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Hormone Replacement Therapy and Height Loss: Does Estrogen Prevent Shrinking?

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by

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Dedication

This thesis is dedicated to my grandmother, Marie L. Hall, who taught me that education and honor are two of the greatest goals.

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Chapter I

Introduction

My mother and I were recently laughing about a comment made to explain the bent-over appearance of the old Chinese women who bustle down the busy streets in San Francisco's Chinatown; "The reason they are so bent over," my aunt said matter of factly, "is because they don't feel like standing up straight anymore." My mother, who is a registered nurse, has an assuredly different explanation. It is her conviction that most of them suffer from vertebral osteoporosis that has resulted in their kyphotic dowagers' humps.

The subject of this master's thesis, height loss and estrogen replacement therapy, has grown out of my interest in both women's health and the course of normal aging. Aging is accompanied by tremendous physical and emotional changes that are described as normal, pathological, or perhaps a combination of the two. The distinction between normal and pathological aging is becoming increasingly blurred, especially as medicine develops more sophisticated methods of preventing what used to be thought of as normal age-related phenomena. The question of what causes height loss in aging women is one example of this tension, and the vignette above describes two polar views on the subject.

This thesis takes a closer look at one explanation of age-related height loss, vertebral osteoporosis. It tests whether a well-advertised therapy that prevents osteoporosis, post menopausal estrogen replacement, also prevents loss of height. A perhaps less clinically relevant question than many others that might be asked about estrogen replacement therapy, this investigation is fueled by implications that height is preserved among long-term estrogen users that are made particularly by the companies that manufacture estrogen itself. Although it is one of the more cosmetic reasons to use estrogen therapy after menopause, height preservation is nonetheless depicted as an implied benefit.

The thesis is organized into five chapters, each written to highlight a specific aspect of the debate. This introduction is chapter one. Chapter two is a brief review of menopause, its epidemiology, "symptoms", and a literature review of one of the risks that is medically believed to result from long term estrogen deprivation, osteoporosis. Chapter three details the methods and results of an epidemiologic study that was conducted from June to October of 1992 through the Kaiser Division of Research. The retrospective cohort study entailed measuring height in 70 women who were in their 60s and 70s and were either long-term estrogen users or non-users. Subjects' current height was compared with their previous measures of height that were taken under standardized conditions. The results of height measurement were analyzed in conjunction with data collected by questionnaire that assessed each individual's risk factors for osteoporosis. Chapter four is a sociological and historical foray into the medical profession's involvement in defining and treating menopause as a disease entity. Finally, chapter five contains brief closing remarks.

Chapter II

Menopause and Osteoporosis

Menopause was once medically viewed as the end of a woman's fertility that caused mainly bothersome and temporary side effects. Now, however, it is recognized that menopause marks the transition of women to a period of increased risk of chronic diseases such as heart disease and osteoporosis. This chapter will present the epidemiology and physiology of menopause, and then turn to one of the most concerning long term side effects of menopause, osteoporosis. A brief description of bone physiology will follow, as well as the epidemiology of osteoporotic fractures, especially vertebral fractures. It will conclude by describing methods of quantifying and measuring osteoporosis, and finally the rationale for using estrogen replacement to prevent bone loss among post menopausal women.

Epidemiology of menopause:

There are few well agreed upon and precise definitions of menopause. The World Health Organization issued a report in 1981 that suggested these definitions[1]:

Menopause: The permanent cessation of menstruation resulting from the loss of ovarian follicular activity.

Perimenopause/climacteric: The period immediately prior to the menopause that includes the endocrinological, biological and clinical features of approaching menopause, and at least the first year after the menopause.

Postmenopause: The period dating from the menopause that is established by at least twelve months of spontaneous amenorrhea.

Most studies looking at the average age at menopause have been conducted in Europe and the United States. They indicate that the average age for the final cessation of menses in Caucasian women is around 50 years old.[2-7] Other studies conducted in

non-western countries such as Papua New Guinea and India show the average age at menopause to be much earlier, ranging from 43.6 to 47.3 years.[8-11] Some variation in the average age at menopause is in part explainable by differences in nutritional status. In fact, within Papua New Guinea, malnourished women experienced menopause approximately four years earlier than well nourished women. However, not all of the difference in age at menopause between western Caucasian women and women in developing countries is accounted for by nutritional factors alone. Further studies are needed to identify the factors creating differences in the average age at menopause between women of western and non-western countries.

Besides nutritional status, cigarette smoking also affects age at menopause; Regular cigarette smokers experience menopause 1-2 years earlier than non-smokers.[15,16] Postulated mechanisms include an accelerated rate of estrogen clearance in the liver, and accelerated oocyte aging due to toxins within the smoke, such as aromatic hydrocarbons.

PHYSIOLOGY/Endocrinology OF MENOPAUSE:

The WHO definition of menopause focuses on the cessation of ovarian function. However, it is the reduction of the hormone estrogen resulting from the waning ovarian function that is at the heart of the medical discussion of menopause.

Estrogen is a steroid hormone which is synthesized from free cholesterol and readily passes through the cell membrane. Once in the cell, estrogen joins to a nuclear receptor complex that binds to DNA and modifies transcription.[17] Females synthesize many forms of biologically active estrogen. In women of reproductive age, the predominant estrogen is estradiol-17ß which is made from androgenic precursors within the ovarian granulosa cells.[18] After menopause, estrogen is still produced. However, the estrone made from the peripheral conversion of adrenal androgens predominates. Peripheral conversion of androgens to estrone occurs primarily in adipose tissue by an enzyme called aromatase, which has led to the the conclusion that body fat affects the

amount of estrone levels in post menopausal women.[12,13] A comparison of estrogen and androgen levels in premenopausal and post-menopausal women is as follows:

	Mean Plasma or Serum Concentration	
	Premenopausal	Postmenopausal
Estradiol (pmol/l)	620	40
Estrone (pmol/l)	440	110
Androstenedione (pmol/l)	6300	3100
Testosterone (pmol/l)	1000	800
Dehydroepiandrosterone (nmol/l)	17000	5500
Dehydroepiandrosterone sulphate (nmol/l)	5400	1000

In reproductive aged women, ovarian estrogen synthesis is controlled by a feedback loop that involves the hypothalamus, the anterior pituitary and the ovary itself. Follicle Stimulating Hormone (FSH) is a two unit glycoprotein derived from the anterior pituitary. It is stimulated by GnRH released from the hypothalamus, stimulates the ovaries to produce follicles, and facilitates granulosa cells' secretion of estradiol via cyclic AMP production to increase aromatase activity in the cells. Estrogen feedback on the pituitary inhibits production of FSH.

Up to 10 years prior to and 3 years following menopause, serum levels of FSH are elevated up to 10 times normal levels. This progressive elevation of FSH is thought to result in part from increasing ovarian resistance to FSH, which prevents negative estrogen feedback on the pituitary.[18,19] Serum levels of FSH serve as a useful laboratory assay to assist in determining womens' reproductive status. In contrast to FSH, LH rises only slightly during the same period, increasing to 2-3 times the level seen in reproductive aged women.

Medical Explanations/Consequences of Menopause:

The physical consequences of declining levels of ovarian estrogen production can be broken down into two temporally observable effects: immediate effects of estrogen deficiency, and long term effects. Both have been characterized to varying degrees epidemiologically, although the mechanism of how estrogen deficiency creates the symptoms is not always well understood.

Estrogen deficient effects may occur immediately during the perimenopause. They include symptoms relating to both vasomotor instability and the loss of trophic stimulation to target tissues. Vasomotor instability results in sensations of hot flashes, night sweats, palpitations and headaches, and are estimated to affect up to 75% of women in the west.[20] A study from the Netherlands reported that 65% of perimenopausal women experienced hot flashes, and 40% of women experienced night sweats[21] and a study from Canada also reported a 65% historical recollection of hot flashes.[22] Direct target tissue effects of lowered estrogen levels may include vaginal dryness, atrophic vaginitis and dyspareunia, although their prevalence and age at onset are not well characterized.

Research has recently focused on chronic conditions that are thought to be related to menopause. It is difficult to separate age related disease from disease caused by lack of ovarian estrogen, however after menopause the pattern of risk of dying from various diseases changes; There is an increase in coronary heart disease-related deaths, and bony fracture related deaths, and a decrease in cancers of the breasts and genital tract.[23] The current trend in research is to investigate how much of the changing risk of these diseases are attributable to estrogen deficiency.

It has been noted that large secular and geographic variations exist in many of the conditions associated with the menopause, such as hot flashes, and heart disease. If estrogen deficiency were the definitive and universal risk factor for these conditions, then the variation should be small. While the menopause may be a risk factor for these

diseases, there are other determinants which are likely to have a more profound influence.[24]

Tissues directly stimulated by estrogen are the vaginal mucosa, the cervix, urethral mucosa, the uterus, ligaments supporting the uterus, breast tissue, liver via synthesis of carrier proteins and clotting factors, and fibroblasts in the skin.[31] In the absence of estrogen, these tissues may atrophy and cause clinically perceptible problems.

Along with a trophic effect on the various tissues detailed above, estrogen also has an effect on the hypothalamus, although it is unclear whether this effect is direct or indirect. Vasomotor instability, a temporary condition which involves peripheral vasodilation with an increased rate of cutaneous blood flow and rapid heart rate, is caused by stimulation of autonomic nerves via the hypothalamus and is affected by estrogen deficiency.[32] Theories that have been proposed to explain the role of estrogen in vasomotor instability include disregulation of brain amines resulting from estrogen withdrawal[33], a direct hypothalamic response to rapid estrogen withdrawal[32], and the direct effect of raised gonadotrophins on the vasomotor center[18].

Lack of estrogen also adversely affects bone density on a tissue level, although the cellular mechanisms of the interaction are still being elaborated. An explanation of bone physiology will help clarify the presentation of what is known about estrogen's action on bone.

PHYSIOLOGY OF NORMAL BONE:

Bone is a specialized form of connective tissue that is composed of a collagen matrix with mineral salt deposition. Bones serve many purposes: support of muscular structures, locomotion, protection of internal organs, housing of developing blood cells and storage and release of calcium and other minerals. For the purposes of this paper, the support function of bone will be highlighted.

Bone is a tissue in continuous metabolic flux. It is constantly being made and destroyed in a process known as remodelling. During early life the process is in equilibrium; Constant remodelling allows bone to be laid down at the points of greatest weight bearing loads, or stress, and resorbed where loading and stress are not as great.[36] However, as aging progresses in both men and women, the rate of destruction, also known as resorption, increasingly outpaces the rate of formation and equilibrium in remodelling no longer exists.

Two populations of cells within bone are responsible for the processes of remodelling: osteoclasts resorb bone, and osteoblasts lay down new bone. Each type of cell is responsive to different hormonal signals. Osteoclasts are stimulated by parathyroid hormone, and inhibited by calcitonin, bisphosphonate, and possibly by estrogen. It is the current theory that osteoblasts are stimulated by estrogen.

Every bone in the body consists of varying proportions of two histological subtypes: cortical bone and trabecular bone. Cortical bone is arranged in a series of longitudinal units called osteons that serve to maintain the strength and integrity of the intact bone.[18] Trabecular bone is composed of delicately arched spicules that run parallel to the weight bearing forces, and houses developing blood cells, the bone marrow. Long bones such as the bone of the thigh, the femur, are predominantly composed of cortical bone, while hematopoietically active bones such as the clavicle and vertebrae contain proportionally more trabecular bone.

Bone metabolism occurs on bony surfaces and trabecular bone has more overall surface area than cortical bone. While trabecular bone constitutes only 20% of the entire skeleton, it is more metabolically active than cortical bone. And, as a metabolically more active bone, trabecular bone is also more vulnerable to imbalances between bone resorption and reformation. During aging of both men and women, bone resorption and formation no longer equal each other. Resorption occurs at a faster rate than formation. The higher metabolic rate seen in trabecular bone may partly explain the observation that

age-related trabecular bone loss appears to be more pronounced than cortical bone loss, and occurs at an earlier age.[37, 38]

In addition to increased resorption, many other age related bone changes may cause weakness. Microfractures accumulate in the bone due to critical mechanical stress, changes in the mineralization of bone cause some areas to become hypermineralized and brittle, changes in crystallinity influence biomechanical properties and physiochemical dynamics of bone tissue, and the protein content of the extracellular matrix of bone tissue may change or decrease.[39] Furthermore, lifestyle factors may negatively influence bone status in the elderly and include dietary deficiencies, and reduced mechanical loading on the bones in general.[40, 41]

Osteoporosis

When the bone loss observed in aging people diminishes to a critical range, there is an associated increased risk of fracture. Osteoporosis is defined as: **the reduction in bone mass that increases susceptibility to fracture** .[43] A more exact definition is elusive.

There has been refinement of techniques available to measure bone mass and bone density. However, there is little agreement about which bone densities ought be considered osteoporotic. Some researchers use the average bone density of 30 year old women as normal, and define densities that fall beyond a standard deviation from that number as osteoporotic.[44-47] Others define the average bone density for the age and height of the person being measured as normal, and a standard deviation below that value as the threshold for osteoporosis.[48] More discussion about the interpretation of bone density will follow.

Before bone density technology was available, clinical diagnosis of osteoporosis was based on the presence of osteoporotic fractures themselves. This created a disease whose diagnosis was based on the existence of the outcome of the disease, a fracture.

Some contemporary researchers still prefer this conceptualization of osteoporosis, arguing that disease is more appropriately characterized by the presence of pathological fractures than by the presence of risk for fractures.[48]

Considering the lack of consensus about the definition of osteoporosis, it is not surprising that few studies have adequately characterized the existence of osteoporosis per se. The epidemiology of osteoporotic fractures is better characterized than the epidemiology of osteoporosis itself.

Despite the existence of 206 bones in the body, osteoporotic fractures are classically thought of as fractures resulting from minimal trauma occuring at the hip, the distal forearm (Colles fracture), and the vertebrae.[49,50] Hip fractures are associated with more deaths, disability, and medical costs than all other osteoporotic fractures combined.[51,52] Nearly 210,000 hip fractures occur in the United States every year. Their incidence is greater in women,[53] and risk rises dramatically with age.[52]

Hip fractures are associated with a 12-20 per cent mortality rate in the first year after the event, although the very high rate of preexisting morbidity makes it difficult to ascertain the direct contribution of the fracture itself to mortality.[25-29] The morbidity attributable to hip fractures is not trivial, and as many as 50% of previously ambulatory and independent persons suffering from hip fractures may be institutionalized, or dependent upon other people for mobility. [14,30,34,35]

Lifetime risk estimates are calculations that define the probability of developing the condition in question before death. It is estimated that the lifetime risk of hip fractures is 12-15% for 50 year old white women compared with 5.2% for 50 year old white males. In African American men and women, the lifetime risk is much lower.[50] 50 year old African American women have a 5.6% lifetime risk of hip fracture compared with a 2.8% risk of lifetime hip fracture for 50 year old African American males. The median age for first hip fracture is 79 years.[50]

Before age 75, Colles fractures are the most common fractures among post menopausal white women. They are associated with little morbidity and are rarely fatal. Lifetime risk for this type of fracture among white 50 year old women is 15%, with the median age at fracture being 66 years old. [50]

Vertebral fractures

Vertebral fractures are more difficult both to detect and confirm than colles and hip fractures. Three vertebral deformities are usually described as resulting from a partial or complete compression fracture of the vertebral body. They are: wedge deformities, in which either the anterior or posterior aspect of the vertebrae is shortened, biconcave deformities, in which the midregion of the vertebral body is decreased both superiorly and inferiorly, and crush fractures, in which the entire vertebral height is reduced. Wedge deformities account for 80% of vertebral deformities while crush fractures contribute 20%.[58] Estimates of the prevalence of biconcave deformities were not found.

While some vertebral fractures become clinically apparent after an episode of acute back pain that is confirmed by radiologic evidence of fracture, the majority are either asymptomatic or cause insufficient symptoms to initiate medical investigation.[48,56] Because of the high prevalence of silent fractures and the many different etiologies of back pain, attempts to estimate the prevalence of vertebral fractures based on clinical evidence of pain are unreliable.

