INTRAUTERINE SPONGE BIOPSY - A NEW TECHNIQUE FOR THE DETECTION OF EARLY INTRAUTERINE MALIGNANCY

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SUMMARY

This thesis presents a new technique for obtaining samples of endometrium and endocervix, suitable for a histological diagnosis. It employs the principles of sponge biopsy and the introduction of intrauterine contraceptive devices. A piece of dry, abrasive polyvinyl sponge is passed through the cervix within a standard intrauterine contraceptive device introducer. It is expelled into the uterine cavity and withdrawn immediately. The sponge scrapes off pieces of endometrium and endocervix from all sites within the uterus. It absorbs the abrased tissue into itself and the entire sponge containing the biopsies is processed as a routine histological specimen.

Endometrial and cervical carcinoma now occur in equal frequency. The decreased incidence of cervical cancer has resulted from the general improvement in the socio-economic status of the population, together with the detection and treatment of preinvasive cancer by asymptomatic population screening with cervical cytology. The incidence of endometrial carcinoma has increased with affluence and

has not been affected by attempts at earlier diagnosis. There have been no satisfactory screening techniques for asymptomatic intrauterine cancer. Formal curettage of symptomatic women has failed to improve the survival from endometrial carcinoma in the last thirty years.

The previous attempts at detecting early endometrial cancer on a significantly large scale, relied on cytological methods, uterine lavage or limited site biopsy with small curettes. These methods are described and critically reviewed.

An acceptable screening procedure must be safe, simple and inexpensive. It must be performed as an outpatient procedure, without anaesthetic, prior dilatation of the cervix or undue discomfort to the patient. It must reliably sample the endometrium and detect or suspect malignant or premalignant change if present, by obtaining random samples from the entire uterine cavity suitable for a histological diagnosis.

To evaluate the suitability of the new technique, intrauterine sponge biopsies were correlated with endometrial biopsies obtained by formal uterine curettage, which is the accepted standard of intrauterine diagnosis. The correlation between the two methods was satisfactory. Sponge biopsy detected or suspected endometrial cancer in all but one case, where the malignant change was at the base of an atrophic endometrial polyp. It readily biopsied hyperplastic and potentially premalignant conditions. Adequate tissue

for a histological diagnosis was obtained in 98 per cent of sponge biopsies.

In addition to its ability to detect endometrial cancer, the leading "V" of the sponge selectively biopsies the cervical canal as it is withdrawn from the uterus. Cervical biopsies were present in one third of the sponges and these included all cases of invasive cancer of the endocervix and ectocervix. This aspect of the technique overcomes the recognised inability of cervical cytology to reliably detect malignant change of the endocervix and inaccessible ectocervix.

The extensive international experience of inserting contraceptive devices in unanaesthetised outpatients, proves that the identical technique of intrauterine sponge biopsy is an acceptable outpatient procedure for widescale implimentation.

Sponge biopsy satisfies all the criteria of a screening technique for endometrial cancer and has the additional ability of screening the cervical canal.

It is proposed that intrauterine sponge biopsy bears the same relationship to endometrial cancer as cervical cytology has to cervical cancer. In view of the similar roles and objectives of the two techniques it is logical to integrate sponge biopsy into existing cervical cytology programmes. This would overcome the deficiences of cervical cytology and would provide the asymptomatic female population with a total uterine cancer screening programme. A pilot

study confirms that sponge biopsy can be readily integrated into existing cytology programmes.

Without radical changes in the treatment of uterine cancer, the improvement in early diagnosis which will result from a combined screening programme, offers the only real chance of reducing the incidence, the morbidity and mortality of uterine cancer.

Other possible applications of intrauterine sponge biopsy technique in gynaecological practice are discussed as an appendix to the thesis.

I N D E X

CHAPTER 1

INTRODUCTION

The success of the current treatment of cancer is directly related to early diagnosis. Interest in techniques for detecting early gynaecological cancer was stimulated by the pioneering work of Papanicolaou, thirty years ago. He demonstrated that exfoliative cytology of the cervix uteri could detect cervical cancer before it was clinically obvious and indeed prior to invasion. The application of cervical cytology to an asymptomatic population at risk has greatly reduced the incidence and mortality of invasive cancer of the cervix.

In addition to cytology screening, a reduction in the incidence of cervical cancer has resulted from improved social standards with a consequent fall in parity. The incidence of endometrial cancer may actually have increased during the same period, as a result of this fall in parity and a rise in the population age. It has not been influenced by attempts at earlier diagnosis.

The present treatment of endometrial carcinoma depends on a combination of surgery and radiotherapy. While refinements of these techniques may effect some improvement in the survival from this tumour, without radical changes in therapy, advances in earlier diagnosis offer the only real

chance of a reduction in morbidity and mortality. Today's patient has virtually the same chance of survival from an endometrial tumour as her grandmother had, unlike her chance with a cervical lesion.

Formal dilatation of the cervix and curettage of the entire uterine cavity, under adequate anaesthesia, is at present the only available method of obtaining reliable samples for the detection of endometrial cancer. This procedure is justified in the presence of suspicious signs or symptoms. Endometrial tumours can, however, be present for a considerable time before symptoms develop and it must be realised that curettage of symptomatic women has failed to improve the earlier detection and therefore the survival for endometrial tumours in thirty years.

A simple outpatient method of reliably obtaining random samples from the entire uterine cavity of asymptomatic women at risk from endometrial cancer is required.

This thesis presents a new technique for obtaining samples of endometrium and endocervix suitable for a histological diagnosis. It uses an abrasive polyvinyl sponge passed through an undilated cervix within an intrauterine contraceptive device introducer. The abrased tissue is absorbed into the sponge as it is withdrawn from the uterus and

the entire sponge is processed as a routine histological specimen. This technique can be performed without anaesthesia, with minimal discomfort to the patient.

It is intended to demonstrate this technique's ability to reliably suspect and detect intrauterine cancer, and to propose that it is suitable to be used as a routine screening procedure for asymptomatic intrauterine malignancy. It could then be combined with existing cervical cytology programmes to provide total uterine cancer screening of a population at risk.

CHAPTER 2

CANCER OF THE ENDOMETRIUM

Endometrial cancer has been considered to be the second most frequently encountered malignancy of the female genital tract for many years. It was preceded by cervical cancer. It is probable that this situation no longer exists and endometrial cancer is now the commonest gynaecological cancer.

Fifty years ago, deaths from cervical cancer were between six and eight times more frequent than deaths from endometrial cancer. Ten years ago they were twice as frequent and at present they occur in equal frequency. Treatment now offers a better survival from endometrial cancer than cervical cancer and therefore endometrial cancer will now be more frequently encountered.

It is appreciated that these statements are by necessity, vague generalisations. The official registration of the incidence and mortality of cancer during the last fifty years, has been notoriously inaccurate. As recently as 1961, the Registrar General's Annual Report (Volume 12) presented incidence and mortality statistics from both uterine tumours. One hundred and five institutions had furnished data on cervical cancer and only 36 of these had reported on endometrial cancer. Considering this degree of inaccuracy and the well recognised regional and racial variations in tumour incidence, it is not

valid to make comparisons or extract detailed information from national and international statistics. It is possible, however, to recognise trends of tumour behaviour from these registers.

Uterine cancer has followed clearly defined trends in the last fifty years. The incidence and mortality of cervical cancer have both fallen progressively and dramatically during this time. Meanwhile, the incidence of endometrial cancer has increased and its overall mortality has remained virtually unaltered.

The explanation for this changing pattern is complex. Carcinoma of the cervix is a disease of younger women. It is associated with high parity, poor standards of personal hygiene and early marriage. As a result of the changing social pattern and a general improvement in socioeconomic status of the population as a whole, in the last fifty years, the size of the families has been greatly reduced, early marriage occurs less frequently and hygiene standards have risen. These factors alone will explain a major reduction in the incidence of cervical cancer. In addition, general gynaecological health has improved, primarily due to the expansion of maternal welfare programmes, where the patients at maximum risk, namely the poorer parous women, can be examined routinely and minor gynaecological conditions detected and treated. Antenatal clinics have also contributed to a breakdown of the reluctance of women to present at gynaecological clinics with potentially

serious signs or symptoms. Pelvic examination is no longer feared.

Having encouraged women to present more readily for gynaecological examination, the introduction of cervical cytology has immeasurably increased the value of these examinations. The detection of preinvasive cancer and its treatment prevents the development of invasive cancer. While there remains some controversy as to whether all these preinvasive lesions would have progressed to invasive tumours if untreated or whether some invasive tumours never pass through a preinvasive stage, there is no doubt that cervical cytology has reduced the incidence of invasive cancer and results in earlier detection and therefore better prognosis from already invasive tumours.

The improved methods of treatment, particularly the modern combinations of surgery and radiotherapy, have resulted in improved survival and reduced morbidity from cervical cancer.

These factors, therefore, explain the reduction in the incidence, mortality and morbidity of cervical cancer in the last fifty years.

As this thesis is concerned with endometrial cancer, the factors contributing to the increased incidence and unchanged morbidity and mortality of this tumour must be analysed.

The Factors Contributing to an Increase in the Incidence of Endometrial Cancer

A. Population Age

Endometrial cancer is a disease of older women, although a significant number of tumours occur before the menopause. Roberts (1961) described 223 patients of whom 27 per cent were premenopausal. In the West of Scotland, out of 1110 patients with endometrial tumours, presenting between 1960 and 1969, 179 (16 per cent) were over seventy years of age, 768 (69 per cent) were between fifty and seventy years and 163 (15 per cent) were under the age of fifty years (Leslie, 1971).

The average age of the population is increasing annually and therefore more women are living long enough to be at risk from endometrial cancer.

B. Parity

Endometrial tumours are associated with low parity, unlike cervical cancer. In the majority of series, thirty per cent of women are nulliparous. In the West of Scotland 36 per cent of women with tumours are nulliparous, sixteen per cent had had one baby and the remainder (48 per cent) had had more than one baby, although it was exceptional for them to have had more than three babies.

The reduction in family size that has resulted from intensive

family planning programmes and a change in social habit related to relative affluence, results in more women remaining at risk from endometrial cancer and less women progressing to being at risk from cervical cancer.

C. Hyperoestrogen Effect

A definite relationship between a hyperoestrogen state and the development of endometrial cancer, has not been demonstrated. There has been considerable controversy as to whether cystic glandular hyperplasia of the endometrium, following prolonged unopposed oestrogen stimulation, is a precursor of malignant change. Novak and Yui (1936) examined 104 women with endometrial cancer. Twenty four per cent of the patients had co-existing cystic glandular hyperplasia. McBride in 1959, however, followed up 544 women who had had cystic glandular hyperplasia at or about the menopause, for up to twenty four years. Only two of these women developed endometrial cancer (0.4 per cent). This showed that unopposed oestrogen stimulation did not seem to pre-dispose to malignant change.

Uterine carcinoma has been reported in association with the oestrogen secreting granulosa and theca cell tumours. Both these tumours occur very rarely and it makes a true correlation with endometrial tumours almost impossible.

Gusberg and Hall (1961), however, reported twenty three women with endometrial carcinoma who had been taking oestrogens

continuously for various reasons for varying periods of one to twenty years. As a possible result of persistent stimulation, the endometrium had produced a characteristic low grade carcinomatous pattern resembling adenomatous hyperplasia. The growths were particularly well differentiated, but in six there was considerable invasion of the myometrium and in two there were widespread metastases.

The relationship between obesity, prolonged oestrogen stimulation and endometrial cancer is discussed later.

Despite the inconclusive evidence concerning cystic glandular hyperplasia, it is probable that a definite relationship exists between a hyperoestrogen effect and endometrial cancer.

The endemic administration of oral contraceptives, despite their small oestrogen content, and the widespread and indiscriminate prescribing of potent oestrogen preparations for menopausal symptoms, is undoubtedly resulting in new states of exogenous hyperoestrogen stimulation of the endometrium which have the potential of increasing the incidence of endometrial cancer.

D. Obesity

It has always been a clinical impression of surgeons that obesity is associated with endometrial cancer. This is undoubtedly due to the fearsome memories of horrible

hysterectomies down small holes in enormous abdomens. Twombly et al (1961) attempted to demonstrate scientifically a relationship between these two conditions. They suggested that obese women tend to store oestrogens in their fat and therefore the action of these hormones on the endometrium is prolonged and possibly carcinogenic. These workers labelled oestradiol with radioactive carbon - 14, and injected it into the gluteal muscles of women and measured the radioactivity of the urine excreted following the injection. Thin women excreted the injected radioactive carbon much sooner than fat women.

Assuming that a hyperoestrogen effect is carcinogenic, then obesity is indirectly associated with endometrial cancer.

Obesity is a disease of affluence, particularly poorly directed affluence. The improved socioeconomic status of the population as a whole has resulted in increased obesity and perhaps an increase in endometrial cancer.

E. Early Diagnosis

There have been no successful widescale screening programmes for the detection of asymptomatic endometrial carcinoma, and therefore premalignant conditions and preinvasive tumours are only detected by chance or if they cause symptoms which would lead to investigation. Unlike cervical cancer with cytology screening, the detection and treatment of these

preinvasive states is so infrequent that it has not influenced the incidence of endometrial cancer.

The Effect of Treatment on the Morbidity and Mortality from Endometrial Cancer

Effective treatment does not affect the incidence of endometrial cancer, but it will reduce the morbidity and mortality associated with the tumour.

Extended total hysterectomy and bilateral salpingo-oophorectomy removing a generous cuff of vagina, has been the basic treatment for the last twenty years. Table I shows the results of treatment of endometrial cancer with this operation alone. The cases operated on all had tumours which were confined to the uterus without serosal invasion (stage 1). The five year survival of all patients with endometrial cancer seen at the same time is also shown.

In the last twenty years, extended total hysterectomy has been supplemented by radiotherapy, given by a variety of techniques. This has produced a marked improvement in the survival of patients with early tumours (stage 1), as shown in table 2.

It must be noted that while a combination of surgery and radiotherapy has resulted in improved survival of patients with

Table 1. Results of Extended Total Hysterectomy for Carcinoma of the Endometrium

Author	Total No. of cases seen	No. of cases treated by hysterectomy	5 yr. survival rate of cases operated on (per cent)	5 yr. survival rate of all cases seen (per cent)
Bourne et al (1955)	209	142	74	59
Corscaden & Tovell (1954)	251	195	64	53
Roberts (1961)	223	127	72	64
Gusberg et al (1960)	360	121	66	54

Table 2. Results of Radiotherapy and Surgery for Carcinoma of the Endometrium

Author	Total No. of cases seen	No. of cases treated by surgery and radiotherapy	5 yr. survival rate of cases treated with surgery and radiotherapy (per cent)	5 yr. survival rate of all cases seen (per cent)
Miller (1960)	342	115	86	57
Montgomery et al (1960)	297	120	87	65

early tumours, the five year survival of all patients with endometrial cancer has not altered in the last 20 years. The five year survival of all tumours in the Western Region of Scotland (Leslie 1971) is 63 per cent, which is in agreement with the series described above. It is obvious that many tumours are still being diagnosed at a stage where they are too advanced to benefit from these improvements in treatment.

The patient, the doctor and the tumour are all responsible for this delay in diagnosis.

The patient may ignore suspicious symptoms but as mentioned previously, improved health education of the public is reducing this factor.

The doctor may delay in referring the patient with suspicious symptoms for specialist consultation, particularly perimenopausal women who may be tragically misinformed that irregular bleeding is to be expected at their age and that no further investigation is indicated. Delays of this kind are a result of malpraxis and it can only be hoped that they will no longer take place.

The failure of the tumour to produce symptoms for a considerable time and often after extensive invasion has taken place, is a most unfortunate characteristic of endometrial cancer. This delay is unavoidable.

Summary

The incidence of endometrial carcinoma is increasing. Advances in treatment can be expected to help only those patients who have tumours diagnosed at an early stage. As those tumours can be present and grow without symptoms, a reliable outpatient technique for screening the asymptomatic population at risk would be the only way to detect preinvasive and early invasive tumours. This would reduce the incidence, morbidity and mortality from invasive endometrial cancer.

CHARACTERISTICS OF ENDOMETRIAL CARCINOMA

Adenocarcinoma of the endometrium has been found to originate in every possible site within the uterine cavity. There is also no uniformity in the extent to which the endometrium is involved in the malignant change. In some cases, a small localised area of glandular epithelium can become malignant and remain confined there for a long time. These lesions may project above the endometrial surface but have limited lateral or downward spread. In other instances, several isolated malignant foci may develop, each separated by normal endometrium. As growth continues, these multiple foci may coalesce.

In contrast to single or multiple focal origin, there may be simultaneous involvement of all or the majority of the endometrial surface. This may occur without endometrial thickening or gross alteration of the surface. The factors governing the particular type of origin and therefore presentation of a tumour are not known.

There has been considerable argument over the years, concerning the type of endometrium in which carcinomatous change develops. No semblance of agreement has been reached and it suffices to say that while some patterns may be more frequently found in association with malignant change, it is impossible to prove a positive pattern of progression from one to the other. Malignant change has been demonstrated in association

with normal postmenopausal atrophic endometrium, with postmenopausal adenomatous hyperplasia and with postmenopausal oestrogen stimulated hyperplasia. In younger women who are still menstruating, there has been carcinoma associated with normal proliferative endometrium, with cystic glandular hyperplasia and even with normal secretory activity. The uninvolved endometrium frequently responds to the cyclical oestrogen and progesterone stimulation in the normal manner.

In view of the unpredictable origin and the variety of possible precursors of endometrial carcinoma, attempts to diagnose this tumour before symptoms develop have been singularly unsuccessful. It is obvious that a satisfactory method must sample the entire uterine cavity including the endocervical canal, unlike cervical cytology where the early malignant change is almost always confined to the mucocutaneous junction and can therefore be consistently sampled. Carcinoma in situ and severe dysplasia of the cervix are the well recognised precursors of invasive cancer of the cervix. As there is no clearly defined precursor of endometrial cancer, the earliest reliable diagnosis that can be hoped for is to detect actual malignant change but before it penetrates the endometrium or if focal before it spreads to involve adjacent healthy endometrium.

These principles must be borne in mind when considering

the value of screening methods for intrauterine malignancy and in particular when considering the principle of intrauterine sponge biopsy.

CHAPTER 3

PREVIOUS METHODS OF DETECTING EARLY INTRAUTERINE MALIGNANCY

Introduction

Curettage of the uterine cavity to remove potentially pathological tissue has been practised since pre-Christian times. The ancient Greeks used metal curettes for the evacuation of incomplete abortions (fig. 1). These curettes are strikingly similar to those in use to-day.

The cervix must either be open or be dilated to allow a curette to be passed into the uterus. Dilatation of the cervix requires anaesthesia.

Dilatation of the cervix, using graded dilators, and systematic curettage of the entire uterine cavity, under a general anaesthetic, is the only accepted technique of exploring the uterus and endocervical canal to detect intra-uterine cancer. It is standard gynaecological practice throughout the world, to perform a diagnostic curettage on all women presenting with abnormal uterine bleeding over the age of thirty five years, to detect or exclude intrauterine malignancy. If curettage does not detect a tumour, it is accepted that no tumour exists. It is recognised, however, that even careful curettage can miss an isolated tumour or polyp, but the operator's experience will reduce this risk to a minimum.

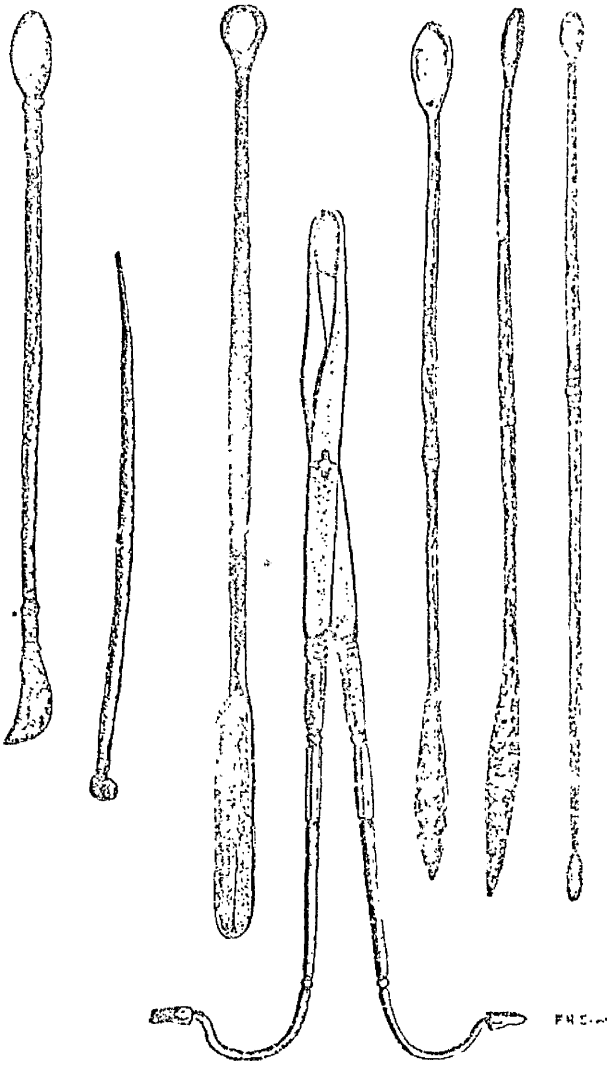


Fig. 1 GREEK ABORTION INSTRUMENTS.

circa 300 BC.

The accepted reliability of diagnostic curettage to detect cancer, enables it to be used as the standard against which all new methods of detecting intrauterine pathology can be compared. In the author's opinion any claims of cancer detection which are not the result of a correlated study with formal curettage are unacceptable.

Education of the public, particularly by the lay press, has resulted in a reduction in the time between the onset of suspicious gynaecological signs and symptoms and presentation for investigation. This has reduced the morbidity and mortality from cervical cancer by diagnosing invasive tumours at an earlier and more treatable stage. Unfortunately endometrial cancer can be present and undergo invasion for a considerable and unpredictable time before bleeding starts and little improvement in survival will result from earlier presentation with suspicious signs.

It must be realised that formal curettage of symptomatic women has failed to detect tumours at an earlier stage of invasion, and therefore has not reduced the morbidity and mortality from endometrial cancer in the last thirty years.

Although formal curettage is the absolute standard of diagnosis, it is not justified to subject asymptomatic women at risk to repeated general anaesthetics to permit curettage in the off chance of detecting an early cancer. This is contrary to the basic principle of asymptomatic cancer screening,

that the technique itself must not be a threat to the patient's wellbeing. The real risk of general anaesthesia, in each individual patient, is greater than the theoretical risk of that patient having an early tumour.

An ideal method of screening asymptomatic women for intra-uterine cancer must therefore be as reliable as formal curettage but must not require general anaesthesia. Various techniques have been tried to achieve this ideal method. These will be described in detail below.

Cytological Techniques

In 1927 Dudgeon and Patrick described "A New Method for the Rapid Microscopical Diagnosis of Tumours". They made smears from the cut surfaces of tumours and examined the cells. By this method they correctly correlated the cytological and histological findings in 106 out of 110 tumours. They were concerned with the potential of this idea, to give a rapid laboratory diagnosis on biopsy material, but in so doing they established the principle of exfoliative cytology; that examination of individual cells, shed by an epithelial surface, could give an impression of the histological structure of the parent tissue.

George Papanicolaou developed this idea and applied the principle to cells naturally shed from epithelial surfaces. He devised specific staining techniques to enable a more detailed

study of the characteristics of individual cells. The science of exfoliative cytology was born.

