smears can not as yet be judged.

14) Various methods used to facilitate the interpretation of the smears, such as fluorescent microscopy, have been tried but

as yet the simplest and most reliable is the Papanicolaou technique.

15) The cost, in Aberdeen, of detecting each case averaged about £60, the same as the cost of detecting a case of tuber-:culosis by a Mass Radiography Campaign.

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