

Menopausal Disorders

Treatment Is Now More Commonplace

Executive Summary

The number one complaint of women undergoing menopause is a vasomotor instability that presents as hot flashes and sweats. A hot flash is a sudden onset of intense body heat with profuse perspiration and reddening of the skin over the head, neck and chest. Flashes last from a few seconds to several minutes and are more frequent and severe at night, when they awaken women from sleep. The frequency varies greatly.

After menopause, the mortality rate from CHD increases greatly. In fact, it is the leading cause of death in older women. As experience is gained in tracking women on hormone replacement therapy, the positive effects of treating women with estrogen are becoming apparent. In 1992 Grady et al. published a study in the Annals of Internal Medicine that analyzed 32 epidemiologic studies. All but one showed that estrogen use lowers the risk of CHD by 35%.

A study published in January 1996 in the Journal of Obstetrics and Gynecology provided additional evidence of benefit to postmenopausal women of taking estrogen. In women over the age of 80, the rate of death from all causes was 46% less in the group receiving hormone replacement therapy. This group had a 60% reduction in coronary heart disease and 73% reduction in mortality related to stroke.

In addition to women undergoing natural menopause, every year a large number of women undergo the removal of their uterus, or hysterectomy. This is the second most performed surgery in the US; only cesarean sections are performed more often. There are many clinical reasons for this procedure. It is often done as a life-saving procedure in order to remove cancers, to stop hemorrhaging ,or to treat infections.

Women who have undergone a surgical menopause caused by the removal of their ovaries are also considered to be candidates for therapy. In fact, because surgical menopause is more abrupt than natural menopause, women who undergo hysterectomies have more symptoms and a greater need for therapy. A majority of physicians believe that, because these women do not have an endometrium, it is acceptable to give unopposed estrogen.

Disturbingly, in the June 15, 1995 issue of the New England Journal of Medicine, results were published from the Nurses' Health Study that was initiated in 1976 and extended to qualify the relationship between the use of hormones and the risk of breast cancer in postmenopausal women. The women in the study group were asked to fill out questionnaires every two years to update information on their menopausal status, use of HRT, and any diagnosis of breast cancer. The risk of breast cancer was significantly increased among women who were currently using estrogen alone or estrogen plus progestin, as compared with post-menopausal women who had never used hormones.

Intravaginal rings are under development by several companies. The advantage of these delivery systems is the ability to provide continuous delivery of estrogen and progestin for up to 3 months. This is especially appealing in treatment of women who are unable to see a physician as often, or who may have difficulty remembering to take a daily medication, as in the case of certain women in a nursing home environment, or those suffering from Alzheimer's or other dementia.

Menopausal therapy is one of the truly exciting growth markets of the future. The population in the age segment that is most affected is projected to increase by 40% between 1994 and 2010. The percent of women seeking therapy and the physicians who believe that therapy is necessary is also expected to increase as evidence of the benefits mounts. The number of women under 50 with ovariectomies will also contribute to this growing market.

Natural Menopause

As women enter their forties, ovulation becomes less frequent. The number of follicles decreases and those that remain become less sensitive to gonadotropins. As this happens, less and less estrogen is produced. As time goes by, there is not enough estrogen to bring about a build-up of the endometrium and menstruation. The time from the beginning of this event leading up to the cessation of menstrual periods is termed the perimenopause. A woman is said to have undergone menopause when she has not had a menstrual period for one year. Menopause, generally, takes place in women in the US between the ages of 48 and 55. The median age is 51.

Menopause is usually diagnosed by the lack of menstruation and the presence of hot flashes. Sometimes the physician will confirm the diagnosis by measuring LH and FSH. After menopause, both of these hormones are greatly elevated over premenopausal levels. In women in perimenopause, FSH is elevated while LH usually remains in the normal range. In the past there were problems differentiating between pregnancy and menopause by diagnostic methods because of the cross reactivity between FSH, LH and hCG; however, newer assays utilizing monoclonal antibodies are much more specific. Levels of estrogen are, obviously, lower in menopausal women but these are not usually measured because the assays are more difficult to do.

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Although some women and physicians consider menopause to be a natural transition that does not require treatment, most opinion leaders in women's health care now recommend therapy to at least alleviate problematic symptoms.

The number one complaint of women undergoing menopause is a vasomotor instability that presents as hot flashes and sweats. A hot flash is a sudden onset of intense body heat with profuse perspiration and reddening of the skin over the head, neck and chest. Flashes last from a few seconds to several minutes and are more frequent and severe at night, when they awaken women from sleep. The frequency varies greatly. They occur in most women over a one- to two-year time frame, but can occur over a period of more than five years.

While the cause of hot flashes is thought to be in the hypothalamus, the exact mechanism is unknown. Hot flashes are known to coincide with LH surges, but these are not believed to be causal.

Women undergoing menopause experience a number of psychological and physical symptoms. Among these are increased tension, depression, anxiety and irritability. The relationship between these symptoms and estrogen is difficult to establish. They also have a higher incidence of headaches, muscle pain, and insomnia. The latter can be caused by the hot flashes and night sweats.

In addition, women undergoing menopause exhibit various atrophic conditions. Low estrogen production in late menopause causes atrophy of all mucosal surfaces. Atrophy of the vaginal lining is common and can cause itching and painful intercourse. Genitourinary atrophy leads to urinary difficulties such as urgency incontinence, urinary frequency, urethritis not caused by bacteria, and cystitis.

Finally, there are health problems that are secondary to long-term estrogen loss. The most important of these are osteoporosis and coronary heart disease (CHD).