Most studies estimating the prevalence of vertebral fractures do so using radiologic films of the spine. They yield highly variable estimates of prevalence, depending on the definitional criteria of vertebral fracture, the age of the group measured, and the area of the spine examined. One commonly used radiologic protocol for assessing vertebral fractures is to consider a 15-20% reduction of height in vertebral body pathological when it is observed either anteriorly, posteriorly, or centrally. With this protocol, Melton et al[63] estimated a 27% prevalence of vertebral fractures among

Caucasian women in the northeast who were 65 years and older. Conversely, a study looking at the thoracic spine among 80 year old Finnish women estimated the prevalence of thoracic vertebral fractures to be only 2.9%.[59] Lifetime risk for vertebral fracture among white 50 year old women has been estimated to be 32%,[50] although this estimate must be viewed with caution, due to the lack of consensus about what constitutes a vertebral fracture.

Consequences of symptomatic vertebral osteoporosis include back pain, kyphosis, and rarely, hospitalization. Pain following an acute vertebral fracture may last from two weeks to approximately 3 months, and is characterized as deep intense pain at the site of fracture, with palpatory tenderness over the site.[55,60,61] Kyphosis may occur as a result of wedge fractures[57,62] and was observed in up to 50% of patients known to be osteoporotic who had previous vertebral fractures.[55]

Because so few vertebral fractures are symptomatic and require hospitalization, the medical costs of osteoporotic vertebral fractures are difficult to estimate. One researcher estimated vertebral fractures to contribute 1-2% of the total cost of all osteoporotic fractures.[65] Another demonstrated that hospitalization for vertebral compression fracture amounted to 10% of the cost of hospitalized hip fractures.[60] Not included in these calculations are individual physician visits for non-specific back pain, which would skew estimates in the direction of overestimation of actual cost.

Osteoporosis and bone mineral density measurement:

The dependence of current definitions of osteoporosis on the quantitative measurement of bone mineral content has been fueled by the increasing availability of technology to measure bone density. Bone mass may be quantified using either radionucleotide or X ray imaging to measure the tissue absorption of photons. Results are reported in units of mass (grams of mineral), or units of mass divided by the area scanned (grams of mineral per cm2). While appendicular sites such as the radius and

ulna are well characterized using a single beam, areas surrounded by soft tissue necessitate more sophisticated technology such as dual beams, a technology that helps correct for error due to non-specific soft tissue absorption.[66]

Technologies that are available to measure bone density include Radiogrammetry, Single Photon Absorptiometry (SPA), Dual Photon Absorptiometry (DPA), Dual X ray Absorptiometry (DXA), and Quantitative Computed Tomography (QCT). Of the density assessing technologies delineated above, Dual X-ray absorptiometry, which has been commercially available since 1987, is considered the most practical and precise tool for examining axial bone densities.[66, 67, 68] It offers low patient radiation exposure, low in vitro precision error, high image resolution and high sensitivity. Dual photon absorptiometry is criticized for having poor in vivo precision, and low sensitivity. Quantitative computed tomography has the greatest capacity to measure spinal trabecular bone and discriminate postmenopausal women with mild vertebral deformities from those with definite fractures but it requires sophisticated calibration, positioning and relatively high amounts of radiation exposure compared with other techniques.[67, 68] High replacement costs also make it an unlikely candidate for following the progression of bone density changes.[67-69]

Interpreting the results of bone density is a confusing task. Since bone density is a continuously distributed variable, there is no absolute cutoff point that separates low density from normal density, or high risk of fracture from low risk of fracture. The gaussian distribution of bone densities among those with hip fractures is shifted only .5 standard deviations from the gaussian distribution of bone density of age matched controls.[70] Lack of consensus in the definitions of which bone densities are considered "osteoporotic" is due to the lack of a dichotomous distribution of bone densities[7]. Nonetheless, studies show that relatively low bone mass is an important risk factor for osteoporotic fractures.[71-73]

The exact clinical applicability of bone density studies is also a subject of considerable controversy. There is great debate about whether to use bone densitometry to screen women at risk for osteoporosis at the time of menopause, and recommend treatment options based on the results. In 1990, Tosteson et al. concluded that screening asymptomatic, perimenopausal white women to detect low bone mass and to target hormone replacement therapy at women who are at the greatest risk for fracture is a reasonably cost-effective use of health care resources.[74] In contrast, in 1991 Law, Wald and Meade pronounced bone density measurement to be a poor screening test, and concluded that there is at present no scientific case for screening.[70] In 1991 Johnston, Slemenda, and Melton recommended that bone density measurement be made in women who are deficient in estrogen, but then added that not all menopausal women are included in this recommendation.[66] In short, the lack of consensus about definitions of osteoporosis are echoed in the lack of agreement about appropriate use of the technology that exists to diagnose it.

Osteoporosis: Risk factors and treatments:

Although bone loss in women starts around 25-30 years, it is accelerated around the time of menopause. There are many well established risk factors for bone loss. They include female gender, low body weight, family history of non-traumatic fractures, low calcium diet, low physical activity and prolonged immobility, cigarette smoking, medications such as thyroid hormone and steroids, metabolic disorders such as diabetes, hyperthyroidism, hyperparathyroidism and Cushings syndrome, malabsorption syndromes, and, as pertains to this study, loss of estrogen stimulation to bone such as is seen beginning with menopause.[43,70,77]

Considering the well established risk factors for osteoporosis, both prevention and treatments rely on correcting any predisposing pathology, such as hyperthyroidism, or Cushing's syndrome, and preventing further loss with more aggressive medical therapy.

Non-medical treatment options include calcium supplementation and weight bearing exercise, which together have been shown to halt bone loss, if not increase bone mass slightly.[77,78,79] Medical options include calcitonin and estrogen therapy.

The pathogenetic basis of estrogen deficiency and bone loss appears to occur by a number of different mechanisms. First it has been shown that lack of estrogen reduces intestinal absorption of calcium to below the threshold for maintaining a positive calcium balance.[80] Second, an increase in bone turnover has been observed.[81] Finally, estrogen receptors have been isolated on osteoblasts, which led Lindsey et al to conclude that osteoporosis is a primary disorder of the skeleton consequent upon loss of estrogen, and that estrogen deficiency is the major factor that causes bone loss among the aging female population.[82]

Estrogen therapy prevents bone loss for as long as the therapy continues. Once it is stopped, bone loss proceeds in the pattern that is seen around the menopause. That is, rapidly at first, and then flattening out .[83] In quantitative terms, white women appear to lose as much as 1-10% of their trabecular bone mass per year during the first few years after menopause, and about 1% of their cortical bone per year during the first decade following menopause. By the age of 70, however, bone loss is no longer observed, regardless of estrogen therapy. [84-86]

In spite of the highly experimental explanations for the mechanisms of bone physiology and estrogen, the epidemiology of post menopausal estrogen's effectiveness in preventing fractures is the most compelling argument for considering its use. Epidemiologic studies have shown continued post-menopausal estrogenic stimulation to protect against fractures of the hip, spine and radius, [42,75] although data on prevention of spinal fractures is weak. An overall 50% risk reduction in hip fractures has been estimated in women who have used estrogen for at least five years, beginning at the time of menopause. Prospective data suggests that estrogen therapy of at least 10 years duration will also reduce vertebral deformity by 75-90%.

Menopause is a universal concomitant of aging in women. It may be accompanied by transient signs of estrogen deficiency such as hot flashes, and night sweats. In women, the estrogen deficiency that accompanies menopause is the cardinal risk factor for osteoporosis, a rather vaguely defined condition that carries with it a predisposition to fracture. The great personal and economic cost of osteoporotic fractures of the hip are well documented, while the epidemiology of vertebral fractures is less so.

Estrogen experimentally affects the rate of bone resorption, intestinal calcium absorption, and increased bone density. Epidemiologic studies show that long term estrogen replacement instituted immediately after menopause unequivocally reduces the risk for osteoporotic fractures in multiple sites.

This may seem like a closed case argument for the universal recommendation of use of post menopausal estrogen replacement therapy. However, many significant questions remain. There are no randomized trials examining the long term effects of estrogen replacement therapy. And new evidence suggests that estrogen's protective effects against hip fracture may be lost after the age of 75.

Furthermore, considering the liberty that pharmaceutical companies take in advertising their products, and the commitment that lifetime post-menopausal estrogen replacement represents to any woman choosing to comply with the regimen, the subtleties of advertised beneficial effects of estrogen deserve the same scrutiny that the more profound effects receive. An advertisement showing a hunched old postmenopausal woman standing next to a ruler is just one example of the tactics employed to promote estrogen use. It preys on peoples' fears of becoming shriveled and hunched over and it presents a highly negative physical image of the aged. It is this representation of one of the beneficial effects of estrogen, the implied preservation of height, that motivated the research that is to be discussed in the next chapter.

References: Menopause and Osteoporosis

1. World Health Organization. "Research on the Menopause." Report of a WHO Scientific Group, Series 670, Geneva: World Health Organization, 1981.

2. McKinlay, S, Jefferys, M, Thompson, B. "An Investigation of the Age at Menopause." Journal of Biosocial Science 4 (1972): 161-172.

3. Thompson, B, Hart, SA, Durno, D. "Menopausal Age and Symptomatology in a General Practice." Journal of Biosocial Science 5 (1973): 71-82.

4. MacMahon, B, Worcester, J. "Age at Menopause: United States 1960-62." US Vital and Health Statistics, Series II, No. 19. Washington DC: 1966.

5. Hauser, G, Remen, U, Valaer, M, Erb, H, Mueller, T, Obiri, J. "Menarche and Menopause in Israel." Gynaecologia (1963): 38-47.

6. Treloar, A. "Menarch, Menopause and Intervening Fecundability." Human Biology (1974): 89-107.

7. Frommer, D. "Changing Age of Menopause." British Medical Journal 2 (1964): 349-351.

8. Wyon, J. "Differential Age at Menopause in the Rural Punjab, India." Population Index 32 (1966): 328.

9. Burch, P, Bunz, F. "The Distribution of Menopausal Age in New Zealand. An Exploratory Study." New Zealand Medical Journal 66 (1967): 6-10.

10. Frere, G. "Mean Age at Menopause and Menarche in South Africa." South African Journal of Medical Science 31 (1971): 21-24.

11. Abramson, J. "Age at Menopause of Urban Zulu Women." Science 132 (1960): 356-357.

12. Siiteri, P, MacDonald, P. "Role of Extraglandular Estrogen in Human Endocrinology." In Handbook of Physiology, Vol 2, Part 1, pp. 615-629. Edited by R. Greep, E. Astwood. Baltimore: Williams and Wilkins, 1973.

13. Nordin B, Crilly, R, Marshall, D, Barkworth, S. "Oestrogens, the Menopause and the Adrenopause." Journal of Endocrinology 89 (1981): 131P-143P.

14. Miller, C. "Survival and Ambulation Following Hip Fracture." Journal of Bone and Joint Surgery 60A (1978): 930-4.

15. Lindquist, O, Bengtsson, C. "The Effect of Smoking on Menopausal Age." Maturitas 1 (1979): 191-199.

16. Jick, H, Porter, J. "Relation between Smoking and Age of Natural Menopause." Lancet (1977): 1354-1355.

17. Webster, N, Green, S, Jin, J, Chambon, P. "The Hormone-Binding Domains of the Estrogen and Glucocorticoid Receptors Contain and Inducible Transcription Activation Function." Cell 54 (1988): 199-207.

18. Al-Azzawi, F. "Endocrinological Aspects of the Menopause." British Medical Bulletin 48 (1992): 262-275.

19. Vagenakis, A. "Endocrine Aspects of Menopause." Clinical Rheumatology 8 (1989): 48-51.

20. Studd, J, Watson, N, Henderson, A. "Sympoms and Metabolic Sequelae of the Menopause." In HRT and Osteoporosis, pp. 23-34. Edited by J. Drife, J. Studd. London: Springer Verlag, 1990.

21. Lock, M. "Contested Meanings of the Menopause." Lancet 337 (1991): 1270-1272.

22. Jaszmann L. "Epidemiology of the Climacteric Syndrome." In The Management of the Menopause and Post-Menopausal Years, pp. 11-24. Edited by S. Campbell. Proceedings of the International Symposium, 1975. Baltimore: University Park Press, 1976.

23. Grady, D, Rubin, S, Petitti, D, Fox, C, Black, D, Ettinger, B, Ernster, V, Cummings, S. "Hormone Therapy to Prevent Disease and Prolong Life in Post-Menopausal Women." Annals of Internal Medicine 117 (1992): 1016-1036.

24. Khaw, K. "Epidemiology of the Menopause." British Medical Bulletin 48 (1992): 249-261.

25. Kenzora, J, McCarthy, R, Lowell, J. "Hip Fracture Mortality: Relation to Age, Treatment, Preoperative Illness, Time of Surgery, and Complications." Clinical Orthopedics 186 (1984): 45-46.

26. Weiss, N, Liff, J, Ure, C. "Mortality in Women Following HIp Fracture." Journal of Chronic Disease 36 (1983): 879-82.

27. Ceder, L, Thorngren, K, Wallden, B. "Prognostic Indicators and Early Home Rehabilitation in Elderly Patients with Hip Fracture." Clinical Orthopedics 152 (1980): 173-84.

28. Ceder, L, Elmquist, D, Svensson, S. "Cardiovascular and Neurologic Function in Elderly Patients Sustaining a Fracture of the Neck of the Femur." Journal of Bone and Joint Surgery 63B (1981): 560-566.

29. Nieman, D, Mankin, H. "Fractures About the Hip in an Institutionalized Population." Journal of Chronic Disease 36 (1983): 879-82.

30. Katz, S, Heiple, K, Downs, T. "Long Term Course of 147 Patients with Fracture of the Hip." Surgical Gynecology and Obstetrics 124 (1967): 1219-30.

31. Mishell, D. Menopause, Physiology and Pharmacology. Chicago: Yearbook Medical Publishers, 1987.

32. Braga, C. "Actions of Ovarian Hormones and their Loss on the Central Nervous System." Mimeographed. University of California, San Francisco: University of San Francisco, 1992.

33. Yen, S. "The Biology of Menopause." Journal of Reproductive Medicine 18 (1977): 287.

34. Thomas, T, Steven, R. "Social Effects of Fractures of the Neck of the Femur." British Medical Journal 3 (1974): 456-8.

35. Cobey, J, Cobey, J, Conanct, L. "Indicators of Recovery from Hip Fracture." Clinical Orthopedics 117 (1976): 258-62.

36. Rodan, Gideon. "Introduction to Bone Biology." Bone 13 (1992): S3-S6

37. Lips, P, Courpron, P, Meunier, P. "Mean Wall Thickness of Trabecular Bone Pockets in the Human Iliac Crest: Changes with Age." Calcified Tissue Research 26 (1978): 13-17.

38. Compston, J, Mellish, R, Croucher, P, Newcombe, R, Garrahan, N. "Structural Mechanisms of Trabecular Bone Loss in Man." Bone Mineral 6 (1989): 339-350.

39. Kiebzak, Gary. "Age-Related Bone Changes." Experimental Gerentology 26 (1991): 171-187.

40. Riggs, B, Melton, L. "Involutional Osteoporosis." New England Journal Medicine 314 (1986) 1676-1686.

41. Schneider, V, McDonald, J. "Skeletal Calcium Homeostasis and Countermeasures to Prevent Disuse Osteoporosis." Calcified Tissue International 36 (1984) S151-S154.

42. Krieger, N, Kelsen, J, Holford, T, O'Connor, T. "An Epidemiological Study of HIp Fracture in Postmenopausal Women." American Journal of Epidemiology 116 (1982) 141-148.

43. Cummings, S, Kelsey, J, Nevitt, M, O'Dowd, K. "Epidemiology of Osteoporosis and Osteoporotic Fractures." Epidemiologic Reviews 7 (1985): 178-205.

44. Krolner, B, Pors Nielsen, S. "Bone Mineral Content of the Lumbar Spine in Normal and Osteoporotic Women: Cross-sectional and Longitudinal Studies." Clinical Science 62 (1982): 329-336.

