# EXOGENOUS ESTROGENS AND ENDOMETRIAL CANCER†

by

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*Introduction*

Menopause was very rarely seen in the early part of 20th century but increase in the age of survival has led to a greater number of patients being seen with this disorder. Today women spend about one third of their years in the climacteric. When Gardanne first described the menopausal syndrome in 1812 the average life span of a woman was far less than 50 years and few experienced the perturbations associated with this syndrome. Menopause is a hormonal deficiency state and like all endocrinopathies, should be treated with estrogen replacement as need be. The manifestations of the menopause are manifold although hot flushes and senile vaginitis are the commonly accepted symptoms of the menopause by most physicians. Greenblatt (1979) has shown that relief of headaches was seen when menopausal patients had implantation of estradiol pellets at regular intervals. Osteoporosis is another condition in the post menopausal women which has gained much importance due to the high incidence of fractures leading to increase in morbidity and mortality in this age group. Nachtigall *et al* (1979) have observed that estrogens are beneficial in preventing osteoporosis if therapy is started early in the climacteric. In our study we have shown that the ratio of total tryptophan to free tryptophan was .reversed after using estrogen therapy in women who had post menopausal depression.

*Estrogen-Cancer controversy*

Do estrogens cause cancer? It is well known that unopposed estrogens in susceptible individuals, has the potential of causing hyperplasia and even carcinoma of endometrium. Use of exogenous estrogens has increased tremendously over the past decade, especially in the United States. Several reports appeared in mid seventies which implicated estrogen therapy for post menopausal women as a possible cause of endometrial cancer (Ziel ond Finkle 1975; Weiss *et al* 1979). These retrospective and epidemiologic studies indicated that there was 3.1 to 8.0 times increased risk of endometrial cancer for estrogen users. In most of these reports the estrogens were used alone. Other studies have shown that use of cyclic progestogen with an estrogen seems to have a protective action and even reduction in the development of endometrial cancer Maturitas 1978; Greenblatt *et al* 1979).

In the proliferative phase of a normal menstrual cycle, estradiol increases the growth of the endometrium about 10 times but the secretion of progesterone from the corpus luteum results in the arrest of mitosis, necrosis, decidualization of endometrium and arrest of growth.

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This is probably due to the antiestrogenic action of progesterone which results in reduction of uterine nuclear and cytoplasmic estradiol receptors (Evans *et al* 1980).

*Scanning Electron Microscopy Studies (SEM)*

Studd *et al* (1980) from England have shown that in a group of 855 women, patients who received estrogens alone without a progestogen developed endometrial hyperplasia in upto 56% of cases but those who received a cyclic progestogen for 13 days each month did not develop cystic hyperplasia.

In normal proliferative endometrium the SEM studies have shown that the cells are of uniform size and are covered with cilia of uniform length. Numerous microvilli are allso seen. Similar findings were seen in a woman who was taking cyclic estrogen—progestrogen therapy for two years. In the patient who had omitted the progestogen the findings revealed proliferation of cilia of variable length and typical findings of hyperplasia were seen on histology. After progestogen was given for 21 days the number of cilia were reduced the microvilli were fused and hyperplastic changes were reversed.

*Receptor Studies*

A receptor is a protein present in all the target cells in both cytoplasm and nucleus and is responsible for the specificity of the reaction of tissues to steroid hormones. Liver, kidney, uterus etc. respond similarly to steroid hormones due to the presence of a specific receptor. The free hormone present in the circulation diffuses into the cell across the cell membrane and binds to a specific cytoplasmic receptor. The hormone-receptor complex then diffuses into the nucleus. The hormone separates from the cytoplasmic-receptor (which diffuses back into the cytoplasm) and binds to the nuclear receptor. This results in the reaction between the hormone receptor complex and DNA, resulting in synthesis of messenger RNA. This ultimately results in the synthesis of protein and specific cellular activity. Estradiol has been shown as an example in the figure 1.

