REVIEW OF LITERATURE
The post menopausal endometrium has been classified by Novak and Richardson (1941) as follows:

I. **ATROPHIC ENDOMETRIUM**: Endometrium is thin, the surface and glandular epithelium is either of normal or less fibrotic and the glands sparse and most infrequently cystic. This is not commonly found.

II. **PROLIFERATIVE ENDOMETRIUM**: Similar to that found in follicular phase of menstrual cycle during reproductive period.

III. **ACTIVE HYPERPLASIA**: Characterised by Swiss-Cheese pattern, an intact epithelium with often dark staining nuclei and abundant compact stroma.

IV. **RETROGRESSIVE HYPERPLASIA**: The Swiss-Cheese gland pattern is perfectly marked here. Epithelium is often low and atrophic and the stroma is obviously fibrotic and inactive. The fibrotic appearance of the stroma appears to be a more reliable indicator of hormonal inactivity than does the epithelium which may remain tall and inactive for many years; after the menopause even when the stroma is very fibrotic.

Endometrial cancer is a disease that occurs primarily in postmenopausal women and is increasingly virulent with advancing age. The role of estrogen in the development of most endometrial cancer has been established.
clearly, any factor that increases exposure to unopposed oestrogen increases the risk of endometrial cancer (Novak's Gynaecology, 12th edition).

**ENDOCRINOLOGICAL CHANGES IN THE POST MENOPAUSAL WOMEN**

With approach of menopause, the oestradial levels in the blood may be low (50-100 ng/l) as compared to 150 ng/l in younger women. The FSH levels may be elevated to twice the level seen during the follicular phase of younger women. There is no significant alteration in the LH levels. After menopause, due to very low levels of oestradial (10-15 ng/l) caused by ovarian follicular failure, the FSH levels get markedly elevated to 10-20 times higher than in younger women with LH about three times higher. The circulating oestrogen in postmenopausal women is mainly oestrogen rather than oestradiol unlike in the young. Most of the oestrogens are now derived by the peripheral conversion of androteno-dione to oestrone. The adrenal cortex (which produces the androtenodione) and the ovarian cortical stroma are the main sources of steroids. As the ovary is responsible for 50% of testosterone production, the plasma testosterone falls only slightly after menopause from about 300 ng/l to 230 ng/l. This fall may be more marked in those who had oophorectomy. The hormonal levels may vary depending upon the time of the day, the number of years following menopause and type of menopause whether spontaneous or surgically induced.

Endometrial hyperplasia represents a spectrum of morphologic and biologic alteration of the endometrial
gland- and stroma, ranging from an exaggerated physiologic state to carcinoma in situ. Endometrial hyperplasia are important clinically because they may cause abnormal uterine bleeding, may be associated with estrogen producing ovarian tumour, may result from hormonal therapy and may precede or occur simultaneously with endometrial cancer. Endometrial hyperplasia has been classified by the International Society of Gynaecological Pathologists into the simple hyperplasia, complex hyperplasia and atypical hyperplasia.

Simple hyperplasia is characterised by dilated or cystic glands with round or slightly irregular shapes, an increased glandular to stromal ratio without glandular crowding and no cytologic atypia. Complex hyperplasia has architecturally complex (budding and infolding) crowded glands with less intervening stroma without atypia.

Atypical hyperplasia refers to cytologic atypia and can be categorised as simple or complex, depending on the corresponding glandular architecture. Criteria for cytologic atypia include large nuclei of variable size and shape that have lost polarity, increased nuclear to cytoplasmic ratio, prominent nucleoli and irregularly clumped chromatic with parachromatric clearing.

The risk of endometrial hyperplasia progressing to carcinoma is related to the presence and severity of cytologic atypia. According to Kurmar et al (1987) progression to carcinoma occurred in 1% of patients with simple hyperplasia, 3% with complex hyperplasia, 8% of patients with
atypical simple hyperplasia and 2% of patients with atypical complex hyperplasia. Most of the hyperplasia seems to remain stable (18%) or regress (7.4%). The premalignant potential of hyperplasia is influenced by age, underlying ovarian disease, endocrinopathy, obesity and exogenous hormone exposure. In patients with atypical hyperplasia detected during endometrial biopsy or in a curettage specimen, approximately 25% will have an associated usually well differentiated endometrial carcinoma, if hysterectomy is performed.