In 1941, Papanicolaou described the staining of cells aspirated from the posterior vaginal pool and showed that by this method early invasive and even preinvasive carcinoma of the cervix could be detected before clinical symptoms or signs develop. From this work the concept of examining asymptomatic women for cervical cancer developed. The initial results were most encouraging, but it soon became apparent that some tumours were being missed, and too many smears were unsuitable for cytological diagnosis. Ayre, in 1947 and 1948, showed that cells scraped directly from the cervix, before they were naturally exfoliated, were much fresher and allowed for a more accurate opinion to be given, with many fewer unsatisfactory smears. The widescale use of Ayre's spatula has resulted in more efficient screening programmes.

Boyes et al (1962) demonstrated the value of population screening to reduce the incidence of invasive cancer of the cervix. They examined approximately one third of the women in British Columbia, Canada, and treated all Stage 0 (carcinoma in situ) cervical lesions. Invasive cancer was reduced by 30.6 per cent between 1955 and 1960, its incidence falling from 28.4 per hundred thousand to 19.7. By 1963 it was 15 per hundred thousand. The success of cervical cancer screening

resulted in the World Health Organisation Cancer Committee stating in 1963 that "Cancer of the uterine cervix is now regarded as a preventable disease". This has proved to be over optimistic, and there has been recent controversy as to the absolute contribution of cytological screening to the reduction in cervical cancer, but the advantages of earlier detection of cervical cancer cannot be doubted.

Encouraged by the success of cervical cytology and the need for a technique for the early detection of endometrial cancer, it was logical to explore cytological methods first. It has been noted that endometrial cells were frequently seen in cytology smears for cervical cancer, particularly in posterior vaginal pool preparations. As malignant cells are more readily exfoliated than healthy cells, it was hoped that a specific study of endometrial cells in cervical smears might reliably detect intrauterine tumours. The feasibility of this idea was demonstrated by Wachtel and Plester in 1952. They claimed to have detected seven endometrial tumours out of 1853 vaginal pools smears examined. They did not correlate the smear results with formal curettage, except where there were suspicious symptoms or suspicious cells were seen. Only five of their seven claims were substantiated histologically. The remaining two patients were never curetted. This work demonstrated that it was possible to detect intrauterine tumours by vaginal cytology, but did not prove that it was in any way a reliable

method.

In 1959, Anderson described his experience of cervical cytology in Edinburgh. In his series he had twelve patients who were suspected of having endometrial cancer on clinical grounds. Four of these patients had cancer at curettage but had normal smears; four patients had malignant cells in their smears and subsequently were shown to have cancer; and the remaining four patients had malignant cells reported in the smears, but curettage failed to demonstrate cancer. Only patients suspected of having intrauterine pathology had the smear results correlated with formal curettage. Anderson concluded that while, like Wachtel, he could detect endometrial cancer in vaginal smears, this method had no practical application.

Following these disappointing studies with exfoliated cells aspirated from the vagina and cervix, it was felt that cells obtained directly from the endometrial cavity itself should improve the detection of intrauterine tumours.

Intrauterine endometrial cells can be obtained by a variety of methods, including aspiration, lavage, intrauterine brushes and tampons.

Papanicolaou and Marchetti, in 1943, described aspiration of cells from the uterus using a syringe and a glass rod. They were able to demonstrate the cytological patterns of endometrial cancer for the first time.

Since then there have been many studies using endometrial

cytology smears obtained by aspiration from the uterus. The great majority of these workers failed to correlate their results with formal curettage and therefore only confirmed that endometrial cancer could be detected by this method but were obviously unaware of tumours that were not. Correlated study did, however, show that endometrial cytology by direct aspiration was a much superior method of detecting intrauterine tumours, compared to vaginal methods.

Hecht, in 1956, reported on 901 smears taken from symptomatic women who subsequently underwent curettage. He used a Killian antrum cannula for aspiration. He detected 48 out of 52 endometrial carcinomas, 92.3 per cent accuracy but only 75.3 per cent of hyperplasias. He had 5 false positive smears.

Shanze, in 1957, presented a correlated series of 180 cases, 150 obtained by aspiration and 30 by a brush technique. He was less successful in detecting malignancy than Hecht. There were eight endometrial cancers and only five were detected on the smears. He also failed to demonstrate hyperplasia and detected only three out of fifteen cases. There were four false positive smears.

Rascoe (1963) described a very large correlated study of 6,416 women who had vaginal and endometrial smears and curettage. There were 103 endometrial tumours. 92.6 per cent were detected on endometrial smears and 74.2 per cent on cervical smears. The results, however, do not include 10 per cent of the tumours

where the smears were unsatisfactory. This factor greatly reduces the reliability of the technique.

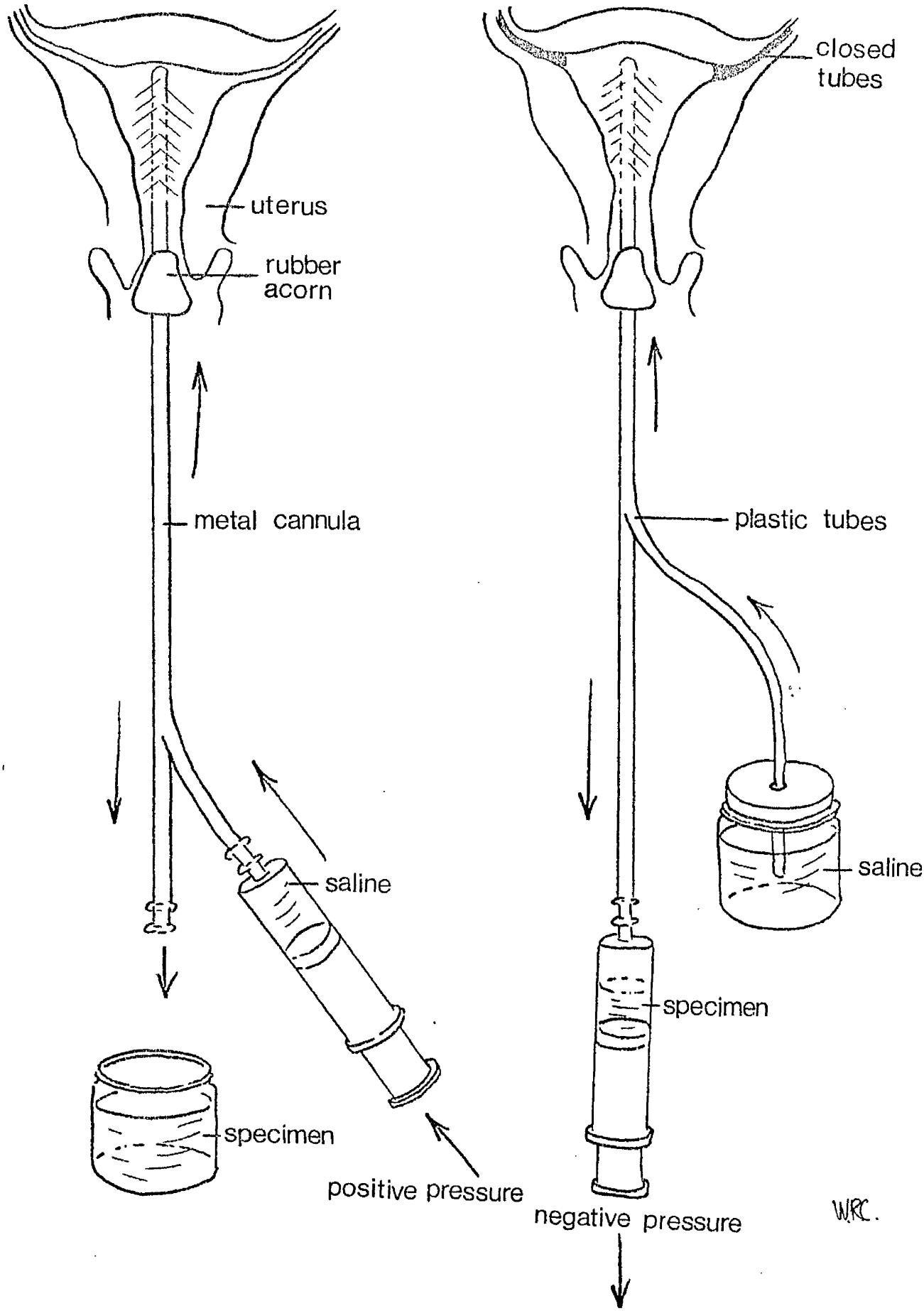
Ayre (1955) used an Adams endometrial brush, rotated in the uterus to collect cells, but did not demonstrate its ability to detect tumours. De Girolami, in 1966, described his experience with Ayre's brush and noted that relatively large groups of cells were obtained by this technique. He mixed the brushings with bovine thrombin and plasma and produced a clot containing all the tissue which could then be fixed in paraffin and sectioned like a routine histology specimen. The tissue is unfortunately very mixed up in the final slides and orientation is very difficult. He has not yet evaluated this promising refinement of the brush technique (De Girolami, 1971). Fox et al (1962) used a much larger and abrasive brush. They also obtained enough tissue to make a cell block preparation which gave a histological pattern in some cases. It was used in 27 cases already known to have endometrial cancer and malignant tissue was detected in the cell block in all cases. There has been no further work carried out with this large brush, apparently due to the difficulty of introducing it without an anaesthetic.

Lavage of the uterine cavity to obtain both cytological and histological material has a very serious objection. It may result in malignant cells being forced along the tubes and into the peritoneal cavity. It is well known from our experience of laparoscopic hydrotubation that fluid passes very freely along

patent tubes. Tumour cells may also be forced into a damaged blood vessel in the uterus and into the general circulation.

After many simple, but unsatisfactory attempts to inject saline into the uterus and collect the cell rich fluid from the vagina, Boutselis and Ullery (1962) described a cannula, made from a modified tubal insufflator, which allowed saline to shower the uterine cavity under pressure (fig. 2). This obtained washings containing cells and small pieces of endometrium which were passed through a millepore filter and a paraffin wax cell block made. This composite tissue was a major improvement on pure cell preparations. The objection to this positive pressure lavage system was too great, however, and its ability to detect malignancy was never tested. The technique was not developed.

Following on this principle, Dowling and Gravlee (1964) devised the Gravlee Jet Washer. It uses a double plastic tube inserted into the uterus and the cervix sealed by an acorn of rubber. To eliminate the risk of emboli along the tubes, a negative intrauterine pressure is created before sucking saline through the uterus. This theoretically closes the tubes before lavage begins. He has not satisfactorily proved the validity of this theory and in addition the risk of haematogenous emboli persists. This rather elaborate and expensive apparatus (fig. 2), obtains washings similar to those of Boutselis, which allow for a histological diagnosis to be made from a cell block



1. BOUTSELIS CANNULA.

2. GRAVLEE JET- WASHER.

in the majority of patients.

In 1969 Gravlee described nine years' experience with his method. He performed 1481 jet washings and correlated them with formal curettage done at the same time. There were 56 patients who had endometrial carcinoma diagnosed at curettage. Jet washings diagnosed 53 of these tumours. In the remaining three, preparations from the washings were unsatisfactory and no opinion was given. There were a total of 397 (27 per cent) of these unsatisfactory washings, although he explains that the number reduces considerably as the laboratory staff become familiar with the relatively complicated preparation of the cell blocks. There were 16 false positive washings. It is interesting that vaginal cytology performed on this same group of patients only detected 26 per cent of the endometrial tumours.

So-Bosita et al (1970) described their experience with the Gravlee Jet Washer. Their study, however, was very small and included only three endometrial carcinoma found at curettage. The washer detected all three tumours and in general, the cell blocks compared very favourably with the curettage material. They found tissue from two ovarian carcinoma in the washings, where the uterus was uninvolved. They considered that while the technique could be performed on outpatients, the tissue handling was too complicated to enable it to be applied as a screening technique.

At the Fourth International Congress of Cytology in London in 1971, Wachtel and Gordon from London, and Fortuno and Barbaro from Melbourne, Australia, described their experience with a simpler negative pressure lavage system, designed to obtain cytological tissue only. While the technique was attractive and in their skilled hands the malignancy pick up was good, they had not correlated all their results and it had failed to distinguish between hyperplastic and malignant tissue. This results in undesirably high false positive results.

Brunschwig and Papanicolaou (1957) reported on their experience of detecting endometrial tumours, using a Draghi vaginal tampon designed to take cervical smears. They left the tampon in the vagina overnight and made preparations from the cells trapped in the porous nylon cover of the tampon. They used it in 23 women already proven to have endometrial cancer. Despite the cytological skill of Papanicolaou himself, they only obtained an 87 per cent tumour detection. Unfortunately this deficiency prevented the development of what was potentially a very ingenious technique, which could have been easily applied to a population at risk.

As the diagnosis of endometrial carcinoma and its possible precursors demands careful assessment of glandular and stromal changes in addition to cellular changes, then purely cytological methods of screening for these tumours must have limited

potential. It has been seen that exceptional cytological skill coupled with efficient collection of good cytological material can reliably detect the majority of endometrial tumours. This level of skill is not universally available. In addition, all cytological methods failed to identify possible precancerous changes without relying on a high false positive rate, which results in unnecessary distress and risk to the patient before she is reassured, and extra work for the gynaecologists. For these reasons, cytological screening programmes for endometrial cancer have never been established on a significant scale.

The ability of the brush-thrombin and negative lavage methods to obtain tissue suitable for histology, overcomes these problems. The conglomeration of individual cells and tissue from any site in the uterus, all crowded together into a cell block preparation, allows obviously malignant tissue to be recognised, but, in the author's experience it makes more sophisticated histology very difficult. The complicated handling of the tissue has not yet been simplified, and as yet this has delayed the setting up of asymptomatic screening programmes with these techniques. Their value remains unproven.

Aspiration Curettage Techniques

When it was realised that a histological diagnosis of endometrial cancer was desirable and that cytological diagnosis had unsurmountable limitations, methods of outpatient direct

endometrial biopsy were reviewed. Their ability to detect malignancy was assessed and their suitability as screening techniques considered.

Small curettes that can be passed through an undilated cervix were developed to obtain single strips of endometrium to provide information on the hormone balance and the confirmation of ovulation, without resorting to formal curettage.

The earliest description of an outpatient aspiration curette was by Klinger and Burch in 1932. Palmer (1950), however, mentions that Howard Kelly advocated the aspiration of endometrium through a narrow tube around 1920. The original curette consisted of a flexible metal tube perforated at one end and attached to a suction source. This obtained small strips of tissue.

In 1935, Randall described a rigid metal tube with a sharp cutting tip for dislodging endometrium (fig. 3). This was five millimetres in diameter and could be bent to accommodate the uterine position. It is interesting that Randall stated that because of the small biopsy site, "this instrument is not used for diagnosis of malignant conditions".

In the same year, Novak independently described a similar curette (fig. 3). Both these instruments, although modified over the years, remain the accepted outpatient endometrial biopsy curettes.

Recently, a disposable aspiration curette (the Vibra

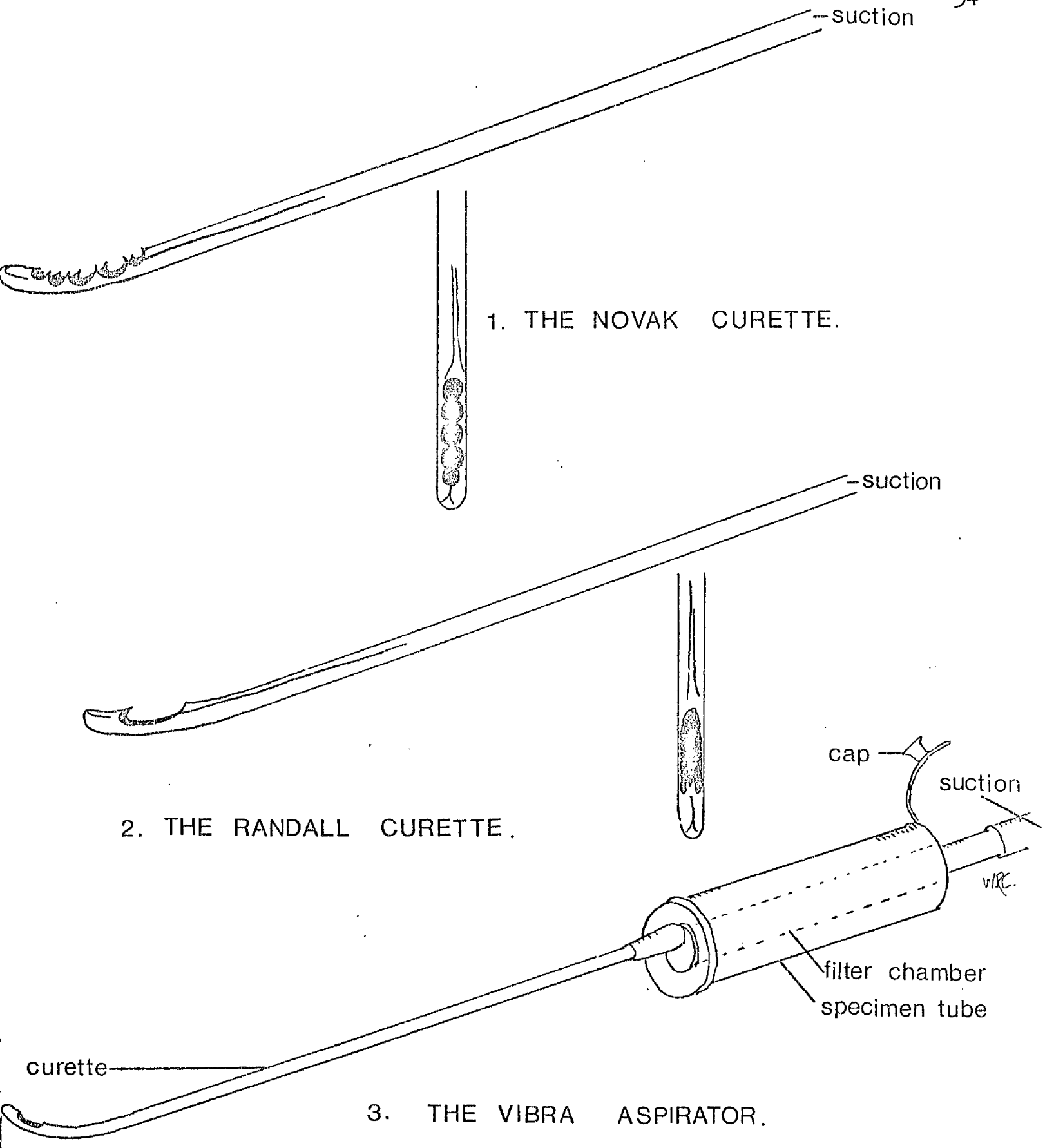


Fig. 3 ASPIRATION CURETTES.

aspirator) described by Jensen (1970) has been introduced. It incorporates a filter and collection chamber for the aspirated tissue (fig. 3). The diameter of the curette is three millimetres, being smaller than the Novak or Randall curettes. This was designed to replace formal diagnostic curettage and not as a specific screening technique.

Male metal catheters, antrum cannulae and a variety of metal tubes have all been used for aspiration curettage.

Before considering the application of these established techniques of aspiration biopsy to the detection of early endometrial cancer, it must be realised that the limited biopsy site of all small curettes is an obvious unavoidable disadvantage in the detection of isolated tumours. Repeated biopsies from the entire surface of the cavity will not be well tolerated by the unanaesthetised outpatient.

There have been many studies, both correlated and uncorrelated with formal curettage, which demonstrate that direct endometrial aspiration biopsy using both Randall and Novak curettes, can detect the majority of symptomatic endometrial tumours.

In 1956, Jordan et al, detected 23 out of 25 endometrial tumours. McGuire in 1962, using a Novak curette and taking eight strokes in each patient, detected 33 out of 38 tumours, in a well correlated series. Wildhack and Graham (1964) were less successful. Out of 131 endometrial cancers they had

negative biopsies in 17 patients.

Nugent, in 1963, demonstrated the theoretical point that the more extensive the biopsy technique the more reliable the tumour detection. In 166 cases he perfozmed a four quadrant technique and failed to detect three out of nine tumours. In the remaining 244 cases he employed a careful circumferential technique involving about ten strokes of the curette, and detected all seven tumours.

Hofmeister et al, in 1959, described their ten years experience of outpatient endometrial biopsy of both symptomatic and asymptomatic women. They employed a circumferential biopsy technique. In the first 240 patients they detected nine out of twelve known tumours. In the next 4320 patients there were 29 endometrial cancers. They detected 26 of these tumours. It is of particular interest that four of these tumours were asymptomatic when diagnosed. In 1964 they published a further 4402 cases in which they detected 24 out of 25 tumours and of these, six were asymptomatic. Although these are basically uncorrelated series, they illustrate the feasibility of detecting asymptomatic endometrial cancer by a screening technique.

In all these studies, hyperplastic endometrium was recognised easily on the histological biopsies and as a result, the false positive diagnosis rate was much less than with cytological methods.

The Vibra aspirator has not yet been applied to cancer

screening. Holt (1970) described experience with it and incidentally demonstrated the detection of one tumour. As it is technically a more efficient device than either the Novak or the Randall curettes, it may well be worthwhile to determine its value as a cancer screening procedure, although it still has the limited biopsy site of all small curettes and it will therefore be subject to the same limitations of accuracy.

These studies confirm the theoretical role that aspiration curettage might be expected to take in the screening for endometrial cancer. It can detect the majority of tumours, particularly if the growth involves much of the uterine cavity. It will fail to detect a number of tumours, presumably when they are small and isolated. The number of failures will be governed by the chance of biopsying a small area with a small instrument, but it will be reduced by extending the area explored.

The limiting factor for the suitability of aspiration curettage as a screening technique will be the patient's tolerance of repeated circumferential biopsies. In the hands of enthusiasts like Hofmeister, it has been shown to be a valuable technique, but the patient discomfort associated with adequate exploration has prevented it being established on a significant scale.

CHAPTER 4

THE PRINCIPLE OF THE INTRAUTERINE SPONGE BIOPSY TECHNIQUE

SPONGE BIOPSY OF THE CERVIX UTERI

In 1948, Gladstone first described the principle of scraping an epithelial surface with an abrasive sponge to obtain pieces of tissue suitable for histological examination. He wanted a simple outpatient procedure which would give more reliable information than cervical cytology and in some cases be an adequate alternative to formal surgical biopsy in patients with clinically suspicious cervices.

At that time exfoliative cervical cytology had not yet been recognised as a very valuable screening technique. This was due mainly to the persistent inaccuracy of the earlier vaginal pool sampling methods. Ayre, however, (1948) described better results from smears made after scraping cells off the cervix with a wooden spatula, rather than awaiting natural exfoliation. Despite this improvement, Gladstone was convinced that sponge biopsy would help bridge the gap between cytological and formal histological methods.

Sponge was selected for this purpose because of its unique ability to absorb into its substance any epithelial tissue that it scrapes off. It can then retain the biopsies despite immersion in fixative. The sponge containing the

tissue is soft enough to be fixed, stained and sectioned as a routine histological specimen.

Gladstone described his experience of sponge biopsies of suspicious cervices, using cubes of gelatin foam sponge. He demonstrated a reasonable correlation between the histological findings of the sponge biopsies and the formal surgical biopsies. He compared these results with vaginal pool exfoliative cytology and concluded that his new method was superior to exfoliative cytology because it provided fresh cells and allowed study of their arrangement and relationship to each other. He had achieved a histological diagnosis without admitting the patient to hospital and submitting her to the risks of anaesthesia and a surgical operation.

Gladstone experimented with various sponge materials before selecting gelatin foam. In particular he tried natural and cellulose sponges. They had poor abrasive properties, irregular pore size and presented problems to routine processing. Unfortunately the gelatin sponge proved to be very friable, it was difficult to handle and was not particularly abrasive. Probably as a result of this, there was surprisingly little interest in this promising technique following the initial work.

