Medical Decisions, Estrogen and Aging

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The book is dedicated to Virginia and Bob Hurt, and Laurie Quarles and Marc Schulkin. Thank you so much for the kindness you have always extended to my family; it has made all the difference here in Washington.

Foreword

If you are a woman between the ages of 45 and 75 and are trying to decide whether to try, or stick with, hormone therapy (HT), or if you are a physician with patients fitting this description, this book is for you – unless you are looking for a simple answer. If you are looking for a simple answer, you can go to the web site of one of the companies that manufactures hormones or makes money by administering hormone therapy (e.g., AntiAgingGroup.com), or you can go to the we bsite of an organization that advocates 'natural' aging (e.g., the Inter National Organization to Reclaim Menopause; Inorm.org). Any impartial advisor, however, is going to admit that the answer isn't at all clear-cut. Jay Schulkin, I believe the reader will find, is such an impartial advisor, and he is going to take you several steps beyond simply acknowledging the ambiguity; he's going to educate you about the biology, history, sociology, business, and ethics of hormone replacement therapy. As a prominent scientist doing research on hormones, a medical researcher, an expert on decision making, he is the ideal guide to the intricacies of the topic.

You might think that all of this sounds superfluous for making an informed decision: "Just the facts, please. Is HT helpful or not?" But you'll quickly discover that, much as reading a novel gives you insights that a plot synopsis can't convey, understanding these many dimensions is essential for making sense of the nuances of available information, and ultimately for making an informed decision. After reading this book, your decision won't necessarily be easier, but whatever decision you finally arrive at is going to be one that reflects your personal values and that is as free as it can be from the vast amount of misinformation disseminated by marketers and the media.

And, in the process of gaining information relevant to HT, you are going to acquire a lot of knowledge of other useful topics: What are hormones? To what extent are the symptoms of menopause culturally determined (the answer summarized in Tables 3.4 and 3.5, is quite shocking)? What are the strengths and weaknesses of different types of experimental (and non-experimental) research designs? What is 'evidence-based medicine,' what is 'decision analysis,' and how do these two approaches, both oriented to giving physicians and patients treatment advice, differ? And how do conflicts of interest affect the advice one receives from doctors?

Why can't Jay Schulkin, one of the foremost experts on the topic of hormone replacement therapy, give you a simple answer? First, and foremost, the science isn't clear on many critical points. Different studies using different methodologies and

subject populations have produced often conflicting results on some of the most basic questions that should inform your decision, e.g., the effect of HT on the risk of breast cancer and on cognitive functioning. Moreover, maddeningly, two of the studies that held out the promise of providing close to definitive answers on some of the most critical questions – the WHI (Women's Health Initiative) in the United States and the Million Women Study (MWS) in Great Britain – were terminated before they ran their course – on the dubious grounds that their early findings provided a clear case against administration of HT. Schulkin will walk you through the evidence, drawing attention to the limitations of different studies, and explaining what findings appear to be robust and which are at best suggestive.

Schulkin is also going to explain why much of the information you receive about HT should be challenged and questioned empirically – even that coming from your own personal physician, who is very likely to be receiving various forms of gifts from the companies that market hormones. He is also going to tell you that one ought to question your own decision making processes. He will teach you about a series of common human decision errors, such as paying too much attention to vivid information (e.g., the risk of contracting BREAST CANCER) and not enough attention to more pallid information (e.g., the impact of HT on bone density), or the tendency to worry too much about errors of commission (things you did that you shouldn't have done), and not enough about errors of omission (things you should have done that you didn't do). As Schulkin notes, the avoidance of HT "may be guided by the understandable wish to avoid causing rare but very undesirable outcomes at the price of exposing patients to far more likely, but somewhat less undesirable, hazards."

Even if all of these scientific issues were resolved, if you could adjust for the biases in the information you receive and eliminate your own decision biases, the decision of whether to take HT would still be far from straightforward because it involves balancing different types of health risks, occurring at different points in a lifetime and resulting in outcomes ranging from dementia to death. Thus, even if we felt confident in the current received wisdom that HT therapy increases the lifetime risk of breast cancer from approximately 45 in 1000 (about 4.5%) to approximately 57 in 1000 (about 6%), would this alone warrant shying away from HT? Not necessarily. A far more robust finding than that relating to breast cancer is that HT decreases the loss of bone density that normally accompanies aging. How important is bone density relative to breast cancer? Breast cancer seems scarier, but one study of 1,042 British citizens aged 65 years and over found that 35% (n=356) reported one or more falls in the preceding year, that the ratio of female fallers to male fallers was 2.7:1, and that mobility was significantly impaired in those reporting falls. Clearly, given such a high prevalence of falls, having strong bones is desirable, but how important is this relative to the possibility of being the 12 in 1,000 who contract breast cancer but would not have absent HT therapy?

And such health–health tradeoffs are the *easy* part. Suppose one is 55, has enjoyed proficient cognitive functioning until now, but has recently begun to experience problems with memory and reasoning. If HT therapy could significantly

delay the inevitable cognitive decline, would that be worth a 2.2% increase in one's lifetime chance of contracting breast cancer? There is no agreed-upon basis for trading off such incommensurable quantities. And breast cancer, bone density and cognitive functioning are only the tip of the iceberg of diverse effects of HT.

Moreover, beyond such 'tangible' effects as changes in the likelihood of contracting breast cancer or in the speed of cognitive decline, one's decision is likely to also be informed by moral or ethical values. As Schulkin notes, the decision of whether or not to obtain HT depends in part on value judgments that we make about aging in general and menopause in particular – e.g., whether menopause should be considered a 'natural' dimension of aging, and whether such naturalness has any value in its own right. Is HT more like cosmetic surgery, or is it more like insulin for someone who is diabetic?

Although Jay Schulkin isn't going to make up your mind for you, I can tell you how the book changed my own perspective on the issue of HT; it made me more positive. The evidence for benefits ended up seeming more robust, and the benefits themselves more substantial than I had realized from being exposed to little more than the publicity surrounding the WHI and MWS. At the least, this book should give pause to the massive numbers of women who went off of HT, perhaps some in a reflexive, uninformed fashion, since the release of those studies.

However, the book also made me acutely aware of the likelihood that HT has diverse and potentially momentous effects that remain undocumented. Hormones, as Schulkin notes, have global impacts across the body, and steroid hormones such as estrogen affect a wide range of functions, including metabolism, immunological functions, cell growth and differentiation, cognition and behavior. The long and continuing history of mass-adoption of drugs and treatments of dubious or often extremely negative value, should give any informed decision making pause when it comes to accepting any kind of drug or invasive treatment.

Even more than shifting my position on the balance of costs and benefits from HT, however, the book made me acutely aware of the need for further research on its effects. Although a researcher myself, I am generally pessimistic about researchers' abilities to make even-handed tradeoffs between risks to subjects on the one hand and the advancement of science (and, incidentally, the advancement of their own careers) on the other. Based on these misgivings, and my knowledge of the magnitude and ubiquity of conflicts of interest in research and especially medical research, I advise my friends and family to steer clear of medical experiments of all types. Yet, despite this distrust of researchers' abilities to balance the interests of science and their careers against those of their research subjects in an even-handed fashion, I nevertheless wonder about the wisdom of the controversial decision (see Chapter 6) to halt the two most definitive trials of HT (the WHI and MWS) before much of the most important data had been collected. Not only was it unclear, in my opinion, that the women in these trials were better off being taken off of HT, but the premature termination of the studies has left millions of women worldwide who face this predicament each year to do so without adequate information about the costs and benefits of HT. If and when such ambiguities

become resolved, I hope that Jay Schulkin will produce an updated version of this book reporting the new findings and, who knows, perhaps even making a specific recommendation!

