



By David W. James, MD
Commentary by Reva Winkler, MD

Kaiser Permanente Medicine 50 Years Ago Management of the Menopause

The reprint in this issue from Vol. 2, No. 3; July, 1944 of the Permanente Foundation Medical Bulletin, edited by Dr. Morris Collen from 1943 to 1953, is "Management of the Menopause," by Dr. David James. Dr. James was then a member of the Department of Obstetrics and Gynecology of The Northern Permanente Foundation, in Vancouver, Washington, but he left our organization shortly after to practice elsewhere. Dr. Reva Winkler of the Southern California Permanente Medical Group Department of Obstetrics and Gynecology has written not only a Commentary on Dr. James' article but a beautifully constructed, brief, personalized update of the topic which will be very helpful to practicing physicians. She is undoubtedly correct in concluding that many physicians of Dr. James' era readily dismissed the sufferings of menopausal women. I am reminded of my first introduction to the subject 45 years ago (not too long after Dr. James wrote his article). It was by a lecturer in my second year of medical school pharmacology course, who told us that it was easy to deal with any unexplained symptoms in a woman between the ages of 40-50. He said "Just call it the menopause, and give her hormones." I believe that, in this area, we have come a long way.
— Arthur Klatsky, MD, Section Editor

Management of the Menopause

The intent of this paper is to present a helpful, though by no means authoritative or exhaustive summary of the present trend in the management of the menopause with particular reference to the use of estrogens. Although the menopause and the climacterium are not actually the same, they will be treated as a single entity for the purpose of discussing therapy. A survey of the literature on the relative potency and effectiveness of the estrogens available, impresses the reader at once with the variance in conclusions reached by not only those workers using different methods of analysis and procedures but also those using identical methods.

The Menopausal Syndrome

The menopausal syndrome itself should perhaps first be reviewed¹ in order to establish certain facts which are considered important. A convenient but not entirely accurate classification is presented (Table 1).

There is value in reviewing the generally accepted manifestations of the menopause because of the occasional tendency in clinical practice to treat as menopausal certain other conditions which produce simi-

lar symptoms. Furthermore, there is a younger group of patients with symptoms suggesting estrogen deficiency which should not be treated as menopausal unless definite evidence of the menopause has been established. Careful study will usually permit accurate determination of the underlying etiology. When ovarian failure in the early age group cannot be shown to be secondary to either local disease or disease elsewhere, its treatment should consist of cyclic administration of estrogen and progestin such as outlined by Smith.² This is in contradistinction to the use of estrogen alone. The detrimental effects of non-physiological administration of estrogens in normal women on the rhythmicity of the menstrual cycle has been demonstrated by Hamblen and co-workers.^{3,4} It may be concluded that this type of administration should be generally limited to substitutional therapy in intrinsic ovarian failure such as occurs at the menopause, or in the control of prolonged and excessive episodes of bleeding.

The hot flush is the most characteristic symptom of this condition and is noted by at least 75 percent of the patients. It is typically described as a sense or spread of warmth or redness over the chest, neck, face and head, usually accompanied or followed by a sense of chilliness. These flushes may occur repeatedly during the night and account for much of the insomnia of which these patients complain. The hot flush is so typical of this condition that one hesitates to make the diagnosis in its absence. In view of this, its disappearance and recurrence may be used as a therapeutic index of the efficiency of treatment. It may be said that if the hot flush does not disappear with adequate estrogen therapy, then it is not the hot flush of the menopause, and the condition is probably not due to the menopause.

Vertigo frequently brings the patient to the doctor. Symptoms of cardiac disease such as dyspnea and palpitation are also a part of the syndrome and with the co-existing instability of the nervous system give rise to acute anxiety on the part of the patient. Hypertension, though a manifestation of the menopause in some cases, should be ascribed to the menopause only if it responds to estrogenic therapy since pathological changes in the heart and blood vessels tend to occur at this period and may account for the increased blood pressure.