In 1954, however, Faulds in Carlisle took up the search for a more suitable material for the biopsy technique. He considered that the ideal sponge had to be firm, abrasive, of

fine regular texture, not friable and able to be processed in a routine "Histokine" system and be easily cut by a standard microtome. Synthetic polyvinyl chloride sponge satisfied these criteria. This sponge is marketed as a bath sponge in sealed polythene envelopes, in a soft moist state. When it is exposed to the air it dries out and becomes very hard and abrasive and can be cut into any required shape.

Faulds reported his ten year experience of cervical sponge biopsies in 1964. The biopsies were obtained by rubbing the cervix with wedges of polyvinyl sponge held in a volsellum forceps. He was interested in using this as a method of making cytological smears and only processed the sponges if the smears were unsatisfactory due to blood or infection or if they showed atypical cells. He showed that the sponge made as satisfactory smears as Ayre's spatulae, and that the subsequent histological examination of tissue in the sponges enabled him to eliminate the majority of the "doubtful" smear results, with an obvious clinical advantage. Unfortunately he did not present correlated results of sponge biopsy, cytological smears and formal surgical biopsy. He again stressed the advantages of a histological diagnosis and noted that this brought the interpretation of cervical screening techniques within the sphere of routine pathologists without specialised cytological training.

As a result of Fauld's work, polyvinyl sponge biopsy of the cervix was introduced into the Department of Gynaecology of the Western Infirmary, Glasgow in 1964, as the method of taking cervical smears in all women attending the outpatient clinic and the technique of eliminating the "doubtful" smear results. Watson reported on their findings in the first 1029 sponge biopsies in 1966. Adequate tissue for a histological diagnosis was obtained in 983 of these cases. One hundred and sixty contained full thickness epithelium and twenty two of these showed malignant or premalignant changes. The remaining 138 cases included dysplasias, chronic endocervicitis, atrophic vaginitis and normal tissue. When these findings were correlated with surgical biopsy specimens and cytological smears, it showed that sponge biopsy made possible the detection of one case of invasive carcinoma of the cervix, where the smear was unsatisfactory and made a definite diagnosis of one case of adenocarcinoma, six cases of carcinoma in situ and six cases of severe dysplasia, where the smears were merely suspicious or normal. The sponges also corrected the diagnosis in two false positive smears, the benign nature being confirmed at surgical biopsy. These impressive results were adequate confirmation of Fauld's impression that cervical sponge biopsy taken in parallel with exfoliative cytology resulted in an improved accuracy of screening for cervical cancer and in particular reduced the number of recalls and repeat smears, so worrying to

the patients. This technique is now established in many centres.

INTRAUTERINE SPONGE BIOPSY TECHNIQUE

Exfoliative cytology of the endometrium and endocervix from vaginal pool, cervical or intrauterine samples is an unsatisfactory method of detecting intrauterine cancer. As cervical sponge biopsy had been shown to improve the accuracy and value of cervical cytology, it was reasonable to expect a similar improvement if the same technique could be applied to the endometrium and endocervix. Endometrial cytological techniques failed to reliably detect malignancy because the high mitotic activity of normal endometrium made the study of individual cells unrepresentative of the basic histological pattern. The tissue suitable for histological examination that is offered by the sponge technique should, therefore, result in a major improvement in the diagnostic accuracy. Watson achieved a 95.6 per cent adequate biopsy rate from cervical sponge biopsies. The endometrium and endocervix are much softer epithelial surfaces than the stratified squamous epithelium of the cervix. The abrasive sponge could be expected to scrape off more tissue, more consistently, so making the histological diagnosis even easier.

Gladstone had postulated that it might be possible to detect endometrial cancer by the sponge technique, but he did

not try to obtain biopsies from within the uterus.

Unfortunately there were many problems to be overcome before obtaining intrauterine sponge biopsies as an outpatient screening procedure, similar to cervical biopsy. It required the introduction of a relatively large piece of polyvinyl sponge through the undilated cervix of an unanaesthetised woman. The sponge could not become wet as it was passed into the uterine cavity or it would lose its abrasiveness and fail to biopsy. It required to be placed in the uterine fundus to ensure obtaining biopsies from the entire uterine cavity and endocervix as it was removed from the uterus. This multiple random sampling is necessary to detect isolated malignant lesions. The biopsy sponge had to be sterile.

In 1968, the author devised a technique which overcame these problems and forms the basis of this thesis (Chatfield and Watson, 1970). It employs the principle of the introduction and removal of intrauterine contraceptive devices. The relatively large, but flexible contraceptive device is drawn into a thin plastic introducer tube. The tube is passed gently through the undilated cervix. Once inside the uterine cavity the coil is expelled from the introducer with a plunger, where it occupies the entire uterine cavity. The device is removed by simply pulling it out of the uterus against the natural resistance of the cervix and the resiliance of the preshaped coil. This procedure is now practised on an endemic

scale and causes minimal or no discomfort to the patient (fig. 4).

Intrauterine sponge biopsy is achieved by replacing the coil with a strip of polyvinyl sponge bent into a "V" shape. The apex of the "V" is attached to the plunger of a standard coil introducer and the sponge is withdrawn into the introducer tube. It is passed through the cervix into the uterus, like the coil. The sponge is expelled into the fundus, the introducer removed and the sponge briskly withdrawn from the uterus (fig. 5). This ensures that the abrasive sponge is rubbed over the entire uterine cavity and the leading surface of the "V" specifically biopsies the endocervix. This system obtains the random biopsies for histological examination, necessary to detect intrauterine cancer in any site.

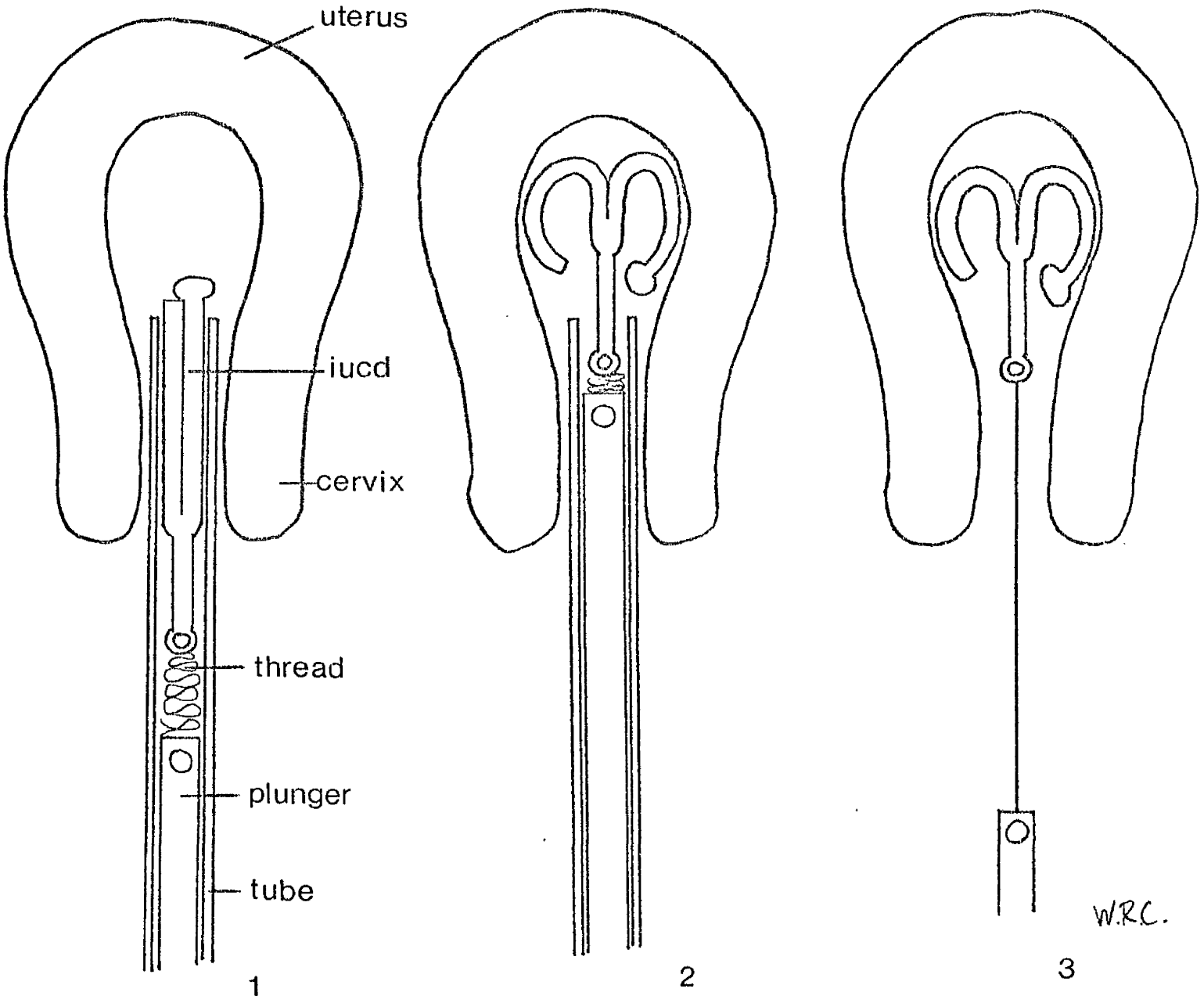


Fig. 4 THE PRINCIPLE OF THE I.U.C.D.

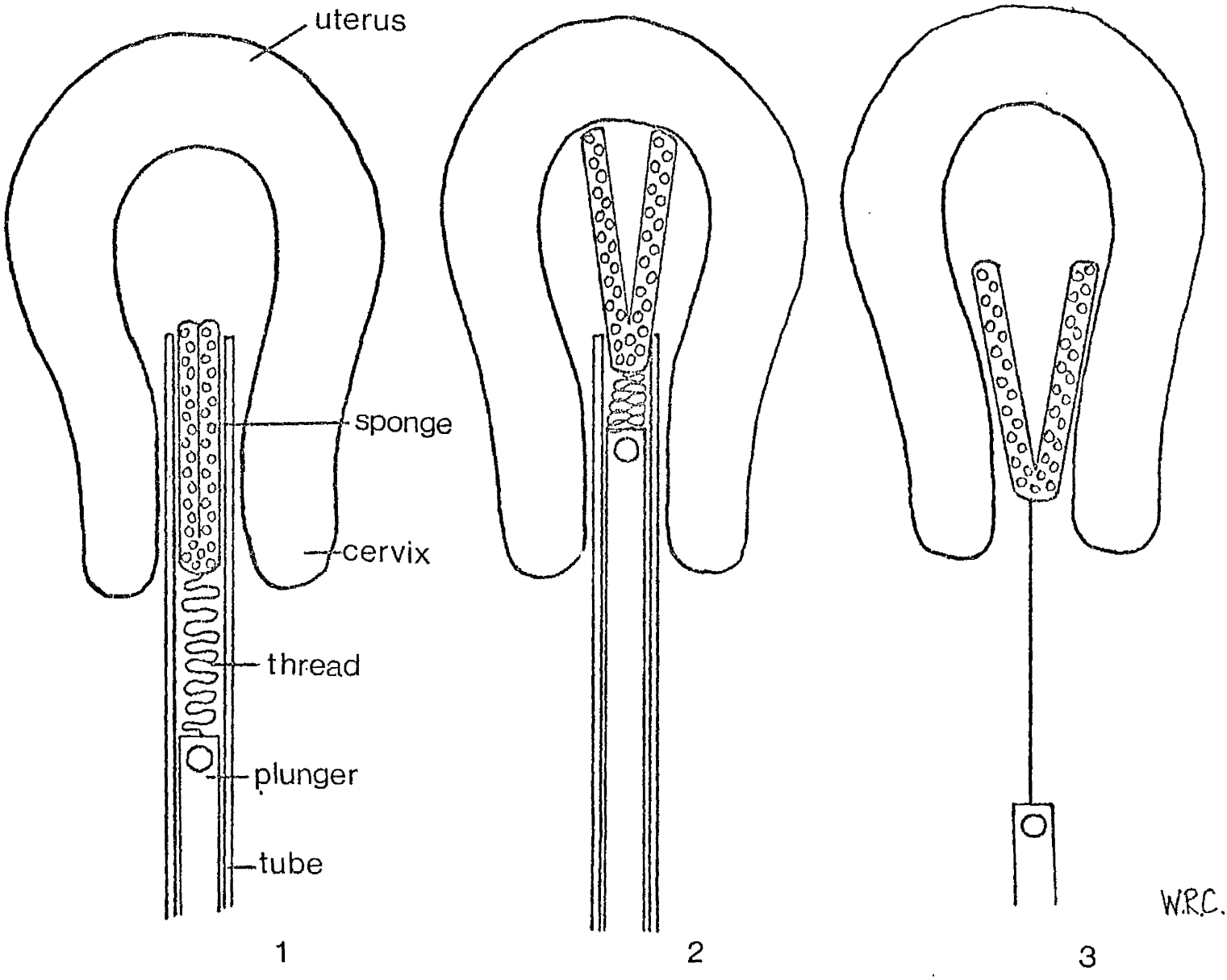


Fig. 5 THE PRINCIPLE OF INTRAUTERINE SPONGE BIOPSY

CHAPTER 5

MATERIALS AND METHODS

A. MANUFACTURE OF THE INTRAUTERINE BIOPSY SPONGE DEVICE

After experimenting with numerous makes of polyvinyl chloride sponges, it was concluded that the Ramer Baby sponge used by Faulds was the most satisfactory for obtaining intrauterine biopsies. This particular sponge material is manufactured for domestic purposes by the Ramer Chemical Company Ltd., 147 Frimley Road, Camberly and is marketed by T. Christy and Company Ltd. It has a small pore size of remarkably uniform diameter, which enables thin strips of the sponge to be cut without them breaking at the site of large pores, as was the problem with all other sponges tried. They can be obtained in various colours. Faulds considered that colour was significant to the appearance on the final stained section. He advised blue sponges which he redyed with 1 per cent aqueous Alcian blue. In our experience, the original colour of the sponge or the subsequent dying to blue, made no difference to the appearance of the sponge on the final sections. The colour was therefore considered to be of no importance.

The Ramer sponge is marketed wrapped in sealed polythene envelopes. This keeps it soft and pliable while damp, so increasing its commercial appeal. When it is exposed to the

air, however, it becomes so hard and abrasive that it can be easily cut with a razor blade into any required shape or size. For our purposes the sponge was exposed in a warm dry atmosphere for 48 hours, after which time it was suitably hard and dry. The outside rind of the circular sponge is then cut off with a razor blade and used for making intrauterine sponges. The inner core is initially discarded but is subsequently cut into cubes to take cervical sponge biopsies. The rind is cut into thin strips, 6 centimetres long, by 3 millimetres wide by 2 millimetres thick. The rind of the sponge is smooth and provides a firm backing for the strip of sponge. The strip is then bent into the shape of the letter "V" with the smooth rind innermost and the abrasive surface outside.

After preparing the biopsy sponge, its introducer is assembled. This consists of a clear plastic tube twenty centimetres long and four millimetres in diameter, through which can pass a solid plastic plunger, twenty two centimetres long and three millimetres in diameter, which has a hole pierced in it at one end. This arrangement is identical to the introducer supplied for the insertion of the Saf-T-coil contraceptive device, manufactured by the London Rubber Company. (Fig. 6 shows a scale drawing of the component parts).

The biopsy sponge is connected to the hole in the plunger by a soft plastic thread four inches long, attached to the apex

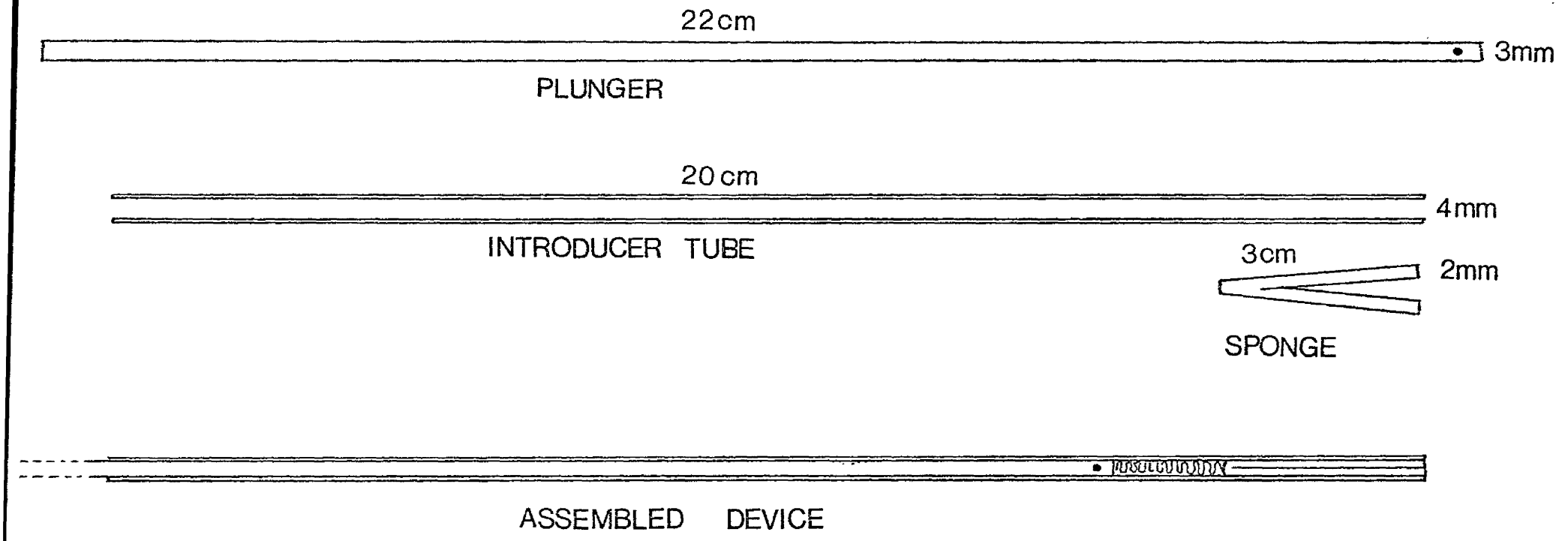


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Fig.6 SCALE DRAWING OF SPONGE BIOPSY DEVICE

of the "V". The sponge and the plunger is then withdrawn into the introducer tube (Fig. 7).

The completed device is parked and sealed in double polythene and sterilised.

The Sterilisation of the Biopsy Devices

The sponges used in this thesis were sterilised with Ethylene oxide gas, in the Victoria Infirmary Model Steriliser. This method is particularly suitable for sterilising small numbers of devices like the sponges which cannot withstand heat or moisture. The sterilisation was performed by the Regional Central Sterile Supply Department at Knightswood Hospital, Glasgow.

Commercially manufactured devices would be sterilised with gamma radiation. This is the ideal method for prepacked plastic products. It is, however, very expensive, unless a large number of devices are sterilised to reduce the individual cost.

Improvements in the Manufacture of the Intrauterine Biopsy Sponge

The biopsy sponges used throughout this thesis were manufactured by the author as described previously. From the experience gained the following modifications have been made and have been incorporated into the biopsy sponge now being manufactured commercially.

Thread Cut Through

While the thickened rim of the sponge resisted the threads

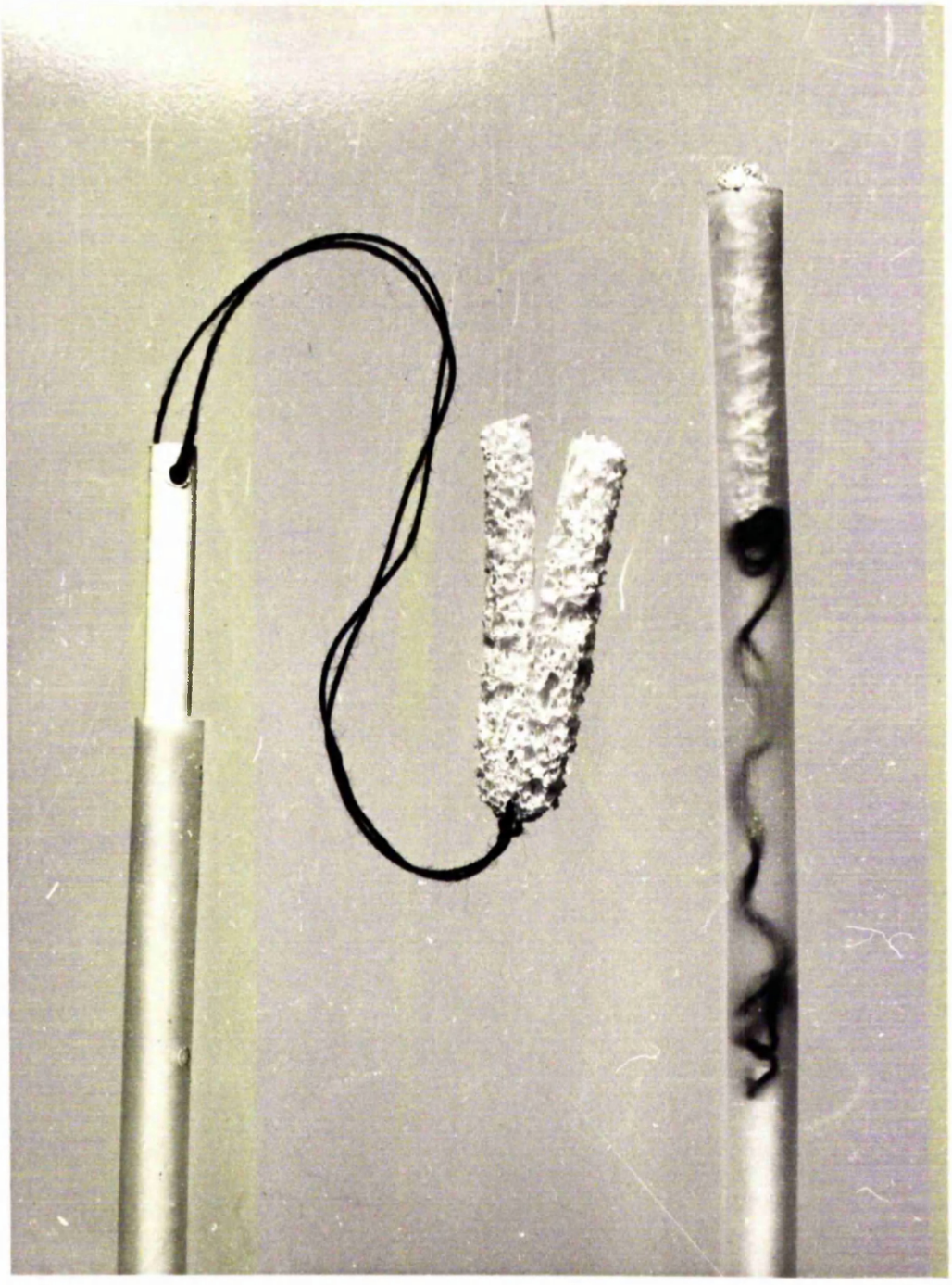


Fig.7 Assembled Intrauterine Sponge Biopsy Device

- as used throughout the study.

cutting through the sponge when traction was applied, it did not entirely prevent it. This problem was overcome by backing the "V" of the sponge with a small strip of zinc oxide tape. The adhesive was soluble in formalin and the tape floated off the sponge during transport to the laboratory in formol saline. No cutting through has been experienced since making this simple modification. The plastic backing strip described below replaces the tape and also eliminates the problem.

Contact Between the Sponge and the Endometrium

The normal uterine cavity is a potential cavity with the anterior and posterior walls lying in apposition. In a pathologically enlarged or distorted cavity, the walls may lie apart and the sponge may make inadequate contact with the endometrium to obtain a biopsy. The natural resiliance of the sponge material ensures that the "V" of the sponge opens up as it is ejected from the introducer into the uterine cavity. This resiliance is decreased, however, if the sponge is left unduly long in the introducer.