45. Nordin, D. "The Definition and Diagnosis of Osteoporosis." Calcified Tissue International 40 (1987): 57-58.

46. Ott, S, Kilcoyne, R, Chesnut, C. "Ability of Four Different Techniques of Measuring Bone Mass to Diagnose Vertebral Fractures in Postmenopausal Women." Journal of Bone Mineral Research 2 (1987) 201-210.

47. Purdie, D, Horsman, A. "Population Screening and the Prevention of Osteoporosis." In HRT and Osteoporosis, pp. 251-264. Edited by J. Drife, J. Studd. London: Springer-Verlag, 1990.

48. Kanis, J, McCloskey, E. "Epidemiology of Vertebral Osteoporosis." Bone 13 (1992): S1-S10.

49. Kanis, J, Pitt, F. "Epidemiology of Osteoporosis." Bone 13 (1992): S7-S15.

50. Cummings, S, Black, D, Rubin, S. "Lifetime Risks of Hip, Colles', or Vertebral Fracture and Coronary Heart Disease Among White Postmenopausal Women." Archives of Internal Medicine 149 (1989): 2445-2448.

51. Haupt, B, Graves, E. "Detailed Diagnoses and Surgical Procedures for Patient Discharges From Short-stay Hospitals: United States, 1979." Hyattsville, MD: US DHHS publication no. 82.-1274-1, 1982.

52. Lewinnek, G, Kelsey, J, White, A. "The Significance and Comparative Analysis of the Epidemiology of Hip Fractures." Clinical Orthopedics 152 (1980) 35-43.

53. Gallagher, J, Melton, L, Riggs, B. "Epidemiology of Fractures of the Proximal Femur in Rochester, Minnesota." Clinical Orthopedics 150 (1980): 163-171.

54. Melton, L. "Epidemiology of Osteoporosis: Predicting Who is at Risk." Annals New York Academy of Sciences 622 (1992): 295-306.

55. Finsen, V. "Osteoporosis and Back Pain Among the Elderly." Acta Med Scandinavia 223 (1988): 443-9.

56. Gershon-Cohen, J, Rechtman, A, Schraer, H, Blumberg, N. "Asymptomatic Fractures in Osteoporotic Spines of the Aged." Journal of the American Medical Association 153 (1953) 625-7.

57. Saville, P. "The Syndrome of Spinal Osteoporosis." Clinical Endocrinologic Metabolism 2 (1973): 177-85.

58. Melton, L, Chao, E. "Biomechanical Aspects of Fractures." In Osteoporosis: Etiology, Diagnosis, and Management, pp 111-131. Edited by B. Riggs, L. Melton. Newport: Raven Press, 1988.

59. Harma, M, Heliovaara, M, Aromaa, A, Knekt, P. "Thoracic Spine Compression Fractures in Finland." Clinical Orthopedics 205 (1986): 188-194.

60. Silverman, S. "The Clinical Consequences of Vertebral Compression Fracture." Bone 13 (1992): S27-S31.

61. Leidig, G, Minne, H, Sauer, P. " A Study of Complaints and Their Relation to Vertebral Destruction in Patients with Osteoporosis." Bone Mineral 8 (1990): 217-219.

62. DeSmet, A, Robinson, R, Johnson, B, Lukert, B. "Spinal Compression Fractures in Osteoporotic Women: Patterns and Relationship to Hyperkyphosis." Radiology 166 (1988): 497-500.

63. Melton, L, Kan, S, Frye, M, Wahner, H, O'Fallon, W, Riggs, B. "Epidemiology of Vertebral Fractures in Women." American Journal of Epidemiology 129 (1989): 1000-1011.

64. Kleerekoper, M, Nelson D, Peterson E, Tilley B. "Outcome Variables in Osteoporosis Trials." Bone 13 (1992): S29-S34.

65. Norris, R. "Medical Costs of Osteoporosis." Bone 13 (1992): S11-S16.

66. Johnston, C, Slemenda, C, Melton L. "Clinical Use of Bone Densitometry." New England Journal of Medicine 324 (1991): 1105-1109.

67. Sartoris, D, Moscona, A, Renick D. "Progress in Radiology: Dual Energy Radiographic Absorptiometry for Bone Densitometry." Annals New York Academy of Sciences 622 (1991): 307-325.

68. Lang, P, Steiger, P, Faulkener, K, Gluer, C, Genant, H. "Osteoporosis: Current Techniques and Recent Developments in Quantitative Bone Densitometry." Metabolic Bone Disease 29 (Jan 1991): 49-76.

69. Hansen, M, Hassager, C, Overgaard, K, Marslew, U, Riis, B, Christiansen, C. "Dual-Energy X-ray Absorptiometry: A Precise Method of Measuring Bone Mineral Density in the Lumbar Spine." Journal of Nuclear Medicine 31 (1990): 1156-1162.

70. Law, M, Wald, N, Meade, T. "Strategies for Prevention of Osteoporosis and Hip Fracture." British Medical Journal 303 (1991): 453-459.

71. Seeley, D, Browner, W, Genant, H, Cummings, S. "Which Fractures are Osteoporotic?" In Proceedings of the Third International Symposium on Osteoporosis October 14-18, 1990. Vol 2, pp 463-464. Edited by C. Christiansen, K. Overgaard. Copenhagen: Osteopress, 1990.

72. Hui, S, Slemenda, C, Johnston, C. "Baseline Measurement of Bone Mass Predicts Fracture in White Women." Annals of Internal Medicine 111 (1989): 355-361.

73. Gardsell, P, Johnell, O, Nilsson, B. "The Predictive Value of Bone Loss for Fragility Fractures in Women: A Longitudinal Study over 15 years." Calcified Tissue International 49 (1991): 90-4.

74. Tosteson, A, Rosenthal, D, Melton, L, Weinstein, M. "Cost Effectiveness of Screening Perimenopausal White Women for Osteoporosis: Bone Densitometry and Hormone Replacement Therapy." Annals of Internal Medicine 113 (1990): 594-603.

75. Ettinger, B, Genant, H, Cann, C. "Long-term Estrogen Replacement Therapy Prevents Bone Loss and Fractures." Annals of Internal Medicine 102 (1985): 319-324.

76. Weiss, N, Ure, C, Ballard, J, Williams, A, Daling, J. "Decreased Risk of Fractures of the Hip and Lower Forearm with Postmenopausal Use of Estrogens." New England Journal of Medicine 303 (1980): 1195-98.

77. Grove, D, Londeree, B. "Bone Density in Postmenopausal Women: High Impact vs. Low Impact Exercise." Medicine and Science in Sports and Exercise 24 (1992): 1190-4.

78. Gutin, B, Kasper, M. "Can Vigorous Exercise Play a Role in Osteoporosis Prevention? A Review." Osteoporosis International 2 (1992): 55-69.

79. Prince, R, Smith, M, Dick, I, Price R, Webb, P, Henderson, N, Harris, M. "Prevention of Postmenopausal Osteoporosis. A Comparative Study of Exercise, Calcium Supplementation, and Hormone-Replacement Therapy." New England Journal of Medicine 17 (1991): 1189-95.

80. Compston, J. "HRT and Osteoporosis." British Medical Bulletin 48 (1992): 309-344.

81. Heaney, R, Recker, R, Saville, P. "Menopausal Changes in Bone Remodeling." Journal of Laboratory Clinical Medicine 92 (1978): 964-970.

82. Lindsay, R, Cosman, F. "Estrogen in Prevention and Treatment of Osteoporosis." Annals of New York Academy of Sciences 622 (1991): 327-333.

83. Christiansen, C, Christiansen, M, Transbol, I. "Bone Mass in Postmenopausal Women after Withdrawal of Estrogen/gestagen Replacement Therapy." Lancet 1 (1981): 1325-7.

84. Mazess, R. "On Aging Bone Loss." Clinical Orthopedics 165 (1982): 239-52.

85. Krolner, B, Nielsen, S. "Bone Mineral Content of the Lumbar Spine in Normal and Osteoporotic Women: Cross-sectional and Longitudinal Studies." Clinical Science 62 (1982): 329-36.

86. Seeman, E, Wahner, H, Offord, P. "Differential Effect of Endocrine Dysfunction on the Axial and the Appendicular Skeleton." Journal of Clinical Investigation 69 (1982) 1302-9.

Chapter III

Hormone Replacement Therapy and Height Loss: Does estrogen prevent shrinking?

Abstract:

Post-menopausal estrogen therapy prevents bone loss. Prior studies suggest that estrogen replacement also prevents age-related loss of height which is believed to be a manifestation of spinal bone loss. This study took advantage of the availability of information on height measured under standardized conditions among women who entered the Walnut Creek Contraceptive Drug Study 20 years ago, to assess the relationship between long-term estrogen replacement therapy and height loss. Loss of height among all participants averaged 0.85 inches over 20 years. Estrogen users lost slightly less height than non-users (0.77 inches v. 0.94 inches), a difference that was not statistically significant (p=0.11). The variability and spread of height change was essentially the same in both groups. While this finding does not contradict the possible protective effect of post-menopausal estrogen against spinal deformities, it suggests that estrogen therapy does not prevent clinically significant height loss over a period of 20 years.

Introduction:

Prevention of bone loss and its attendant adverse health consequences such as fracture are one of the main clinical justifications for placing menopausal women on long-term hormone replacement therapy.[1,2] Estrogen supplementation prevents the post-menopausal loss of trabecular bone[3,4,5] and epidemiologic studies have shown a correlation between estrogen use and lower incidence of hip fractures.[6,7,8,9] Although bone density studies indicate that postmenopausal estrogen replacement therapy has a beneficial effect on spinal trabecular bone preservation, the effect of estrogen in preventing vertebral fractures is less well researched.

Aging is normally associated with a loss of height.[10, 12] Just how much height loss is normal is a question of considerable debate, as are the actual mechanisms of height loss. Many researchers posit that the major factor in height loss is vertebral osteoporosis [10,12,13] and the associated kyphosis resulting from anterior wedge fractures.[14,15,16] Only a handful of studies have specifically investigated whether the known density preserving effects of estrogen actually translate into a prevention of loss of height among post-menopausal estrogen users.

Prior studies of height loss and estrogen replacement treatment have yielded mixed results. Lafferty and Helmuth[17] found that height loss greater than .5 inches appeared with twice the frequency among controls as among estrogen-replaced subjects. Lindsay, Hart, Forrest and Baird[18] found a difference in height loss among estrogen treated oophorectomized women and non-estrogen treated oophorectomized women of .8 cm that was not statistically significant. Hernberg[16] reported that postmenopausal loss of height among osteoporotic women ceased during estrogen therapy; Wallach et all[19] described a group of 90 post menopausal long-term estrogen users followed for 25 years about half of whom lost between 0.5-6 inches of height, and half of whom lost no height; and Henneman and Wallach[15] noted that women treated with estrogens at the time of menopause failed to develop loss of height.

This study took advantage of the availability of information on height measured under standardized conditions among women who entered the Walnut Creek Contraceptive Drug Study 20 years ago to assess the relationship between long-term estrogen replacement therapy and height loss.

Methods:

Subjects in this study were chosen from women who had been in the Walnut Creek Contraceptive Drug Study, a cohort study whose main goal was to assess the long-term effects of oral contraceptive use. The Walnut Creek Study enrolled 16,638 women who

were members of the Northern California Kaiser Permanente Medical Care Program during the period from 1969-1972. At entry, subjects had a complete health examination, including measurement of height and weight under standardized conditions. They also completed detailed questionnaries about their past and current use of oral contraceptives and other steroid hormones (Refer to Appendix). Information on oral contraceptive and hormone use was obtained yearly throught 1977, when active follow-up of the cohort ended.

Considered eligible for this study of height loss were women in the Walnut Creek cohort who had been 45-54 years of age at entry to the study, were still members of the Kaiser Permanente Care Program in 1992, had never used oral contraceptives, and, as of 1977, had either never used estrogen or had used estrogen for 5 or more years. There were 558 never estrogen users and 582 long-term estrogen users (5+ years of use) who met these criteria. 50 never estrogen users and 50 long-term estrogen users who lived within easy driving distance of the Walnut Creek or Oakland examination facility were chosen at random from among these women and asked to come to a clinic to have their height measured.

The number of subjects asked to participate in the study was based on a formal sample size calculation with height loss as the outcome measure. The study was designed to detect a 1 inch difference in height loss between the long-term estrogen users and non-estrogen users with a statistical power of 0.80 using a two-sided statistical test. In these calculations, we assumed that 90% of women asked to participate would agree. The standard deviation of height used in the sample size calculation was the published standard deviation of height among the women recruited to the Walnut Creek cohort in 1969-1972.

Height was measured with the subject standing erect on a horizontal platform with her ankles together and her heels against a vertical wall, looking straight ahead. A t-square was placed on the top of the subject's head and height measured using the scale on a

vertically mounted metal ruler. Weight was measured with the subject wearing light clothing.

At the time of examination, 6 women who had been classified as never-estrogen users on the basis of their histories through 1977 stated that they had used oral estrogen in the interim. Virtually all (91.4%) of the women who were classified as long term estrogen users on the basis of their histories stated at the time of their height examination that they had used estrogen. The mean duration of oral estrogen use reported at the time of the height examination was 2.0 years in the women classified as non-users, and 18.8 years in the women classified as users. Analysis was done based on initial classification of estrogen use.

The unpaired t-test and chi-quare analysis were used to asses the statistical significance of difference in estrogen users and non-users at entry to the cohort and at the time of the height examination. Repeated measures analysis of variance was used to assess the significance of differences in height loss between estrogen users and non-users. Repeated measures analysis of covariance was used to assess the significance of differences in height loss between estrogen users and non-users adjusting for known risk factors for osteoporosis. In all analyses, differences were considered to be statistically significant if the two-tailed probability value was less than 0.05.

Results:

Of the 50 long-term estrogen users asked to participate in the study, 2 were in another country, 1 was dead, 3 were too ill to drive, and 8 refused, leaving 36 (72%) whose height was measured. Of the 50 non-estrogen users asked to participated in the study, 2 were in another country, 1 was too ill to drive, and 14 refused, leaving 34 (68%) whose height was measured.

The characteristics of the participants at time of entry to the Walnut Creek Study and at the time of the current height examination are shown in table 1. The estrogen-users are

approximately two years older than the non-estrogen users, and more likely to have had a bilateral oophorectomy. Estrogen users were also taller and heavier at entry, but these differences were not statistically significant.

At the time of the height examination, all of the women had undergone menopause. The estrogen users experienced menopause approximately three and one half years earlier than non-estrogen users, and they were still more likely to have had a prior hysterectomy and/or bilateral oophorectomy.

Estrogen users lost a mean of 0.77 inches, and non-users lost a mean of 0.94 inches (table II). The difference (0.17 inches) was not statistically significant based on repeated measures analysis of variance ($p=0.11$). Mean height loss for both groups was 0.85 inches. After adjustment for variables known to be related to bone mineral density, the mean difference in height loss was 0.21 inches, which was still not statistically significant. Height of estrogen users and non-users at baseline and at the time of examination is shown in figure I.

Figure 2 shows box plots of height loss in estrogen users and non-users. The box plot, also called a box-and-whiskers plot, visually conveys the level, the spread, and the amount of symmetry of the data. The median value for height loss in the two groups is indicated by the horizontal line inside each box. The middle 50% of values of height loss in estrogen users and non-users define the ends of each box. The vertical line is drawn from the middle of each of the cross-bars of the box to the most extreme upper and lower values of height loss in the two groups. Height loss variability was great in both groups. It ranged from a gain in height of 0.8 inches to a loss of 3.3 inches in the estrogen users and from a gain of 0.3 inches to a loss of 3.4 inches among non-users. The median height loss, and the symmetry were essentially identical in estrogen users and non-users.

Discussion/conclusions:

Post menopausal estrogen replacement therapy prevents bone loss in both the hip and the spine. Although height loss is considered a manifestation of vertebral bone loss[11] studies examining the association between long term post menopausal estrogen use and post menopausal bone loss are limited. Our study found no significant difference in the amount of height lost over a twenty year follow up period in a group of very long term estrogen users and a group of non-users.