Some of the more distressing and serious manifestations of the menopause are expressed through the nervous system. These vary from increased nervousness and irritability to a definite psychosis or involutional melancholia. Such changes may result in transforming a placid, well controlled and well adjusted

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(not pictured) DAVID W. JAMES, MD was, at the time of his article's original publication, a member of the Department of Obstetrics and Gynecology of The Northern Permanente Foundation, in Vancouver, Washington. REVA WINKLER, MD received her medical degree from the UCLA School of Medicine and did her Residency at the Kaiser Foundation Hospital in Los Angeles. She has practiced Obstetrics and Gynecology at the SCPMG from 1986 to the present.



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woman into one who is excitable, irritable, and emotionally unstable. As a result, she may be easily angered, argumentative, suspicious, apprehensive, tending to worry over trivial things, and frequently confused and frightened by the changes taking place. These symptoms may be so mild that the patient is able to conceal them entirely. On the other hand, the symptoms may be so marked that unless their significance is understood by her family and friends, there may be disruption of domestic and social ties. Headaches, pressure sensations, and occipitocervical pain are frequently the symptoms responsible for the patient seeking medical attention.

Personality changes may occur and these may be either minor or approach a true psychosis. That involuntional melancholia is part of the syndrome and is produced by the same endocrine dysfunction which is the apparent causative factor responsible for the rest of the menopausal state is not completely accepted.⁵ However, the divergent views held in regards to this point seems to rest largely on definition or diagnosis. The consensus seems to be that estrogenic therapy in involuntional melancholia of the milder type is of value and is indicated certainly in those cases presenting many of the other symptoms of the syndrome.^{6,7}

Sex changes may occur and these may be manifested as an increased or decreased desire. When combined with a sense of loss of charm, these changes account for much of the mental distress, worry and emotional instability. Such changes may also lead to sexual incompatibility, even in couples previously well adjusted, and may be the underlying factor responsible for divorce, immorality and

unhappiness. Although menstrual irregularities occur commonly during the menopause, an atypical uterine bleeding at this time is best considered as abnormal. Functional menorrhagia may occur as a result of endocrine imbalances due to ovarian failure but any increase in menstrual flow must be considered as evidence of malignancy until proved otherwise. Acyclic bleeding is more suggestive of malignancy than cyclic and necessitates further diagnostic study.⁸ In suspicious cases the value of uterine curettage and cervical biopsy cannot be overstressed. Organic disease accounts for at least 50 percent of abnormal bleeding at this time and requires thorough investigation.

The existence of a true menopausal arthritis has not been proved and possibly joint pains occurring at this time should be designated as arthralgias. However, definite improvement in 30 to 50 percent of cases treated has been reported;⁹ consequently, arthralgia developing coincident with the menopause should receive the possible benefits of estrogen therapy.

Obesity, which adds so much to the patient's discomfort, occurs frequently at this time and results not only from metabolic changes but also from psychic factors manifested by a tendency to overeat. In some cases estrogen therapy alone will produce satisfactory weight loss.

Changes in thyroid function occur in the menopause as a result of the disturbance of anterior pituitary function and may respond indirectly to menopausal therapy. The differential diagnosis of hyperthyroidism must be carefully considered during the menopause particularly because similar symptoms are common to both conditions.

Table 1. The Menopausal Syndrome

Vasomotor	Neuropsychiatric	Others	Associated States
Hot flushes Vertigo Faintness Vicarious hemorrhages Cardiac symptoms •Dyspnea •Palpitation Hypertension	Nervousness •Excitability •Anxiety •Irritability Fatigue Emotional instability Impairment of memory Confusion Tinnitus Headaches and pressure •Occipitocervical •Pain Insomnia Paresthesias Psychosis •Personality change •Involuntional melancholia	Sex changes •Frigidity •Nymphomania Change in menses •Amenorrhea •Hypomenorrhea •Oligomenorrhea •Menorrhagia •Metorrhagia Arthritis and Arthralgia Obesity	Hyperthyroidism Diabetes Cancer Genital change •Atrophy of organs •Atrophy of vaginal mucosa •Atrophy of endometrium Senile vaginitis Pruritus vulvae Kraurosis vulvae



The onset of diabetes at the menopause, and the effect of hormone therapy upon its course, suggests that there is more than a coincidental relationship between these two conditions.

Genital changes, atrophic in nature, occur due to loss of the stimulating effect of the ovarian hormone. Senile vaginitis responds to estrogen therapy but it is doubtful whether pruritus vulvae and kraurosis vulvae will permanently benefit by such therapy.

