

# THE VAGINAL SMEAR AS AID TO CLINICIAN IN CANCER

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## *Introduction and Aim*

The aim of this study is to explore the potentiality of the vaginal smear from the clinician's point of view, to help him in dealing with his patients with special reference to cancer. This study has been prompted by the following observation made at the Civil Hospital, Ahmedabad.

(1) Very rarely cases are seen where a cervical biopsy has come negative for cancer when a subsequent biopsy from the same case has shown undoubted malignancy.

The three conditions: (1) Simple technic, (2) High degree of reliability, (3) Easy of interpretation, have been adhered to, as far as possible, in this study as it is felt that if the vaginal smear, like any other clinical investigation, is to be of more widespread use, it must fulfil these conditions.

## *Review of Literature:*

The application of the vaginal smear in the diagnosis of cancer has been largely pioneered by Papanicolaou and accurate descriptions of the different cell types encountered in malignancy of the genital tract have been described by him.

Slate and associates have shown that even invasive squamous cell carcinomas of the cervix can be

missed by careful history and pelvic examination, because out of 20 cases of invasive cancers detected by the vaginal smears three had benign lesions.

They concluded in a study based on the analysis of 104 consecutive positive and suspicious smears from 8,148 private patients that 5% of invasive carcinomas would be missed if cervical and vaginal smears are not taken.

## *They used the classification:*

- (1) Negative for malignant cells (not suspicious of cancer)
- (2) Definite atypical cells (not suspicious of cancer)
- (3) Highly atypical cells present (repeat smear and biopsy)
- (4) Suspicious for borderline lesions-pre-invasive lesions
- (5) Positive (a) for pre-invasive cervical cancer  
(b) for endometrial or endocervical cancer  
(c) for unclassified or classified mature malignant cells.

Watchel and Plester have shown the use of cytological routine investigation as fully justified. In a survey of 2550 vaginal smears an incidence of

false negative smears was 7.8%. Five false positive reports were given.

Ruth Graham prefers the vaginal smear to the cervical smear in the detection of cancer, because (1) the vaginal smear is simpler to take, requiring no dry speculum as is required in taking the cervical smear.

(2) The vaginal smear shows malignant cells from the corpus also.

Cuyller and associates believe that cytologists should offer interpretations as opinion and not as diagnosis. The classification followed by them, is after Papanicolau, as modified by them.

Type 1: Essentially normal epithelium.

Type 2: Benign epithelial abnormalities present.

Type 3: Intra-epithelial carcinoma of cervix.

Type 4: Cells thought to be malignant—few present.

Type 5: Cells thought to be malignant—many present.

#### *Material and Method:*

In the study of cancer of the female genitalia, smears were prepared both by aspirating with the glass pipette from the posterior fornix and with the cotton applicator. The cotton applicator was used with the special purpose of collecting cells from the ulcer or erosion margin. The centre of the growth or erosion was avoided, as far as possible, as it often gives rise to bleeding and the blood in the smear destroyed the clarity of cell structure.

Both methods have their advantages and disadvantages. The cotton applicator gives a fine, thin smear

with cells obtained from the ulcer or growth but the cell structure is often destroyed. The glass pipette on the other hand, preserves the pattern of the cells shed.

Since it is known for certain that cancer cells have a tendency to clumping, and which is a valuable aid in diagnosis, the advantage of studying a smear with a glass pipette is evident. On the other hand, it is also known that exfoliated cancer cells get much diluted in the secretion that collects in the posterior fornix. This means that for an occasional cancer cell there will be numerous normal epithelial cells. This makes the search for cancer cells more difficult and perhaps plays an important part in raising the number of false negatives. After preparing the smears they were immediately fixed in alcohol-ether and stained with Shorr's stain or haematoxyline eosin stain. After the smears, biopsy or specimens of the cervix were taken or made available for sectioning and study. In only one case the growth was not available for study.

#### *Selection of Patients:*

It was not possible to take smears routinely of all patients attending the O.P.D. or of those belonging to the 'Cancer age'.