Despite those theoretical problems of unresiliant sponges in distorted cavities, adequate biopsies of endometrium were obtained in 97.8 per cent of patients biopsied with unmodified sponges.

The sponge-endometrial contact could be improved and therefore better biopsies obtained if the entire "V" of the

sponge was backed with a thin strip of plastic, which had been bent into an exaggerated "V" and the plastic processed to establish a "memory" of this position. This would ensure that the sponge opens up in the cavity, particularly into the cornu and it would resist withdrawal. This modification has been incorporated in the commercial sponge and the quality of the biopsy has been improved.

Ease of Insertion Into the Uterus

Despite exerting gentle traction on the cervix to straighten out the angle of flexion and anteversion of the uterus, occasional difficulty was encountered in negotiating the angle with the device, which is a straight tube. The cervical canals of some elderly and nulliparous patients were also too narrow to allow instrumentation and the rough leading edge of the plastic introducer tended to catch in those narrow cervical canals.

To overcome these problems the following modifications have been made, with good effect.

a) The plastic plunger has been replaced by a rigid metal one and this lends stability to the device and prevents bending when an obstruction is encountered.

b) The plunger and introducer have been bent 7 centimetres from the end to an angle of 120 degrees. The device now resembles a uterine sound.

c) The plastic introducer tube has been made thinner with

an outside diameter of 3.5 millimetres, although the inside diameter remains unchanged.

d) The leading edge of the introducer has been rounded off and smoothed, reducing any friction between it and the cervical canal.

Prolonging the Abrasive Property of the Sponge

Polyvinyl sponge is very abrasive when dry, but it is also extremely hygroscopic and becoming wet it expands and loses all abrasive properties. For this reason, the sponge is protected from cervical and vaginal secretions by the plastic introducer and it is vital that it is withdrawn from the uterus as soon as possible after its release into the uterine cavity, where the uterine secretions will wet it.

To try to prolong its abrasive property in utero, the sponge was coated with plastic spray lacquers of different types, including domestic hair spray. These lacquers had the desired effect of preventing absorption of water and keeping the sponge abrasive in the uterine cavity. In preventing the water being absorbed, however, it also prevented the abrased tissue being absorbed into the substance of the wet sponge, so that the tissue floated off the surface of the sponge when immersed in fixative, so destroying the principle of sponge biopsy. After experimenting with a variety of types and concentrations of lacquers, it was decided that the hygroscopic

action, after obtaining the biopsy with the dry sponge, is an integral part of the technique and further attempts were abandoned.

Fig. 8 shows the modified intrauterine biopsy sponge.

Fig. 9 shows details of the actual sponge, showing pre set plastic backing.

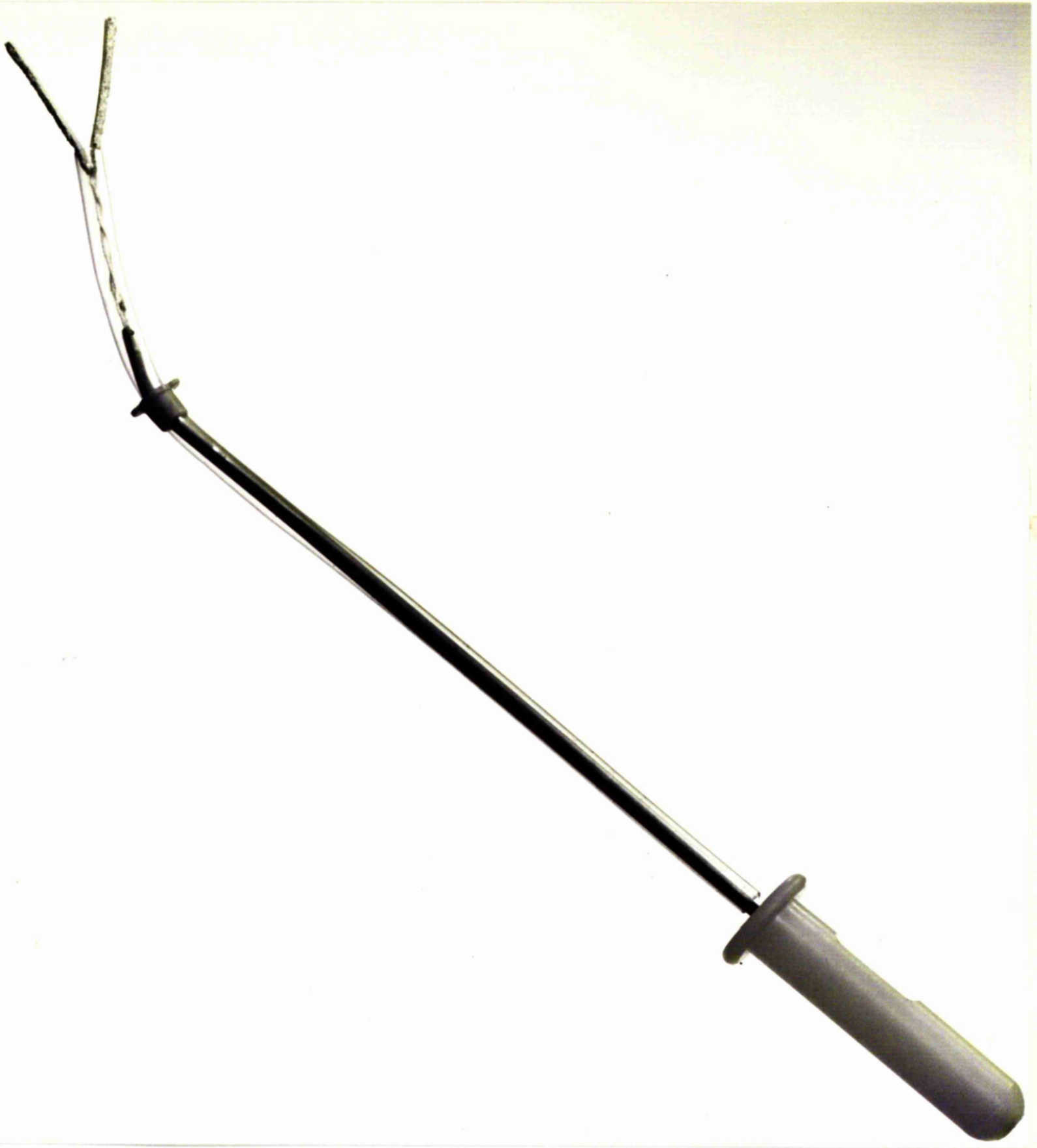


Fig. 8 Modified Sponge Biopsy Device - Prototype actual size.

Fig. 9 Detail of the Modified Sponge.

B. PROCEDURE FOR OBTAINING INTRAUTERINE BIOPSIES

The patient is prepared as for a routine gynaecological examination.

The Position of the Patient

The selection of a particular position for examination will depend on the routine practice of the gynaecologist and the facilities at his disposal. It is necessary to achieve good visualisation of the cervix and adequate retraction of the vaginal walls to allow easy instrumentation of the uterus.

(a) The Lithotomy Position

This position is employed for all minor gynaecological procedures performed in theatre under general anaesthesia in the United Kingdom. It is also the routine position for the outpatient gynaecological examination of conscious patients in North America, Scandinavia and Europe. The patient's legs are supported by stirrups and her buttocks rest on the edge of the table. The cervix is exposed using Sim's duck billed speculum which encourages the vagina to balloon out, as air is allowed to pass in. Although the majority of British patients are at present unfamiliar with this method of gynaecological examination, and may find it inelegant and perhaps initially embarrassing, with a comfortable table and stirrups and careful concern taken for the patient's modesty, this position offers by far the best exposure of the cervix and room for manipulation.

In our opinion it is the most satisfactory position of the patient for the atraumatic intrauterine sponge biopsy.

(b) The Dorsal Position

This position is used in most gynaecological outpatient departments in the United Kingdom for routine vaginal examination and for obtaining cervical cytology smears. The cervix is visualised through a bivalve Cusco's speculum. This position has the advantage of familiarity to the majority of British patients and therefore leads to less embarrassment. In our experience, however, the fixed aperture of the Cusco's speculum makes instrumentation through it difficult. While it is adequate for the introduction of the majority of biopsy sponges or contraceptive devices, if any difficulty is encountered with the minority, it can lead to unnecessary problems and discomfort to the patient.

(c) Sim's Left Lateral Position

This position was described by Marian Sims, to facilitate the passage of his duck billed speculum which allows air to enter and balloon out the vagina. It permits excellent visualisation of the anterior vaginal wall and was described to facilitate the assessment and repair of vesicovaginal fistulae. It achieves maximum modesty for the patient, but in our experience the disadvantage of having to work at the

awkward angulation of the vagina and uterine cavity, makes instrumentation of the uterine cavity difficult and perhaps hazardous.

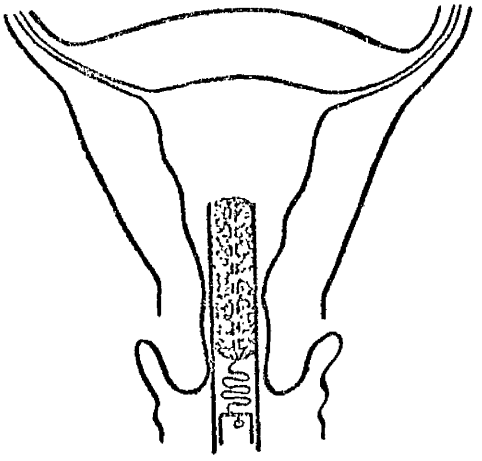
Having positioned the patient, preferably in the lithotomy position, the cervix is exposed. A routine cervical cytology smear is taken, preferably with a wedge of polyvinyl sponge (Faulds, 1964). A digital vaginal examination is made to exclude the presence of pelvic pathology and to determine the size and in particular the position of the uterus. The uterine cavity is sounded and its length and direction carefully noted.

The introducer containing the biopsy sponge is passed through the sponge to a precalculated distance two centimetres short of the uterine fundus. The plunger is pressed home, and the sponge is expelled into the uterine cavity. The introducer is removed and the plunger with the sponge attached is immediately, slowly but steadily, removed from the uterus.

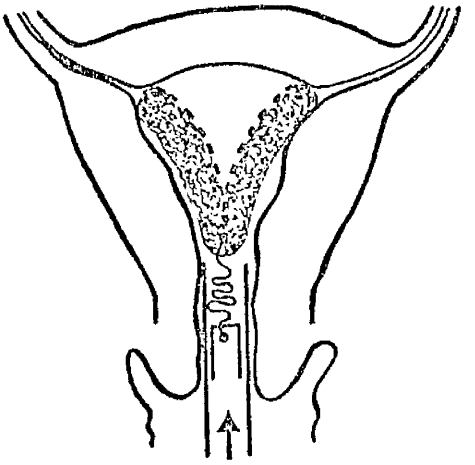
After removing the sponge from the uterus, the string is cut and the entire sponge dropped into a container of formol saline for transport to the laboratory.

The method of taking intrauterine sponge biopsies is illustrated in Fig. 10.

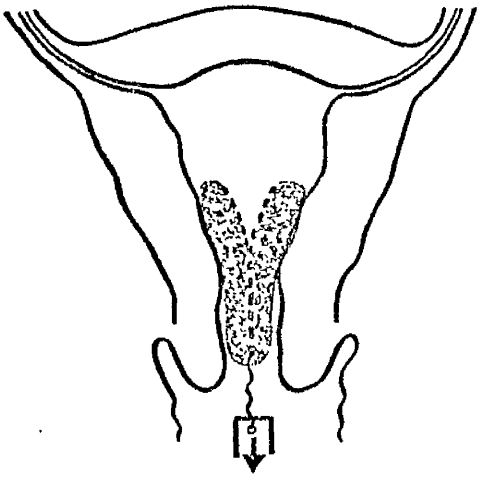
Fig.10 METHOD OF OBTAINING SPONGE BIOPSIES.



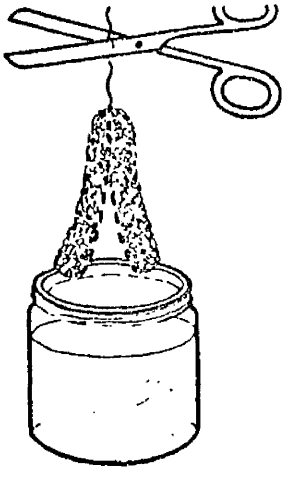
1. Pass the introducer through the cervix, 2cm. short of the uterine fundus.



2. Press the plunger and expel the sponge into the uterine cavity.



3. Briskly withdraw the sponge from the uterus.



4. Cut the thread, and drop the sponge into fixative.

If difficulty is encountered in introducing the sponge, the anterior lip of the cervix is grasped with a single toothed volsellum forceps, or Littlewood's tissue forceps, which produces only minimal discomfort to the patient. This steadies the cervix and slight traction helps to correct the natural flexion and anteversion of the uterus and eliminates the angle that the introducer must negotiate and which is responsible for the majority of hold ups.

The procedure of intrauterine sponge biopsy, if performed by an operator experienced in minor gynaecological surgery and in particular with the insertion of intrauterine contraceptive devices, should produce only slight discomfort to the patient. This is confirmed by the wide international experience gained with a variety of intrauterine contraceptive devices, which is an identical procedure.

It is recognised that any instrumentation of the cervical canal can result in a sudden vasovagal collapse of the patient. In the author's experience of over 500 sponge biopsies, this complication was not encountered.

The risk of perforating the uterus with the introducer exists. As with the introduction of the contraceptive device, careful assessment of the position of the uterus and direction and length sounding of the cavity will minimise this problem. As the sponge is withdrawn immediately after insertion, the

problems of uterine perforation, if it occurred, would be less. We have not been aware of perforating any uteri with the sponge biopsy technique.

As with the insertion of intrauterine contraceptive devices, some patients will be encountered with particularly tight cervical canals which do not permit easy instrumentation. These patients are therefore unsuitable for intrauterine sponge biopsy unless they can tolerate gentle dilatation of the cervical canal to permit the passage of the introducer. In our initial experience, using the less sophisticated home-made biopsy sponges, with the majority of patients in the less satisfactory dorsal position, approximately 10 per cent of patients were unsuitable for biopsy. It is hoped to reduce this figure considerably by using the commercially manufactured sponge which has been specifically modified to ease introduction (see page 55). The initial experience with the new sponge has been most encouraging.

C. THE LABORATORY PROCESSING OF INTRAUTERINE SPONGE BIOPSIES

Tissue Fixative

Formal saline is the standard tissue fixative used in most pathology laboratories. It is, therefore, satisfactory for the endometrial biopsies and our experience has shown that it has no adverse reaction with the sponge tissue.

Experiments were made using formal corrosive as a fixative, to try to achieve clearer nuclear definition. It produced the desired effect on the nuclei but unfortunately the fixative reacted adversely with the sponge tissue, and this resulted in the slides being covered by a peculiar black deposit. The advantage was obscured by the disadvantage and it was felt that formal saline was a satisfactory fixative.

Unfixed sponge biopsies were processed by the Cryostat system of frozen sectioning. The sponge tissue became very hard on freezing and it made cutting of sections impossible. This process was abandoned.

Transport to the Laboratory

The established practice of sending pathology specimens to the laboratory in glass containers containing fixative, is simple and adequate for transporting sponge biopsies.

To set up a large cancer screening programme involving sponge biopsies, where many doctors are taking biopsies over a

wide area, it will be necessary to send the specimens to the laboratory by post. It was a similar situation which resulted in Cytofix sprays being introduced to fix cervical cytology smears and allow them to be posted.

To overcome this problem, it was found that it is sufficient to dip the sponge in fixative and allow it to become saturated. It is then removed and sealed in a small polythene envelope. There is sufficient fixative contained in the sponge and surrounding the biopsies to preserve the tissue during transport to the laboratory.

The Processing of Sponge Biopsies

The original intrauterine sponge biopsies were processed prior to sectioning, by the rapid double embedding method for tissue described by Russell (1956). This involved a 47 hour cycle in which the calibrated disc of the processing machine (Histokinette - Histokine) is changed in mid-cycle. This double embedding method allows these blocks to be cut with the same ease as lung tissue, and was used when the technique was first described by Chatfield and Watson (1970).

After gaining considerable experience with the sponges used in this series, Mr. Kerr of the Pathology Department of the Victoria Infirmary has modified Russell's method. The 47 hour cycle proved to be inconvenient because the process could be commenced only on alternate days and involved the daily changing

of timing discs and in view of the permeability of the sponge it was considered that a more rapid cycle could be evolved.

Using the same processing machine it has been found that the time can be reduced from 47 to 22 hours, without any accruing disadvantages. Indeed, sponges so treated sectioned with the same facility as those processed by the longer method and certainly better than many routine tissue blocks. The details of this method are described below.

Method

After fixation with formal saline the sponges are processed as follows :-

80 per cent industrial methylated spirit 74 O.P.	½ hour
8 per cent phenol in industrial methylated spirit 74 O.P.	1 hour
Industrial methylated spirit 74 O.P. I	1 hour
Industrial methylated spirit 74 O.P. II	1 hour
Industrial methylated spirit 74 O.P. and amyl acetate, equal parts.	
Amylacetate I	1 hour
Amylacetate II	2 hours
1 per cent low viscosity nitrocellulose in methyl benzoate I	5 hours
1 per cent low viscosity nitrocellulose in methyl benzoate II	7 hours
Benzene	½ hour

Paraffin wax 56°C. M.P. I	1½ hours
Paraffin wax 56°C. M.P. II	1 hour

This is followed by vacuum embedding for one hour at 60°C under a negative pressure of -400 mm. of mercury. After processing, the sponges are bisected through the apex and blocked with the two lateral surfaces side by side to ensure maximum tissue concentration on the same histological section. It was found advantageous to cool the paraffin blocks with ice prior to sectioning.

Examples of the sections obtained are shown later.

D. EXAMPLES OF HISTOLOGICAL SECTIONS OF TISSUE OBTAINED BY INTRAUTERINE SPONGE BIOPSY

The following photomicrographs illustrate examples of endometrial, endocervical and ectocervical biopsies obtained by intrauterine sponge biopsy. Malignent, premalignant and hyperplastic conditions of both the endometrium and the cervix are more readily sampled than healthy tissue.

The sponge maitrix is identified as a purple amorphous structure in the sections. All the sections are stained with haematoxylin and eosin.

Fig. 11 Proliferative Endometrium.

Fig. 12 Secretory Endometrium.

Fig. 13 High Power Detail of Secretory Endometrium.

Fig. 14 Cystic Glandular Hyperplasia of Endometrium.

Fig. 15 Endometrial Carcinoma.

Fig. 16 High Power Detail of an Endometrial Carcinoma.

Fig. 17 Polypoidal Endocervicitis.

Fig. 18 Carcinoma in Situ of the Ectocervix.

Fig. 19 Invasive Carcinoma of the Ectocervix.

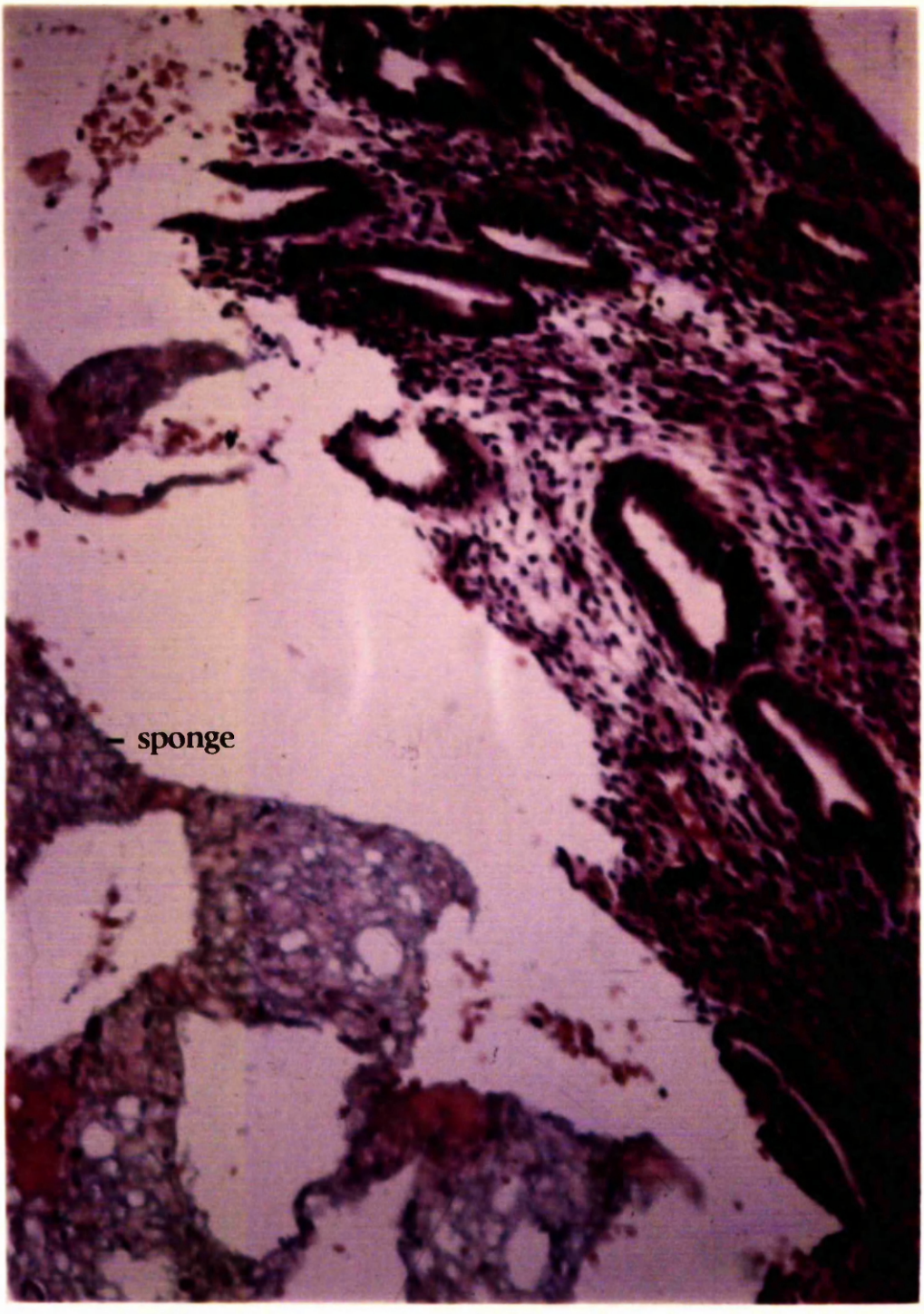


Fig. 11 Proliferative Endometrium. LP.