Management

The diagnosis of the menopause in the typical case presents little difficulty. The average age is 47 years, but characteristic symptoms may arise before, at the same time, or within several years after the cessation of the menses.

Just a few years ago, before the availability of potent estrogenic preparations made the treatment of menopausal symptoms more certain, some clinicians doubted the real existence of the menopausal syndrome. At the present time nearly everyone agrees that such a syndrome does exist and that estrogens provide dependable therapy. There is disagreement as to the exact percentage of women that experience menopausal symptoms severe enough to require treatment. Unquestionably there are many patients suffering from manifestations of the menopause who deserve the relief which accompanies properly administered estrogen therapy.

The severity of these manifestations varies in different women and one finds that co-existing and pre-existing organic lesions and nervous conditions alter the picture presented. Thus, it is important that great care be exerted so that other conditions are not overlooked.

A careful history and thorough physical examination are essential. As already stressed, every precaution should be taken to prevent the possibility of overlooking co-existing organic lesions. If the physician will take the time to obtain a complete sex history he will be rewarded frequently by information which will help explain the patient's symptomatology. A sane discussion with the average menopausal patient concerning the true nature and significance of her symptoms, reassuring her as to their approximate duration and the expected time of ultimate disappearance, is of definite value. General measures which include correction of a secondary anemia, advice regarding an adequate diet, ample rest and relaxation and proper exercise are very important.

Sedation, together with the reassurance, may suffice to satisfy the patient and enable her to carry on in relative comfort. Phenobarbital or an elixir containing phenobarbital and one or more of the bromides is a very useful type of sedative.

The administration of estrogens in the treatment of the menopause may be termed specific therapy. Such therapy produces a change in the vaginal mucosa consistent with the degree of estrogen stimulation, a disappearance of anterior pituitary gonadotropic hormone from the urine, and coincidental improvement in the subjective symptoms. This improvement in subjective symptoms usually appears before a full estrogenic effect in the vaginal mucosa can be obtained.

Estrogens may be administered with one of several purposes in mind. First, administration may be limited to the point of relieving only the more distressing of the symptoms so as to allow the patient to have relative comfort. For many patients, this is sufficient and satisfactory therapy. Second, estrogens may be given in larger amounts with the idea of entirely relieving the symptoms, and here again the value of the hot flush as a therapeutic index may be stressed. After the symptoms are controlled the patient may be carried on a maintenance dose which may be determined by trial and error methods for an indefinite period. It is generally felt, however, that the estrogens should not be given continuously but that rest periods should be provided. These interruptions serve to reduce the incidence of distressing estrogenic bleeding and at the same time permit evaluation of the patient's endocrine adjustment in the absence of therapy. Finally, in the treatment of local disturbances such as senile vaginitis, estrogens may be given since they tend to return the vaginal mucosa to its normal status. The use of the estrogens during the climacterium while the patient is still menstruating has been questioned, based on the contention that it produces and accentuates the menstrual irregularity and that it prolongs this period. Certainly in patients having cyclic bleeding, estrogen administration should likewise be cyclic and the dosage minimal.

Certain methods are used to determine the adequacy of estrogen dosage; however, the relief of symptoms is in most cases the only index necessary. A more accurate means of evaluating the estrogen effect is found in the vaginal smear method introduced by Papanicolaou.¹⁰ In this method the evaluation of estrogen is ascertained by the type of cells seen in the stained vaginal smear. The cells found in these smears vary from the deeply stained immature round cells with large nuclei, and the many leucocytes seen in the menopausal smear, to the cornified cells with pyknotic nuclei and few leucocytes observed in the smears taken from a sexually mature woman. Mack¹¹ has recently modified this procedure by introducing a simple staining

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method which demonstrates the glycogen content of the cells in graded amounts and thereby enables the clinician to accurately evaluate the estrogen response. The slides are stained by laying them face down across a shallow dish containing Lugol's solution. The iodine vapors which arise stain the cells in shades from yellow to brown dependent on the glycogen content. He has used this as a method of estrogen assay.