Cullen (1900) described that endometrial carcinoma began with anovulatory cycles:

Anovulatory bleeding

| Cystic glandular hyperplasia
| Adenomatous hyperplasia

| Adenocarcinoma in situ
| Invasive adenocarcinoma

Backer (1904) first noted that there is an association between endometrial hyperplasia and subsequent endometrial carcinoma.

Gusberge (1947) introduced the designation adenomatous hyperplasia to include the entire spectrum of pre-cancerous architectural and cytological abnormalities of endometrium. It has well been documented that this hyperplasia may be precursor to adenocarcinoma of endometrium in some women. Gusberg (1976) showed that among patients with adenomatous hyperplasia 18.5% with short (5 yrs)
follow-up and 30% after 10 years will develop endometrial cancer.

Precancerous lesions of endometrium are -

1. Cystic hyperplasia.
2. Atypical proliferative hyperplasia, cellular and architectural.
3. Atypical secretary hyperplasia.
4. Carcinoma in situ.
5. Polyps with forgoing changes.

Stromal invasion must be present for diagnosing invasive cancer (Kumar and Morris, 1982).

The new classification formulated by W.H.O. Committee on endometrial tumours breaks down endometrial hyperplasia into 4 stages.

1. Simple hyperplasia without atypia (SH).
2. Simple hyperplasia with atypia (SAH).
3. Complex hyperplasia without atypia (CH).
4. Complex hyperplasia with atypia (CAH).

According to Norris et al (1986), non atypical hyperplasia, glandular or epithelial occur in women with abnormal endocrine milieu. The potential for progression to carcinoma is minimal in these groups (2%). Of these who have atypical hyperplasia it was shown in one study that 23% progressed to carcinoma. It was, therefore, presumed that cytologic atypia signifies a high risk for carcinoma and determines the basis for therapy.
The term atypia refers to cellular atypia and the term complexity refers to severe architectural abnormality close to that seen in cases of well differentiated adenocarcinoma.

Simple hyperplasia: It induces cystic hyperplasia and mild and moderate degrees of architectural abnormality. It is not significantly precancerous.

Simple hyperplasia with atypia deserves further investigation as there has not been enough follow up information. When complex hyperplasia with atypia is diagnosed in a biopsy specimen, a well differentiated adenocarcinoma is discovered in the hysterectomy specimen in 15 to 20% of the cases. Or the lesion will eventually be followed by carcinoma in approximately 30% of the patients (Tavassali F and Krause FT, 1978 and Kurman RI and Norris H., 1982).

ATYPICAL HYPERPLASIA VS WELL DIFFERENTIATED ADENOCARCINOMA

Handerickson et al (1983) and Kurman and Norris (1982) had laid down the criteria *The first group undefined various architectural and cytologic abnormalities some of which may be absent in individual cases, leaving the final decision to the overall evaluation of the lesion. Both pronounced architectural atypia and at least moderate cytologic abnormality are required.*
The second group emphasized architecture qualities stromal and quantitative features. Primary criteria for adenocarcinoma the presence or absence of stromal invasion, which is defined arbitrarily by the presence of at least one of the following features:

1. Desmoplastic stromal response in the vicinity of infiltrating glands.
2. Confluent or cribiform glandular pattern.
3. Extensive papillary pattern and
4. Replacement of stroma by squamous epithelium.

In a retrospective study Hartig and Sommens (1949) observed 32 cases of complex hyperplasia and atypical hyperplasia was found to antecede carcinoma by 1.5 years and in other hyperplasia by 6-7 years. Cystic hyperplasia is only weekly precancerous was presented by Mebride (1959) who followed for 24 years and found that carcinoma develop only in 29% of cases. Normal findings on chromosomal and DNA studies are also consistent with a low malignant potential. Gustilberg and Kaplan (1983) recorded follow up on 191 patients. 80% of the patients were more than 40 years and 12% of patients where hysterectomy was not done, developed carcinoma endometrium (68/101) were followed for one year.