After menopause, the mortality rate from CHD increases greatly. In fact, it is the leading cause of death in older women. As experience is gained in tracking women on hormone replacement therapy, the positive effects of treating women with estrogen are becoming apparent. In 1992 Grady et al. published a study in the Annals of Internal Medicine that analyzed 32 epidemiologic studies. All but one showed that estrogen use lowers the risk of CHD by 35%. The one exception was the prestigious

Framingham Study, which had equivocal results. Estrogen-only replacement is referred to as ERT, while estrogen with another hormone is referred to as HRT.

Estrogen replacement is thought to reduce CHD by multiple mechanisms. Recent evidence points to improvement in a woman's lipid profiles. Results from the multicenter Postmenopausal Estrogen/Progestin Interventions (PEPI) trial were published in the January 18, 1995, issue of the Journal of the American Medical Association. In this trial, 875 postmenopausal women between the ages of 45 and 64 were studied to evaluate the effects of HRT on risk factors for heart disease over a three year period. The study was divided into five groups. One group received daily conjugated estrogen (Premarin) only, the second received daily conjugated estrogen and a natural progesterone for 12 days a month, the third received daily conjugated estrogen and a synthetic progestin for 12 days a month, a fourth received daily estrogen plus daily synthetic progestin, and the last group served as a placebo control.

The four groups that received the hormones had significantly higher average blood levels of high-density lipoprotein (HDL) and lower fibrinogen levels. Both of these results would be considered positive in relation to CHD risk; this was an extensive, well-designed study.

The HERS (Heart and Estrogen/progestin Replacement Study) indicated that HRT did not lower the risk of coronary heart disease in postmenopausal women who already had heart disease. In fact, those women who received PremPro in this study had more heart attacks than the patients on placebo, at least during the first year of study. As the study continued for a longer period time, up to four years, this effect seemed to be less pronounced.

Three different studies have concluded that HRT increases the risk of venous thromboembolism by two to four times. However, it is still believed that the benefits in reducing osteoporosis and coronary heart disease far outweigh the risks. Currently, Premarin/Prempro are indicated for cardiovascular benefits as well as relief of vasomotor symptoms in post-menopausal women in several countries outside the US.

In addition to cardiovascular benefits and the already well-accepted protective effect of HRT against osteoporosis, newly published studies continue to suggest more benefits of hormone replacement therapy to the health of women after menopause.