George Loewenstein
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July 23, 2007

Preface

"Is one enough? Is two too many?" A worried mother in an early 1960s television commercial agonized over a cough syrup for her feverish little girl. Now that little girl, and all those little girls she represented, are women approaching menopause, and as physicians and patients they are caught up in the same kind of decision-making conundrum as that commercial mommy when it comes to hormone therapy (HT). "Should I worry more about my breast tissue or my bones?" "Will my patients with a family history of both cardiac disease and colon cancer do better on HT or off it?" "All these studies seem to contradict each other. Why can't researchers come up with a clear recommendation?" Media coverage of HT research has been extensive. In particular, two recent large-scale studies, one here in the US (Women's Health Initiative or WHI) and the other in Great Britain, have recently cast a negative light on the use of hormone therapy, after years of routine prescription of HT for menopausal women. We have a plethora of information, but we are still caught on that knife-edge between not enough and too much. Part of the problem is certainly inconsistent, incomplete, and contradictory data; but beyond that, our actual decision-making processes are deeply flawed. This is true not merely of HT, but of many if not most health care choices we have to make.

With so much at stake and so much confusion surrounding hormone therapy, I thought I would write a small book on the subject. I am writing as both a basic scientist, having spent many years researching the effects of different hormones on bodily function, and as someone who studies medical decision-making. The audience for this book is a broad one, including people in the biomedical and health-related professions, and individuals in the scientific, social, and philosophical communities. I want to look at the information we have to consider, its contradictions and contraindications and possible flaws and missing pieces, but also at the whole methodology by which we go about making choices based on that information. Hormone therapy choice is a particularly good example of how conflicting perspectives and interests and plain old flaws in our judgment process all affect the medical decisions we make.

I want to thank a set of colleagues in the Decision Sciences at the University of Pennsylvania that initially generated my interest in human decision-making. They include Jon Baron and Paul Kleindorfer. I thank my colleagues at the American

College of Obstetricians and Gynecologists, Georgetown University, and the National Institute of Mental Health. A grant from Heart, Lung, and Blood Institute of the National Institutes of Health is also gratefully acknowledged. I thank Martina Darragh at the Kennedy Institute at Georgetown for her help.

As always I thank my wife, my mother, my daughter, and my son, and the wonderful colleagues who allow me into their world and who provide me with helpful suggestions about my diverse projects, including this one.

I also thank a number of individuals with whom I work: Barbara Bettes, Victoria Coleman, Kristine Erickson, Lauren Hill, Maria Morgan, and Mike Power. Thank you all.

I apologize in advance for those left out. The field is enormous and not everything and everyone can be covered in this book. The views in this book are my responsibility, and not those of any institution or government agency with which I may be affiliated.

Contents

Introduction

Every medical decision is a journey. We pack our bags with facts and head off down a yellow-brick road with many intersections, forks, and divergent paths on the way to our destination. But the road isn't empty. Along the way we run into social attitudes (our own or others') that may give us misleading directions. We are detoured by media reports that tell us a particular road is closed (when perhaps it isn't). Billboards lure us to attractions that distract us from our primary purpose. Large commercial vehicles push our own best interests onto the shoulder of the road. The researchers we consult point us in different directions. Some of the facts we've packed turn out to be useless; others we've left at home, that we later wish we'd remembered to bring with us. It's a wonder we get anywhere at all. And sometimes, when we've gotten where we were going, we find that this is not where we really wanted to be at all.

This text is a guidebook for one particular journey: whether or not physicians should suggest estrogen or progestin or some other combination of related hormones to women during the menopausal period (hormone therapy or HT), and whether women should accept that advice. This decision affects many women in this country and all around the world, and on a wider scale shows what forces influence all medical decision-making, on the part of both doctors and patients.

They say you do not know where you're going until you know where you've been, and in that spirit Chapter 1 will set off with an overview of the history of hormones, hormone therapy, the vicissitudes of HT research, and how that research variously impacted the decisions of patients and physicians regarding its use. We will also meet, for the first time, some of the issues jostling for space along the road.

Societal values: Public attitudes towards women and how they age have changed a great deal in the past century, and those attitudes have all affected how women are persuaded to take or not to take HT. Hormone therapy was initially offered to women as means of being "feminine forever:" retaining youthful vigor and, especially, popular notions of an appropriately feminine appearance. The feminist revolution of the 1970s offered a devastating critique of the ways in which society (de)values women, particularly women who are not young and beautiful, and HT was a major target of that critique – but the feminist movement also raised awareness of the lack of attention paid to women's health and paved the way toward more and better research. The social value of hormone therapy also shifted, to a focus on

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health, rather than beauty. But health is a social value as much as a medical fact, and we still need to look closely at how our values affect the way we evaluate the risks and benefits of hormone therapy.

Commercial interests: Social values are both reflected in and influenced by commercial interests. The drugs that make hormone therapy possible have to be developed and manufactured by someone. It's an expensive and time-consuming process, even with government funding. In our society, pharmaceutical companies have to market their products effectively in order to keep functioning, and that sales effort affects both physicians and patients. Pharmaceuticals have marketed to doctors for many years, with everything from notepads emblazoned with drug and corporate names to expensive junkets. Physicians themselves are nervous over how such advertising affects their judgments. Over the last 10 years direct marketing of prescription drugs to the general public has increased exponentially. "Talk to your physician about xxx," the commercials in magazines and on television urge, and patients do. Commercial interests have inevitably affected our decisions about hormone therapy.

Media coverage: Especially since the advent of 24/7 cable news coverage, media outlets are voracious in their pursuit of newsworthy topics. Medical items have always attracted attention, from the polio threat and the Sabin and Salk vaccines in the 1950s to the war on cancer in the 1960s, to the AIDS and avian flu threats in the 1980s and 1990s and the new century. Public pressure led to greater attention to women's health in the media, and thus to interest in HT; Just as commercial advertising heightens awareness of a particular drug, or treatment regime, so can pervasive media reportage on HT research results can influence doctors and patients. Media thrives on developing the "story" angle of a particular subject. It requires a point of view and a source of tension and conflict, even when attempting to present an unbiased and factual news item. Our views of HT are shaped, perhaps even deformed, by these media pressures.

Physician–patient relations: Historically, the decision to take, or not to take, HT always comes down to a joint conference between women and their doctors. As the medical profession has developed, it has medicalized conditions such as pregnancy and menopause that were once entirely women's issues – in most cases for the better (pregnancy is no longer the leading cause of death among premenopausal women, and good medical care and advice from professionals is a major reason why), but inevitably complicating the process. Today a woman cannot go on HT without a doctor's involvement in obtaining the appropriate prescriptions. Ultimately, however, women control their own bodies and make their own decisions about them – a relatively recent social value in modern Western society that has major repercussions in terms of who ends up on HT and who does not.