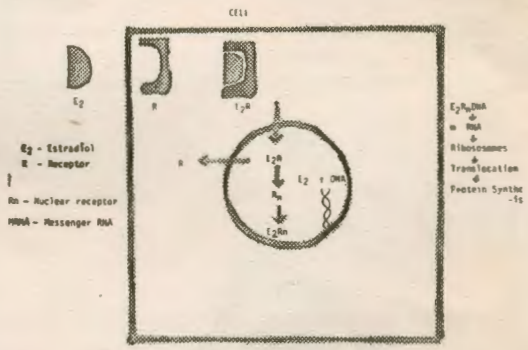
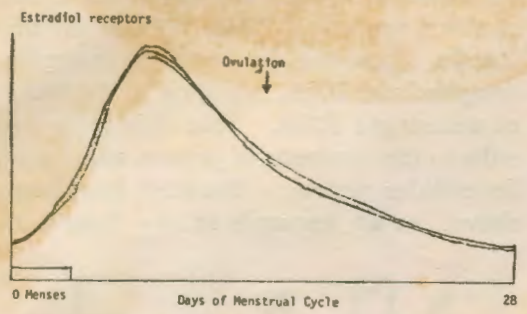


Fig. 1

There are specific receptors for estradiol ($E_2R$) and progesterone (PgR) in the endometrium. It has been shown that estradiol stimulates the synthesis of its own receptor and the progesterone receptor. The levels decline after the respective receptors are occupied by their specific hormone. Estradiol receptor concentrations are highest in early and mid proliferative phase and decline towards late proliferative phase when estradiol levels are high. (Fig. 2) (Bayard *et al* 1978). They are also high in post menopausal hyperplasia and well differentiated carcinoma (Gurpide *et al* 1976). There are few PgR in early proliferative phase but they increase to a maximum at the time of ovulation and return to low levels after ovulation (Rodriquez *et al* 1979). (Fig. 3).

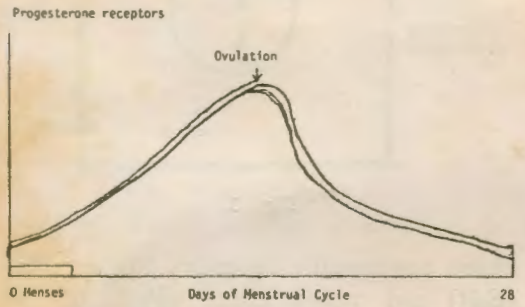
In our studies we have shown that patients who received low doses of estrogen

Figure 2




Estradiol receptors increase till the time of ovulation and fall after ovulation.

Figure 3




Estradiol increases the progesterone receptors, and progesterone secreted by corpus luteum results in the fall of PgR after ovulation

along with a cyclic progestogen for seven to ten days had low $E_2R$ and PgR and these were within the control values. Patients who received estrogen therapy but did not take their progestogen as prescribed or those who took a shorter course of a progestogen had three fold increase n the $E_2R$ and a four fold increase in their PgR. Histology also correlated well as some of the patients who missed their progestogen had endometrial hyperplasia on histology (Natrajan *et al* 1979). From our studies we concluded that a cyclic course of seven to ten days of progestogen each month seems to protect the endometrium from developing hyperplasia by keeping the receptor levels within normal limits.

*Discussion*

From the above studies (clinical, SEM and receptor) it seems that if a patient in the menopausal age group needs an estrogen, she should receive a cyclic progestogen to protect the endometrium and may be breast (Leis 1966). The patients are counselled about the possibility of scant to moderate bleeding from the withdrawal of progesterone and almost all patients accept this if they are told about the beneficial effects of the progestogen in preventing cancer. Many of these patients do not develope withdrawal bleeding, especially if low doses of estrogen are used.

*These are the following recommendations for estrogen therapy*

1. Use the lowest effect dose of a natural or biologic estrogen:—conjugated estrogens 0.6 mg to 1.25 mg or micronized estradiol 1 to 2 mg for 21 to 25 days of each month. Dosage may be increased or decreased depending on the patient response.
2. Cyclic progestogen—Medroxy progesterone acetate 10 mg first 10 days or last 10 days of each month.
3. Endometrial sampling prior to therapy if there is abnormal bleeding and during therapy if abnormal bleeding developes.
4. Counsel patients regarding the pros and cons of using a progestogen.
5. Close follow up of the patients with yearly examination.