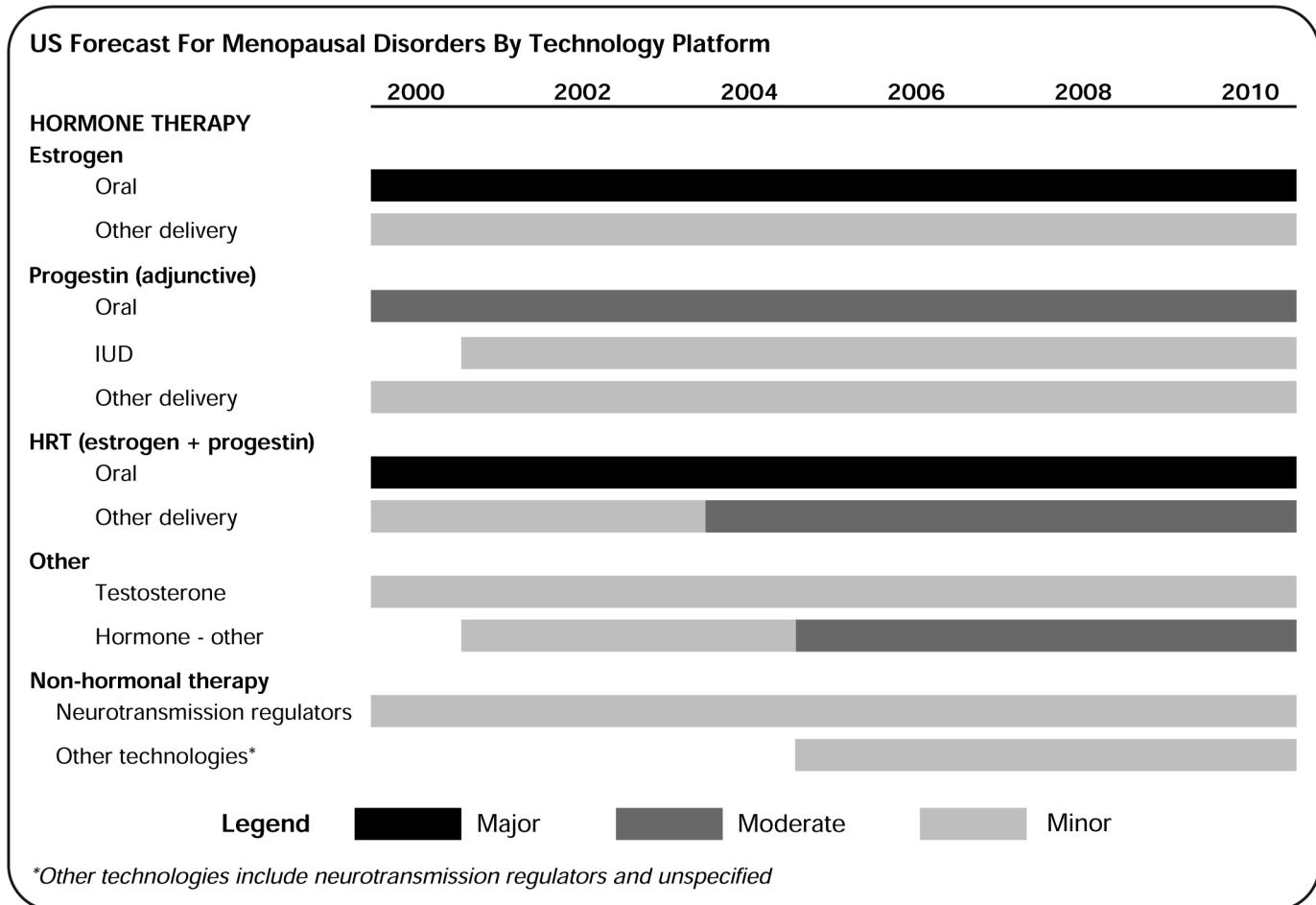
Table 1

US HRT/ERT Demographics – (Thousands of Woman)					
	45-54	55-64	65-74	75+	Total
1990	12,824	11,158	10,139	8,447	42,568
2000	18,477	12,369	10,166	10,553	51,565
2010	22,468	17,949	11,235	11,697	63,349

Source: US Bureau of the Census/Consumer Reports

A study published in January 1996 in the Journal of Obstetrics and Gynecology provided additional evidence of benefit to postmenopausal women of taking estrogen. In women over the age of 80, the rate of death from all causes was 46% less in the group receiving hormone replacement therapy. This group had a 60% reduction in coronary heart disease and 73% reduction in mortality related to stroke.

A study conducted at the US National Institute of Aging from 1990 to 1995 showed that hormone replacement therapy in postmenopausal women had a protective ability against Alzheimer's and Parkinson's diseases. Estrogen is believed to protect neurons from damage. Estrogen appears to act upon the brain by stimulating cholinergic markers preventing neuronal atrophy in the hippocampus and, by increasing cerebral blood flow,

Table 4

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among other mechanisms. The study demonstrated an incidence of Alzheimer's disease that was half the rate in women who were not on hormone replacement therapy. Over five million people in the US have either Alzheimer's or Parkinson's disease. **Wyeth-Ayerst (St Davids, PA)** is expected to conduct a Phase II clinical trial treating Alzheimer's patients with Premarin.

A recent study found an association between hormone replacement and a reduction in risk for colon cancer. An international clinical trial is planned in 30,000 postmenopausal women to determine the benefits of hormone replacement therapy over a period of at least 10 years. This study will compare the relative risks of developing several diseases in women taking estrogen compared to those who do not. Heart disease, stroke, breast cancer, osteoporosis, quality of life and psychological well-being will all be included in this study, called the WISDOM (Women's International Study of Long-Duration Oestrogen after Menopause) Study. There are a number of clinical trials ongoing to examine the benefits of HRT in preventing osteoporosis. Several of these studies so far indicate that administration of postmenopausal estrogen actually increases bone density mass in addition to reducing the loss associated with low estrogen levels after menopause.

Surgical Menopause

In addition to women undergoing natural menopause, every year a large number of women undergo the removal of their uterus, or hysterectomy. This is the second most performed surgery in the US; only cesarean sections are performed more often. There are many clinical reasons for this procedure. It is often done as a life-saving procedure in order to remove cancers, to stop hemorrhaging or to treat infections. There is much controversy surrounding the use of hysterectomies in nonlife-threatening conditions such as fibroids and endometriosis. Fibroid tumors are the most common reason for the procedure and are estimated to account for approximately one-third of all hysterectomies.

There are several techniques for performing a hysterectomy. A vaginal hysterectomy removes the uterus and cervix through an incision through the vagina. In a total abdominal hysterectomy the uterus and cervix are removed through an incision in the lower abdomen. Often the clinical problem requires that the ovaries and fallopian tubes be removed at the same time. When this happens, the woman is put into a surgical menopause because there are no ovaries to produce estrogen.

Therapy

Menopausal symptoms and health problems are generally treated by estrogen replacement therapy (ERT) with an oral or transdermal estrogen. The most widely used type of estrogen is an oral conjugated estrogen, Premarin, which has been on the market for more than 50 years. Conjugated estrogen contains several estrogenic substances, principally estrone and equilin, excreted in the urine of pregnant mares. There are also several brands containing only oral estradiol sold for the relief of menopausal symptoms. In addition to oral estrogen, **Novartis's (East Hanover, NJ)** Estraderm, a transdermal patch containing estradiol, has been on the market for almost ten years. Other estradiol patches include **Berlex's (Richmond, CA)** Climara, **Novartis' Vivelle**, **Warner-Lambert's (Morris Plains, NJ)** Fem-patch, and **Procter & Gamble's (Cincinnati, OH)** Alora.

When estrogen is given alone, it is termed "unopposed." This practice has been out of favor for several years and today estrogen is almost always given opposed by a progestin to women with an intact uterus. This is called hormone replacement therapy or HRT. The progestin most often prescribed in the US is Provera (**Pharmacia & Upjohn (Peapack, NJ)**). When unopposed estrogen is given, it causes a build-up of endometrial tissue. This results in an incidence of endometrial cancer that is two to eight times higher in women on ERT. Progestin therapy causes the endometrium to be shed and not remain built up, thus offsetting (or opposing) the effect of the estrogen.

The warnings against the risk of endometrial cancer are now going to be removed from labeling, per FDA guidance, on estrogen/progestin combination products. The use of HRT for perimenopausal women is under consideration as well; however, a number of clinical trials will need to be performed. It is not clear what degree of protection is gained against osteoporosis when a progestin is added to estrogen.

Most physicians agree that a progestin is needed in HRT, although the oral progestins on the market, that are not in combination products, do not have an official indication for this use. Pharmacia & Upjohn is pursuing such approval for Provera.

All estrogens are approved for the indication of relief of vasomotor symptoms. In the past, only Premarin and Estraderm had indications for the prevention of osteoporosis; however, recently all estradiol products have received approval for this indication. None of the estrogens have a cardio-protective indication, as yet.

