REVIEW OF LITERATURE
The objective of hormone replacement therapy is obviously to enhance the potential benefits and minimize the risks. Over all, the outcome of therapy is reflected in lower mortality rates for those who have received treatment as compared with those who have not (Pititti et al, 1987; Hunt et al, 1987 and Henderson et al, 1991).

It is widely recognised that young women enjoy a significant degree of protection against ischemic heart disease when compared with men of similar age groups (Kannel et al, 1976). This sex difference diminishes with increasing age. This had led to the postulation that the hormonal milieu of the premenopausal woman plays an important cardio-protective role.

Rosenberg et al estimated the relative risk of myocardial infarction among women who underwent bilateral oophorectomy before the age of 55 years to be seven times that of premenopausal woman.

Gordon et al (1978) in the Framingham study showed that there was a significant excess incidence of coronary heart disease in women with surgical menopause.

Lauritsen et al (1973) has shown that the mechanism which occur in connection with hot flushes is better controlled by estrogen than by a placebo. After crossing over to placebo therapy from oestrogen treatment there is a worsening of this symptom.
Emotional function seem to be more favourably influenced than cognitive variables (Rausano et al., 1975).

Anxiety and worry about oneself often disappear (Campbell and Whitehead, 1977).

Kantor et al (1968) and Michael et al (1970) in double blind studies on geriatric patients showed that estrogen therapy over more than 36 months improved learning ability and concentration. During placebo treatment of the same duration these parameters worsened.

Estrogen also improve the readings for the social contact and psychic alertness in aged women (Coldwell, 1952; Dueker, 1957; Evans and Marmorston, 1963; Coldwell and Watson, 1954 and Kopera, 1973).

Fedor-Freybergh (1977) demonstrated in a double blind trial that estrogen medication exerts positive influence on many psychological functions in the climacteric.

Improvement of memory was found by Campbell (1976).

Estriol increases attention and alertness. (Vanhulle and Deud, 1976). Insomnia and anxiety react more favourably to tranquilizer than to oestrogen, they react however, best to a combination of both (Shaffery et al., 1969).

Cooper et al (1976) observed insomnia and arthralgia respond better to oestrogen than to placebo therapy.

Greenblatt et al (1950), Lauritzen (1973), Utian (1975) and Coop (1976) have observed that hot flushes and profuse sweating are quickly and significantly reduced by estrogen treatment.
Ooike et al (1976) observed that after a change from estrogen to placebo in cross over designed studied the hot flushes worsen considerably. After changing from placebo to estrogen the condition is considerably improved.

Estrogen medication also abolishes dizziness and tingling sensation and the concomitant rise of blood pressure which occurs with hot flushes (Lauritzen and Velibese, 1961).

Joswig-Priewe et al, (1973), Lauritzen and Muller et al (1977) observed that a consistent and favourable effect is also obtained by local and parental estrogen administration in atrophic condition, such as vaginitis and kraurosis vulva at .. vaginae when painful intercourse (dysparenic) is the problem.

Urethral carunde (Ectropium urethrae) reacts very readily to estrogen, disappearing completely after a few weeks of estrogen treatment (Foffmann, 1950b; Lauritzen and Muller, 1977).

Smith et al (1977) observed that atrophic cystitis and urethritis with corresponding symptoms can certainly be ameliorated by estrogen medication as shown by urinary cytology and disappearance of the complaints.

Estriol, ethinyl estradiol cyclopentynol ether and estradiol valerate have been reported to improve first and even second degree shows incontinence (Lambillon, 1971; Wallner and Soost, 1971; Bol, 1950; Krong, 1959; Slundery, 1963; Maxelmueller et al, 1954).
Fedor-Freyberg (1977) observed that in some climacteric women libido is decreased because of nervousness, irritability and depressive mood, severe hot flushes and feeling of ill health. In such cases libido and sexual activity can be improved by estrogen treatment.

Master and Johnson et al (1977) observed that vulval or vaginal atrophy and inflammation lead to dyspareunia the treating of these symptoms with estrogens may also restore normal sexual feelings and activity by normalizing the structure and function of the organ.

Semmen and Wegner et al (1982) observed that oestrogen significantly increased blood flow to the vagina and the vulva.

Monly and Dallesy (1977) observed that estrogen improved vaginal lubrication.