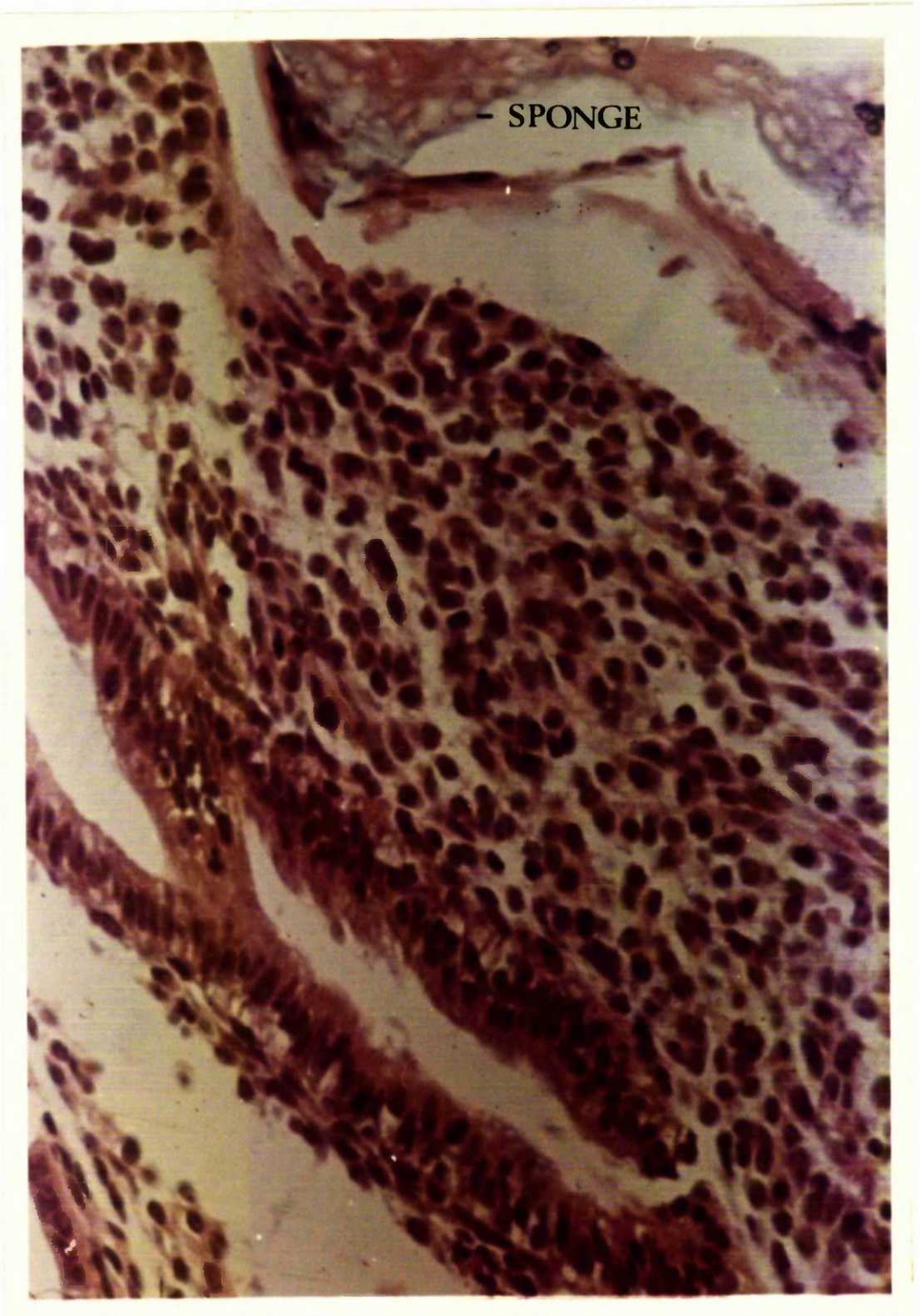


Fig. 12 Secretory Endometrium. LP.

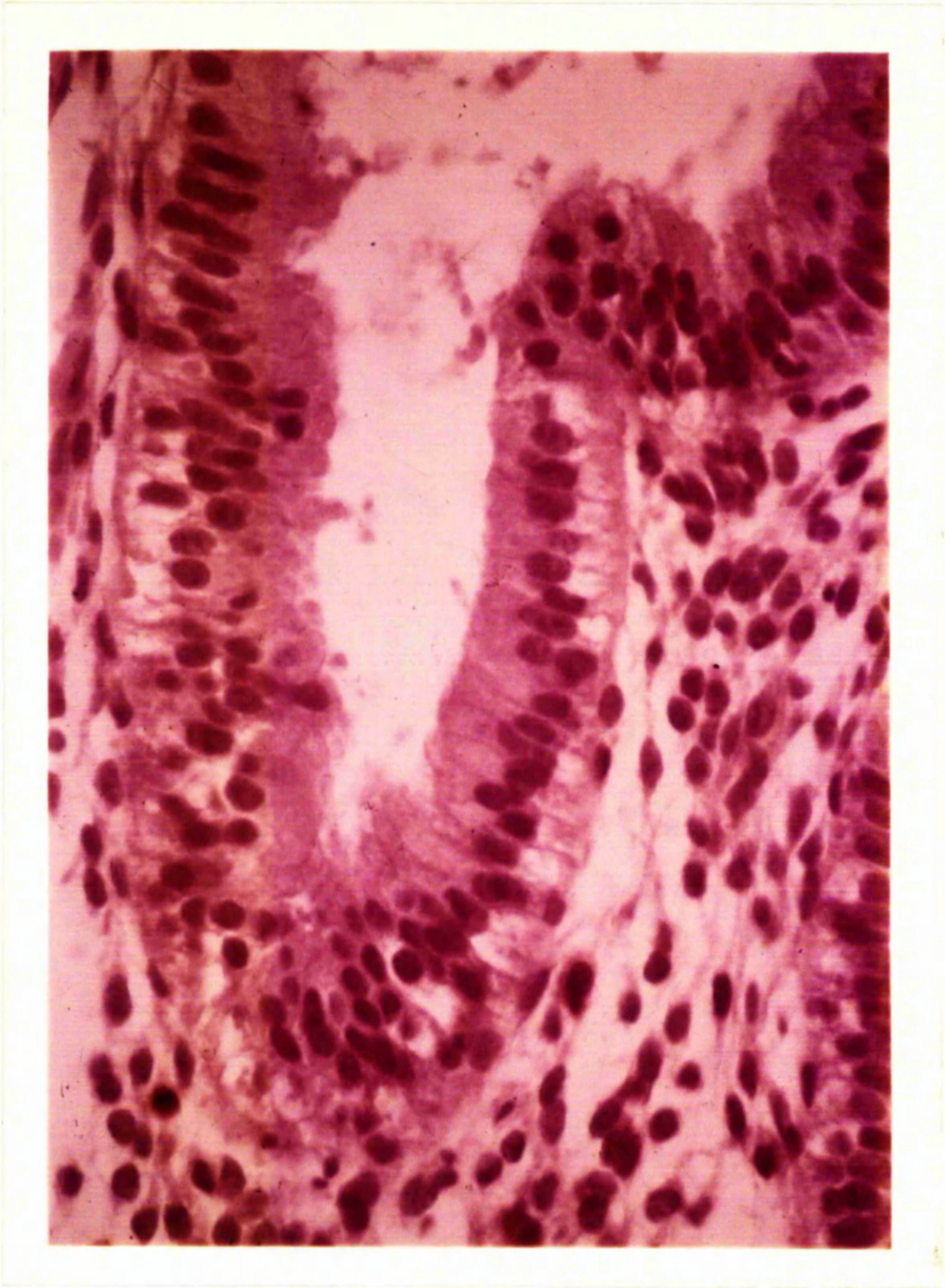


Fig. 13 Secretory Endometrium - HP. Detail.

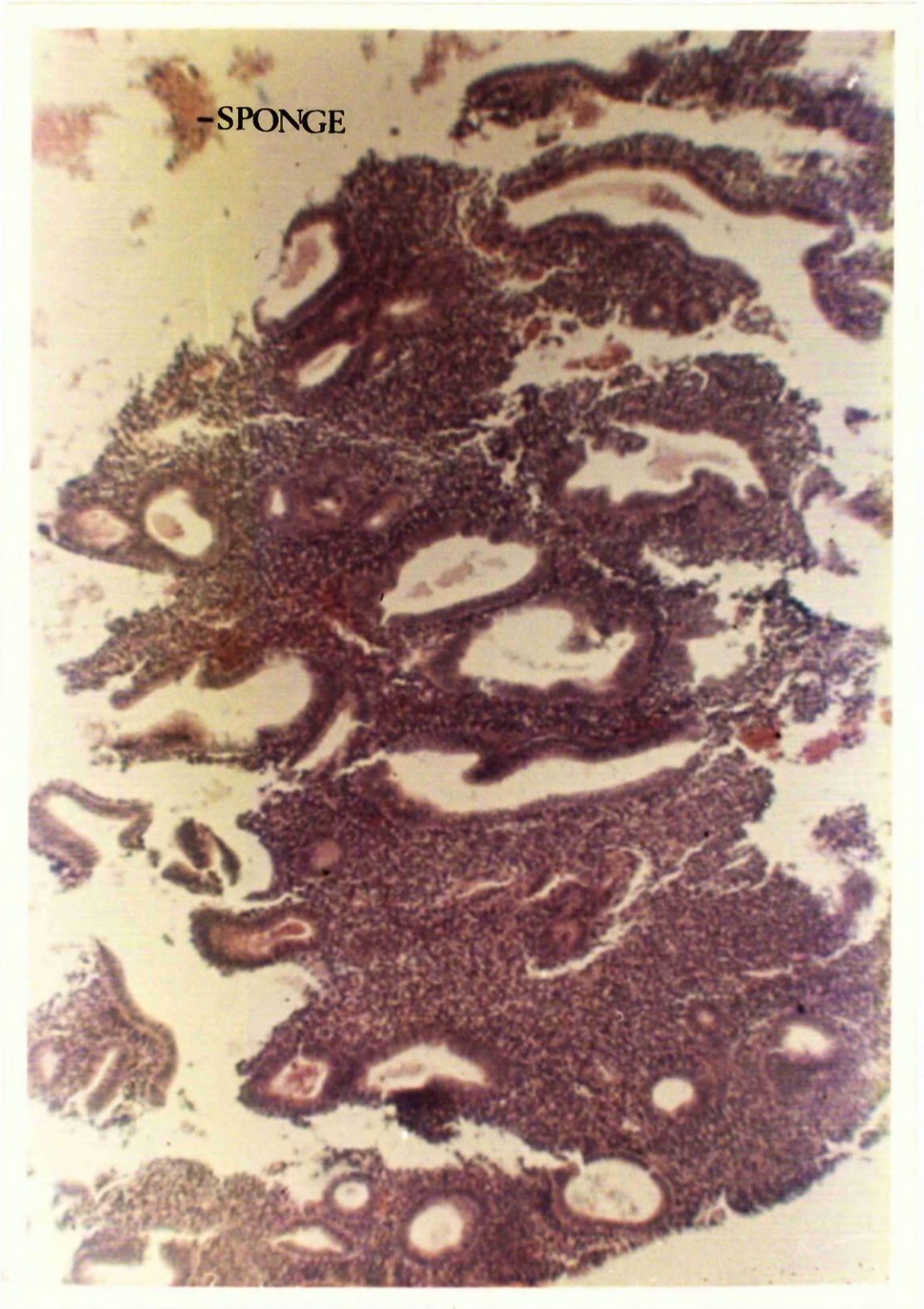


Fig. 14 Cystic Glandular Hyperplasia LP.

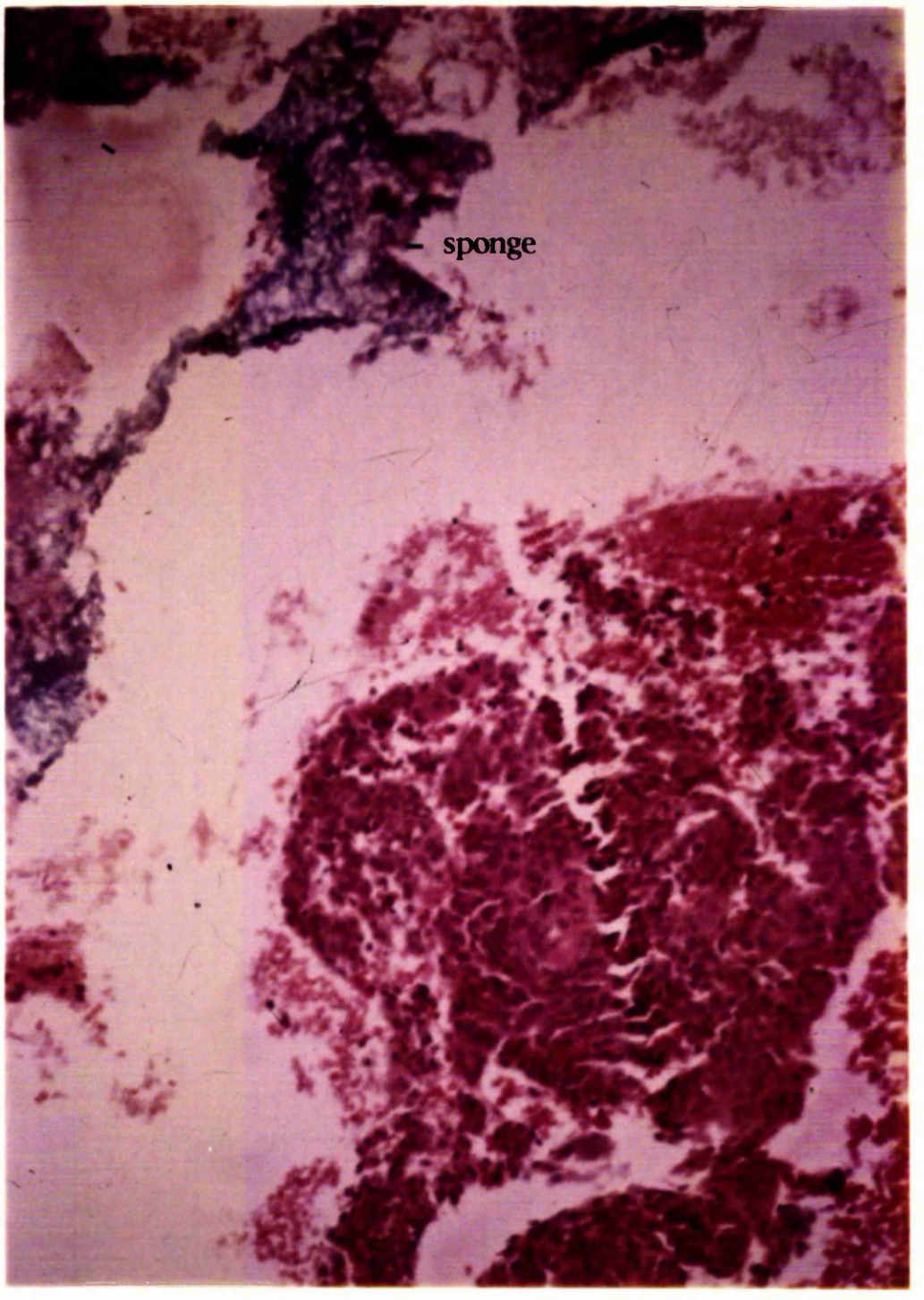


Fig. 15 Endometrial Carcinoma. LP.

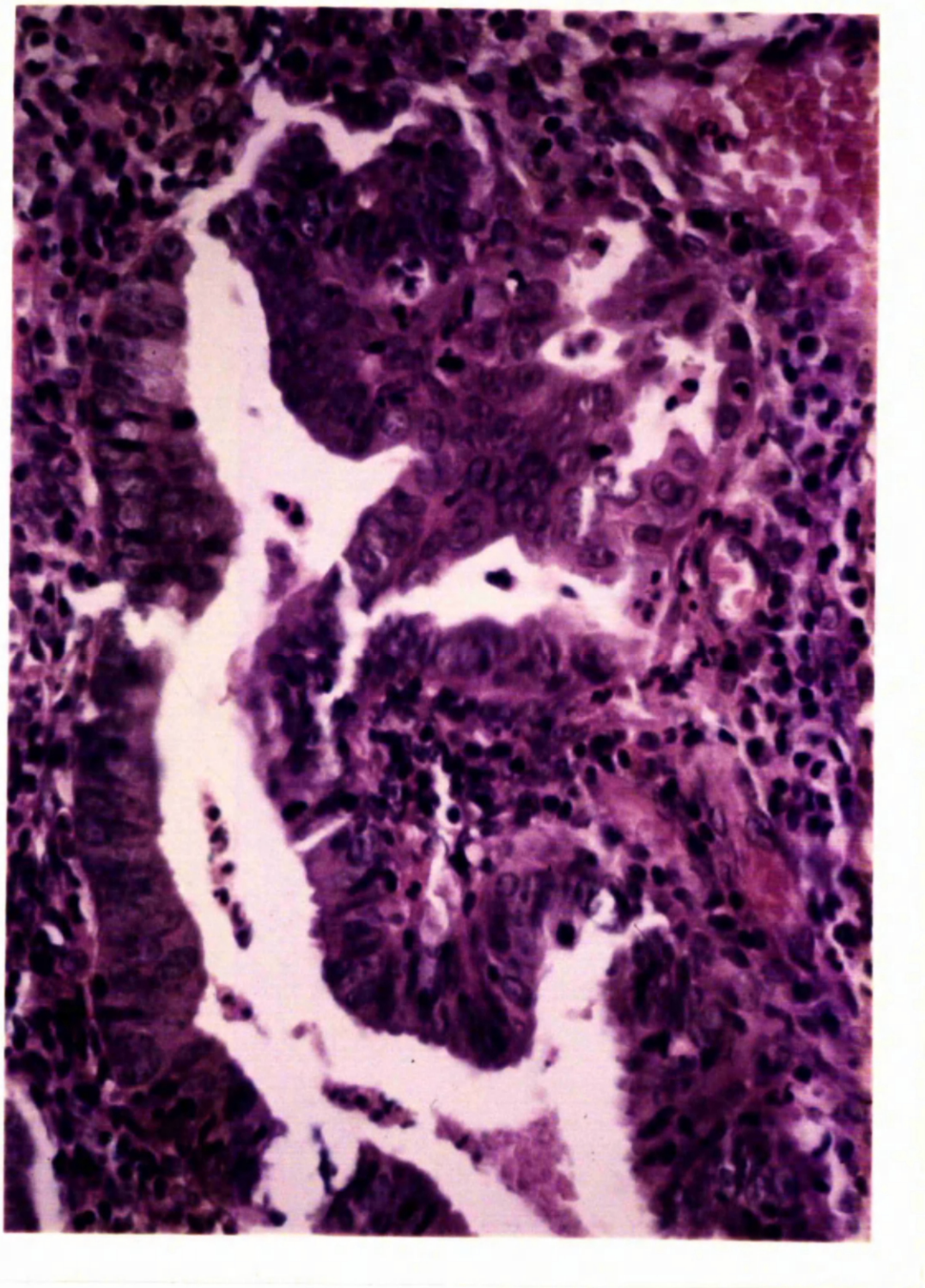


Fig. 16 Endometrial Carcinoma - HP. Detail.

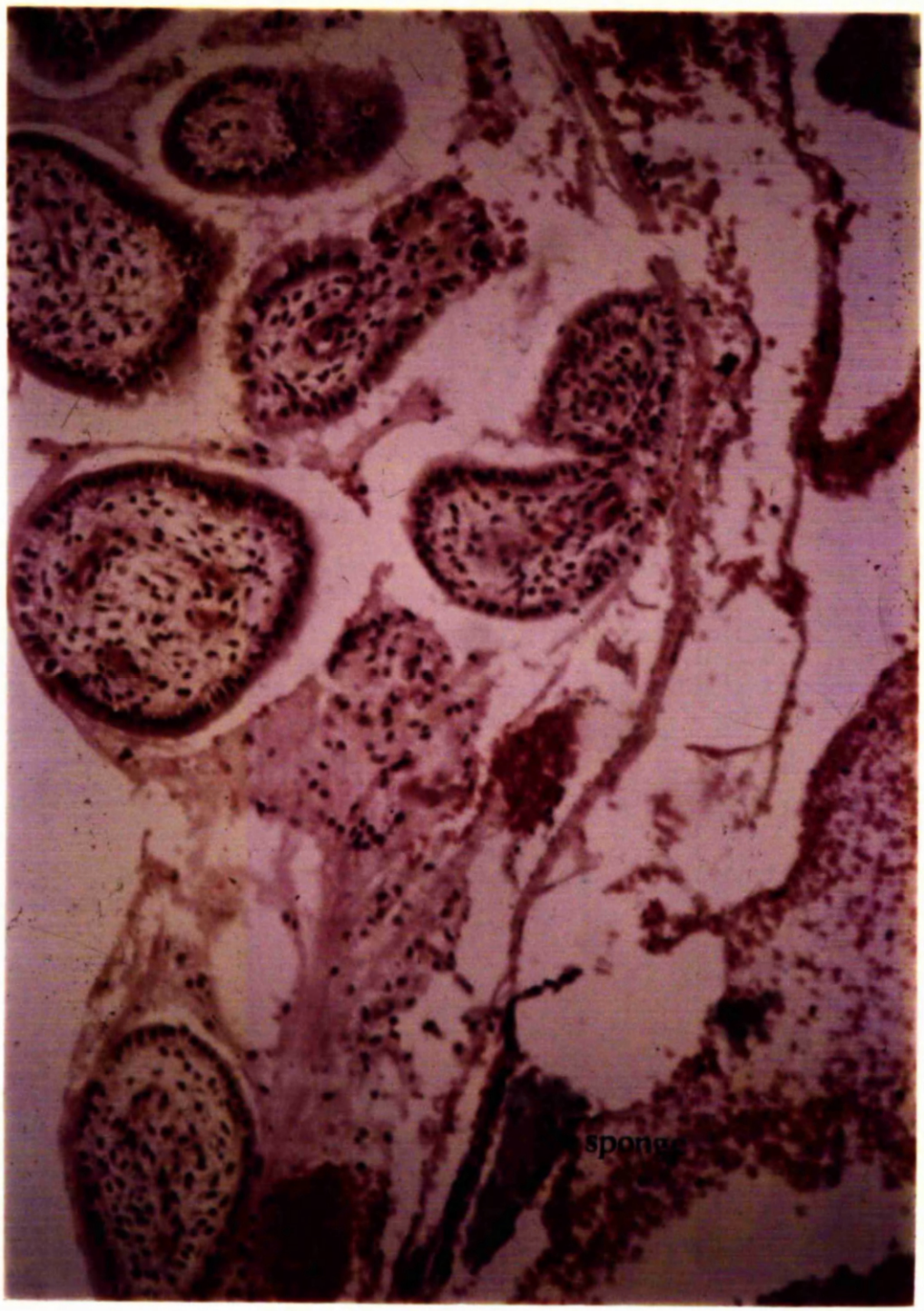


Fig. 17 Polypoidal Endocervicitis. HP.

from the leading 'V' of sponge.