Estrogens Available

The available and commonly used estrogens fall into two classes, the natural and the synthetic estrogens. The natural hormones include the basic substances, estrone, estriol, and estradiol. Estrone (theelin) is prepared in the pure crystalline form, from placental and pregnancy urine extracts. It is of uniform but relatively low estrogenic potency. Estriol (theelol) is of low potency and is at the present time of little clinical value. Estradiol is the estrogenic hormone as it apparently exists in follicular fluid; prepared in pure crystalline form it is said to be twelve times as active as estrone. There are two esterified forms produced by chemical combination with fatty acids; estradiol benzoate and estradiol dipropionate. Variations in chemical composition and physical preparation have resulted in changing the relative effectiveness and rate of absorption of the various estrogens. For example, esterification of estradiol has resulted in estrogenic products with prolonged absorption rates and adding the ethinyl group to estradiol has increased its oral estrogenic potency at least fifteen times. There are three synthetic estrogens commercially available. These are diethylstilbestrol, hexestrol of the stilbene series, and 118B, an unrelated chemical compound.

The preparations mentioned above do not have equal estrogenic effects milligram for milligram. There is no common agreement upon the relative effectiveness of these preparations but much work has been done and general conclusions may be drawn. The potency of estrogenic preparations is measured according to three main standards: weight in milligrams, international units (I.U.), and rat units (R.U.). The international unit by definition is 0.0001 milligram of estrone and expresses the estrogenic activity of that amount of estrone. The rat unit is determined by biologic assay in rats and is subject to the errors of that method. The rat unit represents approximately ten times the estrogenic activity of the international unit. Mack states that estrone is more uniform in its activity than any other estrogen regardless of the route of administration. Possibly in the future, using estrone

as a standard for comparative assay, the estrogenic activity of any estrogen may be determined with reasonable accuracy.

The preparations mentioned will be considered individually and the potency, advantages and disadvantages discussed.¹²⁻¹⁹

1. **Estrone:** Prepared in oil solution and aqueous suspension for parenteral use. The estrogenic activity is low. The oil solution is rapidly absorbed whereas absorption of the aqueous suspension is prolonged. The estrogenic activity of estrone is comparable to approximately half the corresponding weight of stilbestrol or one-sixth the weight of estradiol benzoate. Cost per unit of estrogenic activity is two times that of estradiol benzoate, the aqueous suspension is one and one-half and six times that of stilbestrol.

2. **Estrone sulfate tablets:** Average daily dose is 1.25 milligram or approximately 10,000 I.U. This is more effective orally than estrone, compares favorably in estrogenic activity with oral stilbestrol and has fewer toxic reactions. The cost is ten times that of stilbestrol.

3. **Estradiol:** A potent estrogen prepared in tablet form, in solution for sublingual use (60 R.U. per drop), as a suppository (480 to 4800 R.U.), and for injection (360 to 1800 R.U. per gram). The high estrogenic activity is overshadowed by the high cost per unit of estrogenic effectiveness.

4. **Estradiol benzoate:** This is a potent parenteral product. 1.66 milligrams in oil is equivalent to 10,000 rat units or approximately 100,000 international units. The potency is less than that of estradiol dipropionate and three times as effective as stilbestrol. The cost per unit of estrogenic activity is three times that of stilbestrol.

5. **Estradiol dipropionate:** This is the most potent parenteral estrogen and the chief advantage is the prolonged action. It is two times as effective as stilbestrol dipropionate and more effective than estradiol benzoate; however, a unit of estrogenic activity costs more.

6. **Ethinyl estradiol:** This is a very potent oral estrogen, the average daily maintenance dosage being 0.05 milligram. The toxicity has been reported as approaching that of stilbestrol. The cost is nearly three times that of stilbestrol.

7. **Diethyl Stilbestrol:** (generally referred to as stilbestrol). This preparation is economical and is active by most routes of administration. The oral potency is about half the parenteral potency. The average daily maintenance dose is 1 milligram. Toxic reactions occur in at least 10 per cent of the patients.

8. **Stilbestrol dipropionate:** This preparation is slightly more potent than stilbestrol. There is no difference in cost.



9. **Hexestrol:** This synthetic estrogen of the stilbene series is less potent but less toxic than stilbestrol. Average maintenance dose is 2.5 to 5 milligrams.