We also performed the same analysis looking at height loss in women whose estrogen use and history were consistent, omiting three women who denied ever using estrogen at the time of the height examination, although they had reported using estrogen for greater than 5 years at the time of the original exam, and 6 women who began using estrogen after 1977. Adjusted differences in mean height loss based on the remaining women whose historical and present estrogen use/non-use status were consistent was 0.25 inches ($p=0.48$).

There are a number of other studies looking specifically at height loss and estrogen replacement therapy in women without an established diagnosis of osteoporosis. In 1957, Henneman and Wallach[15] reviewed charts of 200 post menopausal women who used 1-3 mg DES or 1.25-5 mg Premarin/day. They found that patients treated with estrogen at the time of menopause failed to develop height loss for up to 25 years. There were no controls and estrogen users were not characterized. Mean duration of estrogen use was not reported, and the dosages of estrogen prescribed at that time were much higher than the amount that current protocols recommend today.

In 1959, in a different chart review of 292 post menopausal estrogen users, Wallach and Henneman[19] found a more mixed picture of height change among estrogen users. In 94 estrogen using patients who were free of lordosis, lower extremity fractures, degenerated intervertebral disks or kyphosis of arthritic or neuromuscular origin, 41 women experienced no significant height loss, while 53 estrogen-using patients lost

between 0.5-6 inches of height. Again, there was no control group, and information on mean age, mean height lost, entry or ending weight, and use of other medications was not reported. Women used very high doses of estrogens and 66 of the estrogen users also took ethinyl testosterone or methytestosterone.

In 1960, Hernberg[16] conducted a study of 66 estrogen users and 25 non-estrogen using controls. He reported that non-osteoporotic post-menopausal women had a negligible reduction in height during treatment, in comparison to control cases of the same age group. Mean changes in height or duration of estrogen use in both groups were not indicated, and 39 of the estrogen users also used an androgen. Non-users were measured for a longer period of time, and would be expected to shrink more than users for this reason alone.

In 1980, Lindsay et al[18] published a report of a prospective controlled trial of 100 oophorectomized women who were followed for a mean of 9 years. He found that a reduction in height occured among the placebo treated group, but not in the group treated with mestranol. The difference in height loss between estrogen users and non-users was not statistically significant. The study examined only bilaterally oophorectomized women. The difference in height loss over nine years between the two groups was .8 cm, a difference that would not have been detected in our study. The biological importance of this amount of difference in height loss is questionable.

In 1985, Lafferty and Helmuth[17] reported on a prospective cohort study of 61 estrogen users and 63 controls. They reported that height loss greater than .5 inches occured twice as frequently among controls as among estrogen users, and that after the age of 65, the control group lost height twice as rapidly as the estrogen treated group. They also concluded that estrogen was not an absolute protection against height loss, especially after 70 years of age. The authors did not report mean ending heights, preventing comparison of how much height was lost among estrogen users and non-users. 21 elderly post-menopausal women who were not originally in the cohort were added to the analysis

of height change among 70-75 year olds. 16 of the 21 elderly women were included in the estrogen non-using group, whereas only 5 of the 21 elderly women were included in the estrogen using group. This may have introduced bias into the control group, making the control group older and more likely to have lost greater amounts of height than the estrogen using group.

Although our study found that height loss was not associated with estrogen use, this result does not negate the possible protective effects of estrogen against vertebral fractures. One of the few epidemiological studies on vertebral fractures[21] points out the complexity of both defining and studying vertebral fractures, since there is no agreed-on definition of vertebral fractures, and most vertebral fractures are unknown to the patient. In that study, the prevalence of vertebral fractures among 70-74 year olds was 20.9%, and that most of the fractures were of the wedge variety which was defined as a 15% reduction in vertebral body height. According to that protocol, an anterior or posterior change in vertebral height of as little as .5 cm may be the only radiologic evidence of vertebral fracture. If all estrogen users were prevented from having this sort of fracture, this would translate into a preservation of .5 cm X 20.9 people/100 estrogen users, or .1 cm of height preserved per estrogen user. This level of difference would not have been detected in our study.

It is reasonable to consider that mechanisms other than osteoporosis may explain most height loss observed among aging women. Woodhull[22] reports a forward lean associated with aging that may relate to muscular weakness or fear of instability. In a study looking at kyphosis and osteoporosis, DeSmet et al[14] reported that 19% of women with no thoracic fractures still had thoracic hyperkyphosis, which the authors attributed to unspecified contributing non-skeletal factors. Galloway et al[20] suggest that part of height loss may be attributable to the intervetebral disks, which are known to compact, stiffen and become more fibrous with age. In youths, it is reported that the intervertebral disks form approximately 20-30% of total spinal length. Amidst all of these other changes, it is

difficult to determine the specific role of estrogen deficient osteoporosis in causing height loss.

Given the small reduction in height that may be attributable to osteoporosis, one of the limitations of this study is the small sample size. It was designed to detect a one inch difference in height, which was considered a priori to be clinically significant. In both groups, about 22% of women refused to participate for unspecified reasons. This may have led to bias if non-estrogen users who failed to participate were more likely than estrogen users who failed to participate to lose large amounts of height. Another consideration of this particular sample is the possibility that the protective effects of estrogen become more pronounced as aging continues, and thus, measuring women at age 70 years old may be too early to detect the true protective effect of estrogen on height loss of aging women.

These results contradict current beliefs, which attribute the mechanism of height loss to either vertebral compression fractures actually shortening osteoporotic spines, or postural slumping resulting from anterior wedge fractures that cause kyphosis. This mechanism is so widely accepted by some that height loss has been used as a method of estimating the effect of hormone treatment on osteoporosis. It appears from our study that height loss is much more complicated.

This finding is relevant in light of the advertisement of and folklore about post-menopausal estrogen replacement. There are many well established benefits that warrant consideration of HRT. However, biologically significant preservation of height may not be among them. This observation contradicts the implicit claim made in estrogen advertisements showing a woman standing next to a ruler.

Thus, the results of this study suggest suggest that age-related variation in height loss and that height loss per se is not eliminated by long term estrogen use.

Table I

Characteristics of subjects by estrogen use:

At Entry	Estrogen Non-Users (N=34)	Estrogen Users (N=36)	p value
Age in years (mean)	48.4	50.1	.008
Height in inches (mean)	63.6	64.5	.15
Weight in pounds (mean)	134.3	139.7	.26
Current cigarette smoker (%)	23.5	22.2	.90
Married (%)	85.3	86.1	.95
Bilateral Oophorectomy (%)	2.9	19.4	.03

Table I Continued

At the Time of the Height Examination

	Estrogen Non-Users (N=34)	Estrogen Users (N=36)	p value
Age in years (mean)	71.2	73.2	.004
Height in inches (mean)	62.7	63.7	.08
Weight in pounds (mean)	139.8	151.7	.08
Bilateral oophorectomy (%)	13	47	.001
Hysterectomy (%)	24	74	<.001
Both ovaries removed before 50 (%)	2.9	25	.022
Current Smoker (%)	10	19	.97
Ever used estrogen (%)	17.6	91.4	<.001
Length of use of estrogen (mean)	2.0	18.8	<.001
Age at menopause in years (mean)	50.9	47.1	<.001
Age at menarche in years (mean)	13.0	12.9	.082
Ever used calcium supplements (%)	76	65	.37

Table I continued

At the Time of the Height Examination

	Estrogen Non-Users (N=34)	Estrogen Users (N=36)	p value
History of fracture past 50 (%)	36.4	17.1	.13
Diagnosis of underactive Thyroid (%)	21.2	8.6	.14
Milk consumption since the age of 50 years old (% who drink at least one glass every day)	47	56	.21
Body Mass Index	24.97	26.3	.20

Table II

Height Loss in Estrogen Users and Non-Users

	Unadjusted Mean (inches)	P value	Adjusted[1] Mean (inches)	P value	Adjusted[2] Mean (inches)	P value
Estrogen Users	0.94		0.96		0.96	
Non-Users	0.77		0.75		0.75	
Difference	0.17	(0.11)	0.21	(0.19)	0.21	(0.07)

[1]by analysis of covariance for age, age at menarch, age at menopause, ever smoked cigarettes (yes, no), alcohol consumption, history of hypothyroidism, amount of milk consumed at age 50, body mass index, bilateral oophorectomy before age 50.

[2]by analysis of covariance for all of the variables listed above except bilateral oophorectomy before age 50.

Figure I

Mean Height 1972 and 1992: Estrogen Users vs. Non Users

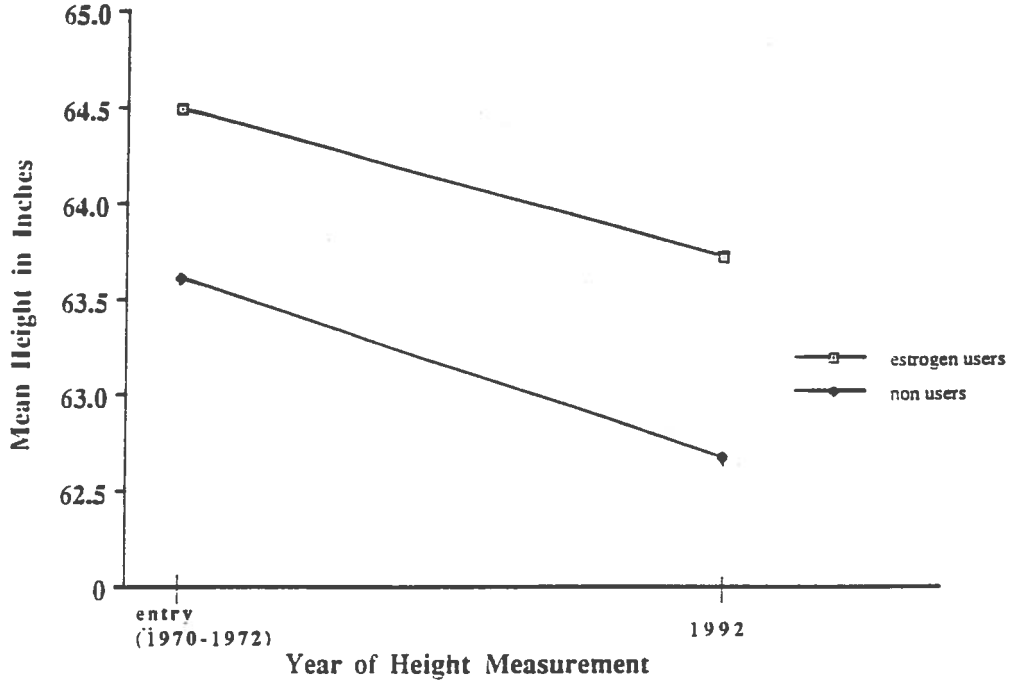
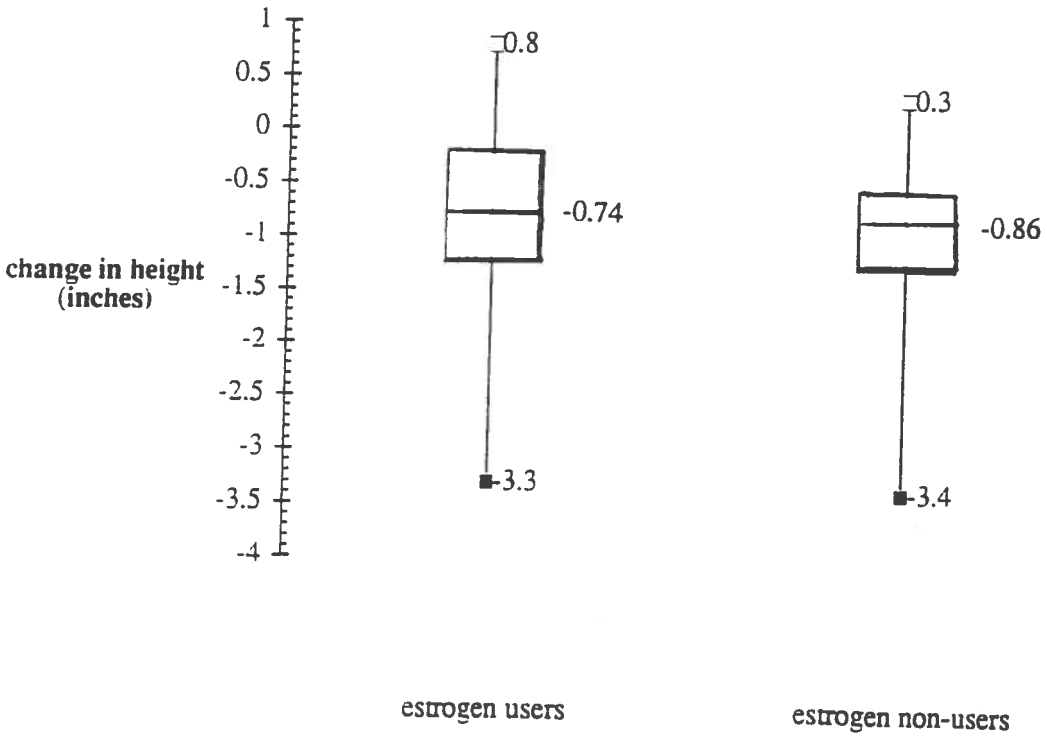


Figure II

Box Plot Showing Height Change in Long-term Estrogen Users and Non-Users from entry (1970-72) to 1992



References: Hormone Replacement Therapy and Height Loss: Does Estrogen Prevent Shrinking?

1. Law, M, Wald, N, Meade, T. "Strategies for Prevention of Osteoporosis and Hip Fracture." British Medical Journal 303 (1991): 453-9.

2. Cumming, S, Black, D, Rubin, S. "Lifetime Risks of Hip, Colles', or Vertebral Fracture and Coronary Heart Disease Among White Postmenopausal Women." Archives of Internal Medicine 149 (1989): 2445-2448.

3. Marslew,U, Overgaard, K, Riis, B, Christiansen, C. "Two New Combinations of Estrogen and Progestogen for Prevention of Postmenopausal Bone Loss: Long-term Effects of Bone, Calcium and Lipid Metabolism, Climacteric Symptoms and Bleeding." Obstetrics and Gynecology 79 (1992): 202-209.

4. Ettinger, B, Genant, H, Cann, C. "Long-term Estrogen Replacement Therapy Prevents Bone Loss and Fractures." Annals of Internal Medicine 102 (1985): 319-324.

5. Munk-Jensen, N, Nielsen, S, Obel, E, Eriksen, P. "Reversal of Postmenopausal Vertebral Bone Loss by Oestrogen and Progestogen: A Double Blind Placebo Controlled Study." British Medical Journal 296 (1988): 1150-52.

6. Kreiger, N, Kelsey, J, Helford, T. "An Epidemiologic Study of Hip Fracture in Post-menopausal Women." American Journal of Epidemiology 116 (1982): 171-8.

7. Hutchinson, T, Polansky, S, Feinstein, A. "Post-Menopausal Oestrogens Protect Against Fractures of the Hip and Distal Radius: A Case-control Study." Lancet 2 (1979): 705-9.

8. Paganini-Hill, A, Ross, R, Gerkins, J. "Menopausal Estrogen Therapy and Hip Fractures." Annals of Internal Medicine 95 (1981): 28-31.

9. Weiss, N, Ure,C, Ballard, J. "Decreased Risk of Fractures of the Hip and Lower Forearm with Postmenopausal Use of Estrogen." New England Journal of Medicine 303 (1980): 1195-98.

10. Davies, K, Recker, R, Stegman, M, Heaney, R. "Tallness Versus Shrinkage: Do Women Shrink with Age or Grow Taller With Recent Birth Date?" Journal of Bone and Mineral Research 6 (1991): 1115-20.

11. Kleerekoper, M, Nelson, D, Peterson, E, Tilley, B. "Outcome Variables in Osteoporosis Trials." Bone 13 (1992): S29-S34.

12. Chandler, P, Bock, R. "Age Changes in Adult Stature: Trend Estimation from Mixed Longitudinal Data." Annals of Human Biology 18 (1991): 433-440.

13. Wahlquist, M, Flint, D. "Assessment of Loss of Height in Elderly Women." European Journal of Clinical Nutrition 42 (1988): 679-682.

14. DeSmet, A, Boinson, R, Johnson, B. Luckert, P. "Spinal Compression Fractures in Osteoporotic Women: Patterns and Relationship to Hyperkyphosis." Radiology 166 (1988): 497-500.