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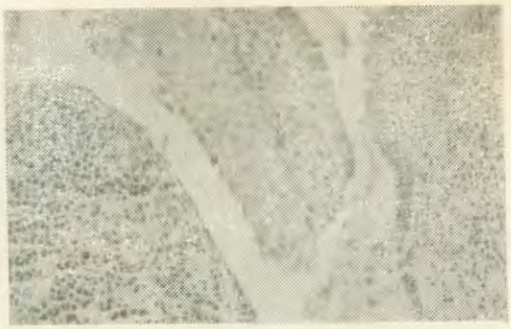

Fig. 1
Squamo columnar junction, left side endocervical mucosal fold showing diffuse lympho-mononuclear cellluar infiltrate. Right side opening of endocervical gland containing mucus material. (H X E x 200).

Fig. 2
Hyperplastic endocervical gland with dark staining IgA (Arrows) producing cells in and around the glands. Upper righthand corner shows columnar epithelial lining of the endocervix (Peroxidase-antiperoxidase stain for IgA with Haematoxylin x 400).

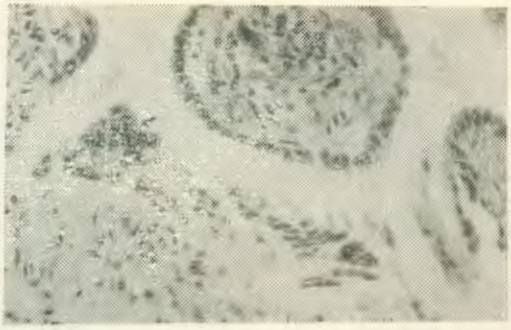

Fig. 3
Endocervix with mucocal fold (Arbor vitae) showing dark staining IgA (Arrows) cells in the upper central part (Peroxidase-Antiperoxidase stain for IgA with Haematoxylin x 400).

*Spontaneous Delivery of Dicephalus at Term—Murty & Roy p.* 265


Fig. 1
X-ray of the Decephalic monster.

*Histopathology of Ovaries during Pregnancy—Sheth et al. pp.* 190-192

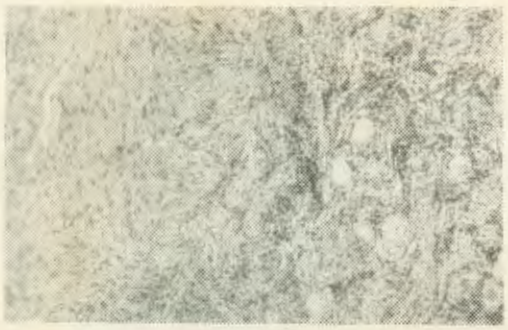

Fig. 1
Ovarian biopsy at III trimester. Note the greatly thcikened fibrous capsule occupying the right half of the field. Few primordial follicles are seen in the cortical stroma on the left side. H & E x 200.

Fig. 2
Scanner view of an ovarian biopsy of sufficient size, but not a single ovum or follicular structure is encountered. H & E x 40.

*Leioyoma of the Ovary—K. Verma et al. p.* 274

Fig. 1
Cut surface of ovarian tumor showing whorled appearance. The arrow points to compressed ovarian tissue at the periphery.

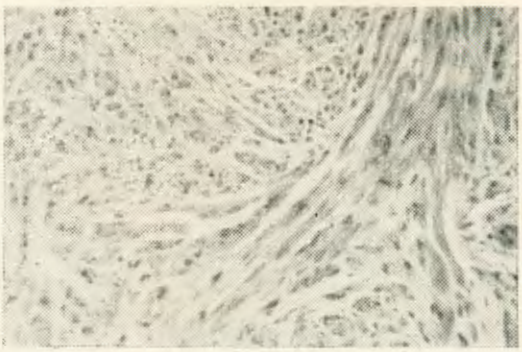

Fig. 2
Microphotograph showing bundles of smooth muscle cells.

*Iniencephaly with Meningoencephalocele—Murty & Roy p.* 266

Fig. 1
Iniencephaly with meningoencephalocele.

*Omphalocele—Purwar & Jawade p.* 267


Fig. 1
Showing fetal liver, intestines and membranes protruding out of vulva.
L—Liver I—Intestine M—Membrane.

*Bilateral Malignant Ovarian Inert Lipid Cell Tumour—Chaudhari p.* 269

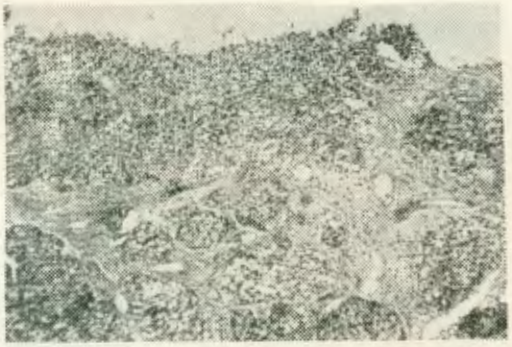

Fig. 1
Bilateral ovarian lipid cell tumour (predominantly hilu-cell type), histologically benign but clinically had metastases. H & E x 80.