10. **118B (Octofollin):** A synthetic estrogen not related to stilbestrol and less toxic than the other synthetic estrogens. The average maintenance dose is 1 to 2 milligram.

Table 2 summarizes some of the facts presented above.

Discussion

From the foregoing and from the standpoint of economical estrogenic therapy, it may be concluded that diethyl stilbestrol, or stilbestrol dipropionate, is the estrogen of choice in patients who can tolerate the drug. The toxic manifestations have not been shown to be associated with intrinsic damage to the liver or to other organs. A serious criticism of stilbestrol is that it fails to give the patient the "lift" produced by the natural estrogens.

Much chemical research is still being directed toward the synthesis of other compounds having estrogenic activity. Stilbestrol may be relegated in the near future to a position similar to that which sulfanilamide now occupies with the sulfa drugs and at that time we will have an economical, synthetic estrogen equally potent and with none of the disadvantages of stilbestrol.

The estrogens may be administered as noted above by various routes. The sublingual drop administration of estrogens in propylene-glycol is said to be a more efficient method than the oral.¹⁸ Implantation of pellets of the pure crystalline substance into the subcutaneous tissues allowing for prolonged, slow absorption either by incision or through a large cannula has had favorable comment as a prophylactic measure in operatively induced menopause.²⁰ The onset of symptoms, following removal of both ovaries, usually occurs some two or three weeks following operation and lasts approximately two years. It has been found that these symptoms could be prevented by pellet implantation of 30 to 50 milligrams of the pure crystalline substance and that the effect lasts from four to six months. This method requires special equipment for making the pellets.

Androgenic preparations have not been mentioned but their use in the therapy of the menopause is limited to those instances where estrogens are not tolerated. The dosage should be kept below 300 milligrams a month to avoid arrhenomimetic effects²¹ and probably should not be used more than twice during a year.

There are three standard methods of administration of the estrogens. First, a method which is gaining favor at present is that of administering small

daily doses over a long period of time.²² This method has the advantage of reducing the incidence of estrogenic bleeding and in many instances it adequately controls the symptoms. The main disadvantage is the long period of time, often six weeks, which is required to relieve the symptoms. The second method is that of giving large initial amounts so as to rapidly control the symptoms (frequently 1.66 mg. of estradiol benzoate is adequate) and then continuing with oral therapy to maintain the therapeutic effect. This maintenance dose is usually in the neighborhood of 10,000 international units, that is, roughly, 1 mg. of stilbestrol, 0.05 mg. of ethinyl estradiol, or 1.25 mg. of estrone sulfate. This may be carried along for not more than two months and then gradually tapered off so as to minimize withdrawal bleeding. After a rest period, and as the symptoms recur, the estrogens may again be administered. Third, a large dose of a long acting estrogen may be given, such as 2.5 or 5 milligram of estradiol dipropionate. This will control the symptoms. The patient is then advised to return as soon as the symptoms recur. By this means the dosage and interval of administration, usually two or three weeks, may be determined for a given patient which will maintain her symptom free.

Summary

An attempt has been made to summarize the manifestations of the menopause and present a simple review of the present trends in the management of the menopausal patient.

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Table 2. Comparative activity and cost of estrogens

Parenteral estrogen	10000 IUs of estrogenic activity equals	Cost factor
Estrone	1.0 mg.	6
Estradiol benzoate	0.166 mg.	3
Diethyl stilbestrol	0.5 mg.	1
<u>Oral</u>		
Estradiol (sublingual)	0.1 mg. or 0.3 cc.	7
Ethinyl estradiol	0.05 mg.	3
Estrone sulphate	1.25 mg.	10
Diethylstilbestrol	1.0 mg.	1

The weights of parenteral and oral estrogens listed above have approximately equal estrogenic activity. With the cost of stilbestrol fixed at 1, the comparative cost of each is indicated by number.

Menopause—Then and Now

*Commentary by Reva Winkler, MD
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Menopause is a 20th-Century condition. Until 1900, a woman's entire life expectancy was less than the average age of menopause today; we now enjoy such improved health that women's lives are almost 40% longer today than at the turn of the century. Today we are overwhelmed with new knowledge and technologies that prolong useful life to its biological limit. The 1944 article by David James, MD, provides us with a midcentury view of this journey toward longevity.