History shows us how we got on the HT path. Analysis of the decision-making process helps us understand the means by which we might travel down that path: whether we should walk or take the bus, as it were. Chapter 2 describes two perspectives, decision sciences and evidence-based medicine, which allow us to fully understand how we make decisions, and provide us with tools for making better ones. While intellectually most of us accept that statistical reasoning is a balance of uncertainties, our Enlightenment past still tends to encourage us to assume on some deeper level that our decision-making is unbiased and based on purely deductive cogitation.

The decision sciences aim to unpack those biases, examine them fully, and provide tools that will allow us to make decisions that correlate more closely with the facts that really matter to us. We may still come to particular conclusions due to emotional needs and the biases of specific value systems, but at least we will be choosing those biases clearly and allowing them to influence our choices at the right point.

Evidence-based medicine (EBM) is a specific medical tool aimed at providing the best possible analysis of research. Medical research studies are many, various, and often contradictory. EBM rates study results based on principles that scientifically judge the comparative value of the evidence provided. Integrating decision sciences and evidence-based medicine means balancing individual choice with collective consensus, patient needs and values with the best medical understanding.

Physicians and medical researchers have often looked at hormone replacement much as they looked at insulin therapy: something is missing, and we just need to put it back. In fact menopause is a complicated aspect of the aging process that involves entire body systems. As research continues, scientists discover more and more implications of HT, some advantageous and some definitely not, all of which must be considered. We used to call these things "side effects," as if the things we put into our bodies have some specific preordained purpose and anything else that happens is a minor inconvenience. But sometimes those "side effects" have more overall impact on the body than the "main effect." Medical professionals now try to address any therapy's effects more holistically. Much recent research has focused on the effects of HT on the heart and other major bodily symptoms.

In Chapter 3 we will look at how HT relates to heart disease, strokes, and related disorders. Chapter 4 considers breast and other cancers, and the benefits that HT brings to the health of women's bones, skin, and teeth – these are the traditional issues associated with long-term HT studies. Chapter 5 broadens the scope to include issues not traditionally associated with long-term HT, focusing on both mood and cognitive phenomena.

Chapter 6 looks at change. Medical understanding is fundamentally knotted to continuous learning and inquiry, and HT is a paradigmatic example of this. Both physicians and patients need to have the will and the desire to acquire new knowledge, to change how they think as new information is generated. Chapter 6 looks at the paradigm shifts in thinking about HT in response to the WHI studies, and considers the role of continuous medical education in a physician's career, as it involves not just learning new skills and absorbing new information, but as it inculcates physicians with the tools to allow themselves to continuously learn.

In the Conclusion I will consider the matter of integrating our values into the medical decision-making process, particularly as they apply to aging. Our society has a vexed relationship with growing old, and that relationship only gets more complicated as the vast Boomer generation has now reached twice that age. What can we expect of ourselves and our bodies as we age? What do we want medical technologies to do for us? What kinds of choices should we make that help the most with what we value the most? Although this book deals only with the ramifications of choosing to prescribe or not to prescribe hormone therapy, the tools and techniques it discusses, the perils and pitfalls it describes, are applicable to almost any complex medical decision-making process.

Chapter 1
Hormone Therapy: Biological, Social, and Medical Context

The question of why or whether women, in consultation with their physicians, should choose hormone therapy (HT) in response to menopause represents a renewed controversy at the beginning of the new century. Conflicting messages regarding the health risks and benefits of HT have been conveyed in the mainstream media, especially information in the media about the results of large-scale studies of the health impact of hormone therapy. Women who have been on one or another of the hormone replacement regimes have been forced to reconsider continuing on HT. Doctors who prescribe these hormones to their patients are somewhat confused, as are perimenopausal women who are considering HT. Pharmaceutical companies that produce these compounds are worried. And public health officials are on the defensive.

Attention to the physiological changes associated with decreased estrogen levels and the search for medical remedies for these changes has been with us since perhaps the coining of the term "La menespausie" in 1816 (see Van Keep, 1990). The definition of menopause ("the climacteric") was first described as a deficiency of the ganglionic regulatory functions, and in the early 1900s researchers recognized that the ovaries were really an endocrine organ. And thus menopause emerged over time as something like a hormone deficiency syndrome associated with decreases in estrogen function (e.g., Van Keep, 1990; Utian, 1997; Watkins, 2002; Houck, 2006). These scientific descriptions both medicalized the state of menopause and labeled it as a disease process, rather than a developmental one.

Women going through menopause frequently suffer from hot flashes, night sweats, sleepless nights, and mood swings accompanying the gradual decline of reproductive hormone levels during the perimenopausal period into menopause. As a woman's body adjusts to this decline, periods of discomfort may be mild or severe, short-lived or seemingly unending. Physicians initially saw hormone therapy as a means of modulating these symptoms of menopause, but soon extended HT's use long-term, to sustain a host of vital biological and psychological functions, and to prevent or reduce vulnerability to a diverse array of diseases such as Alzheimer's disease, heart and bone diseases, and colorectal cancer, which are associated with aging. An impressive inventory of basic sciences documenting the many roles of estrogen and progestin only highlighted the relevance of these endogenous chemical signals to clinical practice (McEwen et al., 2002; McEwen and Norton, 2005).

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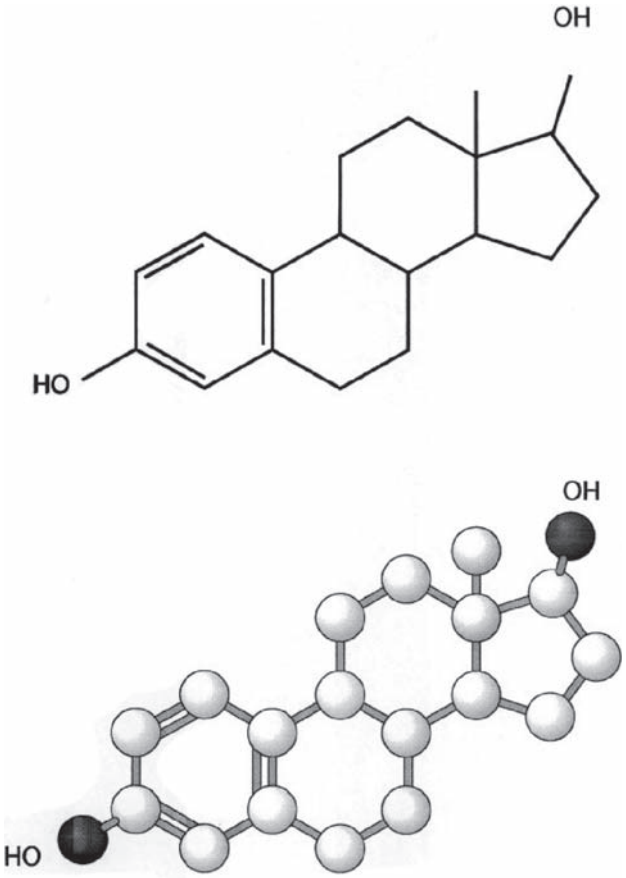

Fig. 1.1 Depiction of the structure of estrogen

As early researchers came to understand hormones better, they identified a number of bodily functions for which hormone therapy might be beneficial, including cardiovascular function, bone metabolism and bone maintenance, a variety of cognitive functions, and energy metabolism.