15. Henneman, P, Wallach, S. " A Review of the Prolonged Use of Estrogens and Androgens in Postmenopausal and Senile Osteoporosis." Archives of Internal Medicine 100 (1957): 715-23.

16. Hernberg, C. "Treatment of Postmenopausal Osteoporosis with Estrogens and Androgens." Acta Endocrinologica 34 (1960): 51-59.

17. Lafferty, F, Helmuth, D. "Post-menopausal Estrogen Replacement: The Prevention of Osteoporosis and Systemic Effects." Maturitas 7 (1985): 147-159.

18. Lindsay, R, Hart, D, Forrest, C, Baird, C. "Prevention of Spinal Osteoporosis in Oophorectomised Women." Lancet 8205 (1980): 1151-4.

19. Wallach, S, Henneman, P. "Prolonged Estrogen Therapy in Postmenopausal Women." Journal of the American Medical Association 171 (1959): 1637-42.

20. Galloway, A, Stini, W, Fox, S, Stein, P. "Stature Loss Among An Older United States Population and its Relation To Bone Mineral Status." American Journal of Physical Anthropology 83 (1990): 467-76.

21. Melton, L, Kan, S, Frye, M, Wahner, H, O'Fallon, W, Riggs, B. "Epidemiology of Vertebral Fractures in Women." American Journal of Epidemiology 129 (1989): 1000-11.

22. Woodhull-McNeal, A. "Changes in Posture and Balance with Age." Aging 4 (1992): 219-225.

Chapter IV

The Medicalization of Menopause

Given an expected female life span of 76 years in the United States and a 95% likelihood of survival past age 50, most women will reach the time in their lives in which they naturally no longer menstruate. The name for this cessation of menses is menopause; meno means menstruation and pause means stop. Menopause refers to the natural and predictable event just described, yet to ask any individual woman to define menopause is to elicit a wide variety of impressions "isn't it when you're without a period?" "It's when the ovaries stop working and you get hot flashes, and cranky, and you don't bleed anymore." Additionally, to study how women of different cultures experience the climacteric, the year in which menstruation ceases, or the social meaning of menopause, is to elicit yet an even wider variety of experience and thought.

It is clear that menopause, an event that defines one part of the normal biology of a woman's reproductive tract, is more than a neutral bodily change. Of great interest is where and how the meanings and perceptions about menopause are generated. Much of the current information available to women is via the popular press, a point of view that is largely informed by the medical profession.[1] This homogeneity might imply that there is near unanimity on the subject and even a monolithic approach to medical treatment of menopause. In fact, among different academic disciplines such as sociology, anthropology, feminist studies, and applied sciences such as medicine and psychology, the study of and discourse about the menopause has become a contentious, and at times highly controversial topic.

This chapter will explore the current literature on menopause, both academic and popular, focusing in particular upon the medical viewpoint. The evolution of medical opinions about menopause since the mid-19th century and current medical "treatment" will

be discussed. Finally brief pause will be given to Western medicine as a culturally defined institution mirroring society's values and concerns in the discourse about menopause.

The Disciplines

Academic disciplines such as anthropology, feminist studies, psychology, sociology and applied health sciences such as psychiatry and medicine all have branches that research menopause. A discussion of each discipline's discourse and a representative example of their research findings will demonstrate the existence of a myriad of ways to look at the subject of menopause.

Anthropology

Within anthropology, study of menopause has been approached from the two distinct subdivisions: cultural anthropology and physical anthropology. Cultural anthopologists examine the interaction of culture and individual in creating the individual's experience of menopause, while physical anthropologists consider the evolutionary significance of menopause, and as such may incorporate "primatologic, historical, cross-cultural and evolutionary views".[2]

Studies by cultural anthropologists have shown that the experience of menopause differs between women from different cultures. For example, cultural anthropologist Margaret Lock investigated the differences in how Japanese women and Canadian women experience the menopause. She found that a common "symptom" of menopause in the west, the hot flash, is experienced by 64.9% of Canadian women, while only 19.6% of Japanese women ever experience the same symptom. Instead, Japanese women are more likely to report the physical symptom of aching shoulders or joints.[3]

While noting that true biological difference between Japanese and European/Western women may underlie the disparate rates of experiencing perimenopausal hot flashes, Lock proposes that economic factors may also have a role. Japanese gynecologists have historically derived most of their income from delivering babies and

performing abortions and they have not historically concentrated on marketing their skills and services to middle-aged women. As a result, Japanese women have not been subject to the medical system's comments about the symptoms of menopause, and somatization of specific symptoms of the menopause are less likely to occur. Lock observes that gynecologists are changing their practices, and some are actively advertising their services to middle aged women with symptoms. 4% of Japanese post menopausal women are currently using estrogen replacement therapy, and Lock suggests that this percent may increase as gynecologists seek new markets.

Cultural anthropologists also compare different groups of women from within the same culture to look at how intracultural differences create disparate experiences. Anthropologist Marcha Flint focused her study entirely within Indonesia, and looked at differences in physical symptomatology of menopause among women of differing socio-economic status and education level. Her study had two main findings. The first is that few post menopausal Indonesian women of any class or education level reported "estrogen dependent symptoms" such as the hot flashes, night sweats, and vaginal atrophy observed in the west. Among the participants who did report estrogen dependent symptoms, differences existed in education level, and residence, ie. urban vs. rural residence. For example, Flint found that 20% of urban educated menopausal women experienced hot flashes while only 7% of migrant non-educated menopausal women experienced the same symptom.

Flint's second notable finding is that Indonesian women have positive symptoms associated with menopause, symptoms that are rarely investigated in the west. Anywhere from 100% to 66% of women report menopausal "feelings of affection" or "well being" or "orderliness".[4]

As cultural anthropologists, both Lock and Flint have shown that cultural environments have a role in determining how women experience menopause. They also show that menopause can be associated with positive feelings and symptoms. This

finding calls to question the cultural influences that shape western women's negative experience of menopause.

Instead of looking at how women experience the menopause, physical anthropologists look at why women experience menopause. The work of Pavelka and Fedigan exemplifies the menopause discussion as it exists in the physical anthropology literature. They write from a life history perspective that "focuses attention on the processes and events that occur in the lives of individual organisms, and questions their evolutionary significance."

It is sometimes explained to women that the existence of menopause in human females is a result of humans outsmarting nature and living unnaturally extended lives. Pavelka and Fedigan emphasize the important distinction between maximal life span and mean life expectancy, to swiftly debunk this myth. Maximal life span is the longest span that an organism can possibly live, and it has stayed relatively constant among humans at about 100 years. The mean life expectancy is the average age that members of any group live to. Although the maximal life span of humans has not changed, humanity has altered is the mean life expectancy.

In any human population sample, there have always been individuals living to the maximal life span, however, a change in the mean life expectancy simply indicates an increase in the size of the post-reproductive population, not the "sudden appearance of individuals in that age group." For example, even though the mean life expectancy in a society such as the Kung may only be 34.6 years old, 40% of that population will live to 50 years and older, and 24% will live to be 65 and older.[2] This example demonstrates that menopausal women are not a recent historical artifact, and that even among peoples with an average life expectancy well below the menopausal age there have always been women who are post reproductive. In short, menopause is neither a recent phenomenon, nor is it a fluke of an extended average life expectancy.

There are no other known species in which the females may be observed to live well past their reproductive ability either in the wild or in the lab. Among primates such as Macaque monkeys, chimpanzees and female Langurs there is evidence of reproductive senescence as the females near the limits of their maximal life span. The human equivalent of this would be akin to a 77 year old women just starting to have reduced menstrual flow, or a lowered fertility. Menopause in humans occurs midway in the maximal life span and appears to be a phenomenon unique to human females.

Thus, Pavelka and Fedigan turn to possible selective advantages to explain why only human females undergo menopause. There are two explainations advanced to explain the evolutionary function of menopause: 1. it is an adaptive feature, or 2. it is the byproduct of some other adaptive feature, a theory known as the "pleiotrophy theory". The risks of reproduction clearly increase with age, and the "grandmother theory" posits that menopause may be a protective adaptation to insure the longer survival of individual members who may then invest their energy on the survival and reproduction of existing offspring and their children. A competing anthropological explaination for menopause is the "pleiotrophy theory." Human ovaries are unique in their ability to produce and store eggs, and may be a trait that is selected for evolutionarily. However, human ovaries may also have inherent limits in function that are time dependent, despite their adaptive value early in life. According to the pleiotrophy theory, a trait resulting in reduced fitness later in the life course will still be selected for as long as they have high adaptive value early in the life course. By this theory, menopause is an epiphenomenon of highly functioning ovaries early in life, and does not, in and of itself, serve any evolutionary purpose.

Although there is little agreement among physical anthropologists about the evolutionary significance of menopause, it can be demonstrated that menopause is not a recent artifact of human industrialization, and that, according to the grandmother theory, menopause may actually be a selective advantage to female humans.

Feminist Studies

Although many of the researchers who have worked on the subject of menopause may well consider themselves feminists, there are few self-identified feminist studies of menopause; One of the few was conducted by Geri Dickson, who is a nurse researcher. She explains that the dearth of feminist scholarship on the menopause exists since "from the feminist perspective, menopause is envisioned as a tabooed subject, veiled in secrecy and silence, in which women's rights are suppressed in the name of biology."[5] The feminist works that do exist are often a reaction to the dominant medical paradigm of menopause, and to the paradigm's assumptions about women's bodies as defective variants of male physiology.

Dickson's study first analyzes the construction of scientific discourse, and then seeks to understand women's discourse about their own menopause as it has been influenced by the scientific voice. She interviewed eleven perimenopausal subjects and found that although each woman anticipated hot flashes and dry vaginas, less that one half experienced hot flashes. Furthermore, while none of the women considered themselves sick, they all wondered about the presence or absence of "symptoms" a word that denotes sickness.[5]

The women in the study were all influenced by the prevailing medical literature on menopause, yet most seemed to use the medical view only as a reference point for their own experiences and didn't necessarily internalize the symptomatology. Dickson's report demonstrates the discordant yet dependent relationship between the female voice and the societal and medical voices that influence each female's experience of her own body at the time of menopause.

Psychology/Psychiatry

As applied health sciences, both psychology and medicine approach menopause as it applies to the complaints of patients, and the illness that is observed or hypothesized to be generated by the process. As such, psychological theories and studies of menopause are

designed to address a subset of menopausal women who show signs of psychological distress around the time of menopause.

Studies show that most women do not experience psychological distress around the time of menopause. Yet the authors of a textbook about female psychology unintentionally reveal their expectation of psychological dysfunction as they report this fact saying "Despite the functional decline that it represents, the majority of women aged 40 to 51 years do not report the menopause to be a major crisis".[6] The explicit information imparted by this statement is much different from the implicit information, which suggests a certain surprise at the lack of problems experienced by women who are undergoing "functional decline."

Psychoanalysts have been alternately inflammatory and affirming towards menopausal women. S. Freud and H. Deutsche, for example, describe menopausal women who "become quarrelsome and obstinate, petty and stingy, show typical sadistic and anal-erotic features which they did not show before," behavior which is explained by another psychoanalyst E. Erickson, as a reaction to the "permanent scar" of lost children, and the forever "empty" womb.[7,8,9] These traditional analytical theories are contrasted by the theories of psychoanalysts C. Thomas and G. Devereaux who note the relative absence of perimenopausal psychological symptoms among women from countries in which their social status actually increases with the onset of menopause, such as the Chinese and the Mohave. They then suggest that the American woman's psychological distress, if it occurs, is largely culturally induced by the prevailing attitudes about aging women.

Although the DSMIII, the diagnostic handbook of psychologists and psychiatrists, formerly included a pathological entity called "involutional melancholia" that was a specific psychological state attributable to menopause, this psychological abnormality is no longer recognized to exist. Psychological research continues to attempt to define an elusive, yet truly pathological state in which mood, behavior, cognitive function and attitudes towards self and others is impaired on account specifically of the menopause. Pharmaceutical companies that manufacture post-menopausal estrogen are currently funding studies

looking for differences in cognitive function in menopausal women. At issue here is whether researchers will assert a biological, social or psychological basis for the psychological disturbances they are seeking. If the studies funded by pharmaceutical companies show any results, the recommendations will likely be based on a presumed biological etiology, with medical/pharmaceutical antidotes.

Medicine

Like psychology, the medical profession focuses on the disabling and pathological features of menopause affecting the body that are thought to benefit from medical intervention. According to medical dogma, some menopausal women can expect to experience immediate symptoms of estrogen "deficiency" such as vaginal dryness, urinary incontinence, hot flashes, and a lowered libido, and most menopausal women will be at risk for diseases/effects attributable to long term estrogen deficiency such as osteoporosis, heart disease, height loss, and wrinkled skin.

Medically speaking, menopause renders women vulnerable to a host of present and future health problems. Thus, many medical studies about menopause are designed to assess the effectiveness of various treatments for the symptoms and long term effects of estrogen "deficiency." For example, a medical literature search using the keyword "menopause" reveals titles such as "Beneficial effects on serum lipoproteins by 17 beta-oestradiol-dyhrogesterone therapy in postmenopausal women; a prospective study" and "Postmenopausal screening for osteopenia."

Given the many ways to look at and understand menopause, ie natural life process, culturally determined experience, pathological failure of the ovaries, it is noteworthy that the medical paradigm of "deficiency disease" has recently become the most widely understood. It is the task of medical sociologists to explain how the medical view of menopause has become the cultural model of menopause, or how society has come to understand a biological phenomenon as a pathological deficiency disease.

Medicalization

The sociologic term for defining and treating human experiences as medical problems is "medicalization".[10] Diverse human phenomena such as alcoholism, homosexuality, childbirth, violence and menopause have been systematically claimed as medical problems at one time or another, and have thus been medicalized. One sociologist refered to thiscontinuing trend as "the medicalization of life".[11]

In theorizing about what motivates the process of medicalization, sociologists have offered many explanations that range from venal to altruistic. Kohler-Reissman bluntly suggests that "physicians seek to medicalize experience because of their specific beliefs and economic interests".[12] McCrea also remarks that the "disease definition of menopause has served the interests of both the medical profession and the pharmaceutical industry" .[13] Conrad more optimistically observes medicalization to be motivated by "humanitarian impulses and effects"[10], while Zola argues that an increasingly complex technical and bureaucratic society has led to a reluctant reliance on scientific experts.[14] Whatever the motivation, the results of medicalization are manifold, and include mystifying human problems with medical language[15], and dimming awareness of social causes of disease by focusing on medical and biological explanations.

Medicalization occurs on three levels: the conceptual, the institutional and the interactional.[16] The conceptual level is the point at which problem is defined in terms of medical language. For example, menopause was at one time considered a physiologic state within the female life span. As will be shown, it was transformed through various medical "discoveries" into a conceptual disease state. The institutional level of medicalization occurs when the medical profession legally controls a problem (Conrad and Schneider 1980). For example, the medical profession legally controls childbirth, and it also claims the exclusive right to "diagnose (menopause) and to treat these symptoms with estrogen available only by prescription".[10] Finally, the interactional level of medicalization occurs when physicians actually apply the medical concepts as defined above in the treatment of

individual patients. It is a step that varies constantly, as there is a large variation in physician practice patterns for any given set of presenting symptoms. The following historical account of menopause and the medical profession are intended to make these concepts of medicalization more vivid.

Women and Medicine in the 19th century

The roots of the current medical conceptualization of women and menopause are evident in the medical practices of the 19th century, a time in which science was used to explain and sanction the status quo. "Would be scientific arguments were used in the rationalization and legitimatization of almost every aspect of Victorian life, and with particular vehemence in those area in which social change implied stress in existing social arrangements".[17]

One increasingly urgent challenge to the social fabric was female agitation for increased educational opportunities, and reproductive freedom. These ideas would become scientifically refuted on the basis of woman's innate biological capacity and incapacity. In other words, rational scientific arguments were used to substantiate the existing social order.

The ideal Victorian female was nurturing, patient, moral, domestic and passive, qualities which were "assumed to have a deeply rooted biological bases".[17] Specifically, many doctors and scientists thought that it was some unspecified feature of the female reproductive tract that endowed women with their nurturing qualities. In addition to shaping the female character, the womb and ovaries were also blamed for almost every physical ailment that a female could have, since the reproductive tract was physiologically thought to be "connected to the central nervous system."