There are two dosing methods for HRT - sequential and continuous. In sequential dosing, estrogen and progestin are given in a monthly cycle. The two main sequential methods of dosing are:

- Estrogen is given on days 1 to 25, and progestin is given on days 14 to 25. No medication is given on days 26 to 30, and then the cycle begins again.
- Estrogen is given on days 1 to 30 and progestin is given on days 1 to 12, and then the cycle begins again.

The majority of women (80%) on these regimens experience menstrual bleeding. The usual dose for the conjugated estrogen is 0.625 mg, but this is sometimes titrated to the individual patient. The progestin dose is 5 to 10 mg.

The continuous dosing method is newer and continuing to gain favor in medical circles. The estrogen dose is the same as in sequential therapy, but the progestin is lower, usually in the 2.5 to 5 mg range. As the name implies, they are given together continuously for days 1 to 30. After approximately four months, bleeding ceases and studies show an atrophic endometrium.

Women who have undergone a surgical menopause caused by the removal of their ovaries are also considered to be candidates for therapy. In fact, because surgical menopause is more abrupt than natural menopause, women who undergo hysterectomies have more symptoms and a greater need for therapy. A majority of physicians believe that, because these women do not have an endometrium, it is acceptable to give unopposed estrogen. A few believe that the progesterone still has a purpose in cancer and CHD prevention and add the progesterone to the therapy regimen.

Others believe that progesterone may actually negate some of the cardiovascular benefits of estrogen therapy. A follow-up study to the Nurses' Health Study examined the relationship between cardiovascular disease and utilization of HRT 16 years after initiation of the study. This study concluded that adding progestin to estrogen therapy did not increase the risk for cardiovascular disease over women on estrogen therapy alone.

Generally, women who stay on hormone replacement therapy are healthier than those who do not. The effects range from lowering of blood pressure to fasting insulin levels to higher HDL cholesterol.

The PEPI (Postmenopausal Estrogen/Progestin Interventions) Trial indicates that estrogen alone increases bone

marrow density. In the PEPI Trial, women who were on continuous combined estrogen and progesterone actually had a greater increase in bone mass density than with estrogen alone. The CHART (Continuous Hormones as Replacement Therapy) clinical trial indicates that a continuous regimen of both estrogen and progestin also protects against bone mass density decreases.

There is much concern over the effect of ERT and HRT on an increase in the incidence of breast cancer. However, recent studies are not conclusive. Completion of the Women's Health Initiative in 2007 will surely yield data enabling decision.

Disturbingly, in the June 15, 1995 issue of the New England Journal of Medicine, results were published from the Nurses' Health Study that was initiated in 1976 and extended to qualify the relationship between the use of hormones and the risk of breast cancer in post-menopausal women. The women in the study group were asked to fill out questionnaires every two years to update information on their menopausal status, use of HRT, and any diagnosis of breast cancer. The risk of breast cancer was significantly increased among women who were currently using estrogen alone or estrogen plus progestin, as compared with post-menopausal women who had never used hormones. This risk was especially significant in women who had used therapy for more than five years. The reader is referred to the original article for discussion beyond the scope of this article.

A study developed by Solvay (Paris, France) demonstrated that combination estrogen/androgen products have a positive effect on vasodilation. There was concern at one time that the addition of androgens would negate the effect of estrogens. Progestins have been found to diminish the positive cardiovascular effect of estrogen. Estrogen/androgen therapy may be beneficial in women who do not obtain complete relief of the effects of menopause from estrogen alone.

Obviously, the optimum HRT regimen is continuing to evolve. The final information as to the best method of therapy may not be available until the results of the Women's Health Initiative are announced in 2007.

Incidence and Prevalence

Menopause is a condition that is the result of women living longer lives. At the turn of the 19th century, the average life expectancy for women was 50 years and therefore most women died before the symptoms of

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menopause became a problem. Today, women can live thirty years, or more than one-third of their lives, beyond menopause.

The population of menopausal women is projected to increase greatly over the next 15 years. At present, there are approximately 95 million postmenopausal women in the US, Canada, and Europe. Only 10% to 20% of these are believed to be currently on continuing HRT.

Most women stay on HRT only for approximately one to two years during and after menopause. The numbers of women in postmenopause may represent a theoretical ideal, but not have practical value for forecasting. The market is probably better estimated by data from the National Council on Patient Information that says in 1986, 6.2 million women visited their physicians for "menopausal symptoms" and 81% received medication. Out of 43 million American women who are in the age range for menopause, approximately 75% to 80% experience symptoms such as hot flashes and night sweats. Approximately 6.5 million women are on HRT in the US today. Only clear-cut studies that indicate that women should be on HRT indefinitely would have much chance of changing the prevailing prescribing habits, and it will be many years before this information will be available.

In addition to the natural menopause patients, there are close to 600,000 hysterectomies in the US every year according to CDC (figures from 1990). Hysterectomies are decreasing due to a constant questioning of the medical need for the procedure, and the current number represents a decline of 21% since the mid-'70s. Approximately 60% are in women 15 to 44 years of age, 30% are in women 45 to 64, and the remaining 10% are in women 65 and over.

While there is no breakdown by type of hysterectomy, many of the indications for the surgery given below also cause women to have an ovariectomy.