1.1 What are Hormones?

Hormones are best understood as chemical signals in the body; they can act locally or travel great distances to end organ systems. Hormones and hormonal messages are phylogenetically ancient (Strand, 1999; Pfaff et al., 2002); they are found in both invertebrates and vertebrates. Hormones in insects, for instance, produce molting and other dramatic changes, or evoke odors that attract others. Hormones

are distributed diversely in the body (see Table 1.1). They are found in skin, heart, and brain, as well as elsewhere (Schulkin, 1999).

The word "hormone" was first used by physiologists around 1905 (see Bayliss and Starling, 1902), derived from a Greek word meaning "to stir up." While initially scientists concentrated on the physiological effects of hormones, by the 1920s, adrenal medullary hormones (neurepinephrine and dopamine) were known to contribute to the regulation of emotional states and adaptation to regulatory duress, stimulating such behavioral reactions as the "fight or flight" response (Cannon, 1929).

Table 1.1 Partial list of major hormones secreted and endocrine glands

Endocrine Gland	Major Hormones Secreted
Anterior pituitary	Growth hormone
	Prolactin
	Adrenocorticotropin (ACTH)
	Luteinizing hormone (LH)
	Thyroid-stimulating hormone (TSH)
	Follicle-stimulating hormone (FSH)
Neurointermediate lobe/posterior pituitary	Arginine vasopressin
	Oxytocin
	Endorphins, enkephalins
Pineal	Melatonin
Thyroid gland	Thyroxine
	Calcitonin
Parathyroid gland	Parathyroid hormone
Heart	Atrial natriuretic factor
Adrenal cortex	Glucocorticoids
	Mineralocorticoids
	Androgens
Adrenal medulla	Epinephrine
	Norepinephrine
Kidney	Renin
Skin/kidney	Vitamin D
Liver/lung	Preangiotensin/angiotensin
Pancreas	Insulin
	Glucagon
Adipose tissue	Leptin
Stomach and intestines	Cholecystokinin
	Vasoactive intestinal peptide
	Bombesin
	Somatostatin
	Ghrelin
Gonads: ovary	Estrogen
	Progesterone
Gonads: testis	Testosterone
Macrophage, lymphocytes	Cytokines

Hormones are generally separated into two main classes in terms of their physiological actions. Peptide hormones typically are mediated by cellular membranes to produce their effects; steroid hormones act on the nucleus of cells to promote protein synthesis. The first effect is usually fast and the second slow. But we now also know that steroids can work rapidly to produce membrane-related effects that underlie diverse regulatory functions (McEwen, 2002).

Peptides include hormones such as insulin, oxytocin, and prolactin. They are derived from proteins. Steroids, on the other hand, are derived from cholesterol. They include hormones like estrogen and progesterone, testosterone, aldosterone, cortisol, adrenalin Vitamin D, and thyroxin. Testosterone is made by the testes, in men. Estrogen is secreted by the ovaries and acts in the brain, bone, and heart (see Fig. 1.2) Aldosterone, cortisol, adrenalin (neurepinephrine, dopamine) is produced in the adrenal gland, thyroxin from the thyroid gland, Vitamin D from the skin (Holick, 1994; DeLuca, 1998; Jones et al., 1998). That Vitamin D is a hormone confuses people, and it confused early researchers too. It was originally thought to be a vitamin in nutritional substances, and therefore by definition not made in the body; in fact it is a classical steroid.

Hormones are generated by diverse tissues in the body, so it is perhaps not surprising that they are often linked to specific regulatory functions Hormones such as insulin, cholecystokinin, or bombesin, all required for food regulation, are generated

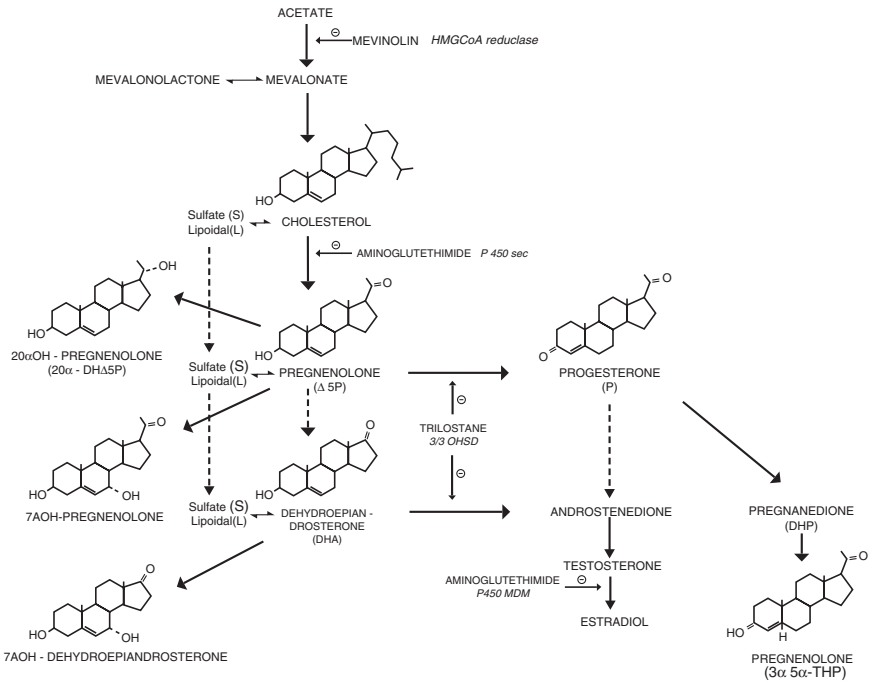

Fig. 1.2 Diverse relationship of estrogen to related hormones

in gastrointestinal organs. Aldosterone, angiotensin, and atrial natriuretic factor, essential for hydromineral and water balance, are produced in the adrenal glands, kidney, and heart. Vitamin D, parathyroid, thyroid, and melatonin, needed for calcium balance, circadian rhythms, and mental health, are produced in the skin, parathyroid, thyroid, and pineal glands. Adrenalcorticotropic hormone (ACTH) and cortisol, vital to adaptation to challenging situations and glucose transport, are produced in the pituitary and adrenal glands. And finally, testosterone and estrogen are fundamental to the expression of both primary and secondary sexual characteristics.

Hormones once were defined as chemical messengers that are blood-borne to distal organs, where they affect development and function. Now we know that hormones can act both proximally and distally (McEwen, 2002). We also know that many peptide hormones produced in the periphery also are created in the central nervous system. For example, hormones such as oxytocin, angiotensin, cholecystokinin, natriuretic factor, parathyroid, calcitonin, dopamine, adrenalin, and serotonin generate in cells in the heart and adrenal glands, and also in the brain. In periphery organs, we call them hormones. In the brain, we call them neurotransmitters, neuropeptides or neuromodulators (Herbert and Schulkin, 2002; Pfaff, 1999).