The strong belief in the centrality of the female reproductive tract as determining female behavior and roles also provided the logical basis for the reverse argument; abberrant female behavior could disrupt the functioning of the reproductive system and

permanently alter the female disposition. Physicians believed that the brain and ovary could not develop at the same time and argued that female scholars depleted their female energy by studying, and would become weak and nervous, perhaps sterile, or more commonly, capable of bearing only sickly and neurotic children.[17] On the subject of female education, one physician remarked, "Their health and that of their children would be inevitably marked by the consequences of such unnatural modes of life."

Given the presumed effect of a female's behavior on her reproductive system, numerous examples exist demonstrating the belief that the symptoms associated with menopause were attributable to women's social behavior. The example that will be used is menorrhagia, or excessive uterine bleeding, a very common symptom associated with the menopause during the nineteenth century. Menorrhagia is no longer included as part of the current clinical syndrome of menopause because it is a complaint, for reasons that are not entirely clear, that has now "virtually disappeared"[18], if not from the individual's experience of menopause then at least from the medical definition.

Historically, menorrhagia began as a peri-menopausal complaint restricted almost exclusively to French upper class women. Awareness of this as a symptom gradually spread to physicians of women of other classes and other countries. Although the medical profession was unable to successfully treat this symptom. it did not lack explanations; "Having abandoned traditional therapy because of its proven iatrogenic effects, especially in provoking uterine hemorrhage, medical men increasingly attributed continuing menorrhagia to their patient's lifestyle".[18] Behaviors thought to contribute to such bleeding included high living, too much meat, too much wine, and sexual promiscuity. Again, science and medicine dictated moral behavior to women with the consequence of disobedience being female medical problems.

The development of an actual treatment for menopause associated symptoms revolutionized the physician's role in treating menopausal women. After abandoning attempts to change their patients' lifestyles, nineteenth century physicians developed

surgical methods to treat menorrhagia, such as bilateral oophorectomy and hysterectomy. The first abdominal hysterectomy occurred in November 1843, and despite the 80% fatality rate, "demand for the abdominal operation grew. It was as if housebound women, constantly bleeding, rejected by husbands and lovers, saw in hysterectomy a new hope for recovery, a promise of a few years of sexual youth, of being noticed and loved".[18] In an abrupt change of policy, rather than utilizing a female's behavior to explain her health, physicians were now using medicine and surgery to restore women to former states of femininity. The introduction of estrogen therapy added yet another piece of armamentarium in the physicians' ability to treat menopause, and all but cemented the physician's role in treating menopause.

Estrogen and the changing attitudes about menopause

Estrogen was first isolated in 1923 from the ovaries of sows. It was next crystalized from the urine of pregnant women in 1932[19], and synthetic estrogen, diethylstilbestrol (DES), was developed in 1938.[7] The discovery of DES advanced the general understanding of sexual endocrinology and also influenced physicians' perceptions of menopause, recommendations for treatment, and the final definition of menopause as a deficiency disease.[16] In the first few years after its discovery, DES was used sparingly, to "smooth the stormy period" in the minority of women who experienced non physiologic menopauses, estimated at that time to be 15%.[20] In 1941, Robert T. Frank, Clinical Professor of Gynecology at Columbia University welcomed the discovery of estrogen as "a major triumph, second only to the treatment of hypothyroidism by thyroid medication and of diabetes by insulin".[21] DES, however, caused toxic reactions from 5-80% of the time, and researchers could not agree on the long-term safety of the therapy.

In 1943, an estrogen extract from the urine of pregnant mares was developed that had 1/2 the potency of the synthetic estrogen, with fewer side effects. It was and still is called Premarin. In the late 1940s and 50s, both Premarin and DES were used experimentally for the treatment of both severe menopausal symptoms as well as

osteoporosis. By the 1960s Premarin became both widely available and affordable to many women.

The development of estrogen chemistry and production paved the way for greater medical interest and intervention in menopause, and in the final definition of menopause as a "deficiency disease." Thus, the conceptualization step of medicalization had occured, even though no unified definition existed for the signs and symptoms of menopause. Menopause was increasingly the turf of physicians since a "treatment" now existed.

One prominent spokesman for the popularization of estrogen replacement therapy was a physician named Robert A. Wilson. He effectively bridged the gap between the medical professional and the popular understanding of menopause by writing scientific articles published in professional journals such as the Journal for the American Medical Association, as well as writing a popular best-seller, entitled Feminine Forever.[22] Although Wilson's views did not represent the entire gynecologic and medical profession's established dogma, "his writings were crucial to the acceptance of menopause as a "deficiency disease" and the large-scale routine administration of Estrogen Replacement Therapy (ERT)".[23] His research efforts were financially backed by a 1.3 million dollar grant from the pharmaceutical industry that funded the creation of the Wilson Foundation, and his book appealed to women's fears of aging, claiming that estrogen could prevent "sagging and shrinking breasts, wrinkles, absent mindedness, irritability, frigidity, depression, alcoholism and even suicide".[22]

Another bestselling manual written by a physician entitled Eveything You Ever Wanted to Know about Sex, But were Afraid to Ask also described menopause as a pitiful turning point initiating the loss of femininity. Dr. P. Reuben described the typical post-menopausal woman as "not really a man but no longer a functioning woman, these individuals live in a world of intersex, having outlived their ovaries, they have outlived their usefulness as human beings".[24] Like Wilson, Reuben advocated estrogen replacement therapy to "turn back the clock."

Lest one think that physicians were protected from the propaganda that bombarded women via the popular press, one has only to look to medical journals and the content of the advertisements for estrogen replacement therapy within these journals during that time (Fig 1). Indeed, physicians were also the target of estrogen advertisements that propogated stereotypical cliches of menopausal women as defeminized, dried-up and unattractive. The convergence of consumer demand, heavy advertising to physicians and a few medical studies published showing positive effects of estrogen rendered estrogen among the top 5 prescribed drugs in the United States in the 1970s.[25]

Estrogen, health risks and the generation of medical policy

Meanwhile, however, dissent existed among medical researchers about the possible adverse effects of post-menopausal estrogen replacement. As early as 1947, scientists were documenting links between estrogen and cellular abnormalities of the lining of the uterus, also known as dysplasia. Questions about the safety of this therapy exploded in the 1970's with the publication of numerous epidemiological studies demonstrating associations between post-menopausal estrogen use and endometrial cancer. A look at the way the medical and pharmaceutical industries both reported and reponded to this controversy in the United States between the years 1970 and 1980 shows factors that interplayed in the creation of current medical knowledge and policy.

Estrogen was estimated in one large urban city study, to be or have been used by about 51% of post-menopausal women by the beginning of the 1970s.[26] Much of the clinical practice was based on both the consumer demand generated by the popular press, medical journal articles documenting the successful treatment of menopausal "symptoms" with estrogen, and heavy advertising in medical journals. Little attention had been given to the issue of adverse or long term effects of post-menopausal estrogen usage.

An outstanding article by researchers Kaufert and McKinlay shows the evolution of the estrogen safety debate as it was played out between the years 1970 and 1980s in two of

the most prestigious medical journals in the United States, and the role of public fear in dictating the course of medical policy. They conducted a literature review of the New England Journal of Medicine and the Journal of the American Medical Association under the topics: menopause, climacteric, estrogen, osteoporosis, and endometrial cancer, and monitored the debate as presented within the medical profession itself.

From 1970-1973, literature from these two journals focused on estrogen replacement therapy and proper institution of the clinical regimen. A 1974 JAMA editorial on ERT summed up: 1. menopause is a deficiency disease, 2. as such, estrogen replacement is therapeutically logical.[27] This uncritical acceptance of ERT changed from 1974-1980, as researchers began to show evidence that post-menopausal ERT was associated with long-term health risks. The first demonstrated risk was among women with gallbladder disease, and following that, an increased risk among all women for endometrial cancer.

From the mid to late 1970s, 9 studies in the aforementioned journals showed an association between ERT and endometrial cancer. During the same period, ERT and breast cancer were studied in 4 articles, all with inconclusive results. ERT and coronary artery disease research was also conducted during that period, also with inconclusive results. Research on ERT and osteoporosis was not discussed in these journals until 1980, presumably since researchers in Europe had already shown a protective role.

By 1980, NEJM took a cautious view of ERT, suggesting that only individual women could balance their need for symptomatic relief against the risks of therapy. In contrast, editorials from the same period in JAMA focused on the "protective" benefits of estrogen, such as prevention of osteoporosis, preservation of functional genitalia and the then unproven and hypothetical benefit to the heart.

The roots of the contemporary discussion about menopause and hormones stem from these articles. As was discussed in the previous chapters, ERT is now touted as

having many long term health benefits. There is little information but much controversy about long term adverse health consequences of ERT.

Once the media seized the research results and publicized the data on an increased endometrial cancer risk, estrogen prescriptions began to decline. The US Food and Drug Administration, in what was to become a political debate, ordered pharmaceutical companies to include a package insert with estrogen prescriptions warning women of the documented risks of the drug. The FDA regulations raised the ire of professional medical groups, who viewed package inserts as an intrusion in the patient-physician relationship. The American College of Obstetrics and Gynecology joined in the pharmaceutical companies' legal suit to prevent FDA orders, while other medical professional organizations such as the American College of Internal Medicine declared their formal support for the suit.[23]

Ultimately, the FDA prevailed, inserts were added, and clinicians were encouraged to individualize the estrogen decision for each patient. A trend of increased physician-patient communication and joint decision making was influenced by the fact that doctors were no longer the sole possessors of medical information now that each patient received warnings within the medication itself. This trend has been interpreted as either a "liberalization of the physician patient relationship," or, by the more skeptical, a decision based on the "notion (that) the passive, compliant patient was becoming a legal liability".[25]

From the 1970s to the 1980s, the status of ERT went from the drug promising "femininity forever," to a potential carcinogen with undetermined long term benefits. While the researchers could only advise that the patient and the physician must together weigh the risks and decide upon an individualized treatment together, the clinician herself was left with a confusing debate. Only about 30% of physicians receive JAMA or the NEJM, and many more rely on the industry controlled "free press," or the advice of their colleagues for research news.[25] Medical opinions and practice that are based on scientific facts are still influenced by culture, media, and now, the law.

The Current Situation

Current medical discussion of menopause and hormones has shifted away from the focus on the alleviation of perimenopausal symptoms of acute estrogen "deficiency," and been put into the much more sobering domain of long term health risks of estrogen "deficiency." As was seen in the 1960s, hormones are again being marketed to women in women's magazines, this time as part of an aggressive campaign to combat bone degeneration, or osteoporosis. Wyeth Ayerst Laboratories has a toll-free hotline that women may call to order their free brochure on osteoporosis and its prevention. The mere existence of a hotline conveys urgency to the women readers, and the brochures that arrive in the mail are official looking documents from the Osteoporosis Information Center, and the National Osteoporosis Foundation. This seemingly neutral source of information advises that "While you may experience some uncomfortable symptoms of menopause at first, they can be alleviated with estrogen replacement therapy." It also alerts women to the symptoms of menopause "Irregular periods, hot flashes, etc." and recommends that "You should report these symptoms to your doctor as early as possible," cementing the experience of menopause as a disease process that should be overseen by physicians.

Yet a heartening trend is being seen. As happened in the 1960's and 1970s, the media is again reporting more openly on this once taboo subject, but with a decidedly more liberated spin. And, as women did in the 1960's, women are again empowering and educating themselves about menopause, and about where the flow of information about menopause comes from. Two non-fiction bestsellers are specifically about menopause: The Silent Passage, by Gail Sheehy[28], and The Change, by Germaine Greer[29], which discuss a personal and very white middle class experience of menopause, and analyze the historical discussion of menopause respectively. On a less positive note, women's magazines devote their space to menopause as it is promoted by the pharmaceutical industry.

The transformation of menopause from a once taboo subject to media hot topic has indeed been a mixed blessing for American women. In a positive light, women are no longer expected to stay silent about this part of their biology. Formal support groups such as "the Red-Hot Mamas" are springing up all over the country, and widespread media discussion ensures that more informal avenues of support have also opened up.

However, given the myriad ways of looking a menopause, it is clear that Greer's book aside, the popular media has seized on the medical perspective, and consistently portrayed menopause as a set of symptoms, or as the trailmark for a future set of health risks such as osteoporosis, and heart disease. Furthermore, rarely is menopause discussed without a concomitant discussion about hormone replacement therapy. Largely ignored are "alternative" solutions to the medical/physical aspects of menopause, such as those advanced in Sadja Greenwood's book Menopause, Naturally. She states "Women who exercise daily, eat healthy food, and work on achieving emotional balance usually manage to avoid many of the ills of mid-life. Moreover, adopting such practices can cure many problems more reliably than drugs or surgery".[30] Rarely found in the discussion are questions about menopause framed in a different way. For example, a question rarely asked and inadequately answered in the popular media is "is menopause exclusively a health issue?" And less frequent yet, is discussion about some of the potential positive feelings associated with menopause, such as lack of fear of pregnancy, and freedom from menstruation.

The Newsweek article of April 24, 1992 entitled "Menopause, The Search for Straight Talk and Safe Treatment"[31] despite itself, reveals the medicalized bias of menopause found so prevalently in the media. It attempts to give a voice to some of the many debates within menopause research by questioning whether it is indeed "a disease that requires medical intervention , or a natural passage that should run its course. Is it the beginning of inevitable decline-or the start of a great new phase of life?" However, the pro-medical/disease bias is clearly seen when the article first reports that "A great many

women seem to go through menopause with few, if any complaints" and then the next six paragraphs are devoted to describing and elaborating on the symptoms of menopause. The article perpetuates the incompetent menopausal woman stereotype by stating, "The first symptoms aren't always the telltale hot flashes or menstrual changes. Sometimes they are more subtle shifts in cognitive functions that can leave women doubting their competence, their confidence and even their very sanity." At this point, many readers have forgotten about the great many women who seem to go through menopause with few complaints, and fear for their sanity. The paragraph ends by describing a woman who had a particularly symptom-filled menopause, replete with forgetfullness and joint pain. The woman's functioning fell to such a level that she left a high stress job and took a lower stress job. Using this woman as an example of menopausal symptomotology reinforces the belief and fear that menopausal women are emotionally unstable and incapable.

While the Newsweek article successfully touched on several of the more pithy issues about females, aging, and society's response to aging women, and even mentions the potential "post-menopausal zest" that is described by anthropologist Margaret Mead, it again falls short by pitting the two female authors of the best-selling menopause books against each other, and both undermines Greer's book and takes the more traditional Sheehy's side by quoting her saying "Greer's manifesto is an interesting hat trick, but I don't think it really appeals to women who want to have full rich lives." The article closes with further reference to "medical options" and is followed by another article specifically on medical treatments that states, "The most effective fix for almost all the woes of menopause is estrogen replacement therapy (ERT). " Since most people do not access the more esoteric academic journals of anthropologists and sociologists, many women rely on the press for much of their information about menopause.

Closing/discussion

Of great interest is what makes the medical definition of menopause the acceptable starting point for discussion of menopause within the popular media. One explanation is that science and medicine, as was seen in the nineteenth century, are thought by many to be one of the few arenas in which facts exist and prevail. As demonstrated earlier, however, medical research, while not necessarily erroneous or ill-intentioned, is limited by the very myopic focus of the clinical gaze on pathology, disease or malfunction. Furthermore, as a social institution, medicine is influenced by both societal norms and more recently, economic considerations and incentives. Medical explanations have at worst been both historically influenced by and used to justified some clearly cultural ideals about women's physiology and behavior. In addition, medical practice has been impacted by pharmaceutical company funding in research and advertising, as well as other political and ideological relations.[13]

The issues addressed in the medical discussion of menopause echo some of the those seen in the nineteenth century. Perhaps as a holdover from the traditional belief that women do not belong in the work force or certainly not in high powered positions when they are of a "certain age," the Newsweek article implies that menopausal women may be impaired from working due to the insidious loss of cognitive function that accompanies menopause.