In these series the patients were selected. Smears were obtained from all patients who had erosions, polyps, ulcers etc., and those in whom cancer was diagnosed or suspected clinically. Cases of frank malignancy or large, foul, necrotic, bloody growths are excluded from these series.

Smears which were positive for cancer but where no biopsy was



available were also excluded, except one case of primary carcinoma of the vagina, which is included because of interest. In all these patients, therefore, reports on sections of the cervix were available. Before declaring a smear as negative a minimum amount of three smears were taken and studied. On the other hand if a smear was positive further smears were not considered necessary. In all, 101 patients were thus studied with 263 smears, and reports were available of 100 biopsy sections.

#### *General considerations:*

This study is based upon the fact that exfoliation of cells is proportionate to proliferative activity (Papanicolau and Traut) and that a more pronounced exfoliation occurs in cancerous tissue than normal.

#### *General criteria of malignancy:*

Under general criteria are included (a) changes in cells and their nuclei like hyperchromasia, disproportionate enlargement of the nuclei, aberrant chromatin pattern, mitotic figures, abnormal vacuolation and multinucleation. The cytoplasm may be filmy, syncytial or amoeboid. The cell as a whole may be enlarged beyond the normal range, may show elongation and bizarre shapes.

(b) Irregularity of pattern, e.g., anisokaryosis and anisocytosis, i.e. marked variation in the size of nuclei and cells of the same type within a cluster; dense grouping and crowding.

(c) Indirect criteria: By this is meant presence of blood, leucocytes, histiocytes and polymorphs.

#### *Application of the criteria to the present study:*

In the 101 patients studied, sections of the cervix were available in 100 patients. In 42 patients the sections showed undoubted carcinoma of the cervix. Biopsy of one growth locally showed papilliferous adeno-carcinoma. In the remaining 57 patients they were negative for malignancy.

In 40 patients the vaginal smear was frankly positive for cancer. In this is included one case of papilliferous adeno-carcinoma of ovary and one of primary carcinoma of the vagina. In the last case, no biopsy report is available. Four of the patients showed negative smears repeatedly though the biopsy taken subsequently showed undoubted malignancy. One of these four patients of squamous-cell carcinoma of the cervix, who showed repeated negative smears, was a case of prolapse with a cauliflower growth on the cervix and surface scrapings from it were taken.

Out of the 57 patients, negative for cancer, three showed atypical smears. Two had trichomonas infection locally and the third showed 'Signet-ring Type' of cells as seen in photomicrograph. The biopsy report of this latter case showed acute inflammatory changes in the cervix.

Only the cell types studied in this series are discussed. The clinical picture together with a detailed study of three interesting cases is described later.

#### (a) *Undifferentiated carcinoma of the cervix*

Cells are oval, round, more uni-

form, smaller and more difficult to identify. Nucleus is large compared to the cells. Cytoplasm is scanty, basophilic and stains bluish, or bluish green (Shorr's stain). Nucleus is round or oval and consists of a membrane within which the chromatin is granular. Nucleoli are visible and quite prominent. Photomicrograph 3 shows a smear of undifferentiated squamous-cell carcinoma showing prominent nucleoli in the cells. Mitotic figures are rare. Chromatin may be present in the form of small dense clumps.

(b) *Differentiated squamous-cell carcinoma of the cervix*

Here the cells assume a great variety of aberrant forms. 'Tadpole type' and 'fibre type' cells with tapering ends were common. Many cells showed bizarre and enormous sizes. Spindle, angular and amoeboid types were common, in fact cells of all shapes and sizes were encountered. Cells were often found in 'nests' or clumps. Cytoplasm may be basophilic or acidophilic. Vacuoles were often seen. Nuclei are round, oval, bean-shaped or elongated. They are usually hyperchromatic, at times to an extent as to stain dense black (Papanicolaou). Photomicrograph 1 shows such a group of cells with nuclei stained black.

(c) *Adeno-carcinomas:*

Only one case of a papilliferous adeno-carcinoma of the ovary, secondarily involving the cervix, was encountered. Adeno-carcinoma cells are smaller than the squamous type. Overlapping and grouping of the cells

is extreme at times. See photomicrograph 4.