- Fibroids 32%
- Endometriosis 20%
- Uterine Prolapse 17%
- Cancer 11%
- Other 20%

Market Analysis

The menopausal hormone market consists of estrogen and progestin in oral, transdermal and vaginal (topical) forms, plus other hormones. Annual US sales in this

category increased from \$1.3 billion in 1996 to \$2.3 billion in 2000, an increase of 68%. Later in this **Genesis Report/Rx** article, a forecast through 2010 will be provided. At this date, approximately 50% of the market is held by Wyeth-Ayerst's Premarin, a 50 year old product! The company's Prempro holds a second place share at 16%, and Vivelle, from Novartis, with a 5% share, holds third place.

In December 1994, the FDA approved Wyeth-Ayerst's packaging of Premarin and medroxyprogesterone (generic Provera) in combination calendar packs. There are two versions. The first is Prempro, which is continuous and contains Premarin in 0.625 mg. tablets and the progesterone in 2.5 mg tablets. The other version is Premphase, which is sequential and contains a month's worth of Premarin at 0.625 mg and 14 progesterone tablets at 5 mg.

Wyeth-Ayerst's strategic attempt to retain market share in the face of generic competition will depend on its ability to get physicians to switch to these packages. In addition, like several other pharmaceutical companies, Wyeth-Ayerst has set up a generic division and it is assumed that a generic Premarin will be one of the main products developed by that division. The company launched Prempro/Premphase single-tablet therapy in early 1996.

Premarin, Prempro and Premphase are co-promoted by **Merck (Whitehouse Station, NJ)** and Wyeth-Ayerst, along with Merck's Fosamax for treatment of osteoporosis in postmenopausal women. Under the alliance, Wyeth-Ayerst will promote both Premarin and Fosamax to ob/gyns and Merck will promote both products to other physician specialties - endocrinology and rheumatology. This deal leverages Wyeth-Ayerst's strong position with the ob/gyn community.

Transdermal Estrogen and Estrogen/Progestin Combinations

Transdermal mechanisms for the delivery of estrogen offer several distinct advantages over existing oral therapy. In addition to avoiding the "peak and valley" effect associated with traditional modes of therapy, transdermal devices avoid that "first pass" through the liver to deliver a precise, steady flow of estrogen into the bloodstream. This could have a significant impact on the cardiovascular and cancer effects of hormone administration. Like many other issues in ERT this needs to be researched further to determine the long-term effects. Finally, while Premarin consists of a mixture of various estrogens, the patches employ pure estradiol.

Estraderm was developed by **Alza** (Palo Alto, CA), and has been marketed by Novartis for almost ten years. The patch has a small share of the total HRT market despite drawbacks in design - it is large and awkward to wear, and the estradiol is contained in a bulky liquid reservoir. Vivelle, introduced in the mid-1990s, developed by **Noven Pharmaceuticals** (Miami, FL) and sold through Novartis has quickly amassed a decent share of the overall HRT marketplace due to its design superiority relative to Estraderm. Vivelle is a twice-a-week patch like Estraderm, but the hormone is contained in the adhesive rather than a reservoir.

Another patch was approved in late 1994. It was developed by **3M** (St. Paul, MN) and Berlex (Schering AG) and is marketed by Berlex in the US as Climara. It is a once-a-week patch without an osteoporosis indication. Once-per-week change gives it a presumed advantage versus Novartis' Vivelle. However, Vivelle enjoys a better market position, perhaps because of multiple dosage strengths.

Competition is likely to be even more intense in the estrogen replacement market in the not too distant future. Novartis' Vivelle is the first product developed from second-generation transdermal technology for estrogen replacement. The purpose of second-generation transdermal technology is to alleviate first-generation technology skin irritation, which was reported in up to 20% of patients. In addition to being less irritating, they are also lighter and more flexible.

Vaginal Estrogen

The vaginal estrogen market is less than 10% of the oral market and is relatively stable. Premarin is again the market leader in this category. These products are cream forms of estrogen that are applied to the vagina to treat vaginal atrophy.

Oral Progesterone

The oral progesterone market had shown good growth in the early 90's but has stabilized. The leading product is **Pharmacia & Upjohn's Provera**. Wyeth-Ayerst makes two products - Aygestin and Cycrin - but Cycrin was marketed just to establish the product in anticipation of the introduction of Wyeth's combination products.

Summary

The outlook for menopausal hormones is positive, primarily driven by demographics and increasingly compelling evidence of the value of hormone replacement

therapy. **American Home Products's** (HMP) (Madison, NJ) hold on this market is substantial, with approximately two-thirds of sales. They are a tough competitor and have shown considerable determination to fight very aggressively to defend position. Competitors should be able to find niches, but this will be a difficult market for any competitor to penetrate and gain any sizeable position.

Products in Development or Recently Launched

For product development in hormone replacement therapy, significant efforts are in different delivery methods in addition to development of novel chemical agents. Various delivery approaches include oral, transdermals, intravaginal rings, and topically applied gels.

Current Therapies:

Orally Administered Products

American Home Products has taken an especially aggressive posture relative to developing the menopausal hormone market. The Premarin family of products include Premarin (conjugated estrogens tablets), Prempro (conjugated estrogens/medroxyprogesterone acetate tablets), and Premphase (conjugated estrogens/medroxyprogesterone acetate tablets).

Novo Nordisk (Bagsvaerd, Denmark) has developed an oral tablet containing 25 µg 17beta-estradiol (natural estrogen) for the treatment of atrophic vaginitis, a component of urogenital syndrome associated with the estrogen deficiency of menopause, and for postmenopausal osteoporosis. The formulation has been approved in the US under the name Innofem®, and has been widely launched worldwide. **Pharmacia & Upjohn** has entered into a licensing agreement with Novo Nordisk to market all of Novo Nordisk's hormone replacement therapy formulations in the US.