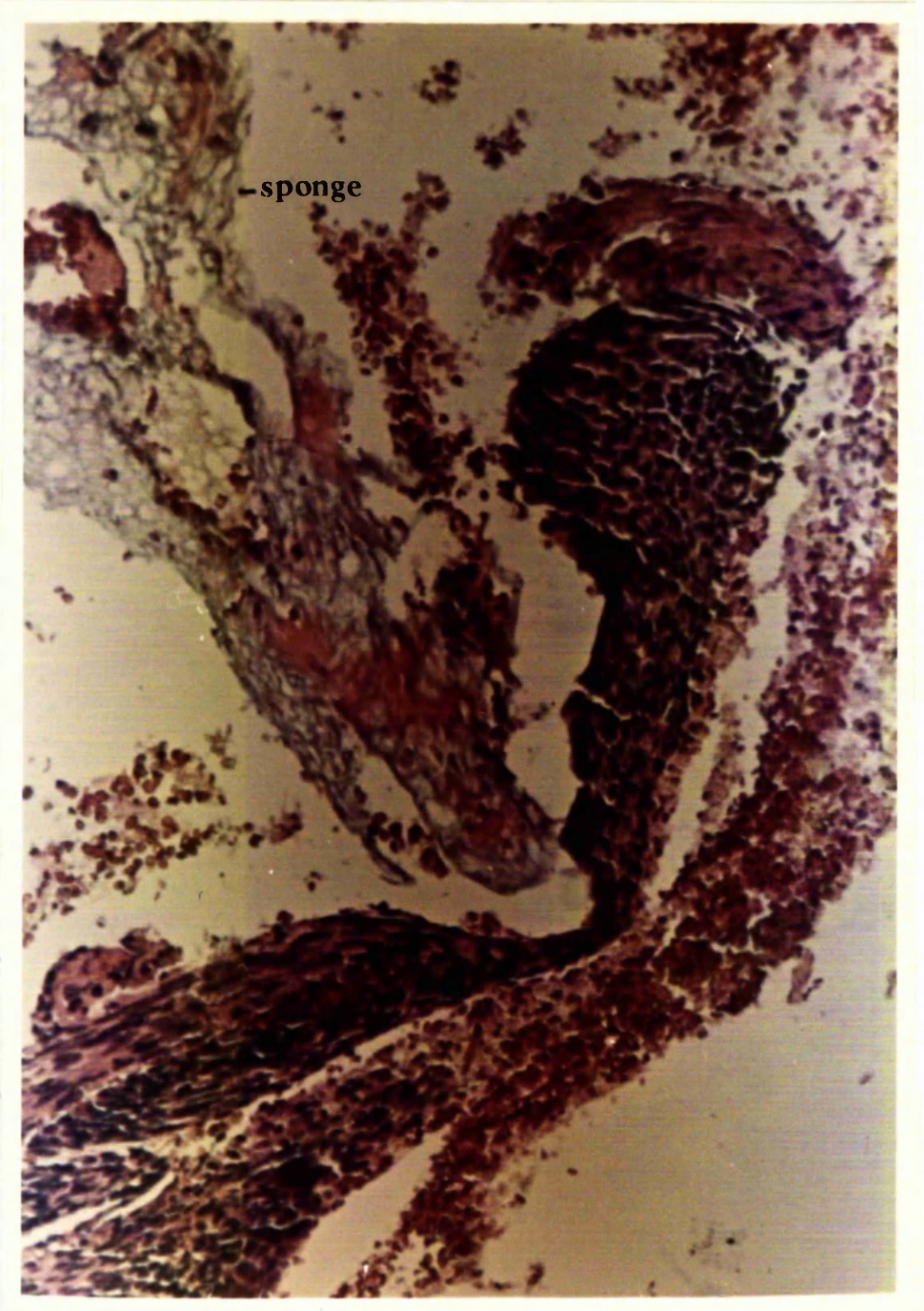


Fig. 18 Carcinoma in Situ of the Ectocervix.

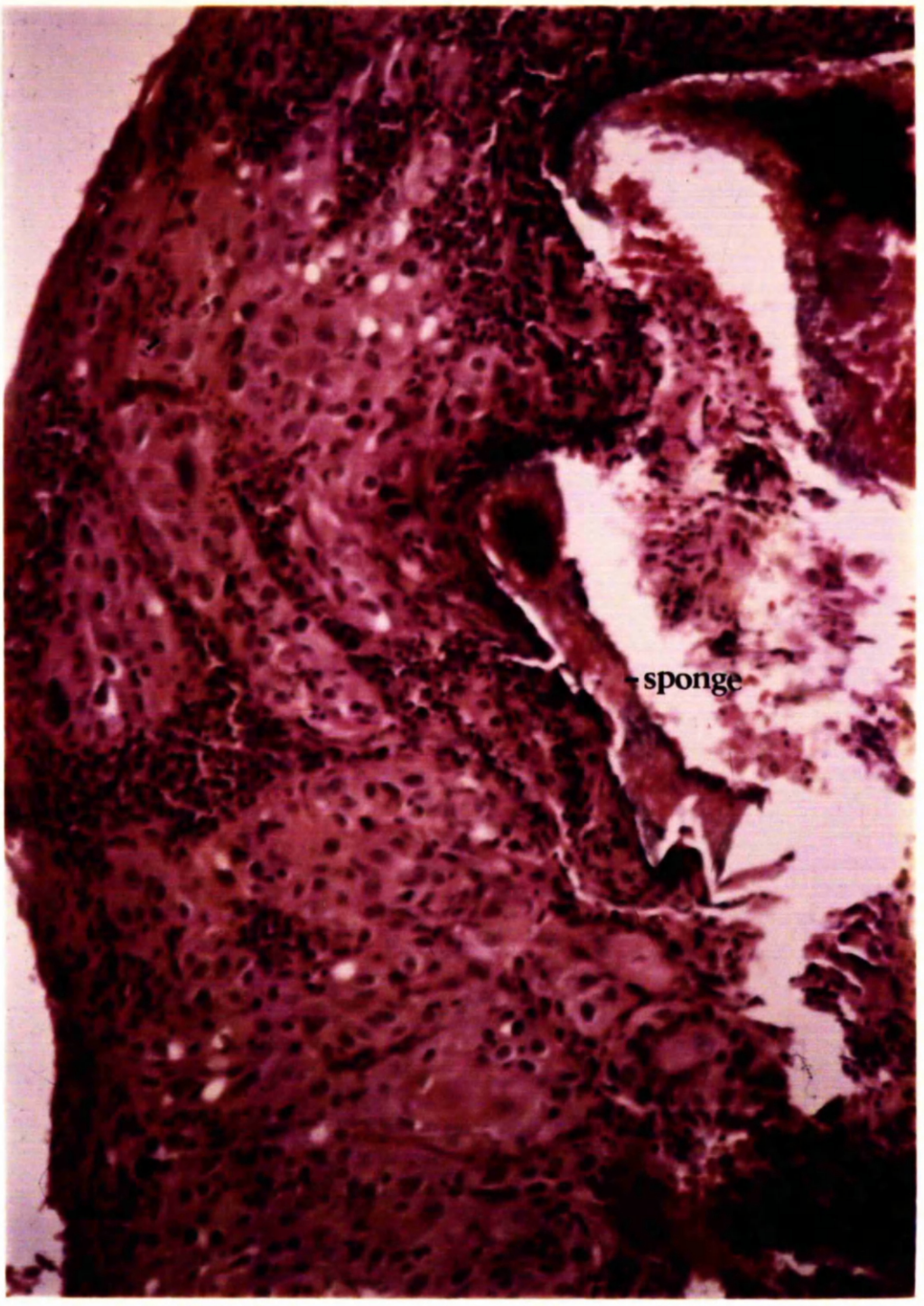


Fig. 19 Invasive Carcinoma of the Cervix.

CHAPTER 6

THE EVALUATION OF THE ABILITY OF INTRAUTERINE SPONGE BIOPSY TECHNIQUE TO DETECT INTRAUTERINE MALIGNANCY

Introduction

Intrauterine sponge biopsy has been designed to detect intrauterine pathology in asymptomatic women in the perimenopausal and postmenopausal age groups, as an outpatient procedure, without anaesthesia.

To assess its ability to effectively perform this function, the results of sponge biopsy must be compared with those of formal dilatation of the cervix and curettage of the entire uterine cavity under general anaesthesia, which is at present the only accepted method of diagnosing intrauterine pathology.

To test adequately the technique's ability to find pathology, the majority of the patients selected for biopsy had symptoms suggestive of intrauterine disease, namely abnormal uterine bleeding and who were subsequently being admitted in the near future for formal diagnostic curettage. The remainder of the patients had normal menstrual histories for their age and could therefore be considered as "asymptomatic" for the purposes of the study. These women had sponge biopsies taken, in the knowledge that they would subsequently be admitted for the treatment or investigation of other gynaecological problems, at

which time a formal diagnostic curettage could be carried out to correlate the findings with the sponge biopsy results. This group of patients included women admitted for the repair of genital prolapse, for diagnostic laparoscopy, for laparoscopic sterilisation and for the treatment of simple cervical pathology. All patients studied were over thirty five, as malignant and premalignant endometrial conditions are extremely rare under this age. Routine cervical cytological smears were taken prior to sponge biopsy.

Before establishing the diagnostic reliability of sponge biopsy by this study, it was considered to be of no value to take sponge biopsies from a large number of asymptomatic women in whom formal curettage could not be performed. It would never be ascertained whether pathology had been detected or not. To demonstrate the techniques acceptability as a routine outpatient screening procedure, suitable for integration into establishing screening programmes, a small pilot study was made of asymptomatic women attending the Glasgow Corporation Well Women Clinics and the follow up clinics of the Family Planning Association. These patients did not have diagnostic curettage.

Selection of Patients

Sponge biopsies were taken from 250 women who subsequently underwent diagnostic curettage in the Western Infirmary, Glasgow.

These were divided into two main groups, premenopausal and postmenopausal women.

A. Premenopausal Women (128 patients)

		Age	Number
Age Distribution		35 - 39 years	35
		40 - 44 years	53
		45 - 49 years	35
		50 years and over	5
		Total	128
Menstrual History	Normal menstrual cycle		45
	Abnormal bleeding		83

B. Postmenopausal Women (122 patients)

		Age	Number
Age Distribution		Under 50 years	23
		50 - 59 years	51
		60 - 69 years	29
		70 - 79 years	18
		80 years and over	1
		Total	122
	No postmenopausal bleeding		26
	Postmenopausal bleeding		96

Method

The sponge biopsies were taken by the method described in detail in Chapter five. The procedure was performed either in the outpatient gynaecological clinic or in theatre prior to diagnostic curettage. In the premenopausal women, both symptomatic and asymptomatic, where even normal endometrium would be expected to be continually changing, it was considered desirable to perform the sponge biopsy and the curettage on the same day, otherwise correlation of the two findings would be of no value. In postmenopausal women, the endometrial changes would be very slow, even if malignant, and a delay of two or three weeks between the biopsies would not be expected to effect the histological pattern.

To make an unbiased correlation between the tissue obtained at sponge biopsy and at formal curettage, the histological interpretation of the sponge biopsies was performed by the author, under the supervision of the staff of the Pathology Department of the Victoria Infirmary, Glasgow. The formal curettage material was examined independently by the routine hospital pathologists of the Western Infirmary, Glasgow. There was no discussion or collaboration between the two reporting teams.

Results

The histological interpretation of material from sponge biopsy and from curettage is presented in the following tables.

Table 3 Premenopausal Women (N 128)

Histological Diagnosis	Sponge	D & C
No tissue obtained	13	8
Atrophic endometrium	11	7
Secretory endometrium	29	42
Proliferative endometrium	62	51
Hyperplastic endometrium	6	16
Suspicious of malignancy	4	0
Carcinoma of endometrium	0	0
Carcinoma of cervix (including in situ ca.)	3	4

Table 4 Postmenopausal Women (N = 122)

Histological Diagnosis	Sponge	D & C
No tissue obtained	28	55
Atrophic endometrium	44	16
Secretory endometrium	2	2
Proliferative endometrium	8	8
Hyperplastic endometrium	12	13
Suspicious of malignancy	5	0
Carcinoma of endometrium	13	17
Carcinoma of cervix	10	10
Carcinoma of ovary	0	1

Correlation of Histological Findings

The histological interpretation of the tissue present in the sponges compared consistently well with the material from formal curettage. There were minor differences of opinion in sixteen cases. None of these involved the presence or absence of malignancy. In addition to variation of interpretation, the larger number of premenopausal secretory endometrium found at curettage could be explained by ovulation occurring prior to admission to hospital and between the two biopsies. The remaining differences concerned the interpretation of whether late proliferative endometrium, at the time of the menopause, was considered to be abnormally hyperplastic. As there was no discussion between the reporters, these differences are considered to be compatible with the normal variation in histological opinion. Agreement of opinion was therefore achieved in 94 per cent of cases.

Pick up Rate of Sponge Biopsy

In the postmenopausal group, no tissue was obtained at curettage of 55 women; the sponge obtained scraps of atrophic endometrium in 26 of these. Excluding these insignificant scraps of tissue, in the entire study, adequate tissue for a histological diagnosis in all but six patients was obtained. This represents a successful pick up of available tissue in 97.6 per cent of cases. The most adequate biopsies were from

women with hyperplastic or malignant endometrium (see chapter 5).

Suspicion of Malignancy

Tissue which was considered to be suspicious of malignancy was present in nine sponge biopsies. Diagnostic curettage was performed in all cases and the position clarified.

Four suspicious biopsies were in premenopausal women. These biopsies contained endometrium with abnormal glandular crowding and hyperchromatism and pleomorphism of the nuclei although frank evidence of malignancy was not seen.

In two women, age 45 and 48 years respectively, the curettage material was similar to the hyperplasia noted in the sponge, but on assessment of the overall glandular architecture, they were considered to be non malignant and were kept under review. The remaining two patients unexpectedly had apparently normal secretory endometrium on curettage. These cases will be described in more detail.

Mrs. H. McN. age 47 years - She complained of heavy regular periods. Despite the suspicious tissue present in the sponge, curettage showed normal secretory endometrium only. A cervical smear was normal. She continued to have heavy bleeding and hysterectomy was performed. The uterus was found to have a necrotic endometrial polyp in the fundus, which had obviously been missed by the curette. Histological examination of this polyp showed tissue identical to the suspicious tissue in the

sponge. It was not considered to be frankly malignant.

Mrs. A.G. age 44 years - This woman had no menstrual upset. She had a cervical smear taken by her general practitioner which contained cells which were highly suspicious of malignancy. She was referred to the gynaecological clinic and the sponge biopsy contained tissue showing a reasonably normal proliferative endometrium but with several collections of crowded glands with pleomorphic hyperchromatic nuclei and with a hyperplastic type of stroma (see fig. 20). These focal aggregates of endometrial tissue were very suggestive of malignant change. Curettage unexpectedly produced normal secretory endometrium only. Biopsy of the cervix showed chronic cervicitis with no evidence of malignancy. On review of the sponge biopsy it was thought that the curette must have missed an area of malignancy and curettage was repeated. This again produced normal secretory endometrium. A possible explanation for the suspicious cells in the smear and the tissue in the sponge was that the sponge scraped off an isolated area of early malignant change. Repeat curettage will be performed at regular intervals in an effort to detect any possible recurrance.

In the postmenopausal group, there were five sponge biopsies with suspicious tissue. Four of these patients were

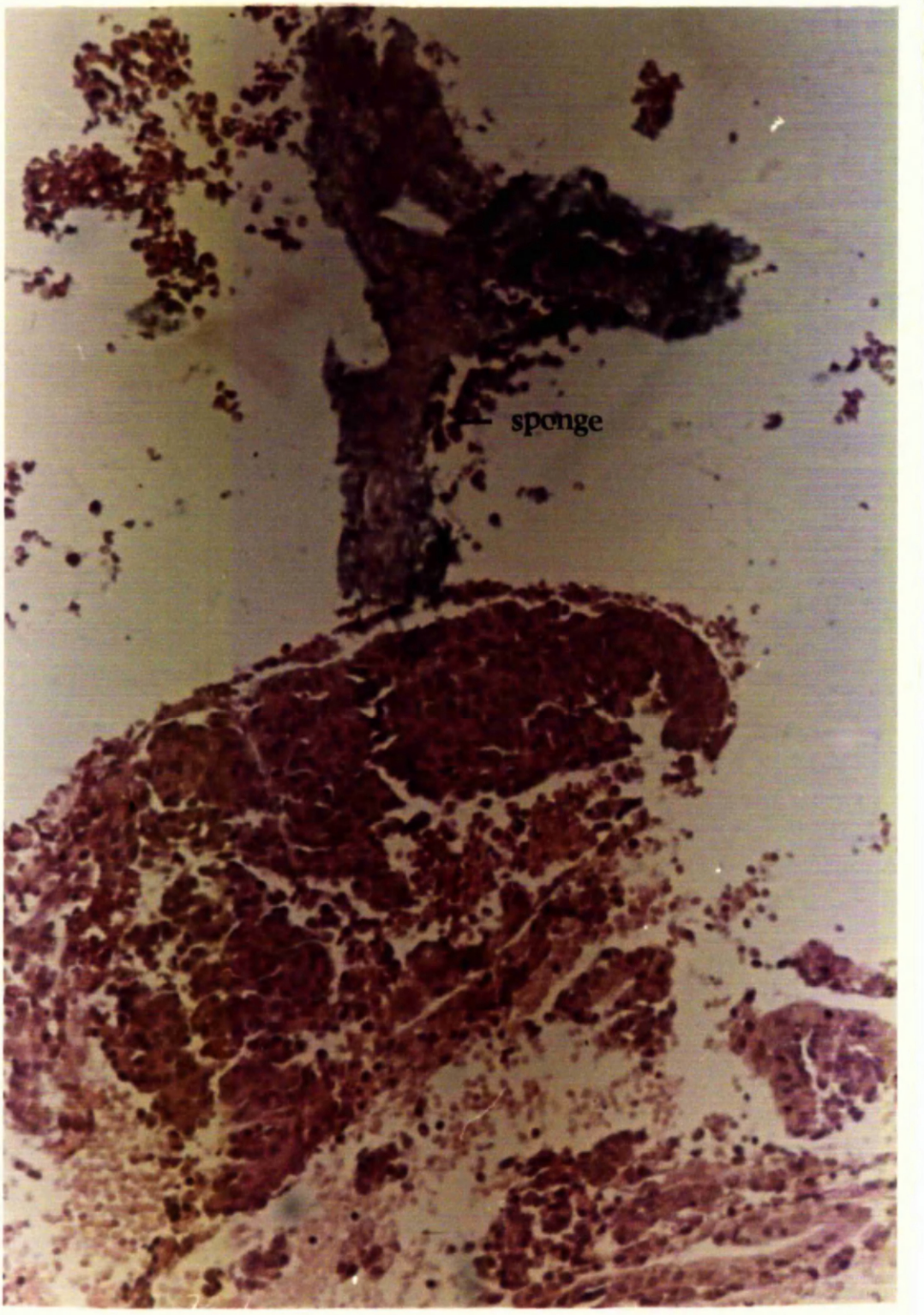


Fig. 20 Suspicious Endometrial Tissue in sponge. Mrs. AG.

subsequently shown to have malignancy.

In two patients, Mrs. D.J. age 47 years and Mrs. A.B. age 52 years, curettage produced tissue similar to that seen on the sponge and on an assessment of the larger sample, they were considered to have carcinoma of the endometrium without significant invasion. Hysterectomy showed no evidence of residual tumour in the uterus, confirming the absence of invasion and the focal nature of the tumour. Radiotherapy was not given to these women.

Mrs. M.H. age 51 years - complained of bleeding twenty months after the menopause. The sponge biopsy contained hyperplastic endometrium with glandular patterns suspicious but not frankly malignant. Curettage produced a scrap of endometrium with hyperplastic glands reported as being of the Arias Stella type and despite her history, was said to be consistent with post-abortal changes.

On reviewing the tissue in the sponge it was felt that there should be discussion between the reporters, in the patient's best interest. The original diagnosis of post-abortal change was reversed and a diagnosis of carcinoma of the endometrium made.

Mrs. H.W. age 50 years - had no postmenopausal bleeding and presented with abdominal pain. She was found to have a pelvic mass. Sponge biopsy showed hyperplastic tissue arranged in a

papillary fashion which was obviously atypical for a postmenopausal women but was not obviously malignant. Curettage obtained tissue reported as being a well differentiated but invasive carcinoma of the endometrium. Laparotomy showed the pelvic tumour to be an adenocarcinoma of ovary with distinct papillary areas similar to those seen in the endometrium and in the sponge. It was concluded that this was a primary ovarian carcinoma with endometrial metastases.

It is interesting to note that no suspicious cells were detected in the cervical smears from these four women.

The remaining postmenopausal patient, Mrs. E.D. age 51 years, did not have the suspicion of malignancy confirmed. She complained of postmenopausal bleeding. A cervical smear was unsatisfactory. The sponge contained a dense inflammatory exudate associated with several areas of hyperplasia and crowding of the glands. There was no frank evidence of malignancy but as it was associated with a pyometra, the degree of suspicion of malignancy was high. Curettage produced an ulcerated, infected and partially necrotic polyp containing hyperplastic but non-malignant endometrium. The endometrium on the remainder of the uterine cavity was atrophic and it is assumed that the sponge biopsied the polyp.

THE DETECTION OF MALIGNANCY

A. Carcinoma of the Endometrium

Seventeen patients in the study had carcinoma of the endometrium. As previously mentioned, three of these women were suspected of having endometrial cancer on the sponge biopsy and the diagnosis was confirmed at formal curettage. A definite diagnosis of endometrial carcinoma was made from the tissue in the sponge in thirteen women. In only one patient was carcinomatous change missed by sponge biopsy. This case is described in more detail.

Mrs. C.C. age 77 years - This elderly lady was admitted for a repair operation for genital prolapse. She had had no postmenopausal bleeding. The sponge biopsy taken before admission to hospital showed scraps of atrophic endometrium only. A cervical smear was normal. Diagnostic curettage performed prior to the repair procedure removed an innocent piece of tissue 0.5 cm. in diameter. It was sent for routine histological examination and the repair completed. Unexpectedly the tissue was reported as being an endometrial polyp with atrophic tissue at the tip and a markedly hyperplastic, crowded, papillary pattern at the base. This was to be regarded as early carcinomatous change. A repeat curettage was performed six weeks and six months later. No tissue was obtained. It is assumed that the sponge only biopsied the atrophic tip of the polyp.

One patient was unfit for general anaesthesia and the diagnosis of endometrial cancer was made on the sponge biopsy alone and confirmed later at post mortem examination.

Pathological Findings

i) Site and Spread of Tumours

Three women were unfit for hysterectomy and were treated by radiotherapy alone. The site and extent of these tumours was never defined. Extensive extrauterine spread was found at post mortem in one case. As discussed above, an isolated endometrial polyp with malignant change at the base was found at curettage. The remaining endometrium was atrophic. Hysterectomy was not performed. The site is therefore unknown.

Carcinoma in situ, presumably of focal origin, was present in two cases. No residual tumour was found in the uterus at hysterectomy.

In four patients there were focal tumours involving the uterine fundus only and which coexisted with normal endometrium. They had minimal myometrial invasion. One tumour involved the lower third of the uterine cavity and resulted in a pyometra (fig. 21).

The remaining five tumours exhibited malignant change involving the entire uterine cavity which had invaded the myometrium extensively in three cases and minimally in two.

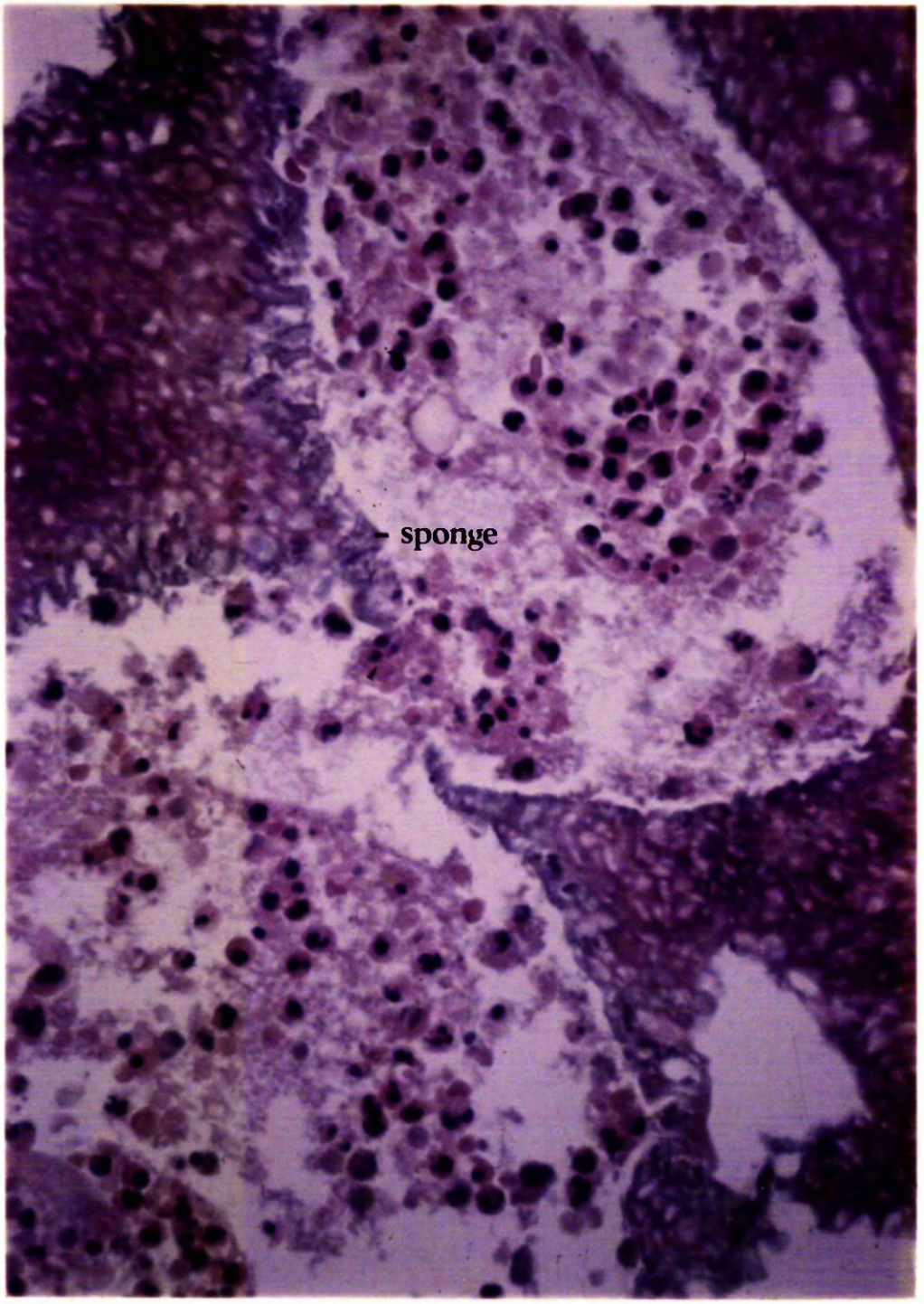


Fig. 21 Pyometra, Inflammatory Cells in Sponge Matrix.

ii) Histological Appearances

There were fourteen adenocarcinomas of endometrium exhibiting varying degrees of differentiation. The remaining three tumours had undergone squamous metaplasia of the adenoacanthomatous type.