(d) *Primary carcinoma of the vagina*

Cells are of the squamous-type as previously described. This case is described later in detail.

(e) *Other cells in the cancer smears*

Normal squamous cells are nearly always seen in varying numbers. R.B.C.'s are nearly always present. Polymorphonuclear leucocytes are numerous and are often found in dense groups.

Histiocytes are also commonly seen. They may at times be confused with malignant cells. They assume a great variety of forms and sometimes reach the size of epithelial cells. They are easy to indentify when they contain engulfed R.B.C.'s. The histiocytes are recognised by the pronounced vacuolisation of the cytoplasm and the foamy appearance. They are often found, like cancer cells, in clumps.

(f) *Atypical smears*

Three patients showed atypical smears. Two were due to *Trichomonas* infection. The 'perinuclear halo' seen in cases of infection was easily detected. Photomicrograph 7 shows another atypical smear. 'Signet ring type' of cells were seen. These are in all probability histiocytes. Polymorphs are also seen in the smears. The cervical biopsy report was acute inflammation of the cervix.

*Three interesting cases*

These cases are of more than ordinary interest and so the smears are described in detail together with a brief clinical picture.



**Case 1**

Mrs. M. B., age 42 years, was admitted in Sept. 1955, for the complaint of bleeding per vaginam. She was admitted with the diagnosis of menorrhagia.

She had 3 F.T.N.D. of which 1 male child was alive. She was in menopause since 10 years. A smear was taken after admission and picture is seen in photomicrographs 2 and 3. Photomicrograph 2 (Shorr stain): It shows a part of the smear. Many of the cells were round and oval and found in clumps. At places there were sheets of cells so that individual cells could not be studied. The cytoplasm was blue or greenish-blue and was scanty as compared to the size of nucleus. The nuclei were round or oval and many of them showed a fine granular chromatin network with nucleoli. Photomicrograph 3 shows the nucleoli distinctly as dark black spots in the nuclei. These cells are more embryonic than the types described under the differentiated squamous cell carcinomas. The cells being cast off, at places, in dense sheets or clumps is suggestive of a rapidly growing tumour.

The cervix was hard and indurated and the biopsy report confirmed the diagnosis of a squamous-cell carcinoma. Radium was given to the patient, but it did not seem to have any effect on the progress of the growth. Nodules could be felt in the abdomen and ascites rapidly developed. The general condition deteriorated and the patient left hospital towards the end of November, 1955. It was later learnt that she expired 4 days after discharge from the hospital.

**Case No. 2**

Mrs. S. B. Age 35 years. She was admitted in the first week of January, 1955. She complained of bleeding per vaginam for one month. She had 5 children and the last delivery was three years ago. She gave history of being operated on for an ovarian tumour in 1953. Only the tumour was removed at that time. She was told a month later that the tumour removed was malignant (papilliferous adenocarcinoma of the ovary) and that she should go to the Indian Cancer Institute, Bombay, for deep X-rays. She took a course of

deep X-rays at the Institute.

A smear was taken a few days after admission and the picture was truly remarkable. The smear consisted of cancer cells in great numbers. They were small, roundish cells with darkly staining large nuclei. The nucleus was round or oval and the cytoplasm compared to the nucleus was scanty. The heaping and clumping of cells was extreme, giving bizarre shapes. At places the nuclei gave a mulberry form, at others a tri-lobed appearance as seen in photomicrograph 4. Mitotic figures were numerous. To the left in photomicrograph 4 are seen two cells in mitosis. The other cells seen in the smear were outer basal cells. These cells could be easily differentiated from the cancer cells. They were round or oval cells with large and well preserved nuclei which were not stained darkly like the tumour cells. Few squamous cells were also present.

Histiocytes, R.B.C.'s, leucocytes and mucous completed the picture of the smear. Though it was known that the smear was positive for cancer, the ultimate diagnosis of papilliferous adeno-carcinoma came from the biopsy report. The biopsy report and the report of the ovarian tumour removed two years previously was the same.