In the last year or so, three new HRT products were launched in the US: Activella (Pharmacia), FemHRT (Parke-Davis (Morris Plains, NJ)/Pfizer (New York, NY)), and Ortho-Prefest (Ortho-McNeil (New Brunswick, NJ)). The new products use either 17beta-estradiol or ethinylestradiol (femhrt) with either norethindrone acetate or norgestimate for the progestin component. The newer products may have reduced side effects, particularly breakthrough bleeding. Each is only available in one formulation, roughly equivalent to the lowest available dose of Prempro.

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Table 2

US Development Programs for Menopause Therapy by Company and Clinical Status					
Company	Preclinical	Phase I	Phase II	Phase III	Total
Schering AG				7	7
American Home Products			1	3	4
Aventis	1	1		2	4
Johnson & Johnson				1	1
Akzo/Nobel	1			1	2
Solvay				1	1
Watson			1		1
Merck	1				1
Merck KGaA				1	1
Glaxo SmithKline			1		1
Others	7	2	3	4	16
Total	10	3	6	20	39

Source: Women's Healthcare Emerging Business Opportunities - Genesis 2000

Table 3

US Development Programs for Menopause Therapy by Platform and Clinical Status					
Platform	Preclinical	Phase I	Phase II	Phase III	Total
HRT	3		2	13	18
ERT	1			4	5
Testosterone	1	1	2		4
Progestin - Adjunctive		1		2	3
Estrogen	1	1			2
Other Hormone	1			1	2
Monoamine Reuptake Inhibitor			1		1
PRM	1				1
SERM	1				1
Serotonin Reuptake Inhibitor			1		1
All Other	1				1
Total	10	3	6	20	39

Source: Women's Healthcare Emerging Business Opportunities - Genesis 2000

Prometrium®, a natural progesterone obtained from wild yam, has been launched in the US for the prevention of endometrial hyperplasia in postmenopausal women who have not had a hysterectomy, treatment of secondary amenorrhoea, and for use in hormone replacement therapy. Prometrium is an oral micronized

progesterone originally developed by Schering-Plough. (Madison, NJ) Solvay Pharmaceuticals has licensed Prometrium® in the US and has formed an alliance with Duramed Pharmaceuticals (Cincinnati, OH) to jointly promote the product.

Transdermal Delivery (Patch)

Several ERT patches are currently on the market. These include Climara from Berlex (Schering AG), Vivelle and Vivelle-Dot from Novartis, Esclim from Serono, and Alora from **Watson (Corona, CA)**. Most of these patches are worn for 7 days and are available in several doses of estradiol. Vivelle-Dot, a second-generation product, is smaller than older products and is applied twice weekly.

Cygnus (Redwood City, CA) and American Home Products co-developed a 7-day transdermal estradiol patch (E2III) for the treatment of menopausal vasomotor symptoms. AHP provided most of the funding for the development of the product and was responsible for the clinical trials as well as the submission of the NDA. In June 1999, AHP did not exercise its option to reacquire the rights to two hormone replacement patches it had been funding with Cygnus, including E2III. The product was approved in the US in September 1999 for the treatment of moderate to severe vasomotor symptoms associated with menopause, and treatment of vulvar and vaginal atrophy. In December 1999, Cygnus sold all the assets of its drug delivery business to Ortho-McNeil Pharmaceutical (Johnson & Johnson).

CombiPatch™ is the only (combination) HRT patch currently marketed in the US. In October 1999, **Aventis (Strasbourg, FR)** and Novartis signed a sublicensing agreement giving Novartis exclusive marketing rights to the product under the name Estalis® in all countries other than the US and Japan; Aventis will continue to market the product as CombiPatch in the US.

Intravaginal Rings

Intravaginal rings are under development by several companies. The advantage of these delivery systems is the ability to provide continuous delivery of estrogen and progestin for up to 3 months. This is especially appealing in treatment of women who are unable to see a physician as often, or who may have difficulty remembering to take a daily medication, as in the case of certain women in a nursing home environment, or those suffering from Alzheimer's or other dementia. The difficulty of installing and removal of the ring in or out of vagina is the major obstacle for broad acceptance of this type of product. The wide acceptance of orally administered HRT puts intravaginal rings into a niche status.

ERT/HRT with Other Modes of Delivery

Estrogel® is a topical estradiol gel developed by **LaSalle Laboratories (Amsterdam, NY)** for the treatment of menopausal symptoms such as hot flashes and night

sweats. Estrogel® is the most widely prescribed estrogen in Europe. Solvay Pharmaceuticals has licensed Estrogel® from LaSalle for the US.

Pharmacia recently launched a new vaginal estrogen preparation, Vagifem. Vagifem is a vaginal tablet containing 25 µg 17beta-estradiol and was developed by Novo Nordisk for the treatment of atrophic vaginitis. The tablet formulation is more convenient than existing estrogen creams for vaginal use.

SERMS

A new class of compounds known as Selective Estrogen Receptor Modulators (SERMs) (exemplified by Evista, (raloxifene) from **Eli Lilly (Indianapolis, IN)**) has undergone studies for HRT.

Future Therapies:

US clinical development program counts are provided by company and by clinical phase in Table 2. A total of 39 programs have been identified for the menopausal disorders category. A total of 26 programs are late-stage programs (Phase II or III).

US clinical development program counts are provided by technology platform and by clinical phase in Table 3. The HRT technology platform leads all other tech platforms with a total of 18 programs.

Hormone Replacement Therapy (Estrogen + Progestin)

Selected programs

- American Home Products has two new HRT products in late-stage clinical development that incorporate a new progestin, trimegestone. One formulation combines trimegestone with Premarin; the other uses 17beta-estradiol.