1.2 History of HT

The roots of HT itself can be traced back to the turn of the twentieth century, when a substance was first derived from the ovaries of cows. The estrogen patch was introduced in the late 1920s, the synthesis of estrogen in the late 1930s and the 1940s, and Premarin in the 1940s (Barrett-Connor, 2003a,b; Seaman, 2005). Hormone therapy enjoyed widespread popularity in the industrialized world by the 1950s. A number of pharmaceutical companies were involved in the research from the start, including Merck, Pfizer, and Ayerst (Seaman, 2005; Watkins, 2002; Houck, 2006). Physicians, provided with these products, started recommending HT as a remedy for the discomfort of menopause on a short-term basis. Once HT was available and affordable to at least some patients, physicians began to recommend HT for longer-term use, meaning over a decade or longer (Barrett-Connor, 2005, 2003a,b; Watkins, 2001; Houck, 2006) But as early as the 1940s studies indicated that HT increased the risk for breast and endometrial cancers, even as it appeared to have definite benefits for bone health. The trajectory was from a short-term medication to a much longer- term control over the aging process. And of course with the expansion of individuals who live longer the idea of retarding aging grew in prominence.

So the question of whether women should choose to go on HT is not a new one, and one reasonable suggestion has always been that women could decide to undertake a course of HT under certain well-defined circumstances. I want to emphasize that the book is not closed on HT now any more than it was in the 1940s. Despite the mounting body of research, our understanding of the physiology of menopause is incomplete, as is our knowledge regarding the connection of estrogen and progestin

with physiological and pathological states. But there are other issues I would like to address that are critical in determining those conditions: a careful exposition of the diverse positive effects associated with HT; heuristics and biases that may lead to over-emphasizing research findings — both positive and negative — with regard to prescribing HT; the role of pharmaceutical companies in testing estrogenic compounds and the promotion of their products; the seduction of physicians and patients with regard to reasonable expectations about menopause and aging; and the kinds of HT regimens that have been tested thus far.

In this age of biology and technology, there are important normative issues that need to be addressed, if not resolved. For example, what are reasonable expectations for how we are to age, and what medicines might we take to enhance, not just our longevity, but our zest for life? Hormone therapy is but one example amongst many other medical treatments that are related to these issues. Further, HT can be seen as a story with elements relevant to many other areas of medical decision-making: the forces that bias how the data are received, understood and collected, how social forces promote an idea of human excellence for bodily performance that may or may not be attainable or even desirable, what constitutes "normal aging" …. With a vast pharmacopeia to treat our every ailment, patients and also their physicians sometimes seem to believe that medicine can not only cure you, but can make you perfect.

A strong and important response to these social and medical issues came from the feminist movement. The women's movement, arising around the same time that menopause was being defined, medicalized, and identified as a disease process, has always been wary of the medical establishment and its intentions and motives regarding the treatment of women (e.g., Greer, 1991; Bell, 1987; Meyer, 2003 Houck, 2003; Elson, 2004). As early as 1792, Mary Wollstonecraft, wrote an essay entitled "A Vindication of the Rights of Women," demythologizing pernicious behaviors and rules that are bad for both genders, amidst a more militant sensibility of the denigration of women's rights (e.g., Mill, 1869). The longer-term social milieu in which women's rights were championed demanded equality of opportunity, diversity of choice, and respect from a larger public culture dominated disproportionately by men. Feminism since the latter part of the twentieth century has played an even more important role with regard to the evolution of patient rights, the participation of patients in decision-making with regard to medical choices, and a recognition of cultural biases that permeate all aspects of the medical and the larger milieu, including those pertaining to HT. Treatises such as *Our Bodies Our Selves* (1973) expressed, in part, the need for control over the choices women made with regard to medical or other decisions that affect their lives. So the evolution of HT and the expansion of patient decision-making is knotted to a cultural recognition and expansion of women's rights. One end point that emerged in the midst of the evolution of HT was a philosophy in which opportunities and respect were a primary concern (e.g., Gould, 1976; Mahowald, 1996; Wolf, 1996), as well as the discernment of the importance of context and social ties and collaborative sensibilities. Feminism made clear that women are not to be identified by their levels of estrogen.

1.3 Unreasonable Expectations about Aging and Menopause: The Lofty Promise of a Magic Bullet

Society's ideas about being a woman and about getting older, however, were not obviously always in sync with the feminist movement. Since the late 1950s and early 1960s, gynecologists such as Robert Wilson laid a very different framework in which HT would serve women well as they grew older. In 1966, at the beginning of the feminist revival of the 1960s, Wilson published a book called *Feminine Forever*. Wilson argued that the revolution in biological knowledge, particularly that of estrogen and progesterone in female regulatory physiological systems, needed to be tied to the pharmacological treatments surrounding women's health. Through hormone replacement therapy, a woman could simulate the hormones of reproduction and thereby stay "youthful" and "attractive" throughout her life span. All the right keywords were in place: youth, vigor, and sex. And Wilson's argument had a real rationale, housed in the discoveries of biology. But Wilson seemed to understand as axiomatic that simulation of estrogen and progesterone is a way to stay feminine and forever young – and, he asserted, healthy. Wilson argued that estrogen therapy is a window into youth, stating that menopause and all of the signs of external aging, including wrinkles, can and should be averted (see Houck, 2006 for an excellent social history).

By the 1970s, pharmaceutical companies had already studied various forms of estrogen or progesterone and promoted a long list of potentially beneficial effects. The basic science indicated that estrogen plays a prominent role in the organization of physiological and behavioral regulation outside of reproduction. For example, estrogen is essential during intrauterine development and throughout the life cycle in maintaining physiological tissue such as bones and the brain (Goy and McEwen, 1980). Since hormones like estrogen and progesterone play functional roles for the duration of one's natural life, as life expectancy (and thus the probability that women will enter menopause) increases, more women are confronted with the fact that there is a natural decline in hormones over time. Although menopause is a normal consequence of living to a certain age, it comes with many physiological changes which are problematic by anyone's definition, and certainly in the eyes of the women suffering debilitating hot flashes and embarrassing mood swings. Therefore, both the basic science and women's own experiences seemed to legitimate HT use, the pharmaceutical companies had the physicians' ears, and the patients had the physicians' attention.

Some of the symptoms of menopause, of which there is wide variability of duration and severity, are hot flashes, vulnerability to urinary incontinence, vaginal atrophy, and reduced sexual desire. These are aversive experiences, and it is easy therefore to justify replacement therapy. Pharmaceutical companies have been in the business of replacement therapy for almost as long as scientists have known about the link between hormones and health, most notably Lilly and the introduction of insulin for diabetics. Thus, if insulin (a hormone that underlies glucose

metabolism synthesized within pancreatic tissue) could be given to repair the consequences of a failure of pancreatic function, surely estrogen and progesterone could be supplemented to sustain the physiological and behavioral functions that reflect their normal role in maintaining health, even though HT provokes complex and diverse physiological actions that perhaps do not easily map onto therapeutic functions (Turgeon et al., 2004). For diabetics, the dramatic decreases of insulin and thyroxin secretion (or pancreatic and thyroid deficiency) are not inevitable natural occurrences. This is not the case for the cessation of ovarian function towards the end of the reproductive years. Menopause, and the loss of estrogen, is not a disease state analogous to diabetes.