Chamberlain and Taylor (1970) investigated 97 patients of adenomatous atypical hyperplasia. 14% developed carcinoma in 1-14 years.
Wentz (1974) reported follow up of 115 cases for 2-3 years. 27% adenomatous hyperplasia, 82% atypical hyperplasia and all cases of carcinoma in situ had developed carcinoma.

Sherman and Brown (1979) followed for 2-18 years, 216 untreated patients of 50 years of age with complex hyperplasia and 39% of cases had carcinoma later on (22% adenomatous, 57% atypical adenomatous, 59% carcinoma in situ). Regression of process of endometrial hyperplasia is certainly more frequent than progression to neoplasia. The risk of developing adenocarcinoma increases with the spectrum of morphology being lowest for cystic hyperplasia, greater for adenomatous hyperplasia and greatest for atypical hyperplasia.

Screening Technique used for detection of endometrial carcinoma

Carcinoma of uterus is one of the common malignancies of female genital tract. Early diagnosis of the disease can lower the morbidity and mortality associated with it. Attempts to identify premalignant and silent cancer of uterus have been made. A single diagnostic procedure has not been uniformly successful. It would appear that multiple techniques using both cytologic and histologic material would increase the possibility of achieving the goal for early diagnosis of uterus cancer.

It was Slauter (1902) who used first endometrial biopsy as a diagnostic procedure for endometrial carcinoma in both symptomatic and asymptomatic post menopausal women.
Papanicalou and Traut (1943) advocated vaginal pool smear technique for early detection of endometrial carcinoma. This method is now abandoned in favour of direct endometrial sampling. The vaginal pool smear techniques was time consuming and was less efficient than the direct endometrial sampling in the detection of endometrial lesion. For screening purpose, the vaginal pool smear should be obtained on every woman who crosses the age of 50, as it may contribute significantly to the diagnosis of endometrial cancer in early stages.

Hering and Sammers (1949) indicated that adenomatous hyperplasia preceded carcinoma. Palmer (1950) diagnosed endometrial carcinoma by endometrial biopsy. He reported about 92% accuracy rate in his study.

Hechte (1954) used aspiration cytology to diagnose endometrial carcinoma. He included 901 patients ranging in from 20 to 71 years, the average being 51 years. 71 cases were post menopausal with bleeding per vaginum. Out of which 38 patients were diagnosed as cases of endometrial carcinoma.

Way (1956) had drawn attention to an interesting fact that carcinoma body uterus was associated with late menopause, obesity, hypertension, presence of fibroid, nulliparity and diabetes in many patients.

Sippe (1962) in his study of 282 cases noted that the endometrial hyperplasia was a common uterine disorder occurring particularly during climatric. He found that 80% of cases were in the age group of about 40-50 years. On histopathological examination, there were large blood
sinuses with inconspicuous wall which were commonly found in the superficial endometrium and rupture of these sinuses had been responsible for uterine haemorrhage.

Devi (1964) stated that endometrial cancer was usually a disease associated with post menopausal women. The peak incidence of endometrial carcinoma in his series was towards the end of the 6th decade of life. 10-15 years after menopause most of the cases diagnosed were in the 50 to 60 years of age group. The disease was rare before 20 years and after 90 years of age.

Coleman (1965) used vaginal cytology to detect uterine malignancy in early stage. He selected 285 patients for study and found atypical cells in 185 patients, 78 patients showed negative report, 22 patients showed unsatisfactory findings.

Robert (1965) pointed out that there was a strong association between persistent unopposed oestrogen action in the absence of ovulation with increased risk of endometrial cancer. Two pathways seemed to be involved in this process.

In first excessive or unopposed 17 extradiol was secreted either continuously over long period of time or in fluctuation. So that the endometrium was stimulated from the stage of normal proliferation to hyperplasia, atypical hyperplasia and eventually to carcinoma in some cases. This would appear to be a major mechanism in those postmenopausal cases in whom progression through atypical hyperplasia to carcinoma takes place. The other pathway involved was the production of oestrone by extraglandular
conversion of androstenedione. This would appear to be the most common root in postmenopausal women. The oestrone may have sufficient estrogenic activity to cause proliferative changes in the endometrium but it provides facultative support in development of cancer. However, when the production of oestrone is increased by any mechanism, the chances of developing endometrial cancer are greatly increased.