Trimegestone is a progestin that lacks androgenic activity. Trimegestone-containing products are expected to have fewer side effects than those containing first-generation progestins. Trimegestone was developed by Aventis in collaboration with Wyeth-Ayerst. Wyeth-Ayerst and Aventis have recently renegotiated their co-development agreement, and Wyeth-Ayerst will now have exclusive rights to develop and market trimegestone for all indications and formulations with the exception of transdermal products.

- **Jenapharm's (Mauschen, Germany)** combination product estradiol valerate/dienogest (Klimodien®) has completed Phase III clinical trials for post-

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menopausal hormone replacement therapy, including treatment and prevention of osteoporosis. An application has been submitted for this product in the European market. Schering AG is also developing HRT products with the progestins gestodene and drospirenone, but US development of this line has not been confirmed.

- Schering AG has developed a 7-day combination transdermal patch, ClimaraPro™ that delivers estrogen and levonorgestrel for prevention of postmenopausal osteoporosis and menopausal symptoms.
- **Merck KGaA (Darmstadt, Germany)** has developed a 7-day transdermal patch that continuously releases estradiol and levonorgestrel from an adhesive matrix. It has been licensed from Merck KGaA to Solvay Pharmaceuticals for the US and Canada and Merck KGaA has the right to co-market the patch in these countries. Phase II/III studies in the treatment of vasomotor symptoms associated with menopause are continuing.
- **Galen Holdings (Rockaway, NJ)** has developed an estradiol- and progestin-releasing intravaginal ring that has completed a dose-ranging Phase II trial in the UK as hormone replacement therapy. The ring releases the hormones at a controlled rate and can remain in place for up to 3 months. This product is indicated for use only in women with an intact uterus. Phase III trials are due to begin in Europe and the US, and the company plans to use a single global study to provide information for filing requirements in Europe and the USA. The company hopes to submit applications for the ring in the UK and US in 2002, and in Europe in 2003.

Other Hormonal Therapies

Selected programs

- **Leiras Oy (Turku, Finland)** has developed a hormone-secreting intrauterine system (Mirena®), a T-shaped plastic intrauterine device (IUD) that releases levonorgestrel 20 µg/day over a period of 5 years. In the US, Mirena is licensed to Berlex Laboratories, which has submitted an NDA to the FDA. Although initially developed as a contraceptive, a smaller version is planned for use in hormone replacement therapy in post-menopausal women.

- Androsorb™ is a topical testosterone cream in development with **Novavax (Columbia, MD)**. The testosterone is encapsulated in a proprietary Novavax micellar nanoparticle cream that allows for transdermal delivery of alcohol-soluble drugs.

Testosterone replacement therapy may prevent osteoporosis, help maintain muscle mass and increase energy and libido. A Phase I dose-ranging and pharmacokinetic trial of Androsorb in post-menopausal women who are deficient in testosterone is being conducted in the US. Androsorb has completed Phase I trials for testosterone replacement therapy in testosterone deficient men.

- **Cellegy Pharmaceuticals (South San Francisco, CA)** is developing Tostrelle™, a topical gel formulation of testosterone, based on the company's proprietary Celledirm™ technology. The gel is delivered using a metered dose system. Cellegy has completed a dose-finding, Phase I/II, pharmacokinetic and tolerability trial of Tostrelle in postmenopausal women with sexual dysfunction resulting from testosterone deficiency. The product was well tolerated. An expanded Phase I/II trial to determine the optimal dosing of Tostrelle in women with surgically induced menopause is planned.

- Tibolone (Livial®) is a synthetic steroid that is indicated for menopausal complaints associated with hormone deficiency, and osteoporosis. It is a tissue-selective estrogen agonist, acting as an estrogen in some tissues including the brain, bone, vaginal tissue and blood vessels, but not acting as an estrogen on the endometrium or breast tissue. It is also weakly androgenic. Tibolone is in development with **Organon (Durham, NC)**, a subsidiary of AkzoNobel.

Tibolone has been launched as a hormonal replacement therapy for the treatment of menopausal disorders and for the prevention of postmenopausal osteoporosis in more than 70 countries worldwide, including most Asian, European and Latin American countries but excluding the US, Canada and Japan.

- **Karo Bio (Durham, NC)** and Merck are collaborating in a research program aimed at developing compounds that act on estrogen receptors alpha and beta. Preclinical studies are under way

investigating the potential of these compounds for the treatment of menopausal symptoms, osteoporosis, cardiovascular disease and cancer.

Product Technology and Sales Forecast

Menopausal therapy is one of the truly exciting growth markets of the future. The population in the age segment that is most affected is projected to increase by 40% between 1994 and 2010. The percent of women seeking therapy and the physicians who believe that therapy is necessary is also expected to increase as evidence of the benefits mounts. The number of women under 50 with ovariectomies will also contribute to this growing market. Finally, new combination therapies and patches should make treatment more convenient and increase the use of therapy. Table 4 depicts shifts in Technology Platforms used in treatment.

Estrogen Replacement Therapy

Strengths and weaknesses: Estrogen replacement therapy effectively relieves the immediate symptoms of estrogen deficiency; namely hot flashes, atrophic vaginitis, and vaginal/vulvar atrophy. Estrogen also has beneficial effects on blood lipids and bone metabolism, and may have a long-term positive impact on the cardiovascular system. Estrogen replacement increases the risk of endometrial cancer by five-fold, and estrogen is no longer given without progestin (unopposed) to women with an intact uterus. Some of the use of estrogen replacement products can be attributed to hysterectomized women; the remainder is used by women who are prescribed a separate progestin.