The Results of Cervical Cytology in the Presence of Endometrial Cancer

Routine cervical smears were taken from all but two of the seventeen women with proven endometrial cancer. In twelve patients the cervical smears were unremarkable. Two smears contained suspicious cells which could have been of endometrial origin and in only one smear were frankly malignant cells seen.

It should be understood, however, that these smears were taken from the mucocutaneous junction with the prime object of detecting cervical cancer. The cytologists had not been specifically asked to concentrate on abnormal endometrial cells and no attempts were made to obtain intrauterine or posterior fornix smears.

B. Carcinoma of the Cervix Uteri

The leading "V" of the sponge specifically biopsies the endocervical canal and the high ectocervix as it is withdrawn from the uterus. Biopsies of the endocervix and ectocervix were present in 32 per cent of all sponge biopsies examined.

Twelve women in the study were found subsequently to have

invasive cancer of the cervix. Malignant tissue was present in the sponge in all twelve cases. This supports the principle that malignant tissue is more friable than healthy tissue and is selectively biopsied.

A definite diagnosis of invasive cancer was made from the sponge biopsy in eight cases. An example of malignant tissue from the cervix is shown in fig. 19 . In three patients, due to the limitations of the size of the tissue in the sponge, it was only possible to diagnose changes amounting to carcinoma in situ. Formal biopsy of the cervix demonstrated that they were invasive. The remaining patient had carcinoma of the endocervix and will be described in detail later.

One patient was found to have a suspicious smear. The sponge biopsy failed to obtain any cervical tissue and formal cervical biopsy showed changes of carcinoma in situ.

In a similar case, the sponge contained normal endometrium together with several clumps of hyperchromatic cells, which were considered to be abnormal but not obviously malignant. Biopsy of the cervix diagnosed carcinoma in situ and it was assumed that the sponge failed to obtain enough tissue to establish a diagnosis.

One sponge biopsy showed changes amounting to carcinoma in situ (fig. 22) which were not substantiated. The patient, Mrs. A.W., age 48 years, had menorrhagia and a cervical smear

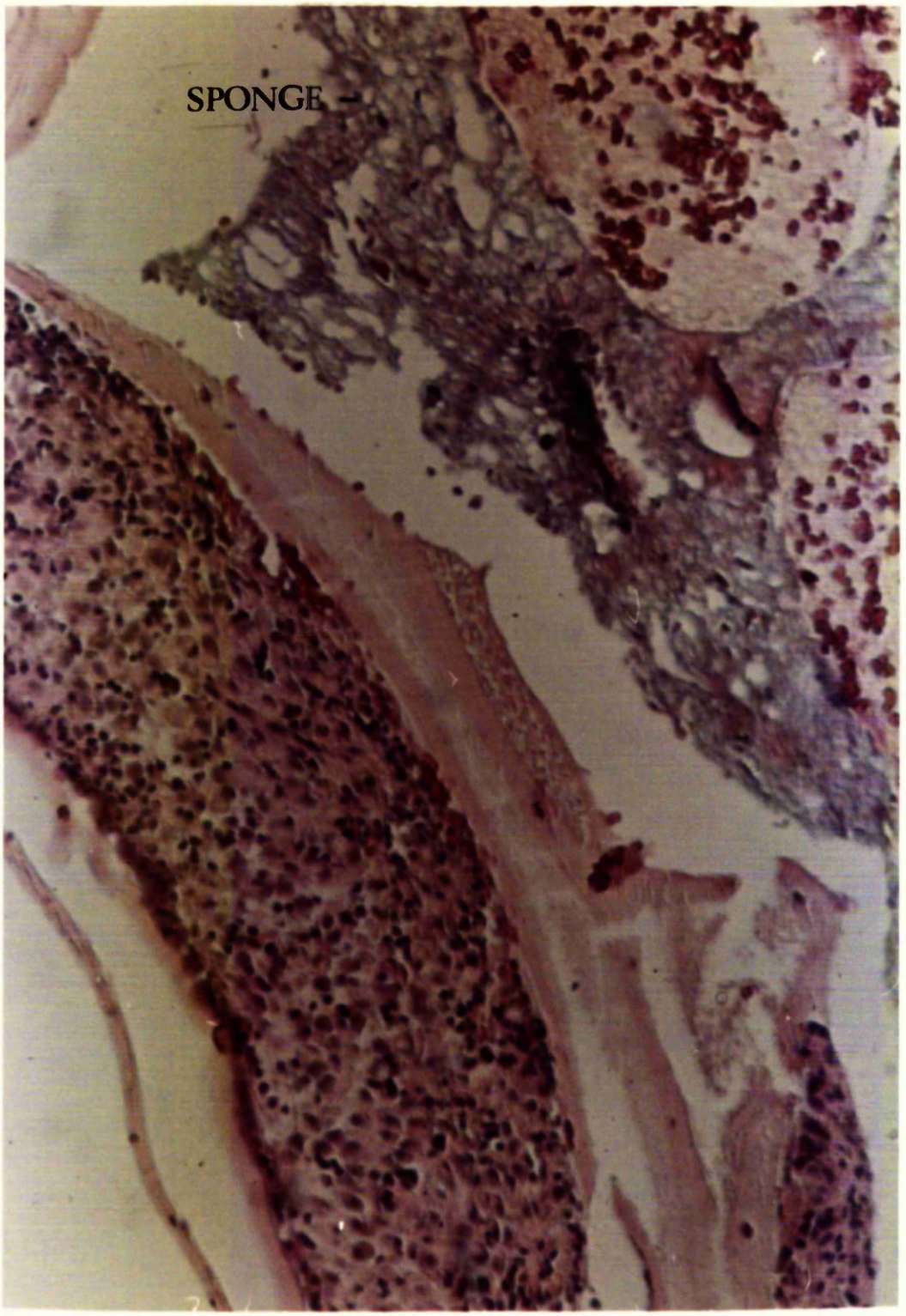


Fig. 22 Ectocervix in sponge with Carcinoma in situ, not substantiated at Biopsy. Mrs. AW.

was spoiled by blood. A biopsy of the eroded cervix failed to detect any malignant change. She will be followed up by smears.

The Detection of Malignant and Premalignant Changes of the Endocervix and High Ectocervix by Sponge Biopsy and Exfoliative Cytology

It is recognised that routine cervical cytology can fail to obtain cells from malignant sites within the cervical canal. Three cases are described to illustrate this problem and to demonstrate the advantages of sponge biopsy in this situation.

Mrs. M.C. age 38 years - had intermenstrual bleeding. The cervix was clinically healthy and a cervical smear was unsatisfactory due to blood contamination. A sponge biopsy contained scanty proliferative endometrium with numerous clumps of malignant cells which closely resembled endocervical cells. A provisional diagnosis of endocervical cancer was made. Fractional curettage obtained tissue from the endocervical canal which was an invasive endocervical cancer. The endometrium was in the proliferative phase.

Mrs. A.S. age 55 years - complained of genital prolapse. She had no postmenopausal bleeding and the cervix was clinically healthy. A routine cervical smear showed some abnormal cells associated with a heavy trichomonal infection. A repeat smear

despite treatment with metranidazole was again contaminated and a further course of treatment prescribed. A sponge biopsy, however, taken at her first clinic visit contained several small pieces of ectocervix (fig. 23) with changes that at least amounted to carcinoma in situ. The repair operation was postponed and biopsy of the cervix showed an invasive well differentiated squamous carcinoma of the cervix originating at the mucocutaneous junction which was situated abnormally high inside the cervical canal.

Mrs. M.R. age 56 years - also had a genital prolapse and no abnormal bleeding. A cervical smear showed normal postmenopausal cells. The sponge biopsy, however, contained a large piece of ectocervix with extensive foci of severe dysplasia with brisk mitotic activity. It was not frankly malignant. Biopsy of the cervix confirmed the diagnosis of a severe dysplasia which was not yet malignant, present at the mucocutaneous junction only.

Sponge Biopsies from Asymptomatic Women Attending "Well Women" Clinics

Fifty sponge biopsies were taken from healthy women with normal menstrual histories for their age. The findings were not correlated with formal curettage material.

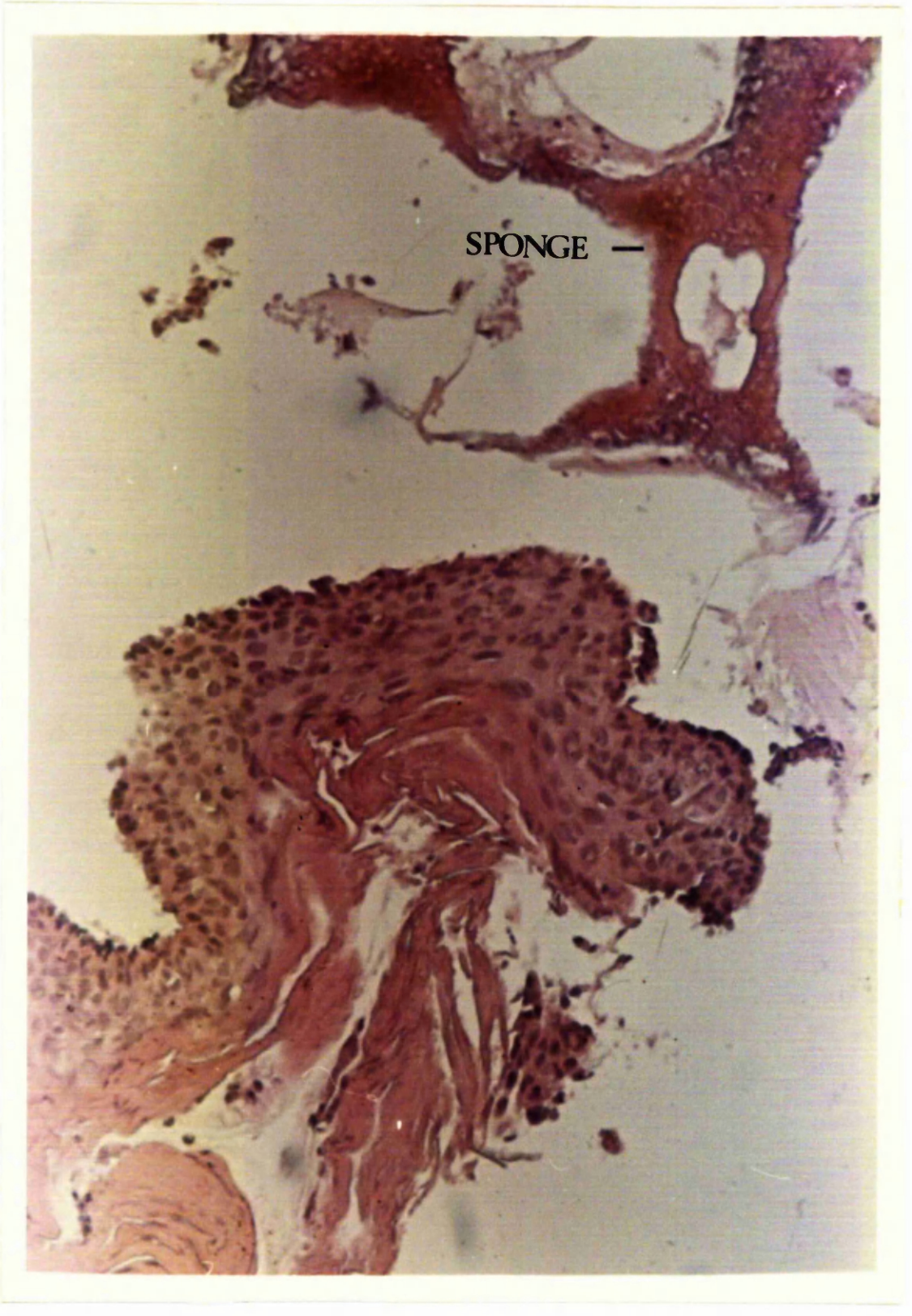


Fig. 23 Ectocervix in sponge with Carcinoma in situ, Invasive Cancer on Biopsy. Mrs. AS.

Age Distribution	Age	Number
	under 40 years	14
	40 - 49 years	24
	50 - 59 years	9
	60 years and over	3
	Total	50

Results : The histological interpretation of the sponge biopsies is shown in table

Table 5 Asymptomatic "Well" Women (N = 50)

Histological Diagnosis	Number
No tissue obtained	4
Atrophic endometrium	11
Secretory endometrium	7
Contraceptive "pill" effect	6
Proliferative endometrium	15
Hyperplastic endometrium	5
Postmenopausal hyperplasia (suspicious)	2
Total	50

There was no tissue in four sponge biopsies. Three of these were in postmenopausal women and only one was premenopausal.

Two postmenopausal women had markedly hyperplastic endometrium which was considered significantly abnormal. They

were admitted for curettage which confirmed the abnormal glandular activity but examination of the larger biopsies excluded malignancy. Endocervical and ectocervical tissue was present in fifteen biopsies (30 per cent) and included a small endocervical polyp.

CHAPTER 7

THE SUITABILITY OF INTRAUTERINE SPONGE BIOPSY AS A SCREENING PROCEDURE FOR INTRAUTERINE CANCER

Thirty years ago, Papanicolaou demonstrated that exfoliative cytology of the cervix could detect cervical cancer before it was clinically obvious and indeed prior to invasion. The application of cervical cytology to an asymptomatic population at risk has greatly reduced the incidence and mortality of cervical cancer. The logical result of this work was an attempt to develop a similar technique to detect asymptomatic intrauterine cancer, which in combination with cervical cytology could screen the entire uterus for malignancy.

Unfortunately the two tumour sites presented different problems of diagnosis and a satisfactory technique of detecting early intrauterine cancer has not yet been established.

The cervix is easily visible and can be scraped under direct vision. This ensures that the entire surface can be sampled and in particular cells can be obtained from around the mucocutaneous junction, where the majority of premalignant and malignant changes develop. Obviously malignant cells are shed from the epithelial surface at a very early stage in the tumour's development. For these reasons cervical cytology can achieve a high degree of accuracy in cancer detection. It is

recognised, however, that lesions of the endocervix and abnormally situated ectocervix, where the mucocutaneous junction lies within the cervical canal, can be missed. In these cases, naturally exfoliated cells may be present in a smear taken from the surface of the cervix, but they may not. This is the one major deficiency of cervical cytology.

By comparison, endometrial and endocervical tumours lie within the uterus and are therefore invisible. They are also inaccessible. The undilated cervix will only admit a sound of approximately four millimetres in diameter without producing discomfort. Elaborate exploration of the uterine cavity will require dilatation of the cervix and therefore an anaesthetic. Unlike the relatively constant site of origin of cervical tumours, endometrial cancer can arise from an isolated focus at any site within the uterine cavity. The entire cavity must therefore be sampled to ensure adequate screening.

The normal endometrium is such a potentially active structure that the examination of exfoliated cells requires extraordinary skill to interpret the significance of the cellular changes. This skill is not universally available and attempts at developing cytological methods of diagnosis have consequently been abandoned. Even the histological diagnosis of endometrial cancer tests the most experienced histologist. It depends on an analysis of the sum of the

glandular architecture, the epithelial structure and the stromal changes, all of which may vary widely in the same endometrium.

Multiple samples of endometrium obtained from the entire uterine cavity suitable for a histological diagnosis are required to diagnose endometrial cancer.

A technique to reliably detect early asymptomatic intrauterine cancer, in a population at risk, must therefore fulfill the following criteria, if it is to be accepted as a screening procedure.

1. It must be safe for the patient.
2. It must be simple - both for the clinician and the pathologist.
3. It must be inexpensive to facilitate widescale application.
4. It must be performed as an outpatient procedure, without a) an anaesthetic, b) prior dilatation of the cervix, and c) undue discomfort to the patient.
5. It must reliably sample the endometrium and detect or suspect malignant and premalignant change if present.

<u>To achieve this,</u>

6. It must obtain samples of tissue from the entire uterine cavity to enable it to detect any isolated focus of malignancy.

7. It must obtain sufficient tissue to allow for a histological as distinct from a cytological diagnosis to be made.

The screening techniques at present available for the detection of asymptomatic endometrial cancer, have been described in detail in Chapter 3 . They failed to satisfy all these criteria for a variety of reasons, which will be considered below.

It was hoped that cervical and vaginal pool cytology, introduced to screen a population for cervical cancer, would also detect exfoliated malignant endometrial cells. This hope was unfounded. Less than a quarter of endometrial tumours were picked up by this method. In our own series, out of fifteen women with endometrial cancer, twelve had normal smears, two had suspicious smears and only one smear contained malignant endometrial cells. This method has consequently been generally abandoned.

Following this initial failure, cytological studies of cells obtained directly from within the uterus were explored. Numerous ingenious techniques were developed to obtain the cells, including aspiration, lavage, intrauterine tapes and brushes. Whatever the method used to obtain the cells, the

diagnosis depended on cytological methods, which had the unavoidable limitations described previously. Although intrauterine cytology improved the detection of malignancy, it remained too unreliable to be of clinical value. Despite these techniques being safe, simple and inexpensive, without reliability of tumour detection they remain unacceptable.

It was eventually recognised that an acceptable degree of accuracy could only be achieved with a histological diagnosis. A variety of small endometrial biopsy curettes were used to obtain tissue for histology without dilatation of the cervix. These included the Randall, the Novak and the Sharman curettes, and more recently the quality of the biopsy was improved by applying suction to the curette, as in the Vibra aspirator. The biopsies taken at each scrape are very small and are difficult to handle, both by the clinicians and the pathology technicians. Whatever the individual advantage of each model, they all failed to overcome the problem that the introduction and withdrawal of a curette biopsies only a limited site, and therefore the critereon of requiring to sample the entire uterine cavity can not be satisfied. They were therefore liable to miss isolated tumours. Despite using histological techniques, the limited biopsies still failed to obtain clinically valuable detection rates for endometrial tumours. Some authors have managed to achieve

acceptable results, however, particularly if they employ systematic scraping of the entire uterine cavity. In our experience, it requires at least six introductions of a small curette to explore convincingly the whole uterus and this caused considerable discomfort to an unanaesthetised patient. Limited endometrial biopsy with small curettes is therefore also unacceptable as an adequate method of detecting intrauterine cancer.

Intrauterine lavage with normal saline can obtain endometrial washings suitable for histological examination, which theoretically come from the entire uterine cavity. When positive pressure was used to instil the saline, it increased the intrauterine pressure and posed the theoretical risk of disseminating tumour cells along the fallopian tubes or through a damaged vein into the blood stream. Gravlee produced his "jet washer", which obviates this problem by creating a negative pressure in the uterus. This should close the tubes before saline is sucked through the uterine cavity. This theoretically safe method achieves very satisfactory results. It detected 53 out of 56 endometrial tumours. The technique is suitable for outpatient use. In his initial study, however, there were 27 per cent (397 patients) unsatisfactory washings, when inadequate tissue was present to give an opinion. This included thm three missed tumours. He claims to have reduced

this figure to 5 per cent by familiarising the clinical and laboratory staff with the technique. He makes no reference to any inability to pass the canula through the cervix of an unanaesthetised patient and washing was not possible.

The main practical problem with the technique is that the tissue in the washing must be filtered from the saline into fixative within four hours, or the cells are destroyed. This demands that the laboratory is close to the clinic and prevents sending specimens to the laboratory by post. The preparation of a cell block from the filtered tissue and its histological interpretation demands extra effort and skill from the laboratory staff. The device is at present available only in the United States of America. It is expensive and costs $ 14 (approximately £6) for one device, which is disposable and is used only once. This expense has been a serious obstacle to the application of the technique to wide scale screening programmes.

Intrauterine sponge biopsy has been specifically designed as a technique for screening a large population at risk, for intrauterine cancer. It must therefore satisfy all the criteria of acceptability.

Safety

Any technique of screening for gynaecological cancer must be performed by clinical staff who are able to perform a

satisfactory pelvic examination and visualise the cervix. Having defined the position and approximate size of the uterus, it is safe to pass a uterine sound followed by the sponge introducer which resembles it closely. If the biopsies are taken by staff with this basic gynaecological experience, and preferably by practising gynaecologists or family planners experienced with coil insertions, then the chance of accidental perforation of the uterus is minimal. If perforation did occur, the fact that the sponge and the introducer are immediately withdrawn from the uterus would minimise its significance. In our experience of over five hundred biopsies, perforation of the uterus has not occurred.

Like all intrauterine manipulations, passing an introducer through the cervix of an unanaesthetised patient could induce a vasovagal attack. In our series, this has not been noted to be a problem.

Ascending pelvic infection could theoretically be introduced at the time of biopsy. As the sponge device is sterile and the cervix has been cleaned, assuming that the principles of asepsis are adhered to, there should be even less risk of introducing infection, than at formal dilatation and curettage where the cervix is opened and the cavity repeatedly sounded. As the sponge is removed immediately from the uterus, the risk of infection must not be compared to the contraceptive coil, where a foreign body with a cervical

"tail" lies for an indefinite period within the uterus. In our experience no cases of pelvic sepsis were attributed to sponge biopsy.

Any intrauterine manipulation in the presence of malignancy has the theoretical problem of disseminating malignant cells. This must exist with sponge biopsy but will be considerably less than curettage methods, where small veins in the myometrium are liable to be opened.

Simplicity

The clinical problems of taking a sponge biopsy are identical to the insertion of a contraceptive coil and has been discussed above, and requires only basic gynaecological experience.

In the laboratory, the entire sponge is processed in precisely the same way as a routine histological specimen. It is fixed in formal saline, stained with haematoxylin and eosin, processed in a Histokine/Histokinette system, paraffin embedded and cut with a standard microtome. The advantage of processing the entire sponge is that the sponge absorbs and retains the multiple small biopsies and it is not necessary to handle individual minute pieces of tissue. This greatly reduces the time and skill required in the laboratory. It also allows the histologist to give an opinion as to the

probable site of a lesion; for example, all endocervical and ectocervical tissue is found in the leading "V" of the sponge. The pathologist who reports on the slides must obviously have experience of endometrial histology and become familiar with the size of biopsy and the sponge maitrix in which they are contained. He does not, however, require any specialised training, unlike a cytologist.