Yet as I indicated above, menopause was "medicalized" to conform to the model of diabetes. The physical manifestations of menopause were transformed into symptoms, and women increasingly demanded – and gynecologists prescribed – replacement hormones. This occurred in spite of that fact that the safety of HT was up for debate. Some very early data suggested greater vulnerability to breast cancer (e.g., Colditz et al., 1995). The public debates were spirited, but in the end the FDA and other government agencies lent credibility to the safety of HT (Watkins, 2002). The stage was set for millions of women to go on HT.

In the high stakes game of health, beauty, and agelessness, pharmaceutical companies seemed to have hit a home run; women were sold the prospect of staying young forever. Indeed, advertising from pharmaceutical companies has always significantly contributed to HT use (Institute of Medicine, 1993; Watkins, 2002), and once the Federal Drug Agency (FDA) legitimated hormone therapy, the advertising campaigns became even more intense (Watkins, 2002). By the early 1970s, HT was widely available and very popular in Western Europe (especially in countries like Germany, Italy, France, and United Kingdom), as well as in the United States (World Health Foundation in Geneva, 1971; Van Keep, 1990). For example, in San Diego in the 1980s and 1990s, over 70% of gynecologists prescribed HT to their patients for longer-term use (Barrett-Connor, 1986).

1.4 Continuing Concerns

But concerns about HT continued to arise. One study in the middle 1970s, published in the New England Journal of Medicine, revealed an increased risk of vulnerability to endometrial cancer for HT patients – a condition that was also exacerbated by age. In another case-controlled study published in the same journal (Smith et al., 1975; Ziel and Finkle, 1975), investigators found an increased vulnerability for endometrial carcinoma in women on diverse forms of estrogenic compounds. The use of estrogen went up dramatically from 1962 to 1973, but following the publication of these studies prescriptions and use of HT subsequently declined (Holzman et al., 1984). The decline in HT use was, however, not permanent.

It was already known that diverse estrogenic compounds induced growth factors in tissue. Estrogen's function in sustaining different end-organ systems, like ovarian and uterine tissues, would become a stable theme in the basic science of research into biological material (McEwen et al., 2001). But estrogen was linked to a wider range of function. Intimations about the preservation of bone tissue by estrogenic compounds would rekindle the wider use of HT for an aging population.

To counteract the increased risk for the induction of cancerous tissue, progestin – which was known to have inhibitory effects on tissue growth, as well as being a prophylactic against some of the stimulatory effects of estrogen – was given along with the estrogen (e.g., Whitehead et al., 1981). Thereafter, evidence of the positive effects of HT on physiological systems, which included heart, bone, teeth, and mood (Institute of Medicine Report, 1993), accumulated rapidly. The combination of estrogen and progestin (Premarin, a drug produced by Wyeth-Ayerst Laboratories, Inc. was the major product used by women in the United States) would become a prescriptive treatment (Watkins, 2002; Hersh et al., 2004).

Premarin
- Estrogen product extracted from pregnant mares' urine (PMU).
- Manufactured by Wyeth-Ayerst Laboratories, Inc.
- Most commonly prescribed for estrogen replacement therapy (ERT) to relieve hormonal deficiency symptoms associated with menopause or hysterectomy.
- Premarin is the most widely used ERT drug, marketed for more than 50 years, and currently administered to more than nine million American women.

Thus hormone therapy took shape around estrogen or estrogenic compounds (often derived from horse urine, Cox, 1996), given alone or in conjunction with progesterone or synthetic progestins such as medroxyprogesterone acetate (MPA, e.g., Hapgood et al., 2004). The synthetic progestin, MPA however is also a glucocorticoid agonist and thus should have more effects on diverse end-organ systems. In other words, it is not a pure progesterone-related molecule (MPA is glucocorticoid and androgen agonist, Hapgood et al., 2004; Koubovec et al., 2005). Nevertheless, this compound is used in many large studies of HT (e.g., Rossouw et al., 2002). This fact may have implications for understanding this literature, since picking the right compound on which to base any study is obviously an important component in the validity of the study.

But there are diverse arrays of compounds that women use; a subset is depicted in Table 1.2.

Table 1.2 Examples of oral estrogen and estrogen/progestin products

Estrogen pills		Progestin pills		Estrogen-plus-progestin pills	
Brand	**Generic**	**Brand**	**Generic**	**Brand**	**Generic**
Premarin	conjugated equine estrogens	Cycrin	medroxypro-gesterone acetate	Premphase	conjugated equine estrogens and medroxyprogesterone acetate
Cenestin	synthetic conjugated estrogens	Provera	medroxypro-gesterone acetate	Prempro	conjugated equine estrogens and medroxyprogesterone acetate
Estratab	esterified estrogens	Aygestin	norethindrone acetate	Femhrt	ethinylestradiol and norethindrone acetate
Menest	esterified estrogens	Norlulate	norethindrone acetate	Activella	17-beta-estradiol and norethindrone acetate
Ortho-Est	estropipate (piperazine estrone sulfate)	Prometrium	progesterone USP (in peanut oil)	Ortho-Prefest	17-beta-estradiol and norethindrone acetate
Ogen	estropipate (piperazine estrone sulfate)				
Estrace	micronized 17-beta-estradiol				
Estinyl	Ethinyl estradiol				

1.5 Medical Decisions, Conflicts, and the Marketing of HT

If the science around HT has been gray, the marketing is too often not. Direct marketing of hormone therapy has been very lucrative for pharmaceutical companies, and the line between *persuade* and *inform* is not always clear (Berndt, 2005). There is no mythology here; the drug companies are out to make money with regard to HT. But the situation should not be reduced to a one-dimensional picture of corporate greed. One must also acknowledge that pharmaceutical companies have invested a great deal of time and money to find ways to enhance quality of life, combat diseases, and save people from early death through therapeutic innovations. Many individuals, doctors, scholars, researchers, and care givers have contributed substantially to the growth of biomedical knowledge from within pharmaceutical companies, or with research funds provided by them.

But financing that research requires a lot of funding, and even not-for-profit pharmaceuticals require a healthy income to function. During a peak period in the 1990s, advertising with regard to HT on television and elsewhere increased substantially (Katz, 2003). In 2002, Wyeth spent over $28 million in consumer advertising promoting HT (Katz, 2003). The campaign depicted menopause as a deficiency disease that

could be cured by replacing the hormonal milieu (e.g., McCrea, 1983; Martin, 1988; Watkins, 2002; Meyer, 2001; Elson, 2005). Managing menopause remains a major profit center for the pharmaceutical industry (Dukes, 1997; Moynihan and Cassels, 2005), and exploiting myths of *Feminine Forever* remains a central advertising ploy (Scott et al., 2004; Coney, 1994). As one colleague put it "The Lauren Hutten ads, using a former fashion model, were really incredibly influential on a lot of women. She was respected by many women as a bit quirky and independent (everyone remembers her refusal to fix the gap in her teeth), as well as being thought very hot." (Kate Mertes, August 2006; personal communication).