In 1944, a woman's life expectancy was 65 years. With improving health standards, life spans became longer and the discomforts of menopause thus became more common—and required treatment. Most women in 1944 would spend only 18 years in the postmenopausal years and would be troubled mainly by symptoms of hypoestrogenism. The morbidity and mortality now associated with osteoporosis, cardiovascular disease, breast cancer, and Alzheimer's disease were then mainly in the future. At the middle of the 20th century, medical management of the menopause consisted of providing only short-term, symptomatic relief. Estrogens were newly available commercially and were effective, but the benefits and risks of estrogen therapy would not be well known for another 30 to 40 years.

As a description of the menopausal transition and symptomatology, Dr. James' article is as useful today as it was in 1944. The countless symptoms attributed to the menopause are no fewer today. The hot flush is still the typical symptom described in these same terms by most menopausal women. Disagreement about the relation between depression and hormonal change in menopause continues. Today we have information arguing against a relation between menopausal hormone changes and obesity and diabetes, although these conditions commonly coexist in this age group. I admire Dr. James' careful description of the sexual changes and the "loss of charm" experienced by some women. We know nothing more useful today to assist women in this area than we did half a century ago.

Dr. James clearly felt a need to address the issues presented by menopause and "to present a helpful, though by no means authoritative or exhaustive summary of the present trend in the management of the menopause." Why he felt that need arouses my curiosity. A clue can be found in his comment, "Just a few years ago, before the availability of potent estrogenic preparations made the treatment of menopausal symptoms more certain, some clinicians doubted the real

existence of the menopausal syndrome." Apparently, physicians commonly dismissed the sufferings of menopausal women. This dismissal of women's symptoms is not unique, however; similar medical disinterest was seen for dysmenorrhea, postpartum depression, and premenstrual syndrome until pioneering physicians braved the derision of colleagues to find effective treatments. In 1944, when this information was probably not given high priority by many physicians, Dr. James provided to physicians of the fledgling Kaiser Permanente Medical Group an informative summary and sensitive approach to menopause.

Kaiser Permanente (KP) can be proud of the physicians who have contributed so significantly to understanding menopause. Moreover, the gentle-but-confident presentation by Dr. James in 1944 about the importance of menopause management represents the tradition of scholarship and continuing education that is still strong within the KP Program. In 1975, William Finkle and Harry Ziel (KP, Los Angeles) published a landmark article in *The New England Journal of Medicine*²³ identifying the relation between unopposed estrogen treatment and development of endometrial cancer. Hormone replacement therapy (HRT) has been forever changed by their work. In the 1980s, multiple publications by Bruce Ettinger^{24,25} (KP Division of Research, Oakland) examined the effectiveness of HRT in preventing osteoporosis and fractures and reducing overall morbidity and mortality.

In honor of Dr. James, I will present a personal (though not authoritative or exhaustive) discussion of current management strategies for menopause. After more than 14 years of practice and considerable experience caring for transitional and menopausal women, I know that the scientific literature is helpful but that the most useful information comes from patients, whose insightful and probing questions challenge me every day. I do not always have a ready or simple answer for the patient who asks me such questions. Together, the patient and I combine our knowledge to find an approach that works for her. I will share with you some lessons that my patients have taught me.

Management of the menopause has changed during the past 50 years for many reasons. New hormone preparations, new research information, and a growing—and more demanding—female population have focused greater attention on the menopause and on patients' need for treatment. Education, counseling, and assisting women in sorting through the choices for management of menopause is time-consuming but essential: most women can expect to live to at least age 79 years and to spend 35% to 40% of their lives after the menopause.

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Overview: Transitional Physiology

A female child is born with all the ova she will ever produce. During the reproductive years, the healthiest of the eggs are easily stimulated to ovulate and produce estrogen and progesterone every month; during this time, a woman experiences her most predictable, regular cycles. When a woman reaches her late 30s, the remaining eggs are less easily stimulated and require slightly higher gonadotropin levels to stimulate ovulation. Estrogen production is variable at this stage of life, and cycle length begins to change. Progesterone production may be poor, and the luteal phase is commonly inadequate. Menses become unpredictable because of constantly changing production of estrogen and progesterone. As ovarian resistance to ovulation increases and the egg is not stimulated, anovulation results. Fluctuating estrogen levels without progesterone are responsible for dysfunctional uterine bleeding. As estrogen levels decline, patients may have hot flushes, even though they still have menstrual periods. When the ovary no longer responds to gonadotropins, levels of follicle-stimulating hormone (FSH) are elevated, estrogen production becomes minimal, and menses cease.