Or perhaps as a symptom of this youth aggrandizing culture, aging women are treated as ill and disease prone, and medical viewpoints about menopause are accepted because they closely echo society's view that aging is pathological, especially aging women. A tragic shortcoming of the medical point of view is that rather than forcing insight into why society shuns its elders, it offers "treatment" against the aging process.

This is not to suggest that the medical perspective on menopause is wrong, but to underscore that medicine and the attendant conceptualizations of illness and disease are generated within a specific societal and cultural context. It is not a "shame" as W. Utian,

MD[31] says, nor is it "dangerous" to include disciplines other than medicine in the discourse about menopause. Considering the lack of biological consistency among women from different cultures and even among women from the same culture, medical opinions should be taken as one of the many expert voices about a process that would appear to have significant social and cultural components.

The "menopause as deficiency disease/estrogen debate" is a complicated one. Recent attention has been brought to the medicine profession's neglect in adequately researching female physiology and disease, and instead generalizing the results of male subjects as representative of "normal physiology".[32] In light of this, the interest in menopause as a medical phenomenon may have, on a positive note, influenced and intensified the commitment of greater medical resources to researching women's health. Indeed, the National Institute of Health has earmarked $500 million to a community-based clinical intervention to explore the roles of diet, dietary supplements, exercise, hormone therapy and smoking cessation in preventing cardiovascular disease, cancer and osteoporosis. The results of the 10 year multi-center study, called the Women's Health Initiative (WHI), will hopefully provide more information about the true risks and benefits of post-menopausal hormone replacement as well as no hormone replacement. However, given the preceeding discussion of science and medicine as socially influenced institutions, interpreting the results of the WHI and putting them into clinical practice must be done with care, as there is continued risk of reducing a clearly social/medical issue into a simply medical one.

Ultimately, one of the curent medical solution to menopause, hormone replacement therapy, remains a controversial topic. To singularly focus on whether or not to "treat" the menopause is to regrettably reduce the experience of menopause into a single medical "decision" and eliminate the more complex and individual meanings surrounding the experience. This chapter is intended to reveal some of the complexities and controversies

of menopausal research and medical policies, and to highlight that the understanding of menopause as a medical phenomenon is both historically and culturally influenced.

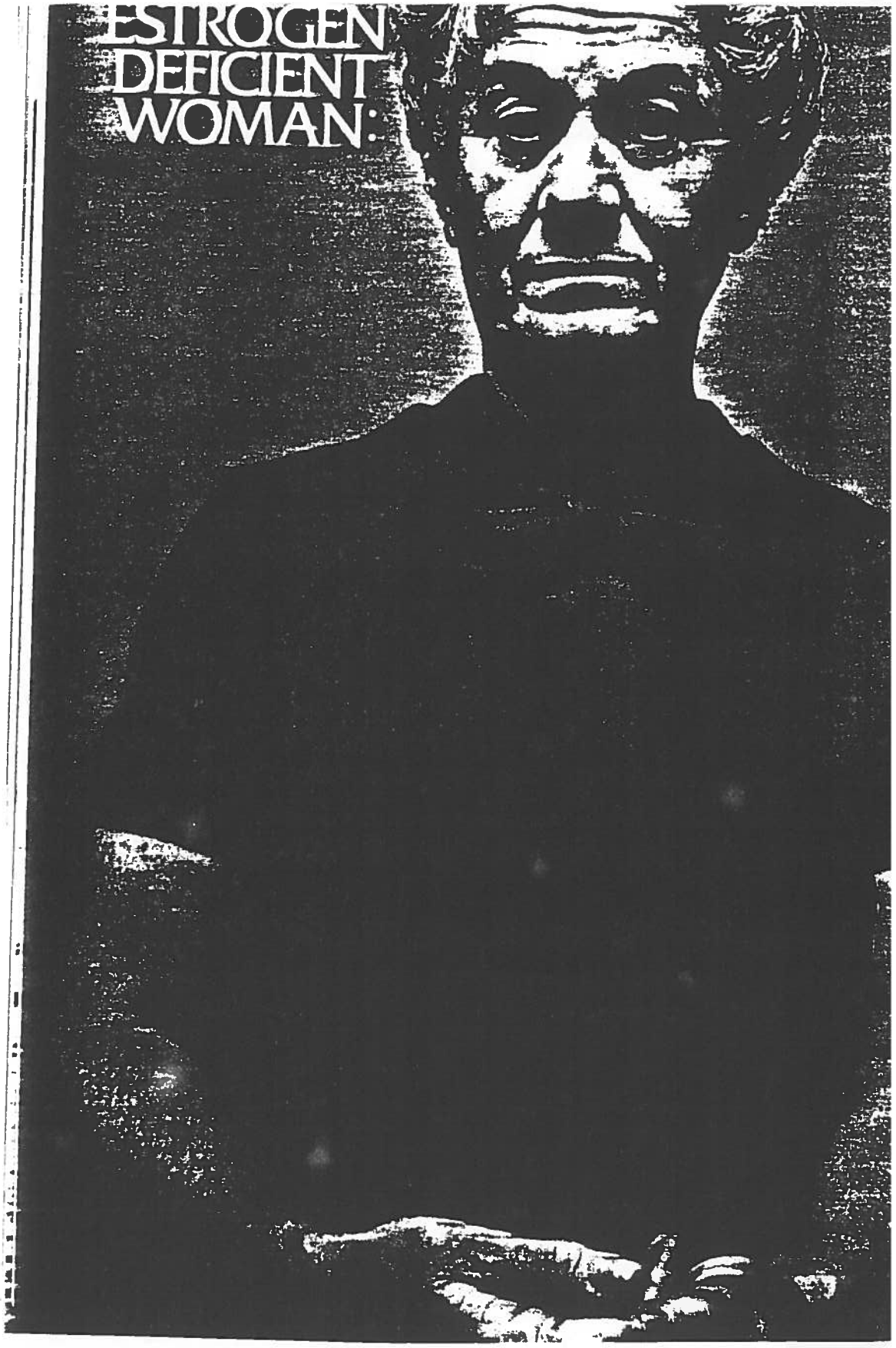


Figure 1. Estrogen Advertisement: Journal of the American Medical Association, 1970

THE ARID YEARS . . .

It is ironic that modern woman's increased life-span may merely add more years of living as something less than a woman. During these added years, postmenopausal estrogen deficiency not only "defeminizes"—with profound cosmetic and psychic effects—but also increases the physical hazards to cardiac, circulatory, bone and other vital metabolic processes.

MUST THEY BE?

Fortunately, technics are now well established to compensate for Nature's premature withdrawal of protective estrogen. Replacement estrogen therapy with natural oral estrogens as PREMARIN® (conjugated estrogens—equine), and based on the patient's own individual needs, now permits the physician to institute a most beneficial program for woman's over-all health and well-being in the postmenopausal years. The following pages describe these therapeutic objectives briefly but thoroughly.

Figure 1b- Estrogen Advertisement: American Medical Women's Association Journal 1965

References: Medicalization of Menopause

1. Rittenhouse, C. "The Emergence of Premenstrual Syndrome as a Social Problem." Social Problems 38 (1991): 412-425.

2. Pavelka, M, Fedigan, L. "Menopause: A Comparative Life History Perspective." Yearbook of Physical Anthropology 34, (1991): 13-38.

3. Lock, M. "Contested meanings of the Menopause." Lancet 334 (1991): 1270-1273.

4. Flint, M, Samil R. "Cultural and Subcultural Meanings of the Menopause." Annals New York Academy of Sciences 592 (1990): 134-149.

5. Dickson, G. "A Feminist Poststructuralist Analysis of the Knowledge of Menopause." Advanced Nursing Science 12, (1990): 15-31.

6. Morse, C. "Psychosocial Aspects of the Climacteric." In Premenstrual, Postpartum and Menopausal Mood Disorders. Edited by L. Demers, J. McGuire, A. Philips. Baltimore: Urban and Schwarzenberg, Inc., 1989.

7. Delaney, J, Lupton M, Toth E. "From Leeches to Estrogen: The Menopause and Medical Options." In The Curse: A Cultural History of Menstruation, pp 213-19. Chicago: University of Illinois Press, 1988.

8. Delaney, J, Lupton M, Toth E. "Psychology and the Menopausal Menace." In The Curse: A Cultural History of Menstruation, pp. 220-24. Chicago: University of Illinois Press, 1988.

9. Delaney, J, Lupton M, Tothe E. ""November of the Body": The Menopause and Literature." In The Curse: A Cultural History of the Menstruation, pp. 225-39. Chicago: University of Illinois Press, 1988.

10. Bell, S. "Sociological Perspectives on the Medicalization of Menopause." Annals New York Academy of Sciences 592 (1990): 173-177.

11. Illich, I. Medical Nemesis: The Expropriation of Health. New York: Pantheon, 1976.

12. Riessman, C. "Women and Medicalization: A New Perspective." Social Policy 14 (1983): 3-17.

13. McCrea, F. "The Politics of Menopause: The "Discovery" of a Deficiency Disease." Social Problems 31(1), (1983): 111-123.

14. Zola, I. "Medicine as an Institution of Social Control." Sociological Review 20 (1972): 487-504.

15. Conrad, P, Schneider, J. Deviance and Medicalization: From Badness to Sickness. Saint Louis: C.V. Mosby, 1980.

16. Bell, S. "Changing Ideas: The Medicalization of Menopause." Social Science and Medicine 24 (1987): 535-42.

17. Smith-Rosenberg, C, Rosenberg, C. "The Female Animal: Medical and Biological View of Woman and Her Role in Nineteenth-Century America." In Women and Health in America, pp 12-23. Edited by J. Leavitt. Madison: University of Wisconsin Press, 1984.

18. Wilbush, J. "Menopause and Menorrhagia: A Historical Exploration." Maturitas, 10 (1988): 81-108.

19. MacPherson, K. "Nurse-Researchers Respond to the Medicalization of Menopause." Annals New York Academy of Sciences 592 (1990): 180-184.

20. Pratt, J. "Sex functions in man." In Sex and Internal Secretions. Edited by E. Allen, C. Danforth, E. Doisy. Baltimore:Williams and Wilkins, 1939.

21. Frank, R. "Treatment of Disorders of the Menopause." Bulletin of the New York Academy of Medicine 17 (1941).

22. Wilson, R. Feminine Forever. New York: M. Evans., 1966.

23. McCrea, F, Markle, G. "The Estrogen Replacement Controversy in the USA and UK: Different Answers to the Same Question?" Social Studies of Science 14 (1984): 1-26.

24. Reuben, P. Everything You Always Wanted to Know About Sex but Were Afraid to Ask. New York: David McKay Co., 1969.

25. Kaufert, P, McKinlay S. "Estrogen-Replacement Therapy: The Production of Medical Knowledge and the Emergence of Policy." In Women, Health and Healing, pp 113-37. Edited by E. Lewin, V. Olesen. New York: Tavistock Publications, 1985.

26. Weiss, N, Szekely, D, Austin, D. "Increasing Incidence of Endometrial Cancer in the United States." New England Journal of Medicine 294 (1976): 1259-62.

27. Kase, N. "Editorial : Estrogens and the Menopause." Journal of the American Medical Association 227 (1974): 318-19.

28. Sheehy, G. The Silent Passage. New York: Simon & Schuster Inc., 1993.

29. Greer, G. The Change: Women, Aging and the Menopause. New York: A. A. Knopf, 1992.

30. Greenwood, S. Menopause Naturally. San Francisco: Volcano Press, 1984.

31. Beck, M,Beachy, L, Mathews, J, Wingert, P, Friday, C, Barrett, T, King, P, Joseph, N, Gordon, J. "Menopause: The Search for Straight Talk and Safe Treatment." Newsweek May 25 (1992): 70-82.

32. Cotton, P. "Women's Health Initiative Leads Way as Research Begins to Fill Gender Gaps." Journal of the American Medical Association 267 (1992): 469-70, 473.

Chapter V

Conclusion

This thesis was undertaken to examine the relationship between long-term estrogen use and height change over a 20 year period. It was dually motivated by my interest in women's health and aging, and questions about the validity of claims made by estrogen manufacturers about the specific benefits of estrogen therapy. The results of this research project show that there is little difference in the amount of height lost over twenty years between long term estrogen users and non-users: the difference was 0.17 inches, which was not statistically significant.

Thus, the work contained in this thesis challenges reports in the medical literature claiming that estrogen has a significant role in preventing age-associated height loss among women. In fact, the results demonstrate that the amount of height loss over twenty years is in general highly variable, and occurs among most women regardless of their estrogen replacement status. This by no means contradicts the well demonstrated effect of estrogen in maintaining bone density. Rather, it calls to question what role the bone preserving effects of estrogen therapy have on height preservation.

This research topic also invites examination of menopause and estrogen replacement within a broader context. As was discussed in chapter four, current medical and popular beliefs about menopause have been influenced by more than simply scientific discoveries. Political, social and economic factors, in addition to scientific advancements, have strongly directed the evolution of medical belief about this physiologic event, and continue to influence our ideas currently.

This paper began with a description of the bent-over women bustling through the streets of Chinatown. It appears from this study that the very medicalized explanation for their height loss as having been caused mainly by osteoporosis is worth reconsidering. While intuition leads me away from the explanation for their shrinking put forth by my aunt, the actual factors causing and preventing height loss deserve further exploration.

Appendix: Documents relating to study
1. Letter of Introduction

July 16, 1992

Dear Mrs. X:

We are writing to you from the Kaiser Permanente Medical Care Program's Division of Research, in cooperation with investigators from the University of California, School of Medicine, San Francisco, to invite you to participate in a study examining factors that affect body size and shape over time. You are being asked to be in the study because you were in the Walnut Creek Study and are still a member of Kaiser. The scientists who conducted the Walnut Creek Study have left Kaiser, but they gave the names of women in the study to the Division of Research so that the information you provided then could be used in later studies.

When you participated in the Walnut Creek Study over twenty years ago, your height and weight were carefully measured and important medical history information was taken and recorded. As an original participant in that study, you are part of a unique group whose potential changes in measurements will contribute important scientific data about what happens to womens' height and weight over time. With your continued participation in this study, we will investigate which factors affect the outcome of these body measurements.

In short, the study we are currently conducting, the Walnut Creek Alumnae Study, will use information you provided when you were in the Walnut Creek Study, along with the results of a new examination, to study the factors that affect changes in body size and shape.

Should you choose to participate, you will be invited to come to the Division of Research's clinical examination facility for a 45 minute visit. During this visit, you will have an examination to measure your height, weight, waist and hip size, which will take approximately 10 minutes. You will also be asked to complete a 20 minute questionnaire on your use of hormones, your medical history, smoking, drinking and diet. Parking and light refreshments will be provided.

The confidentiality of these data will be maintained at all times by study staff, and the information you provide will be used only in statistical analyses with data from the other participants; It will not become part of your medical record. Under no circumstance will you name or other individual identifying information be used in any publication or report.

You will be receiving a call within one week so that we may answer any questions you may have, and to schedule participants for either Monday or Tuesday appointments. Please note that your decision to participate or not to participate will in no way affect your medical care at Kaiser. If you have any questions, please call 1-800-627-2067 during regular business hours and leave a message for Victoria Hall.

Thank you for your consideration.

Sincerely,

Diana Petitti, M.D.
Assoicate Professor
Department of Family and Community Medicine
University of California

Bruce Ettinger, M.D.
Division of Research
Kaiser Permanente Medical Care Program

Steve Sidney, M.D.
Division of Research
Kaiser Permanente Medical Care Program

2. Telephone Protocol

Draft Telephone Protocol for Scheduling Appointments
MEASUREMENT ONLY!!!

Hello, my name is _____. I am calling from the Division of Research at Kaiser Permanente. We are conducting a study of factors that affect body size and shape, with physicians from the University of California, San Francisco. In this study we hope to find out which factors have an effect on the way that height and weight may change over time. Did you receive a letter from us in the mail about this study?

_____yes
*Do you have any questions?
*(Proceed to questions section on the following page.)

_____no

*verify address

* Ask permission to briefly explain the study
"Do you have a few minutes to discuss this study now?"