*Retroperitoneal Cystic Terratoma Simulating Ovarian Cyst—Murty & Murty p.* 270

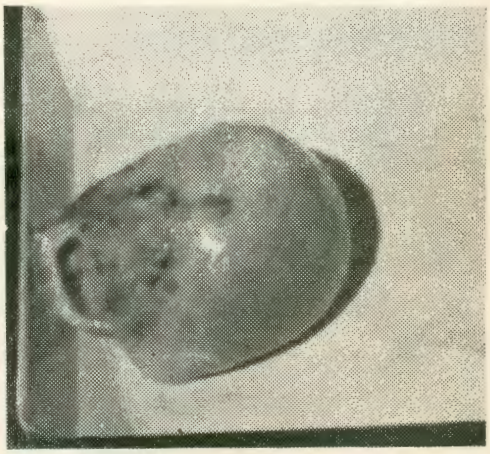

Fig. 1
Photograph showing the retroperitoneal cystic terratoma.

Fig. 1
Vaginogram 3 years after ward mayo operation using condom filled with Ba-sulphate solution.

Fig. 2
Vaginogram in a case procedentia showing whole of the uterus coming outside the vulva after straining.

Fig. 3
Vaginogram without straining in the same case of procedentia 3 months after ward mayo operation, showing restoration of vaginal contour after the operation.

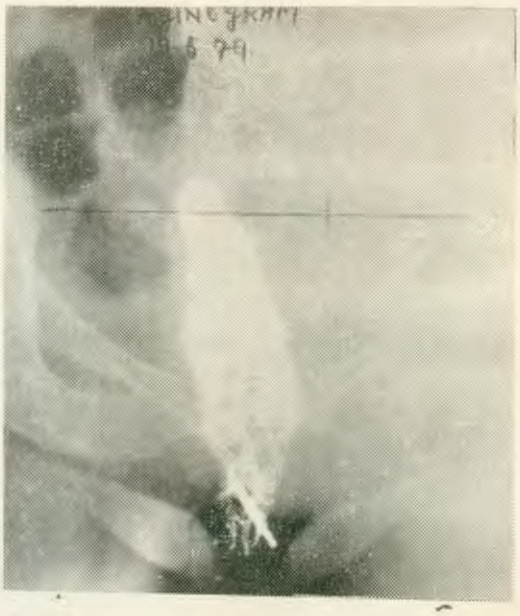

Fig. 4
Vaginogram in a patient of menorrhagia after vaginal hysterectomy without straining.

*Vaginogram—Das & Ghatak pp.* 242-245

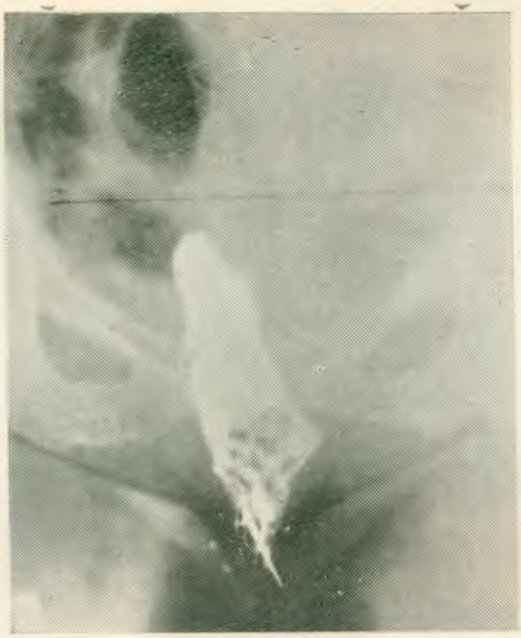

Fig. 5
Vaginogram of the same patient after vaginal hysterectomy with straining showing that the vagina is well supported after operation.