This transition is not necessarily an easy one. A woman who has relied on the regularity and predictability of her body is disconcerted at this unpredictable, constantly changing time of her life. She may skip menses for several months and develop hot flushes, then resume having menstrual periods temporarily while the hot flushes abate. This waxing and waning of ovarian function is common; a woman is not truly menopausal until she has had 6 to 12 months of amenorrhea. Even after this time span, however, some women can have menstrual bleeding from late ovulation stimulated by high FSH levels.

The largest, most comprehensive study of transitional women was published in 1992 and described the experience in 2,570 healthy women.²⁶ In that study,⁴ median age at menopause was found to be 51.3 years, and 90% of women had a transitional time lasting about four years (range, 2-7 years). In 10% of women, menses ceased abruptly without a transition phase. Hot flushes occurred in 10% of transitional women and in 50% of women just after menopause began. In 33% of women, hot flushes continued 4 years after menses stopped. Women who smoked cigarettes had onset of menopause two years earlier than in nonsmokers.⁴

Managing Menopause in 1998

A useful management strategy for menopause is to consider the transitional years differently than the postmenopausal period. Some women experience relatively higher estrogen levels during transi-

tion because of unpredictable ovulation or anovulation and irregular bleeding. Lack of cyclic progesterone can be effectively managed using either cyclic progestin or very low doses of oral contraceptives. For patients receiving cyclic progestin, the hypoestrogenism of true menopause can be identified when progestin treatment by itself no longer relieves symptoms. Estrogen can be added to the progestin for HRT at this time.

Some women experience relative hypoestrogenism with symptoms of hot flushes, even though they have regular menstruation and are ovulatory. These patients can be helped with estrogen treatment alone if they are still producing progesterone from ovulation. For women who are severely troubled and inconvenienced by the typical unpredictable irregularity of this phase of life, oral contraceptives can reestablish control of bleeding, rebalance hormonal levels, and provide contraception. In my clinical experience, using estrogen and progestin daily in the form of combined HRT causes difficulties for patients in the transitional years: use of this therapy may neither control irregular bleeding adequately nor prevent occasional ovulation and may cause both unnecessary anxiety for the patient and unnecessary intervention by the physician.

After a woman has clearly become menopausal, symptoms of hypoestrogenism are common: hot flushes, night sweats, vaginal dryness, and dyspareunia. I do not measure FSH or estrogen levels to document menopause; each patient is the best biological assay of her own overall hormone production.

Use of sequential HRT in the early menopausal years seems to produce less unscheduled bleeding in my patients. During these years, women may have fluctuating levels of estrogen that better respond to regular withdrawal of HRT. In addition, women who have recently stopped menstruating are more amenable to cyclic withdrawal of HRT than women for whom menopausal change is not imminent. After several years, changing to continuous combined HRT may be a more successful treatment strategy. Women who begin receiving HRT sometime after menopause can start with continuous, combined therapy.

The enormous benefits of long-term HRT in preventing heart attack and osteoporotic fracture and reducing overall morbidity and mortality are well known, and widespread recommendation of HRT to women seems essential. However, much research has shown that only 20% of menopausal women receive HRT.

Despite these health benefits, many women are afraid to take HRT. Generally, women are not afraid that they might die from heart attack or become affected with osteoporosis unless they know a rela-

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“Medically, the women who benefit greatly from HRT tend to be hypertensive diabetic patients with high cholesterol levels. Too many of these women are not receiving HRT, either because ‘my doctor told me I couldn’t,’ they are overwhelmed by the numerous medications they are already taking, or they cannot tolerate side effects.”

tive who had a hip fracture and became debilitated. However, women are afraid of cancer, specifically breast cancer. They are afraid of such known risks but are also afraid of unknown risks. Despite this fear, however, many women are skeptical or even cynical about our efforts to assist them: in the past, women have suffered from our good intentions, and such experiences as use of DES to prevent miscarriage and use of the Dalkon Shield IUD for contraception gives these women good reason to be cautious. In addition, many women dislike taking daily medication because they think it indicates they are “sick”: to this way of thinking, healthy people should not need medication, and people take medication because they are psychologically disturbed. Indeed, women generally do not think of HRT the same way they think of vitamins. Women understandably demand to know why menopause cannot be viewed as the normal part of life that it is. Asymptomatic, healthy women often have considerable resistance to “treatment” for menopause.