_____no
If member does not have time for the explanation now, tell her you will send a letter of explanation and call back in 10 days. Ask for a convenient time to call.

_____yes (Proceed to next question)

We are inviting you to participate in the Walnut Creek Alumnae Study because you were a participant in the Walnut Creek Study over fifteen years ago, during which your height and weight were recorded. As an original participant in the Walnut Creek Study, you are part of a unique group whose progress and changes in measurements over the last twenty years will contribute to the scientific data about what happens to womens' height and weight over time. The Walnut Creek Study started in 1969 and ended in 1977. The scientists in that study have left Kaiser, but they gave the names of women in the study to the Division of Research so that the information you provided then could be used in later studies.

The study we are now doing will use information you provided when you were in the Walnut Creek Study, along with the results of a new examination, to study the factors that affect changes in body size and shape.

Should you choose to participate, you will be invited to come to the Division of Research's clinical examination facility for a 45 minute visit. During this visit, you will have an examination to measure your height, weight, waist and hip size, which will take approximately 10 minutes. You will also be asked to complete a 20 inuute questionnaire on your use of hormones, your medical history, smoking, drinking and diet.

The confidentiality of these data will be maintained at all times by study staff. The information you provide will be used only in statistical analyses with data from other participants. It will not become part of your medical record, nor will it affect your medical coverage or care. Under no circumstances will your name or other identifying information be used in any publication or report.

If you choose not to participate, your decision will not affect your health plan coverage or the care you receive at Kaiser.

Do you have any questions about this study?

FREQUENTLY ASKED QUESTIONS:

Who is conducting the study? Dr. Bruce Ettinger and Dr. Steve Sidney, from the Division of Research at Kaiser Permanente, in collaboration with Diana Petitti, from the Department of Family and Community Medicine, University of California, San Francisco, School of Medicine.

How did you get my name? Your name was included in our files of women who were in the Walnut Creek Study.

What would I have to do? We would like to schedule you to come to our examination facility at the Division of Research on a Monday or Tuesday for a forty five minute visit. We are located on Piedmont Avenue near the Oakland hospital. At this visit, you will have an examination to measure your height, weight, waist and hip size. You will also be asked to complete a 20 minute questionnaire you your use of hormones, your medical history, smoking, drinking and diet.

What will I get from participating? You will be contributing to the development of knowledge about factors that affect body size, ~~and bone density~~. You may receive a copy of the results of our study, and parking and light refreshment will be provided.

Questions you cannot answer: Refer to Dr. Sidney: 987-2108

After all questions have been answered:

Recruitment

Would you be interested in participating in this study?

_____yes: Can I schedule you for an appointment?
Enter into the schedule book the date, time, and member's daytime telephone number. Then repeat the day and time to the member.

Advise the member that we will send a letter with a map showing the location of the Division of Research, and that we will call once again, the day before the appointment, to confirm the appointment.

Explain that parking will be available in the visitors spaces in the parking lot adjacent to the building, and that a parking pass will be sent to them.

_____no:

Thank the member for her time, and assure her that her decision will not be noted in her medical record and will not affect her health plan coverage or care.

3. Questionnaire

Kaiser Medical ID _ _ _ _ _ _ _ _

__/__/__
interview date

WALNUT CREEK ALUMNAE STUDY

WELCOME!!

WHAT WE'RE ASKING YOU TO DO:

* *Please answer the questions on the following pages as completely as you can.*

* *If you do not understand some of the questions, please feel free to ask at the front desk for assistance.*

* *Please make only one check for each question, unless the directions indicate otherwise.*

* *Thank you for your participation in this study.*

I. Demographics

A. Self

1. Please check the information below for accuracy. Make any corrections, changes or additions in the spaces provided:

Name_____
Address_____
_____
_____
Telephone_____

1a. Do you expect to move or have a different mailing address in the next year?
_____yes _____no _____don't know

If yes,
If you know your new address, please write it below
_____
_____
_____

2. When were you born?____/____/____
month day year

3. What is your race or ethnic background? (please check only one)
_____Asian or Pacific Islander
_____Hispanic or Latina
_____White or Caucasian
_____Afro-american or Black
_____Other

II. Hormone History

A. Type/Length of Use

1. Have you ever used birth control pills?
_____yes _____no _____don't know

If yes,
1a. how long did you use birth control pills?
_____years (number)
_____I took them for less than a year

HAVE YOU EVER TAKEN ANY OF THE FOLLOWING MEDICATIONS:

2. Estrogen or female hormone pills, such as Premarin, Estinyl or Estrace, sometimes prescribed for women going through menopause?
_____yes _____no _____don't know

If yes,
a. about how old were you when you first took estrogen or female hormone pills?
_____years old

b. Not counting years when you stopped, for about how many years altogether did you take estrogen or female hormone pills?
_____years
_____I took them for less than one year

3. Worn a patch containing estrogen hormones for symptoms of menopause?
_____yes _____no _____don't know

If yes,
a. About how old were you when you first began wearing an estrogen patch?
_____years old

b. Not counting years when you stopped, for about how many years altogether did you wear an estrogen patch?
_____years
_____I wore a patch for less than one year

4. Estrogen or female hormone vaginal cream or suppository?

_____yes _____no _____don't know

If yes,

a. about how old were you when you first used an estrogen vaginal cream or suppository?

_____years old

b. Not counting years when you stopped, for about how many years altogether did you use an estrogen vaginal cream or suppository?

_____years

_____I used them for less than one year

5. Injections of estrogens or female hormones for symptoms of menopause?

_____yes _____no _____don't know

If yes,

a. About how old were you when you first received injections of estrogens or female hormones?

_____years old

b. Not counting years when you stopped, for about how many years altogether did you receive injections of estrogens or female hormones?

_____years

_____I received them for less than one year

6. In the past thirty days, have you used estrogens or a combination of estrogens and progestin?

_____yes _____no _____don't know

If yes.

a. What is the name of the estrogen you are currently using?

_____Estrogen Medication Name

b. What is the dose of the estrogen you are currently using?

_____dose

c. What is the name of the progestin you are currently using?

_____Progestin Medication Name

d. What is the dose of the progestin you are currently using?

_____dose

e. How many days per month do you take a progestin pill?

_____days per month

III. Past Medical History

A. SELF

1. Have you ever been diagnosed with any of the following illnesses or conditions? Please check YES or NO for each of the following

yes	no		year first diagnosed
___	___	Breast Cancer	_____
___	___	Endometrial (womb) Cancer	_____
___	___	Ovarian Cancer	_____
___	___	Overactive thyroid ←	_____
___	___	Underactive thyroid	_____
___	___	Kidney failure/damage	_____
___	___	Fracture, only those after the age of 50	_____
		If so, which bone(s)_____	
		_____	
		_____	
		_____	
___	___	Osteoporosis (thin or brittle bones)	_____

B. Family History

1. Did your mother, sister or any aunt ever fracture a hip, wrist or spine?
_____yes _____no _____don't know

2. Did your mother, sister, or any aunt ever have osteoporosis (thin or brittle bones)
_____yes _____no _____don't know

3. Did your mother, sister or any aunt have a Dowager's hump (upper back that is stooped or bent forward)?
_____yes _____no _____don't know

4. Did your father, brother or uncle ever fracture a hip, wrist or spine?
_____yes _____no _____don't know

5. Did your father, brother or uncle ever have osteoporosis (thin or brittle bones)
_____yes _____no _____don't know

6. Did your father, brother or uncle have a Dowager's hump (upper back that is stooped or bent forward?
_____yes _____no _____don't know

IV. MENSTRUAL HISTORY

1. At what age did your menstrual periods begin? _____years old
(If you cannot remember, please make your best guess)

2. Have you had your uterus removed (Hysterectomy)?
_____yes _____no _____don't know

2a. If yes, how old were you when you had your uterus removed?
_____years old

3. Have you had one or both ovaries removed?
_____yes _____no _____don't know

If yes,
3a. How many ovaries were removed?
_____one _____two (both) _____don't know

3b. How old were you when you had this done?
_____years old

4. At what age did you go through menopause? That is, at what age did your menstrual periods stop or become irregular?
_____years of age

V. HABITS

A. Tobacco

1. Have you ever smoked cigarettes regularly?
(regularly means at least 5 cigarettes per week, almost every week.)
_____yes _____no _____don't know

If yes,
1a. Altogether, how many years have you smoked cigarettes regularly?
_____ years

1b. How many cigarettes did you smoke per day, on the average? (*If you still smoke regularly, how many cigarettes do you smoke, on the average, each day?)*

_____cigarettes per day

1c. Are you still smoking regularly?
_____yes _____no _____don't know

B. Alcohol

1. Did you ever drink alcohol?
_____yes _____no _____don't know

If yes,
1a. On average how often did you drink alcohol of any type, including beer wine or hard liquor, in the last 12 months?
_____Only on special occasions or less than once per month
_____At least once a month but not every week (1-3 occasions/mo.)
_____About 1-3 times per week
_____About 4-6 times per week
_____Daily or almost daily
_____don't know

1b. When you drink (or drank) alcohol, about how much do (did) you usually drink?
please convert to standard drink: one drink = one 4 oz glass of wine
= 1 1/2 oz of distilled spirits
= one 12 oz bottle of beer

_____6 or more (standard) drinks
_____4 or 5 drinks
_____2 to 3 drinks
_____1 to 2 drinks
_____1 drink
_____less than one drink
_____unknown

C. DIET

For the years of your life indicated below, please mark the box next to the words that best describe how often you drank milk. (Include whole, lowfat and skim milk.)

I DRANK MILK:	YOUR AGE: From age 12 to 17	From age 18 to 50 (Not including pregnancies or breast feeding)	During pregnancy or breast-feeding	Since age 50
with every meal (or almost every meal)	☐	☐	☐	☐
almost everyday (or everyday), but not every meal	☐	☐	☐	☐
Every week, but not every day	☐	☐	☐	☐
Rarely or never	☐	☐	☐	☐

D. MEDICATIONS

HAVE YOU EVER TAKEN:

1. Diuretics or water pills for high blood pressure or any other reason?
   _____yes _____no _____don't know

   If yes,
   1a. What is the name of the diuretic?
   _____Diuretic Medication Name

2. Thyroid hormone pills?
   _____yes _____no _____don't know

   If yes,
   2a. What is the dose of the pill?
   _____dose

   2b. At what age did you begin taking the thyroid hormone pills?
   _____years old

3. Medications for seizures, convulsions, or epilepsy?
   _____yes _____no _____don't know

4. Prednisone pills, cortisone pills, or other steroid pills?

   _____yes _____no _____don't know

5. Calcium supplements such as oyster shell calcium, Os-Cal, Tums or Dolomite at least once a week?
   _____yes _____no _____don't know

   If yes,
   5a. How often did you take the Calcium supplement? (please check one)
   _____daily
   _____irregularly

   5b. When did you start taking the calcium supplement?
   _____(years, months, weeks ago)

   5c. For how many years altogether did you take Calcium supplements?
   _____years
   _____I took them for less than one year

In the past 30 days, have you taken:

6. vitamin D or a multivitamin containing vitamin D <u>at least once a week?</u>
   _____yes _____no _____don't know

VI. LIFESTYLE

A. Activity

1. In the last five years, how would you describe your general level of physical activity?

_____Mostly, I sit and work at a desk, read, watch television and/or do needlework.

_____Mostly, I am up and around shopping, cleaning, walking, and doing things that keep me on my feet.

_____Other (please describe)

_____
_____
_____
_____

2. Aside from any work you do at home or at a job, in the last year, have you done anything regularly to help you keep physically fit?

_____yes _____no _____don't know

If yes,

1a. How often in your free time, did you take part in moderate physical activity (such as bowling, golf, light sports or physical activity, gardening, taking long walks)?

_____ more than 4 times a week
_____ 2-4 times a week
_____ about once a week
_____ a few times a month
_____ a few times a year
_____ rarely or never

1b. How often in your free time, did you take part in vigorous physical activity (such as jogging, racket sports, swimming, aerobics, strenuous sports)?

_____ more than 4 times a week
_____ 2-4 times a week
_____ about once a week
_____ a few times a month
_____ a few times a year
_____ rarely or never

B. Overall Health

1. How would you rate your overall health?

_____ Excellent
_____ Good
_____ Fair
_____ Poor
_____ Very poor

4. Consent Form

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
KAISER FOUNDATION HOSPITALS; THE PERMANENTE MEDICAL GROUP, INC.
OAKLAND, CALIFORNIA

CONSENT TO BE A SUBJECT IN A RESEARCH STUDY

FORMAL TITLE: DOES LONG-TERM ESTROGEN PREVENT SHRINKAGE?

Dr. Steve Sidney and Dr. Bruce Ettinger of Kaiser Permanente and Dr. Diana Petitti of the University of California, San Francisco, School of Medicine, are doing a study of the factors that affect bone density and changes in body size and shape. The study involves collection of information about various behaviors, and an examination to measure body size and shape and bone density.

I have been invited to participate in the study because I am a member of the Kaiser Foundation Health Plan who participated in the Walnut Creek Study. I have agreed to participate in the study, which involves the following:

1. My height, weight, the curvature of my spine, and my waist and hip size will be measured. This will take about 15 minutes.

2. The density of my bones will be measured. This will take about 20 minutes.

3. I will complete a questionnaire about my use of hormones, my medical history, diet, and other characteristics. The questionnaire will take about 20 minutes to complete.

Although x-rays in high doses can be harmful, the equipment used to measure bone density in this study uses low dose x-rays. The amount of exposure to x-rays from the examination is very low--less than the amount one would receive taking a cross-country trip in an airplane. No other risks are expected from participation in this study.

Confidentiality will be maintained to the full extent provided by law. I will not be identified in any reports or publications about this study.

I cannot expect to directly benefit from my participation in this study. However, it is hoped that the study will help physicians learn more about what factors affect bone density and body size and shape. This may help future patients.

I have talked with _____ (research investigator obtaining consent) about this study. If I have any questions or if I am concerned about anything after the study, I can contact Dr. Steve Sidney (510-987-2108) or Dr. Diana Petitti (415-476-6840); also, the Institutional Review Board for the Protection of Human Subjects, Kaiser Foundation Research Institute, 1800 Harrison Street, Oakland, CA 94612, telephone (510)987-3236. I have been offered a copy of this consent form and the Experimental Subjects's Bill of Rights to keep.

PARTICIPATION IN THIS RESEARCH IS VOLUNTARY. I may refuse to enter the study or may withdraw at any time without jeopardy to receiving future health care or eligibility for membership in Kaiser Foundation Health Plan.

******

I voluntarily consent to participate in this study as described above.

_____
Signature of Research Subject

Name (please print):

_____

Date: _____

_____
Signature of Research Investigator

Date: _____

AHB:ls
07/01/92

KAISER FOUNDATION HOSPITALS
THE PERMANENTE MEDICAL GROUP, INC.

INFORMATION ABOUT RIGHTS OF MEDICAL RESEARCH PARTICIPANTS

California law* requires that a potential participant in a medical research study or investigation be presented with an "experimental subject's bill of rights." The following list of rights and privileges is intended to satisfy the statutory requirement.

Persons who participate in medical research, investigation, or experimentation are entitled to certain rights, which include (but are not necessarily limited to) the right to be:

1. Informed of the nature and purpose of the study, investigation, or experiment.

2. Given an explanation of the procedures to be followed in the medical study, investigation or experiment, and a description of any drug or device to be used.

3. Informed of any related discomforts and risks reasonably to be expected from participation in the study.

4. Told of any benefits to the participant, reasonably to be expected, if any.

5. Advised of any appropriate alternative procedures, drugs, or devices that might be advantageous to the participant, and the relative risks and benefits of these alternatives.

6. Informed of the availability of medical treatment, if any, to the participant, after the experiment, should complications arise.

7. Given an opportunity to ask any questions concerning the study, investigation or experiment, or about the procedures involved.

8. Instructed that consent to participate may be withdrawn at any time and that the participation in the medical study, investigation or experiment may be discontinued without prejudice.

9. Given a copy of the written consent to participation as a research participant, as signed and dated.

10. Allowed to decide to consent or not to consent to participate in a medical study, investigation or experiment, without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence upon the participant's decision.

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* Health and Safety Code Sections 24170-24178