A speculum examination showed the cervix and the upper anterior wall of the vagina to be eroded. It seemed, therefore, that the growth had secondarily invaded the uterus and upper vagina and cells shed were collected in the vaginal smear.

The patient left hospital after a month and it is learnt that she expired shortly after leaving the hospital. This case is of special interest because of its rarity and because of its certain characteristics which differentiate it from the squamous-cell carcinomas.

**Case No. 3**

Mrs. S., aged 55, was admitted in June, and left hospital the same day against medical advice. She had 1 F.T.N.D.—35 years old.

Patient was in menopause since 15 years. Patient was operated upon for a growth, in the posterior fornix, which was removed.

Patient was referred here for persistent

leucorrhoea following the operation.

The vaginal smear showed definite malignant cells. Photomicrograph 5 shows a part of the smear under low power. There is a 'nest' of cancer cells surrounded by normal squamous cells. The nuclei of these malignant cells were hyperchromatic, large, roundish, or oval and the cytoplasm was scanty as compared with the nuclei. Normal epithelial cells are seen surrounding these malignant cells.

Photomicrograph 6 is the same nest of cells seen under the high power of the microscope. The criteria of malignancy mentioned above are seen better here. Normal squamous cells are seen in the lower right hand corner of the picture. Numerous leucocytes are also seen.

A speculum examination showed the cervix to be normal and hence the diagnosis of primary carcinoma of the vagina was made on the strength of the picture seen in vaginal smear. No biopsy is available of this growth though the gynaecologist who operated did say that the growth was strongly suspicious of malignancy. Even if the patient had stayed in hospital it would have been quite difficult to select a spot for biopsy. On the other hand, the leucorrhoeal discharge was easy to obtain and showed the pictures above mentioned.

#### *Comments and Discussion:*

That cases of the worst type of cancer can be missed by a clinical examination alone is shown in Case No. 1. This justifies the taking of vaginal smears routinely in all suspicious cervixes even though the chances are that only one patient in a hundred will be first brought to the notice of the clinician by the vaginal smear.

There were no false positive smears in the series but that could be explained because the patients in this series were all specially selected. There were four negative smears in cancer patients. The smears were taken repeatedly and they remained

negative. These smears were all haemorrhagic and that did make the study of the smears difficult. It is seen from the above that whereas one negative smear has little value, one positive smear can be looked upon with grave suspicion.

Case No. 3 shows another condition where the vaginal smear is invaluable. The presence of these malignant cells definitely shows the persistence of the malignant growth. Such a patient could be easily followed by the vaginal smears whereas repeated biopsies in such a case would be very difficult. 39 patients showed frankly positive smears for cancer. (1 case of primary carcinoma of vagina in which biopsy report is not available is excluded). The biopsies in all these 39 patients showed malignancy. Does this mean that a frankly positive smear together with a clinical diagnosis of cancer gives a 100% correct diagnosis of cancer?

Does this mean that taking biopsies in these patients is a matter of routine?

There is strong evidence that a frankly positive smear for cancer together with a clinical diagnosis of malignancy does not need the confirmation of the diagnosis by the biopsy which every clinician knows causes bleeding, at times profuse.

39 patients may not be a large group of patients for the above assumption, but surely then one would expect at least one case to be otherwise. The smears may also throw light on the prognosis. In two cases the smears showed malignant cells cast off, at places in sheets. One showed numerous mitotic figures.



Both these patients went down rather fast in their health and expired shortly afterwards. Such criteria in a smear therefore point to a bad prognosis. The only type of smear to which a clinician should attach importance is the frankly positive smear. In these smears the diagnosis is simple.

The role that the vaginal smear can play in India should also be stressed.

39 patients were clinically diagnosed as cancer of the cervix. All showed frankly positive smears. The cervical biopsy in all these cases showed malignancy, also in these cases the biopsy reports did not alter the treatment.