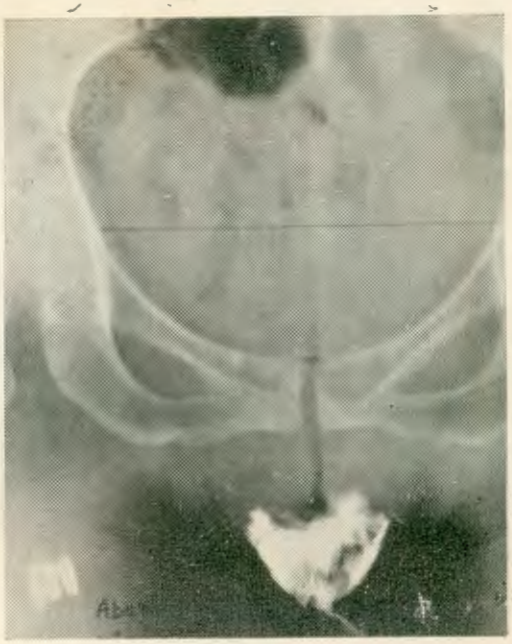

Fig. 6
Vaginogram in a patient of vault prolapse after straining showing that the vaginal vault has fallen down.

*Pre-Operative Excretory Urography in Prolapse Cases—Sandhu et al. pp.* 227-229

Fig. 1
Shows increased amount of residual urine.

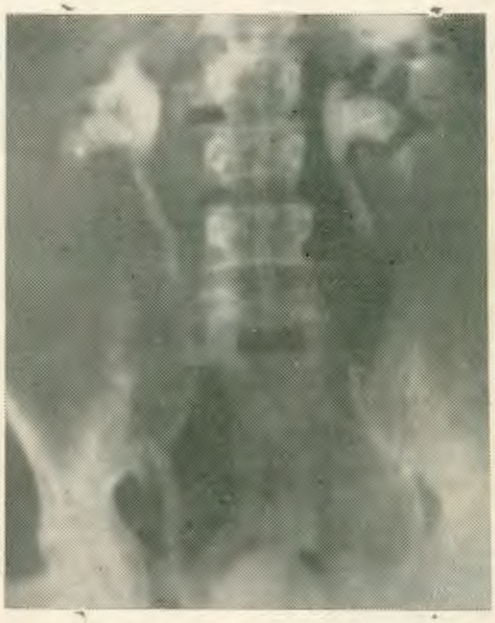

Fig. 2
Shows marked elongation of uterus with descent of bladder.

*Pre-Operative Excretory Urography in Prolapse Cases—Sandhu et al. pp.* 227-229

Fig. 1
Shows bilateral hydroureter and hydronephrosis.

*Amnioscopy and Assessment of Feto-Placental Complex—Ambiye & Alwani pp.* 178-182

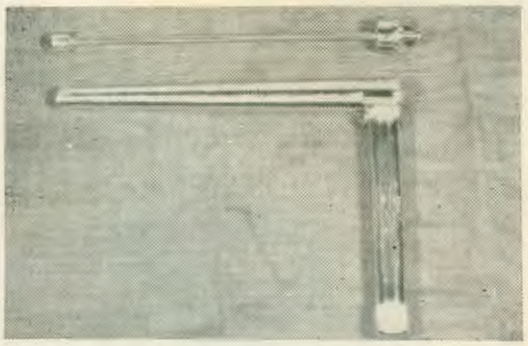

Fig. 1
A 16 mm aminoscope with bult in battery operated light source.

*Tuberculosis of Vulva—Mishra et al. pp.* 276-277

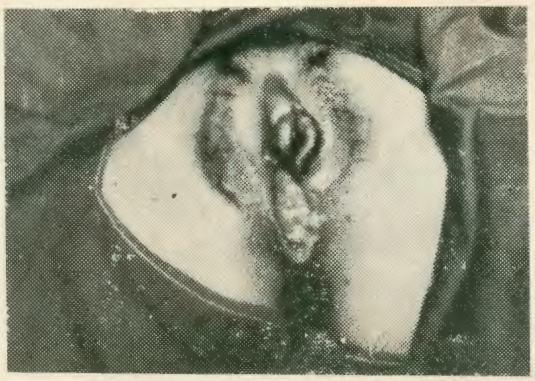

Fig. 1
Showing tubercular ulcer involving lower halves of the labia minora extending upto the posterior commissure.

Fig. 2
Shows squamous stratitied epithelium and fibrous subcutaneous tissue along with tuberculous granuloma.

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