These are prospective studies from Meemos et al (1975), Dequeker and Ferin (1977), Faruhjelhum (1976), Lindsay (1976), Nordin (1976), and Aitken (1974a and b) demonstrating that in non substituted castrated women the bone loss is significantly greater (as measured by the change in cortical thickness) than in patients with ethinyl estradiol or mesteranol in a daily dose of 20–25 ug.

Cristiansen et al (1981) observed that postmenopausal bone loss is primarily oestrogen dependent and may be prevented by oestrogen replacement therapy.

Nordin et al (1981) observed that major cause of postmenopausal osteoporosis appears to be an increase
in bone resorption.

Aitken et al (1971) observed that oestrogen effects on calcium metabolism are primarily mediated through an increase calcitonin activity.

Erikson et al (1988) observed that oestrogen blasts were found to express oestrogen receptors.

Lindsay et al (1980) observed that the protective effect of oestrogens continue for as long as oestrogen is replaced. Stopping the oestrogen therapy results in acceleration of bone loss again. The rate of bone loss being identical to that of which occurs in the immediate postmenopausal layers. The net effect would be to buy time and delay the onset of clinical osteoporosis while oestrogen replacement is provided.

Prill and Lauritzen (1970) observed that estrogen therapy alleviates the periarticular complaints in postmenopausal patients in a high percentage of cases.

Lindsay et al (1984) observed that the minimum effective dose in one study was found to be 0.625 mg conjugated egwine, estrogen (Premarin) or its equivalent for oral therapy.

Ettinger et al (1987) observed that 1.5 gm of total calcium is combined with a reduced dose of conjugated oestrogen (0.3 mg) this offers the same protection as 0.625 mg conjugated oestrogens alone.

Christiansen (1990) observed that oestrogen is also effective when given by parenteral routes,
the serum oestradiol level is sufficient.

Gallaghen et al (1989) observed that addition of progesterone does not impair the bone preserving function of oestrogen. The minimum dose of oestrogen required to prevent bone loss was found by Horsman to be 15 ug of ethinyloestradiol per day. The equivalent dose of conjugated equine oestrogen being 0.625 mg.

The duration of protection of bone mineral content appears to be for as long as oestrogen is administered in sufficient dosage with bones loss occurring again after withdrawal and protection of bone mineral content over at least 10 years of HRT (Lindsay et al, 1980).

Rauramo and Punnonen (1976) have observed that atrophic changes which occur in the skin following oophorectomy can be prevented and reversed by the administration of estrogen.

The antistrophic action of oestrogen is demonstrated by epidermal thickness measurements and by thymidine incorporation rate determinations. These findings have been confirmed to some extent by the radiological measurement of dermal thickness and by measuring the incorporation of thymidine and proline into human skin explants in the presence of estrogen (Sharad and Marks, 1976; Marks and Shahrad, 1977).

Oestrogen treatment abolishes the temporary increase in blood pressure which accompanies hot flashes
(Lauritzen and Velibesi et al, 1961).

Notelovitz et al (1983) observed that oral contraceptives containing synthetic oestrogen in relatively higher doses are associated with an increased risk of spontaneous thrombosis whereas natural oral oestrogen replacement does not alter the clotting factors and has no deleterious effect on coagulation.

Coope et al (1975) showed an increase in factors VII and V and in increase in thrombin induced platelet aggregation after 18 months of conjugated estrogen use.

Stangel et al (1977) reported that 14% of patients in a control group and 57% of oestrogen treated women were found to be hypercoagulable when multiple coagulation factors were measured. A study conducted by Ross (1976) indicated a protection effect of oestrogen in the postmenopausal women with a risk of myocardial infarction of 0.43. This protection effect may not be maintained if a patient smokes, 16 out of 17 postmenopausal women between the age of 29 and 45 years who sustained nonfetal myocardial infarction were found to be smoker and 9 out of these 17 women were receiving conjugated oestrogen. This study suggested a 7.5 fold increase in nonfetal myocardial infarction in the women of this age range who both smoke and taking conjugated oestrogen.

Clinically an increase in thromboembolic events has not been established in postmenopausal women on oestrogen therapy in studies in which other risk factors
are controlled (Studd, 1978).

Utian et al (1977) observed that administration of 2-3 times the substitution doses (4 mg estradiol valerate or 5 mg conjugated estrogens) to 50 castrated women over a period of 1 year influenced diastolic pressure in only 2 patients.

Crane et al (1971) described five women who developed hypertension on low doses of conjugated oestrogen taken from 3-6 months in the menopause. All women subsequently become normotensive often discontinuation of estrogen therapy over a period of 1-7 months. Similar findings were described by Pleffer (1978) and Notelovitz (1979).