Wynder (1966) concluded that obesity was a major risk factor most commonly associated with endometrial carcinoma. In women who were 21-50 pounds over weight, occurrence of endometrial carcinoma has increased three fold. In women 50 pounds or more over the ideal weight the risk was 5 times greater than women of normal weight.

In Peterson's series (1968), a total of 81% patients with endometrial carcinoma weighed over 150 pounds while 63% of the group weighed over 180 pounds and 7% over 230 pounds.

Gravlee (1969) advocated jet washing technique for establishing early diagnosis of endometrial carcinoma particularly in asymptomatic patients. 181 patients were sampled with jet washer. 135 patients out of 181 showed atypical cytology, 10 of which were found to have endometrial carcinoma. On curetting failure rate was 21%.

Bonham (1973) reported from his own clinic that the peak occurrence of this disease was between the age of 50 and 60 years. When diagnosis was made before the menopause, as occur in 20 to 25% of cases. The clinical outcome was definitely more favourable. In general the early onset of this disease was more frequently associated with femini-
zing ovarian tumours and polycystic ovarian disease.

Gushberg (1973) reported that endometrial carcinoma tended to occur one decade later in life than cervical cancer. This occurred because endometrial carcinomas seem to be some combination of hormonal disturbance that occur after menopause or whenever oestrogen activity in excess or is unopposed by activity of progesterone.

Kelly et al (1973) advocated the use of endometrial biopsy as an outdoor procedure in order to obtain adequate endometrial tissue for diagnostic study. Many other authors have also advocated the use of endometrial biopsy as a routine outdoor procedure and in their hands it has become a good screening technique.

Knoll (1974) evaluated the utility of vacuum aspiration method in diagnosis of asymptomatic patients. There were 122 patients evaluated by vacuum aspiration of endometrial cavity. 72 out of 122 patients had abnormal cytology. 10 out of 72 patients were diagnosed as having endometrial carcinoma also proved by endometrial biopsy.

Hofmeister (1974) for the first time used endometrial biopsy as a routine office procedure in more than 20,000 postmenopausal women. He noted that in 17% cases, endometrial carcinoma was diagnosed in asymptomatic women.

Kaplan and Cole (1974) suggested that diabetes mellitus may be associated with increased risk of endometrial carcinoma. He reported that the risk with abnormal glucose tolerance is 2-4 times higher than when it is absent.
Smith (1975) showed positive association between endometrial carcinoma and hypertension. The triad of diabetes mellitus, obesity and hypertension occurs most commonly in patients of the age group of 60-70 years. This triad had been dubbed as "The corpus cancer syndrome".

Out patients diagnostic technique is comparable to the papanicolaou. Smear for carcinoma of cervix, to permit an early recognition of endometrial cancer. Five different techniques of sampling of the endometrial cavity were saline irrigation with antrum cannula, endometrial brush sampling, high vaccum aspirator, Gravlee jet washer and endometrial biopsy. Out of these five methods, endometrial biopsy permitted accurate diagnosis (Davil and Anderson, 1976).

Creasman (1976) studied 640 patients selected from out door and indoor. The age varying from 40 to 70 years. Endometrial cytology was done by Vabra technique. He found that 80% adenocarcinoma and adenomatous hyperplasia could be diagnosed by this technique. He also evaluated the utility of combination of several techniques when brush and endometrial biopsy were combined, 19'out of 21 patients could be diagnosed as suffering from endometrial carcinoma.

David (1976) evaluated the different screening procedures and proposed saline irrigation as a simple outdoor screening procedure which could be utilized to diagnose endometrial carcinoma in early stage. Out of 125 patients who underwent saline irrigation of endometrium cavity, 64 patients were having endometrial hyperplasia. Failure rate of this procedure was 22%.
Second technique used was brush technique. In this group 191 patients were subjected to endometrial brush sampling. There were 11 patients with endometrial adenocarcinoma proved by endometrial curettage. 118 cases were having atypical cytological findings. However, cytology was unsatisfactory in 62 patients. Failure rate of this method was very high about 36%.