In fact, over the last 20 years, there has been an explosion in advertisements for HT, always using, of course, women who appear to be quite young and fit (Katz, 2003; Whittaker, 1998). This explosion coincides with the easing of FDA regulation of pharmaceutical advertising and with the rise of direct consumer advertising, as well as with the recognition of the profitability of products such as Premarin (Watkins, 2001, 2002). For 2001, Wyeth alone reported global sales of Premarin of more than $2 billion, a number that fell to $880 million in 2004.

An advertising campaign directed at physicians that spanned a number of decades was generated by Wyeth for Premarin, first discretely by representatives, then at conferences, then directly and en masse to the physicians' offices. There are diverse kinds of estrogenic and progestin compounds that have been used in HT studies (see Table 1.2). However, the most widely known and certainly the one most often prescribed in the United States is Premarin (Watkins, 2001; Moynihan and Cassels, 2005). Wyeth donated Premarin for both the Heart and Estrogen/progestin Replacement Study (HERS) study (which it also supported in other ways) and Women's Health Initiative (WHI) study (Rossouw et al., 1995). Such donations have helped to further research, but at the same time they have circumscribed its results by limiting its parameters: in this case, by predetermining the type of HT that would be studied.

Pharmaceutical companies (or their products) penetrate our lives, and their promotional activities permeate our decision-making with regard to treatment options (Angell, 2004; Collier and Iheanacho, 2002). A massive amount of advertising was deployed as companies sought ways to induce women and physicians to be interested in HT (Palmlund, 1997; Dukes, 1997). Diverse forms of visual imagery, including media attention, was, and still is, produced to lure both physicians and patients (Scott et al., 2004; Andrist, 1998). The advertising reflects our desires: to stay young, to remain healthy, and to retain sexual desirability (Watkins, 2001, 2002).

Physicians report that they are not comfortable with the way they are marketed to by pharmaceutical companies (e.g., Shaughnessy and Bucci, 1997; Morgan et al., 2006; Chew et al., 2000), but they nevertheless respond to it in a number of ways, depending on the category of advertising. Studies suggest that direct marketing to both women (with regard to HT and other pharmaceutical products) and physicians does influence drug prescription practices (e.g., Avorn et al., 1982; Katz, 2003; Chew et al., 2000; Ubel et al., 2003). Physicians get a vast amount of their information about HT from direct marketing by pharmaceutical representatives (Griffiths, 1995; Power, Rossouw, and Schulkin, 2007), and these representatives are also a major source of gift giving to doctors, which is thought to influence physician behavior and represent

conflicts of interest (e.g., Dana and Loewenstein, 2003; Wazana, 2000; Gibbons et al., 1998; Blumenthal., 2004; Studdert et al., 2004).

Consider one study: Morgan et al. (2006) presented obstetrician–gynecologists with four scenarios describing hypothetical interactions between doctors and pharmaceutical industry representatives. They were asked questions related to the ethical appropriateness of the interaction and how they would respond in such a situation (see Fig. 1.3). The scenarios are listed below:

> Doctor A has been offered a lunch meeting with a pharmaceutical representative. The representative provides a buffet lunch for the doctor and staff at the expense of the company. During the lunch, the representative will introduce the company's new drug, hoping that doctor A will prescribe it.
>
> Doctor B was recently visited by a pharmaceutical representative, who gave the doctor information about one of the company's new drugs. The representative offered the doctor free samples of the drug, for the purpose of distributing to patients free of charge, hoping that doctor B would prescribe the company's drug.
>
> Doctor C was contacted by a pharmaceutical representative who has offered the doctor an anatomical model for the examination room. The model has a monetary value of a little under US$100, and has some patient benefit. It bears the name of one of the company's new drugs, which the representative hopes the doctor will prescribe.

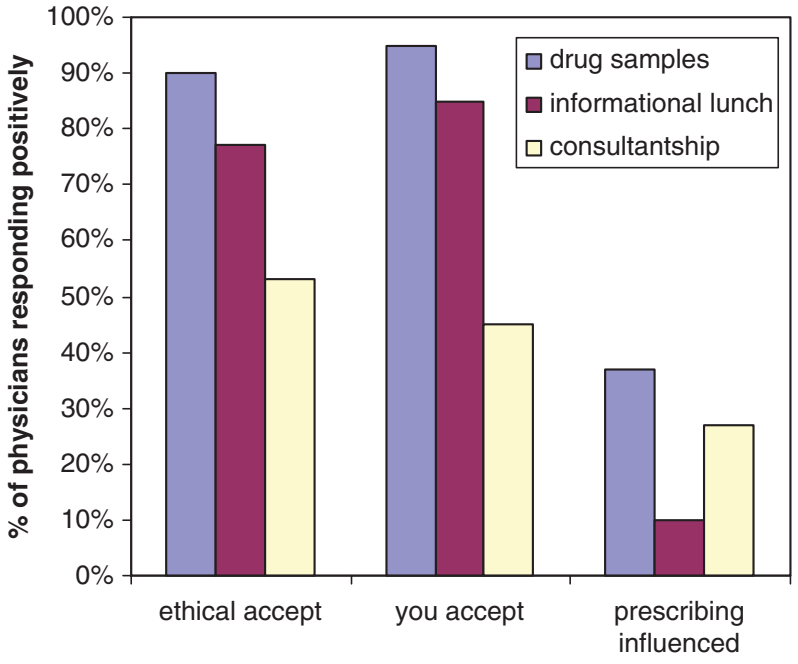

Fig. 1.3 Percent of physicians agreeing that it is 'ethical to accept', they 'would accept', and their 'prescribing would be influenced were they to accept' drug samples, an information luncheon, and a lucrative consultantship (Adapted from Morgan et al., 2006.)

> Doctor D has had a long-standing relationship with a pharmaceutical representative and has been informed that he or she is a "high-volume prescriber" of the company's drug. During a visit, the representative offers the doctor an invitation to sit in as a consultant on a market research meeting. The pay for this is lucrative, although in line with what other companies pay doctors for the same service.

Morgan et al. (2006) found that the majority of obstetrician–gynecologists (92%) reported that they believed it was ethically proper to accept free samples of a new drug from a pharmaceutical representative. Approximately three-fourths of physicians felt that accepting the lunch (77%) and the model (75%) were ethically proper, whereas even fewer physicians (53%) thought it ethical to accept a well-paid consultantship with a company for which the doctor was purportedly a high-volume prescriber of their drugs. A third of the physicians thought that acceptance of free samples might influence the prescription of a drug, yet almost all (96%) respondents said they would probably accept free samples. When asked whether pharmaceutical gift-giving should be regulated, the majority (74%) said that it should. Interestingly, obstetrician–gynecologists reported that "the average physician" would be more likely than themselves to be influenced and to accept the item. Whether this reflects a cognitive bias about one's own behavior being less influenced than that of others is an interesting question (Dana and Loewenstein, 2003), and a reflection of a more general cognitive dissonance and self-deception bias in decision-making. However, those more likely to agree that physician behavior should be regulated with regard to gift-giving were also less likely to accept gifts.

Significantly, 94% of respondents reported that they distribute the samples to patients because of the patients' monetary needs, in addition to building a good relationship with their patients (60%). However, doctors are perhaps more likely to give out samples simply because they have them available. In another study, Morgan and Schulkin (2006) found that physicians who had antidepressant samples available were more likely to indicate treatment with antidepressants than those physicians who did not have samples available.