In a country where good pathological laboratories for sections are few, the frankly positive smears have a definite value. So far this study strongly supports the view that in a case of frankly positive smear for cancer, together with a clinical diagnosis of malignancy, treatment may be started immediately rather than wait for a biopsy report to come in. This is especially true in towns with no competent pathologists. It may be argued that treatment of cervical carcinoma should always be in a big institution, with adequate facilities, but one comes across quite a number of patients who refuse to leave their own towns.

Case No. 2, for instance, could not complete her treatment in the cancer institute in Bombay because of economic conditions. If a patient refuses to leave her town and cannot afford a biopsy report should treatment be withheld even though the clinical

picture and the vaginal smear show positively that cancer is present?

This would surely not be justified and every gynaecologist would do well to have a good knowledge of the vaginal smear, especially for this type of patient who is quite common among the poorer classes in this country. The vaginal smear, if intelligently utilised by the clinician, would prevent much suffering among these patients.

#### *Summary and Conclusions*

(2) A study of 101 patients with lesions of the cervix is presented. (This includes one case of primary carcinoma of the vagina in which biopsy report is not available).

In all these patients the cervix was available for microscopic study except the one case already mentioned.

Biopsy showed definite carcinoma in 43 patients (42 of squamous cell carcinoma, 1 of papilliferous adenocarcinoma of the ovary). The vaginal smear was positive in 40 patients (this includes 1 case of primary carcinoma of the vagina in which no biopsy is available). In 4 patients of definite squamous-cell carcinoma the vaginal smears were negative.

(2) Its utility is shown and its role in this country is discussed.

(3) Numerous mitotic figures and cells cast off in sheets, as seen in the vaginal smears, suggest a bad prognosis.

#### *Acknowledgments*

This work was carried out under the guidance of Dr. S. B. Anklesaria, M.D., Hon. Gynaecologist and Obstetrician, Civil Hospital, and B. J. Medi-

cal College, Ahmedabad, to whom I am grateful. I am particularly indebted to Dr. Y. M. Bhende, M.D., Professor of Pathology, B. J. Medical College, Ahmedabad, for going through the numerous smears and giving invaluable advice during the work and in compiling this dissertation.

I am thankful to Dr. G. V. Barve, M.S. (Bom.), Principal, B. J. Medical College, Ahmedabad, for allowing me to use the photomicrocamera.

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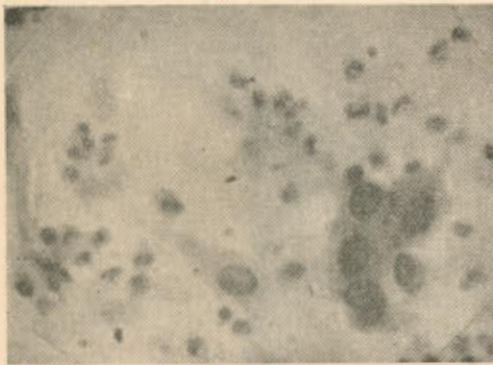


Fig. 1

Shows a cluster of malignant cells. Note hyperchromatic large nuclei. The picture shows that in squamous cell carcinoma, the nuclei are often hyperchromatic at times to an extent as to stain dense black — Papanicolau. Biopsy showed a squamous cell carcinoma of cervix.

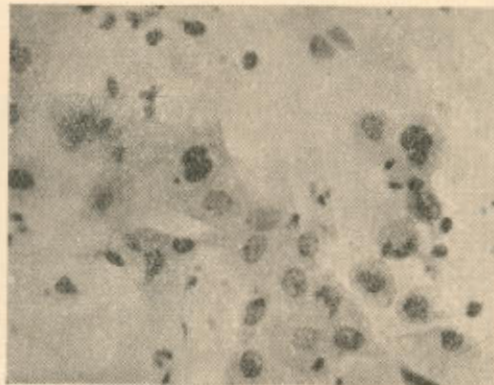


Fig. 2

Shows a smear of an undifferentiated squamous cell carcinoma. Note round or oval cells with large nuclei. Coarse granular chromatin network and nucleoli are seen in some of the cells.