Peter (1976) noted that all endometrial tumour had low progesterone binding capacity. By means of dextron coated charcoal assay, the capacity of various endometrial cytol preparation for specific binding of progesterone was determined. Two out of 7 grade I, 3 out of 8 grade II and 2 out of 3 grade III endometrial carcinoma showed low binding capacity. These data suggested a progressive loss of specific progesterone binding capacity from normal to hyperplastic endometrium and from well differentiated to anaplastic form of adenocarcinoma. The author calculated that the use of progesterone binding capacity may help in diagnosing the asymptomatic and symptomatic patients at risk for endometrial carcinoma.

Cohen (1977) stated that an accurate endometrial cytology screening test would be of particular value in the continuing surveillance of patients with abnormal uterine bleeding in the follow up evaluation of patients with documented atypical endometrium and perhaps as a part of the periodic examination of all menopausal and post menopausal patients.
Welch and Scully (1977) pointed out that stimulation of endometrium by exogenous or endogenous oestrogen resulted in hyperplasia or carcinoma body uterus or to cause abnormal vaginal bleeding. In his study he noted that 25% of cases having hyperplastic endometrium, converted into endometrial carcinoma in five years or more time.

The technique so far discussed for diagnosis of endometrial carcinoma had all been invasive in nature, procedures being relatively unsafe, time consuming, costly and success rate achieved by them have been rather low.

Gambrell et al (1980) gave an illustrated view regarding the quality of outdoor screening procedures for diagnosis of endometrial carcinoma. They stated that the method should be acceptable to the patients, be painless, inexpensive and reliable in the hands of all those doing the pelvic examination. They recognised the need for a technique that would permit early diagnosis of endometrial carcinoma.

Progesterone counter the effect of oestrogen and causes sloughing of endometrium and withdrawal bleeding induced by progesterone intake in an indication of presence of oestrogen in sufficient quantity to proliferative endometrium.

In post menopausal women suspected for endometrial carcinoma administration of progesterone will cause withdrawal bleeding to occur after the progesterone is stopped based on this principle is the progesterone challenge test developed by Gambrell and co-authors at Warfoy Hall, U.S.A.F.
MEDROXYPROGESTERONE ACETATE STRUCTURE
Currently, Hanne et al (1983) noted the use of progesterone challenge test in asymptomatic postmenopausal women. According to them, the presence or absence of withdrawal bleeding aid in detecting premalignant lesion of endometrium. In 1981 they selected 30 women for the study. Both progesterone challenge test and endometrial biopsy were done in all the cases. 25 women exhibited no withdrawal bleeding and had no pathological lesion (Histology was normal). Five women exhibited withdrawal bleeding. Three out of five positive cases had unsuspected hyperplasia, one of which was atypical and two had atypical endometrium. In 1983, they selected 10 post menopausal women with biopsy proved adenomatous hyperplasia who had presented with bleeding symptoms for progesterone challenge test. No specific selection criteria were used. 9 of these 10 exhibited withdrawal bleeding. The purpose of this study was only to establish a false negative rate for progesterone challenge test in known cases of hyperplastic endometrium.

**STRUCTURE OF MEDROXY PROGESTERONE ACETATE**

**Pharmacology of Medroxy Progesterone Acetate**

It is a derivative of 17, 6 methyl medroxy progesterone acetate.

It is a highly active progestational agent, white to off white colourless crystalline powder partially soluble in water.
Physiological Activity

**Medroxy Progesterone acetate** shows exceptionally high progestational activity when administered in tablet form by mouth or in form of Depo provera by intramuscular injection. Comparative studies in immature female rabbit indicate that MPA in 24 to 28 times as potent as other progestational agents.

Clinical Study

The effectiveness of MPA producing secretory changes in endometrium and other progestational effects have been studied in surgically castrated patients with functional uterine bleeding and dysmenorrhoea.

It is used for detection of premalignant condition of endometrium. It causes withdrawal bleeding when administered in patients at risk for endometrial carcinoma or premalignant lesion.

Adverse Effects

It is well tolerated both locally and systemically. There were no estrogenic or androgenic effect after administration. Menstrual irregularity is the main adverse effect when used over prolonged period.

Preparation

MPA is marketed by name of:

1. Devicy - 2.5 mg/5mg/10 mg tabs.
2. Inodin - 2.5 and 10 mg tabs.