Notelovitz (1975) strolfeld (1977), Utian et al (1977) observed that no significant weight increase occurs following therapy with conjugated estrogens or estradiol valerate.

Aartgurts (1972) observed that there was improvement in wrinkles skin appearance elasticity and blood perfusion of skin after 6 and 12 months estradiol succinate treatment (4 mg) in a high percentage of patients. Sanel (1982) observed that oestrogen has an effect on perception and skin sensitivity.

Boyd et al (1973) observed that administration of various estrogens, such as ethinyl estradiol, mestranol, conjugated estrogens, micronized estradiol, estradiol...
mestranol valerate and estrone sulphate nearly always produces a decrease of total lipids and of total cholesterol, especially of beta-lipoprotein cholesterol while increasing the phospholipid.

Ethinyl estradiol, mestranol and conjugated estrogen (in doses of more than 2.5 mg) usually elevate triglyceride levels (Furman, 1969; Lebech and Barggard 1973 and Boyd, 1973).

Estriol and Estradiol may sometimes even decrease triglyceride level if they are elevated (Prroost et al, 1969; Larson-Cohn, 1976; Punnonen and Rauramo, 1976).

Hirvonen et al (1981) studied three groups of post menopausal women with estradiol valerate a dose of 2 mg/day and subsequently added 10 mg of norethindran acetate medroxy progesteron acetate or norgestrel. Total cholesterol decrease in all groups by 10-18% from baseline values. Significantly, both estradiol norgestrel regimen decreased LDL by 20% during treatment. While no significant change in HDL was noted on medroxy progesterone therapy.

Tikaren et al (1978) reported an average 22% reduction in LDL concentration and 30% increase in HDL with administration of estradiol valerate.

Potocki (1971), Burch et al (1974) observed that frequency of coronary thrombosis has been seem to be significantly lower in women on long term estrogen treatment than in nontreated population of similar age and residence.
In the epidemiological study of Rosenberg et al (1976), the relative risk of myocardial infarction in long term estrogen treated patients was slightly lower (relative risk 0.97) than in the control group.


Connor et al (1989) and Miller et al (1991) demonstrated that postmenopausal oestrogen administration lower the serum concentration of LDL cholesterol and increase the serum concentration of HDL cholesterol, particularly the HDL₃ subfraction in both cross-sectional studies and clinical trials.

Miller et al (1991) observed that apolipoprotein A-I which has an inverse relationship to the cardiovascular morbidity.

Spelcey et al (1976) observed that aggravation of glucose intolerance in women taking oral contraceptive is primarily attributable to the progestin component and not the oestrogen component of the oral contraceptives.

Spelcey et al (1987) demonstrated that natural oestrogen replacement has no deleterious effect on the carbohydrate metabolism of postmenopausal women.

Ballejo et al (1983) observed that use of oestrogen actually improve glucose tolerance by enhancement of insulin receptor binding.
Osteoporosis is the rare condition in the young and healthy adults; however by the age of 75 years, fully 50% of U.K. resident females have sustained such a reduction in their bone mineral content that they may be labelled osteoporotic (Nordin, 1984).

Edwin Currie, the former U.K. Junior Health Minister, stated that in 1985, 35,000 women in England and Wales sustained a femoral neck fracture, of whom 26,000 (74%) were aged over 75 years. The age-specific incidence of femoral neck fracture doubles every decade from age of 60 years (Gordan and Vaughan, 1977), and the incidence appears to be showing a true increase after allowance for the present demographic increase of the population at risk (Boyce and Vessey, 1985).

A marked rise in the bone turn over rate occurs at the perimenopause (Heaney et al, 1978). In the human, Eriksen et al (1987) have demonstrated the presence of oestrogen receptors in cultured trabecular osteoblasts. The rate of loss of trabecular bone in the immediate post menopause may near 5% per year for natural menopause and a nearly 9% per year after surgical castration (Gennant et al, 1983).

It has been shown that osteoblasts contain progestogen receptors (Johnston et al, 1978) which also bind glucocorticoids with high affinity. Progestogens may also have a direct effect on the C cells of the thyroid
and promote skeletal protection via calcitonin release (Greenberg et al., 1986) as well as promoting bone formation (Lindsay et al., 1978).

US endocrinologist, Fuller Albright, first proposed that there was a link between ovarian failure and osteoporosis (Albright, 1940).