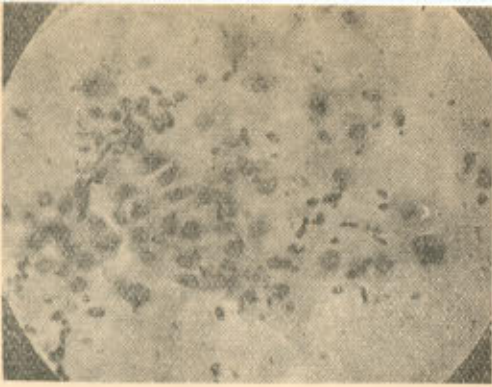


Fig. 3

Shows the same smear as 2 but the nucleoli are seen very distinctly in many of the cells. Biopsy showed a squamous cell carcinoma of the cervix.

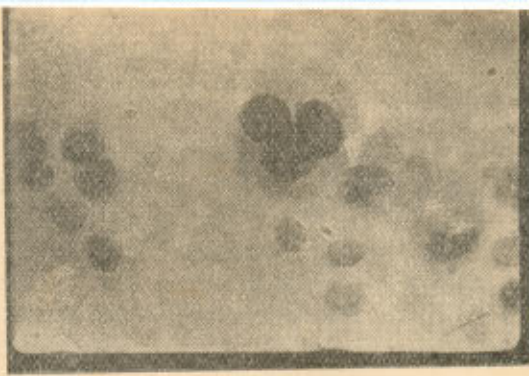


Fig. 4

Shows a smear in a case of papilliferous adeno carcinoma of the ovary. A tri-lobed appearance of the cells is seen. To the left are seen two cells in mitosis.

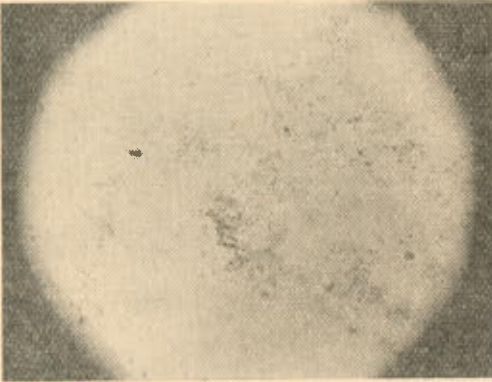


Fig. 5

Shows a low power view of a smear taken from a patient in whom a growth from the vagina was excised five months previously. A nest of hyperchromatic cells is seen surrounded by normal epithelial cells. The same nest of cells is seen under the high power of the microscope in Fig. 6. Smear from a case of primary carcinoma of the vagina.

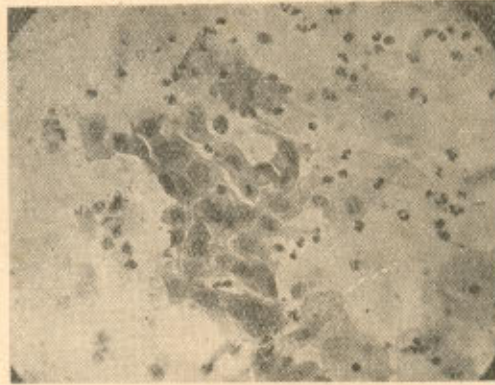


Fig. 6

Shows the same nest of cells as seen in Fig. 5 under high power. The cancer cells are seen together with a few normal squamous cells. Smear from a case of primary carcinoma of the vagina.

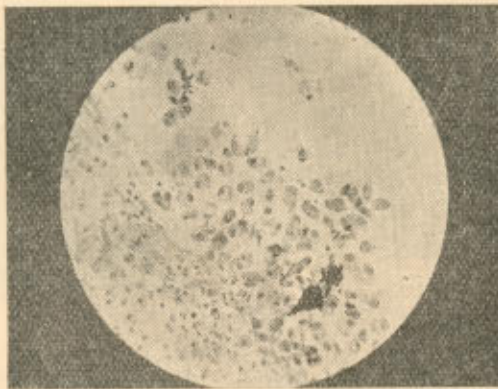


Fig. 7

Shows an atypical smear encountered, "Signet ring type" of cells are seen with numerous leucocytes. Biopsy showed an acute inflammation of the cervix.