The sponges can be transported from the clinic to the laboratory in small bottles containing formalin. Delays in reaching the laboratory are unimportant to the preservation of the tissue. As described earlier, where the specimens must be posted to the laboratory, dipping the sponge in fixative and sending the wet sponge in a plastic bag will overcome any postal problems. This is an important consideration in many screening programmes where a large central laboratory serves a wide area, as in many parts of the United States of America.

Expense

The device is disposable and requires to be pre-sterilised. This increases the production costs. An estimated cost of manufacturing, gamma ray sterilising and packaging a commercial device is 15 pence. It would be hoped that despite the expense of marketing and distribution, the final cost to the clinician would be under 30 pence. This would enable the technique to be applied on a sufficiently wide scale.

Outpatient Suitability

Outpatient Suitability

Intrauterine contraceptive devices have been inserted as an outpatient procedure in endemic proportions for the last decade. The taking of a sponge biopsy is an identical procedure, and therefore the introduction of this technique as an equally large scale should be feasible. It is performed without anaesthesia and with minimal discomfort to the patient. It is our observation that the discomfort to the patient is inversely proportional to the experience and skill of the operator. If undue traction on the anterior lip of the cervix can be avoided, then discomfort is negligible.

As previously mentioned, some patients will be encountered where the cervical canal is so narrow that it will not permit easy instrumentation, without prior dilatation of the os. Unless the patient can tolerate gentle dilatation, to allow the introducer to pass, these patients are unsuitable for intrauterine sponge biopsy.

In our initial studies, it was not possible to pass the sponge introducer through the cervix in up to ten per cent of patients. This figure was reduced considerably by gaining experience with the method and in particular by adopting the lithotomy position for taking the biopsies. More recently, the modifications to the commercially made devices have reduced the failure rate even further. Despite these improvements, a failure rate of 5 to 7 per cent must be expected.

The pilot study performed at the "well women" clinics demonstrates how the technique can be integrated easily into existing cervical cancer screening programmes.

Biopsy of Available Tissue

In a screening programme, sponge biopsies will be performed on many postmenopausal women who have virtually no endometrium and in whom formal curettage produces no tissue. The sponge biopsy picked up scraps of atrophic endometrium in fifty per cent of these patients. Where tissue was available to the curette, the sponges recovered tissue in 97.6 per cent of cases.

It is fortunate that hyperplastic and malignant tissue is more friable and therefore easier to biopsy than normal tissue. If an isolated area of abnormality is present, the sponge will selectively biopsy this area as it is drawn over it. This principle is illustrated well by the sampling of isolated hyperplastic polyps and by the reliable sampling of malignant tissue, particularly localised foci of tumour. It is confidently expected that the preset plastic backing of the modified sponge will improve the endometrial-sponge contact and therefore both the pick up rate and the quality of the biopsies obtained. Initial experience with the new devices has been most encouraging.

The histological interpretation of the tissue in the

sponge biopsies correlated consistently well with the tissue obtained at formal curettage. This confirms the adequacy of the biopsies obtained.

The tissue in the sponges taken from "well women" in the pilot study, was representative of the expected intrauterine findings in the perimenopausal population. Although these findings were not correlated with curettage material, it is most likely that the sponges were obtaining representative samples.

Detection of Malignancy

Sponge biopsy has been shown to reliably detect or suspect malignant and premalignant conditions of the endometrium. By screening the entire uterine cavity, it can detect all known sites and modes of presentation of endometrial carcinoma.

In the present study, however, one case of malignant change occurring at the base of a small endometrial polyp was missed by the sponge biopsy, which only biopsied the atrophic tip of the polyp. It is difficult to devise any way to counter this failure. If the abrasive power is improved with the backing, it is possible that entire polyps could be scraped off. The detection of this site of presentation of early malignancy must remain a defect of the technique.

The type of tumour present in the uterus did not influence

the sponge's ability to biopsy them. Adenocarcinoma, adenoacanthoma and secondary neoplasms from primary ovarian tumours, were all detected.

In addition to satisfying the criteria necessary for the detection of endometrial cancer, sponge biopsy will also detect malignant disease of the endocervix and high ectocervix.

As the sponge is withdrawn from the uterus, the leading "V" selectively biopsies the endocervix and high ectocervix. Biopsies of endocervix and ectocervix were present in one third of the biopsies. Like malignant endometrium, tumours of the cervical canal are also selectively biopsied. All cases of invasive cancer of the cervix were diagnosed in the sponge biopsies.

As discussed previously, cervical cytology frequently fails to detect malignant lesions of the endocervix and inaccessible ectocervix. A carcinoma of the endocervix, an invasive carcinoma of the high ectocervix and a severe dysplasia of the ectocervix were all detected by the sponge in the presence of unsatisfactory or normal cervical smears.

This ability to detect malignant change of the endocervix and ectocervix is a very important aspect of the technique's role in uterine cancer screening. It is not performed by any other method of endometrial screening. It compensates for the only major defect of cervical cytology screening.

If endometrial sponge biopsy and cervical cytology are performed together, then they can be confidently expected to detect cancer of the endometrium, endocervix and ectocervix.

The contact between the sponge and the walls of the entire uterine cavity and cervical canal is demonstrated in Figs. 24 and 25. They show a sponge in a hysterectomy specimen. It will be noted that the expelled sponge lies in the fundus of the uterus and opens up to extend into both cornu. As it is withdrawn, the leading "V" of the sponge is in contact with the entire cervical canal. It is of interest that the uterus shown, had an isolated adenocarcinoma on the right postero-lateral wall and the sponge lies directly over it, ensuring adequate biopsy.

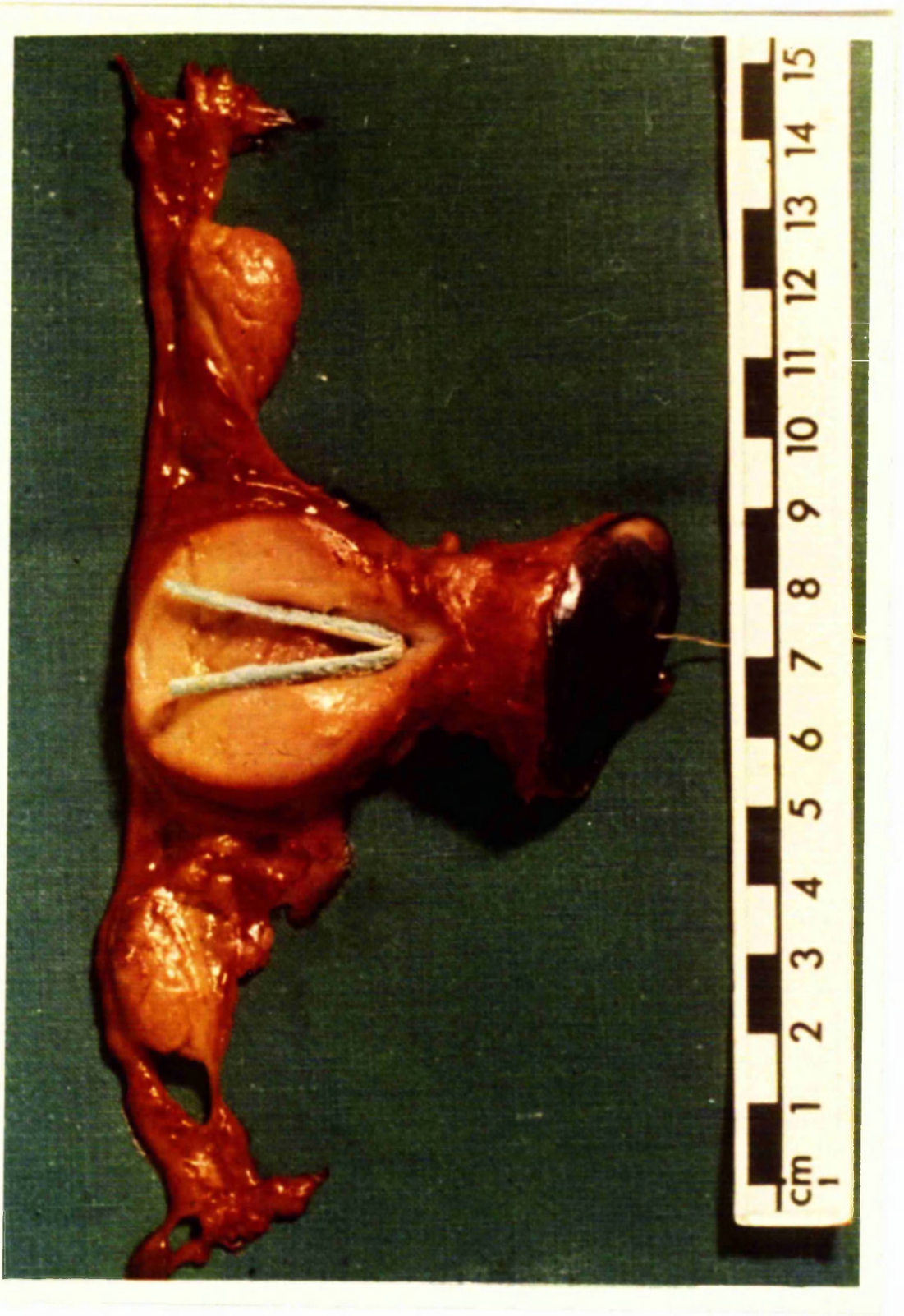


Fig. 24 Sponge Expelled into the Uterine Cavity of a Hysterectomy Specimen.

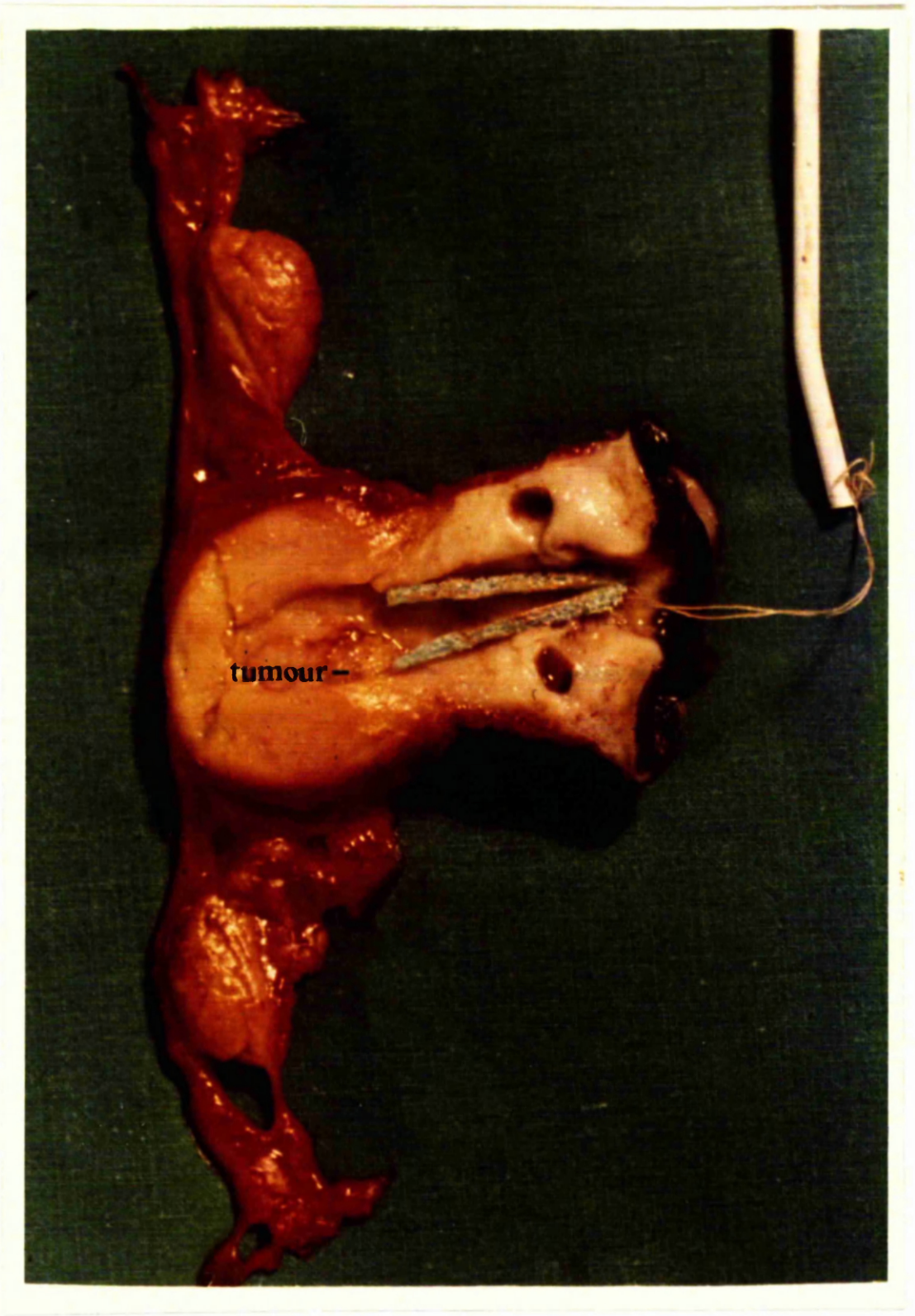


Fig. 25 Sponge withdrawn from the Uterus and lying in the cervical canal.

CHAPTER 8

PROPOSALS FOR THE DEVELOPMENT OF TOTAL UTERINE CANCER SCREENING PROGRAMMES

Intrauterine sponge biopsy would appear to be a theoretically acceptable technique for screening asymptomatic women for endometrial cancer.

It is postulated that sponge biopsy bears the same relationship to endometrial cancer as cervical cytology has to cervical cancer. Its aim is to select from an asymptomatic population at risk, those patients with endometrium which appears to be frankly malignant or is suspicious of malignancy, who therefore require to be admitted to hospital for formal curettage. This allows for a definite diagnosis to be made and the subsequent management planned. This is identical to the role of cervical cytology, where malignant or suspicious cells are seen in the smear and these patients are selected for curettage and cervical biopsy to define the origin of these cells. It must be clearly understood that neither technique is a substitute for formal biopsy in the presence of suspicious signs or symptoms and that definative treatment must not be instigated on their findings alone.

The histological diagnosis of endometrial cancer is difficult and it is imperative that eventually the gynaecologist presents the pathologist with the entire endometrium to enable

him to formulate his final opinion. It must not be considered a failing of the sponge biopsy technique that the pathologist may be unable to give a definite diagnosis on the tissue in the sponge. It is sufficient to arouse his suspicion. It is as important to detect as to suspect malignancy in a screening procedure.

Cervical cytology of asymptomatic women has two main problems. As previously discussed, it can fail to detect endocervical and high ectocervical tumours. The other problem is more subtle. Unfortunately the majority of patients and many of their doctors do not appreciate that while a normal cervical smear means that her ectocervix is healthy, it is not a clean bill of gynaecological health. On the reassurance of a normal cervical smear women may subsequently ignore symptoms of intrauterine cancer. The extent of the area screened is not clearly understood.

In view of the similar roles and objectives of the two techniques, it is logical to integrate intrauterine sponge biopsy into existing cervical cytology programmes. This would overcome the deficiences of cervical cytology and would provide a total uterine cancer screening programme.

As endometrial cancer is a disease of older women, it is proposed to take sponge biopsies from all asymptomatic women over the age of thirty five years. Obese women, diabetics and

women with a late menopause are considered to be at a higher risk of developing endometrial cancer, although the evidence to support this is inconclusive. If biopsy facilities were limited, these women would warrant priority. Women who are known to have unduly active endometrium for their age could be followed up by repeated sponges, as cervical dysplasias are monitored by smears.

The pilot study has demonstrated the feasibility of establishing total uterine cancer screening in existing "well women clinics". The need for the author to make all the devices by hand has inevitably limited the setting up of larger scale programmes. Considerable international interest has been shown in the technique and its application to population screening, following the presentation of this work to the Fourth International Congress of Cytology in London in May 1971. As would be expected, this interest has been predominately from North America, Scandinavia and Germany, whose relatively affluent societies are more conditioned to the concept of "well patient" screening and where the more sophisticated cervical cytology programmes are at present established.

As the devices are being manufactured and will shortly be available in adequate numbers, it is confidently expected that large total uterine cancer screening programmes will be set up by a number of independent workers. In this way, the actual incidence of asymptomatic intrauterine cancer in the population

will be determined. From the completion of these studies, it will require a further five years to elapse after conventional therapy before it will be known what effect this earlier diagnosis will have on the morbidity and mortality from these tumours.

CHAPTER 9

CONCLUSION

Intrauterine sponge biopsy has been shown to be a simple, safe technique which can be performed as an outpatient procedure, without anaesthesia, dilatation of the cervix or undue discomfort to the patient.

It can reliably detect or suspect endometrial carcinoma in any site with the exception of malignant change at the base of a polyp. It achieves this by obtaining the necessary random samples of endometrium, suitable for histological study, from the entire uterine cavity.

It detects malignant change of the endocervix and high ectocervix, overcoming this recognised deficiency of cervical cytology.

Establishing a diagnosis of endometrial cancer before the development of symptoms offers the only forseeable chance of reducing the morbidity and mortality from this tumour, which have remained unaltered for a considerable time. Intrauterine sponge biopsy is a suitable technique to screen an asymptomatic population at risk from endometrial cancer. It can be integrated into existing cervical cytology programmes and together these techniques will detect premalignant and early malignant change of the endometrium, endocervix and cervix, and thus contribute to a reduction in the morbidity and mortality associated with cancer of the uterus.

CHAPTER 10

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CHAPTER 11

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APPENDIX

OTHER APPLICATIONS OF INTRAUTERINE SPONGE BIOPSY TECHNIQUE IN GYNAECOLOGICAL PRACTICE

While intrauterine sponge biopsy was designed principally to detect early intrauterine malignancy, other possible applications to gynaecological practice have been explored.

1. The Use of Intrauterine Sponge Biopsy in the Investigation Of Infertility

The initial investigations of female infertility include an endometrial biopsy and a tubal patency test. It is routine practice in this country to perform these procedures under general anaesthesia which involves formal hospitalisation of the patient.

Endometrial Biopsy

Histological examination of a premenstrual endometrial biopsy, will determine if ovulation has occurred by producing secretory endometrium and will detect tuberculous endometritis if present on histological examination and culture of the tissue.

Tubal Patency

Tubal insufflation with carbon dioxide using Sharman's kymograph, is the standard method of establishing tubal patency. It can be performed as an outpatient procedure without anaesthetic, although it is usually combined with

formal diagnostic curettage under general anaesthesia.

The Detection of Tuberculous Endometritis

In genital tuberculosis, the fallopian tubes are almost always involved and the endometrium is affected by direct extension from the tubes, as shown by the very frequent finding of endometrial lesions in the cornu in continuity with similar lesions in the mucosa of the tubes. Haines and Taylor (1962) consider that tubercles are therefore more numerous in the superficial layers of the endometrium and are more likely to be found in the second half of the cycle, when they are better formed and can be recognised histologically.

The final diagnosis of tuberculosis is made on detecting the tubercle bacillus. Histology and bacteriology are complimentary methods in diagnosis and neither is completely reliable.

To detect tubercle bacilli, Haines (1952) recommended taking multiple endometrial biopsies at formal curettage in the premenstrual phase. He considers that isolated strip biopsies with small curettes are insufficient.

The endometrium is examined histologically. A portion is stained by Ziehl Nielson's method and examined for stained bacilli. Fluorescent microscopy can also visualise the bacilli. The tissue is then cultured. This involves homogenising the endometrium prior to decontamination by Petroff's method. It is then centrifuged and the concentrated deposit is inoculated on Lowenstein-Jensen's medium. The

inoculated medium is then incubated for eleven weeks before it is declared negative.

Intrauterine sponge biopsy can obtain tissue in 97.8 per cent of cases where tissue is available to the curette. It takes random small biopsies from the entire uterine cavity including the cornual and fundal region. It would, therefore, obtain enough tissue to allow for an opinion to be given regarding ovulation (see Fig.13 showing detail of secretory endometrium). As tuberculous endometritis is present in the superficial layers of the endometrium, it should, therefore, be included in the sponge biopsies, and may even be detected histologically. The sponge contains endometrial secretions in addition to the small biopsies and they may also contain tubercle bacilli.

The top half centimetre of the sponge is in closest contact with the fundus and cornu of the uterus. To detect tuberculosis by culture, this piece of sponge is cut off and sent to the laboratory in a dry sterile container, where it is treated in the same manner as endometrium and inoculated on to a Lowenstein-Jensen medium.

This process is theoretically practical. To demonstrate this, sponges were used to transfer bacilli from one known culture to a fresh medium. Five wet sponges were drawn across a weak culture of tubercle bacilli. The sponges were processed

as described above. Positive cultures were obtained on the inoculated medium in all the experiments performed. These studies were carried out by the East African Tuberculosis Centre, Nairobi, Kenya. In the opinion of the medical and technical staff of the Centre, this method of culturing the tip of the sponge could be expected to detect endometrial tuberculosis if present.

Intrauterine sponge biopsy and tubal insufflation performed as outpatient procedures could therefore be expected to provide the same information in the investigation of infertility as at present obtained under general anaesthesia in theatre.

Infertility is a major medical and social problem in East Africa and its detailed investigation is a significant burden on the already overtaxed medical services. The author conducted a prospective study of two hundred patients to attempt to define the extent of the problem and formulate a rational management (Chatfield et al. 1970). A limited endometrial biopsy and tubal insufflation were performed without anaesthesia.

Intrauterine sponge biopsies were taken from thirty of these patients. The sponges were flown to the Western Infirmary, Glasgow for sectioning and reporting by Dr. Watson. The tips of eighteen of these sponges were cultured for tubercle bacilli in Nairobi as described above.

The histological findings of the sponge and the curettage material correlated well in all but two cases. Unexpectedly, the sponge failed to obtain adequate tissue for diagnostic purposes in eight patients where tissue was obtained by the curette. This high figure may have been partly due to the technique being in its earliest stage of development and the tissue could have floated out of the sponge during transport and handling. Cervical and endocervical tissue was present in twelve cases. This relatively high figure would be explained by the tight cervices in nulliparous patients, which would improve the sponge-cervical contact.

Unfortunately no cases of tuberculous endometritis were included in the group who had sponge biopsies. Only three patients in the overall series had tuberculosis (1.5 per cent).

Fifty six per cent of the patients in the series had blocked tubes.

This small study demonstrates that intrauterine sponge biopsy and tubal insufflation can provide an adequate, simple outpatient investigation of infertility, which would be of particular value where theatre time and hospital beds are at a premium.

2. Intrauterine Sponge Biopsies as an Alternative to Formal Curettage in Underdeveloped Countries

In the author's experience in East Africa it was frequently

impossible to admit patients with menstrual disturbances to hospital for diagnostic curettage, due to a chronic shortage of hospital facilities. A similar situation exists in almost all underdeveloped countries. While it is recognised that an examination under anaesthesia and thorough curettage has many obvious advantages, intrauterine sponge biopsy would be an inexpensive, although inferior alternative which would obtain enough endometrium to establish a diagnosis and allow the problems to be managed.

3. The Use of Intrauterine Sponge Biopsy for Monitoring Ovulation Stimulation Therapy

With the recent increase in the use of ovulation stimulation therapy, both with pituitary extracts and Clomiphene Citrate, a simple method of defining if ovulation has actually occured, is required. Temperature methods are inaccurate. In the author's experience, a post stimulation sponge biopsy to demonstrate secretory endometrium is a very simple and satisfactory method of monitoring the therapy.