There is no over representation of highly parous women among patients who later develop osteoporosis and oral contraceptive usage may similarly provide a protective effect (Goldsmith and Johnston, 1975). Indeed calculation of aggregate sex steroid exposure in the period of fertility between puberty and menopause indicates that the longer an individual remains in the fertile 'window', the less her risk of postmenopausal osteoporosis (Lindsay and Hart, 1984).

Christiansen et al (1987) found that a set of plasma and urinary biochemical parameters correlated well with current rates of bone loss measured over a 2 years period by single photon absorptiometry.

The Consensus Development Conference on Osteoporosis held at NIH, Bethesda in 1984, concluded that women should seek advice from a medical adviser in the immediate postmenopause as to whether hormone replacement therapy is or is not indicated.

The use of an added progestogen to induce endometrial shedding is generally seen as prophylactic against endometrial cancer provided that adequate duration
of dose is involved (Hunt et al, 1987).

In summary, they found that there was a relative risk of 1.59 (95% confidence limits 1.18-2.10) of a breast malignancy in HRT users although interestingly less deaths from the disease were observed than would have been expected in the population studied, the relative risk of death being 0.55 (95% confidence limits 0.28-0.96).

Data from the United States have generally shown a protective effect from oestrogen against death due to ischaemic heart disease (Stampfer et al, 1985; Henderson et al, 1986), while in U.K., Hunt et al (1987) have shown a 0.7% relative risk of death from stroke among 'ever users' of HRT.

In the longer term it has been repeatedly shown that hormone replacement therapy by oestrogen alone (Lindsay et al, 1976; Horsman et al, 1977; Nachtigall et al, 1979) or in combination with a progestogen (Munk-Jensen et al, 1988) will halt postmenopausal or post oophorectomy losses of BMC (Bone mineral content).

The newer transdermal oestrogen patch has been shown to be effective in reducing the fasting urinary calcium creatinine ratio in all of its three available doses of 25, 50 and 100 ug. Chetkowski et al (1986) and prospective data on the ability of transdermal oestrogen to protect BMC in the medium term are urgently required.

Lindsay et al (1978) were the first to demonstrate that a progestogen might be capable of exerting a protective
effect on the skeleton. Mirethisterone in a dose of 5 mg daily shows biochemical evidence of being protective to the skeleton (Selby et al, 1985) and Neary et al (1988) have shown prolonged suppression of bone specific alkaline phosphatase by mirethisterone in the postmenopause indicating suppression of bone turnover.

Bone formation has been shown to be enhanced in the spayed beagle (Karambolova et al, 1986) by the use of continuous progestogen in the form of medroxyprogesterone acetate (MPA), and there is good evidence that in the beagle model the drug shortened resorption times in the cortical bone remodelling unit (Snow and Anderson, 1985).

Ettinger et al (1985) found a 50% reduction in the occurrence of spinal and distal fractures in women who had been taking unopposed oestrogen compared with those never exposed to oestrogen.

Weiss et al (1980) showed that the risk of fracture of proximal femur or distal radius was reduced by 50-60% in women who had taken oestrogen as HRT at least 6 years.

Hutchinson et al (1979) found significant protection from oestrogen against femoral and radial fracture.

Using a prospective format, Riggs et al (1982) were able to demonstrate that in 144 patient-years of exposure to oestrogen and calcium, the vertebral fracture was 181 per 1000 patient-years and significantly less than
the rate of 834 per 1000 patient-years found in an untreated and age matched control group.

Exogenous unopposed oestrogen therapy was found to increase the risk of developing endometrial cancer 2.15 times as compared with risk in non users (Henderson 1989).

The increased risk is evident even after use of unopposed oestrogens for a period as short as 12 months and this risk persists long after the treatment is discontinued for as long as 10-15 years (Shapiro et al, 1985; Paganine-Hill et al, 1989).

Recent cohort studies (Paganine-Hill et al, 1989; Persson et al, 1989) supported the findings that increasing duration of oestrogen exposure is associated with increased risk of endometrial cancer but no minimum safe period has been found.

The benefit of adding a progestogen to oestrogen replacement therapy to reduce the risk of oestrogen induced endometrial cancer has been clearly demonstrated in clinical practice (Gambrell, 1988).