Many women stop HRT after only a short trial because the side effects can be troublesome. Breast tenderness—experienced by most women on HRT—can be so severe that being touched is uncomfortable, as is wearing a bra or tight-fitting clothes. This mastalgia can be decreased by not using HRT on Saturdays and Sundays, thus reducing overall HRT dose. For many patients, irregular spotting and bleeding does improve after three to six months of HRT use. Meantime, patients need a great deal of encouragement and support until amenorrhea is achieved, and many women will not maintain treatment. About 5% to 10% of women never achieve amenorrhea while receiving daily HRT. This situation is frustrating for the physician as well as for the patient. Inevitably, such patients have endometrial biopsy, manipulation of hormone doses, hysteroscopy, and dilation and curettage until both give up. A patient may accept scheduled bleeding while receiving sequential HRT, but I am admittedly relieved when she finally asks, “Can’t I just stop taking them?” Yes, indeed, she can.

As a women’s physician, I am not sure if I should encourage all women to take HRT. Recently, a healthy 85-year-old patient brought me a news article on the benefits of HRT and asked me if she should be receiving it. For a healthy woman whose genes and life habits have served her well, who has already surpassed her life expectancy, and who is still “going strong,” what can HRT improve?

Another patient who consulted me about HRT began by saying, “I don’t want to do what you people want me to.” Fine, I say. I evaluated her personal risk assessment profile and suggested nonhormonal alternative approaches for preventing osteoporosis

and heart disease. “You mean I don’t have to take them?” she asked. “No, you don’t,” I replied. Then she said, “OK. But can you give me a prescription anyway? Maybe I’ll give them a try.”

Medically, the women who benefit greatly from HRT tend to be hypertensive diabetic patients with high cholesterol levels. Too many of these women are not receiving HRT, either because “my doctor told me I couldn’t,” they are overwhelmed by the numerous medications they are already taking, or they cannot tolerate side effects. These are the patients I encourage the most, because the risk-benefit decision seems to weigh clearly on the side of benefit. However, when counseling a healthy, normal-weight, active woman with no medical problems and no family history of heart disease, I am not so sure that HRT can do anything for her. How can HRT decrease her risk of heart attack when she has very little risk anyway? If her mother had breast cancer, I think avoiding HRT is appropriate. In general, however, the best way to answer the risk-benefit question is not clear to me.

If HRT is shown to be beneficial in preventing or minimizing Alzheimer’s disease, the risk-benefit balance will change for many women. Women are very afraid of Alzheimer’s disease. Those who are afraid of breast cancer and Alzheimer’s will be very frustrated and not know what to do. They will need much encouragement and support. The availability of SERMs (Selective Estrogen Receptor Modifiers) such as raloxifene will add more to the already confusing mix. Raloxifene reduces bone loss without stimulating the breast or uterus, but it provides no relief for hot flushes or for other hypoestrogenic symptoms. Raloxifene has some effect in cardiovascular disease prevention but may not equal estrogen in this regard. Raloxifene has been initially approved for prevention and treatment of osteoporosis and is a welcome alternative to alendronate therapy.

Management of the menopause is not just a matter of “take two pills every day and everything will be fine.” Each woman has a different risk-benefit balance that should determine whether she should take HRT.²⁷ Alternatives to HRT for prevention of osteoporosis and heart disease must be included in counseling. Above all, physicians must realize that the decision to take HRT is difficult. Each woman must find her way through the dilemma. As a women’s physician, I have a comprehensive knowledge of the facts, reasons, arguments, and statistics. As a woman in her forties who is facing the HRT decision in the near future, I have no idea what I will choose. ❖

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The Cost of Ignorance

"If you think education is expensive, try ignorance."

Derek Bok,

President Emeritus, Harvard University