There is some evidence that estrogen increases the risk of breast cancer based on retrospective analyses; however, this is likely to remain controversial, at least until the

Women's Health Initiative is completed. This is a randomized, prospective study involving 27,000 women, which will examine the incidence of heart disease and breast cancer in women assigned to receive either placebo or estrogen replacement (women with a uterus will also receive a progestin if assigned to estrogen). Other potentially serious side effects of estrogen include blood clots (thrombosis) and gall bladder disease. The latter complication is less likely for women using a transdermal estrogen preparation. Because of the increased propensity for blood clots, women with established thromboembolic disorders should not use estrogen and women who smoke should be considered to be at increased risk.

Forecast: Oral estrogen replacement therapy will remain the preferred treatment option for women without a uterus who are experiencing menopausal symptoms. Despite the theoretical advantages of transdermal delivery, the poor acceptance of patches is not likely to change. Vaginal estrogen may be accepted by women troubled with urogenital symptoms, but concerned about systemic estrogen exposure.

Hormone Replacement Therapy (Estrogen + Progestin)

Strengths and weaknesses: Hormone replacement therapy (HRT) combining estrogen with a progestin combines the benefits of estrogen while reducing the risk of estrogen-associated endometrial cancer. However, many of the unpleasant side effects of HRT are due to the progestin component, and surveys show that women taking estrogen alone are less likely to discontinue therapy than women on HRT. These side effects include mood swings, water retention, weight gain, and breakthrough bleeding. A second generation of HRT products has been developed, which may have fewer side effects and thus higher compliance.

Table 5

Menopause - Forecast US Sales by Technology Platform (\$ millions)				
	2001	2003	2005	2010
Estrogens	1,524	1,589	1,625	1,650
Progesterones	217	271	315	325
Combination Therapies	607	775	850	900
Other Hormonal Therapy	5	5	20	35
Non-Hormonal Therapy	2	2	7	10
Total	2,355	2,642	2,817	2,920

Source: Women's Healthcare Emerging Business Opportunities - Genesis 2000

HRT regimens can supply progestin either continually or sequentially. The most common sequential regimen adds progestin for two weeks of a four-week cycle. Different estrogen and progestin combinations may be used, both in terms of dosage and compound. In addition to CEEs, HRT formulations using either 17beta-estradiol or ethynodiol diacetate are available. Progestins used in HRT include medroxyprogesterone acetate (MPA), norethindrone acetate (NETA), and norgestimate. Other formulations are in development. Ideally, for women unsatisfied with HRT, different formulations should be tried to see if side effects can be reduced.

Transdermal patches providing combined HRT offer some theoretical advantages over oral formulations. There have been significant improvements in this technology, which will lead to greater acceptance by some well-informed women. Although with increased marketing efforts use may increase to moderate levels, patches are still not likely to be major competition for the oral formulations.

Forecast: Hormone replacement therapy will remain the dominant treatment modality for women with an intact uterus. Surveys indicate that use of HRT correlates with level of education and prior use of oral contraceptives, so that overall use of HRT may increase. However, there is a countertrend away from traditional pharmaceutical therapies toward herbal and other OTC remedies may limit growth of this market.

Other Hormonal Therapies

Strengths and weaknesses: Progestins oppose the activity of estrogen in the uterus and reduce the risk of endometrial cancer, but have unpleasant side effects. Newer synthetic progestins may offer some advantages over those currently available as monotherapies. A progestin-secreting intrauterine device is also in development that would offer the advantage of local progestin-delivery and reduced systemic effects.

Testosterone replacement was initially developed for menopausal women as an adjunct to estrogen for the treatment of menopausal symptoms not responding to estrogen alone. Combinations of estrogen and methyltestosterone have been available for this indication since the 1960s. Testosterone replacement may be particularly valuable for women undergoing surgical menopause.

Other products in development which may be important for treatment of menopausal disorders include agents

that selectively interact with hormone receptors. This includes selective estrogen receptor modulators (SERMs), selective progesterone receptor modulators (PRMs), and tibolone. The latter is a complex steroid that undergoes tissue-specific metabolism, resulting in estrogen-like suppression of menopausal symptoms, including bone loss, without stimulation of endometrial growth.

Forecast: Adjunctive progestin use will continue, but products available in combination with estrogen will have an advantage. Testosterone use will be limited as a result of concern over androgenic side effects. New approaches to hormone replacement therapy are needed, and tissue selective agents have great potential. The search for the ideal SERM continues, and a compound with all of the positive effects of estrogen and none of the negative effects could dominate the market and eliminate the use of adjunctive progestins. Tibolone does not appear to be the perfect agent because of negative effects on lipids.

Other Technologies

Strengths and weaknesses: This category includes neurotransmission regulators under investigation for prevention of vasomotor symptoms (hot flashes) in women who cannot take estrogen. Pilot studies in breast cancer survivors indicate that this may be a promising new approach. These agents would not provide any of the other benefits of estrogen replacement, such as reduction in bone loss.

Forecast: The use of neurotransmission regulators will be quickly adopted for treating hot flashes in breast cancer survivors. Because hot flashes are the primary reason menopausal women choose to initiate hormone replacement therapy, they may eventually become an option for women who are reluctant to take estrogen and need relief of symptoms for a limited amount of time.

Market Forecast

Forecast sales through 2010 are listed in Table 5. Sales are projected to increase modestly to a total of \$2.9 billion in the year 2010.

Estrogens were the dominant technology platform of US sales in 1999 (\$1.6 billion) and are projected to occupy the number one position in the year 2010, with a total of \$1.7 billion. Combination therapies are projected to retain their number two position in the year 2010, with a total of \$900 million in sales.