Exogenous progestagens reduce the total content of oestradiol receptors in the endometrium (Bayard et al, 1978; Martin et al, 1979). They also increase the activity of the dehydrogenases that convert oestradiol to oestrone which is a biologically less active oestrogen (Guspride, 1978; King et al, 1981).
The oestrogen-progestogens users were also noted to have significantly lower risks of endometrial cancer when compared to the untreated population (incidence 245.5 per 10,000) (Gambrell, 1988).

The duration of progestogen addition appears to be of great importance. There is a significant reduction in the incidence of hyperplasia from 20% to 30% with unopposed cyclic oestrogens, to 4% when progestogens were added for seven days each month (Whitehead et al, 1979).

Most case control studies fail to find evidence of significant overall excess risk in patients in ever users of ERT when compared to non users (Jick et al, 1980; Ross et al, 1980; McDonald et al, 19860 Brinton et al, 1986 and Wingo et al, 1987).

A meta-analysis of the literature on estrogen replacement therapy and breast cancer published since 1972 (Dupont and Page, 1991) suggested that the overall relative risk of breast cancer associated with HRT was low (1.07).

Several case control studies using population controls indicate that long term oestrogen use is associated with a small to moderate increase in the risk of breast cancer (Ross et al, 1980; Brinton et al, 1986).

Brinton et al reported overall relative risk of breast cancer (1.47) (95% CI : 0.9 to 2.3) after 20 years of use.
It is possible that duration risk relationship is affected by dosage and type of treatment and that the contradictory results could be due in part to these different aspects of therapy (Dupont and Page, 1991).

Hoover et al (1976) in a prospective study of 1,891 patients taking conjugated oestrogens noted increasing relative risk with follow up duration and progressed to 2.0 (96% confidence interval 1.1 to 3.4) after 15 years of use.

The large prospective study by Bergkvist et al (1989a) found increasing relative risk with increasing duration of treatment reaching a relative risk of 1.7 after nine years of treatment (95% confidence interval 1.1 to 2.7).

Dupont and Page (1991) quoted a relative risk of 1.08 (95%) confidence interval(0.96 to 1.2) for women who took 0.625 mg or less of conjugated oestrogen per day. This is consistent with the evidence that low dose conjugated oestrogen therapy does not appreciably increase breast cancer risk.

Bergkvist et al (1989) noted that the use of oestradiol was associated with a 1.8 fold increase in risk after more than six years of use (5% confidence interval 0.7 to 4.6) while no such increase in risk was noted after use of conjugated oestrogens or other types of oestrogens, mainly oestradiol.
Oestrogens in combination with progesterone may actually increase the risk of breast cancer over that associated with exposure to oestrogen alone (Key and Pike, 1988).


The use of an added progestogen to induce endometrial shedding is generally seen as prophylactic against endometrial cancer provided that adequate duration of dose is involved (Hunt et al., 1987).

Hunt and her colleagues (1987) found that there was a relative risk of 1.59 (95% confidence limits 1.18 to 2.10) of a breast malignancy in HRT users although, interestingly, less deaths from the disease were observed than would have been expected in the population studied, the relative risk of death being 0.55 (95% confidence limits 0.28 to 0.96).

Sullivan et al assessed the degree of coronary artery occlusion rising arteriography. They excluded women with mild or moderate stenosis and included only those with more than 70% occlusion. The age adjusted relative risk was 0.44 and this was not greatly influenced by age. Some
protection was observed in high risk groups e.g. the protective effect of HRT was stronger in those with higher as compared with lower levels of cholesterol.

Gruchow et al included a substantial minority with previous myocardial infarction, approximately 32% among oestrogen users and approximately 40% among non users. An occlusion score was derived and women were classified as having a low, moderate or severe score. The relative risk for severe coronary occlusion for current oestrogen users was 0.37 and for moderate occlusion was 0.59.

The nurses health study (Stampfer et al, 1985) is the largest prospective, cohort study to investigate the relationships between arterial disease risk and HRT. In 1976, 121700 females registered nurses completed a questionnaire and were enrolled. A further questionnaire was completed in 1978 and 32317 postmenopausal women without prior coronary artery disease were followed for an average of 3 years. Current users of oestrogens has a relative risk of 0.3, among past users this was 0.7.

According to Ottosson et al (1985) medroxy progesterone acetate causes potentially undesirable lipid effects. In a 3-months prospective study of postmenopausal women taking oral oestradiol 2 mg/day the addition of medroxy progesterone acetate, 10 mg/day reduced HDL-cholesterol by approximately 8% and HDL$_2$ cholesterol by as much as 18%.