The conflicting perspectives are apparent. Physicians are concerned about being influenced on the one hand, and trying to manage a practice on the other. Almost two-thirds (66%) of doctors were familiar with the ACOG guidelines related to relationships with the pharmaceutical industry. Those physicians who were familiar with these guidelines were significantly more likely to agree that they would probably or almost surely accept the consultantship, but not the samples, lunch or model. Further, when physicians were asked whether their patients inquired about a prescription product after an advertisement to the patient, the majority (98%) said they did. And when asked whether direct advertising and consumer marketing was biased, 74% said that it was. Again, physicians are wary about the marketing (Morgan et al., 2006), yet clearly influenced by it. Amidst this worry about marketing are the increased burden of little time, chronic anxiety about lawsuits, and pockets of ambiguity regarding the efficacy of clinical trials and treatments with HT (Power et al., 2006a).

Physicians are also in conflict regarding consumer advertising directed at patients (Lipsky and Taylor, 1997). Interestingly, however, in a study of the effects

of the media on women's decisions about HT (Andrist, 1998), the detection of uncertainty and confusion in what the media reported about hormone therapy reinforced women's doubts about HT rather than encouraging them to take it. This fits the more general findings that status quo effects (staying on the same course, not changing) often appear in contexts of conflict (Baron, 1988, 2003).

Medical societies promote codes of ethics that highlight a range of forms of conflict of interest that potentially undermine patient care, including those from pharmaceutical advertisements (Coyle et al., 2002). In the Morgan et al., study, most physicians (66%) were aware of guidelines for physician–industry relationships, which stress that "physicians have an obligation to go beyond the information provided through advertising or other marketing strategies in selecting the best product for care of the patient" (ACOG 2002). In a follow-up study Anderson et al. (2007, unpublished observations) noted that those physicians that were familiar with ACOG guidelines were less likely to deviate from recommended interactions with pharmaceutical representatives. Medical practice, at many levels, is alert to the problem, and has condemned a number of forms of medical transgressions linked to these issues (e.g., American Medical Association guidelines, 2005, ACOG guidelines, Accreditation Council on Continuing Medical Education on gift giving, 2004). Many medical associations provide guidance with regard to gift giving and its resultant dangers (Coleman et al., 2006).

But whether one likes it or not, drug companies still reach us in diverse ways, and their way is not always in our interests. It is a powerful industry, battling pressures for information transparency amidst profit motives. Motivations to compete fluctuate, perhaps encouraging us to look the other way if the data are not consistent with the product's selling points (Angell, 2004). For pharmaceutical companies, obtaining access to the physicians, getting the physicians invested in the product, and then, in the end, selling the product to the patients is imperative. Hormone replacement therapy has been actively and directly promoted by pharmaceutical representatives to physicians, and more generally, marketing tactics to physicians and patients result in physicians' mixed feelings about the advertising and conflicts of interests that pervade this interaction (Rodwin, 1993; Lipsky and Taylor, 1997; Morgan et al., 2006; Blake and Early, 1995; Chew et al., 2000). On the other hand, the pharmaceutical industry invests billions of dollars (Collier and Iheanacho, 2002) in valuable biomedical research. It is in everyone's interests to make the process of physician interaction with pharmaceutical companies as transparent and medically appropriate as possible.

That transparency requires an evolving sensibility of the language of human rights, including patient rights (e.g., Macklin, 1999; Brody, 1998) and women's rights (e.g., Macklin, 1994; Wolf, 1996; Sherwin, 1996; Tong, 1996; Mahowald, 1996; 2000), and embraces a "right to know" what is in the product, as well as the pros and cons of using a particular product. The right to know is at the heart of taking responsibility for our decision-making (Sarokin and Schulkin, 1991), and underlies, in part, the concept of informed consent (Faden and Beauchamp, 1986; Murphy, 2004) so important to patient knowledge about medical products, including

estrogenic compounds (Watkins, 2002). It is the responsibility of the producers of products, including hormone products, to indicate what is in the product and what its dangers are (Angell, 2004). Still, seductive advertising is an omnipresent reality, and how many unbiased and fully educated expert physicians or consumers are there?

1.6 Recurrent Controversy and Confusion

Three major studies, and any number of smaller ones, conducted since the use of HT became widespread among women in industrialized countries, continue to raise concerns about the effects of hormone therapy. What became known as the Nurses' Study here in the United States was centered on broad based observational studies. Most of the research subjects were nurses, hence the name. The Nurses' Study began in the mid-1970s and aspects of it still continue today (Hankinson et al., 2001). Its aim shared with a number of other studies here and elsewhere around the world, was a comprehensive investigation into what enhances and what harms women's health. At the time of its inception, there was a perceived need to conduct studies devoted to understanding women's health and to promoting good health in women.

The HERS (Heart and Estrogen–Progestin Replacement Study) was a randomized double-blind control study of 2,763 postmenopausal women in outpatient and community settings at 20 US clinical centers over 4 years, with the initial results published in the *Journal of the American Medical Association* in 1998 (a follow-up study, HERS II, was released in 2002). Its objective was to determine if estrogen plus progestin therapy altered the risk for coronary events in postmenopausal women who already had heart disease.

The Women's Health Initiative (WHI), run by the National Institutes of Health (NIH), was launched in 1991 and consisted of a set of clinical trials and observational studies, which together involved 161,808 generally healthy postmenopausal women. The hormone trials included an estrogen plus progestin and an estrogen alone study. WHI, aimed at analyzing the relationship between HT and a wide range of potential risks and benefits, has always attracted considerable attention and respect because it has involved such a large number of subjects (see Chapter 3).

These studies, and many other smaller trials, have alerted both the public at large and physicians in particular to the ramifications of hormone therapy following its widespread use since the 1970s. These concerns center around four major areas: breast cancer, heart disease, ovarian cancer, and bone health.

Breast Cancer: Studies as early as the 1940s raised concerns regarding risk for breast cancer in women on HT, and modern trials have not ameliorated those worries. Despite positive results in some research in the 1990s, overall results are decidedly problematic. These include several studies, begun during the 1970s and 1980s with follow-up into the 1990s, that presaged the HERS and WHI studies. The findings of all these studies suggest that women on HT are more vulnerable to breast cancer;

importantly, the longer the time on HT, the higher the vulnerability (e.g., Colditz et al., 1995; Persson et al., 1996; Sellers et al., 1997; Stanford et al., 1995, see also Bush et al., 2001).

Breast cancer is a leading cause of death among women. One observation noted in the Nurses' Study was the association between excess weight and breast cancer. Another risk factor that was noted was the use of replacement hormones for 5 years or more. (Women on HT for less than 5 years did not appear to be at increased risk for breast cancer.) Further, the increased incidence of breast cancer associated with HT identified in the Nurses' Study was higher among women on both estrogen and progestin compared to estrogen alone.

Cardiovascular Pathology: The Nurses' Study found a weak but elevated risk for strokes among women on HT, and also found that HT provides some protection from heart disease (e.g., Stampfer et al., 1985; Grodstein et al., 2006). However, this finding has since been challenged (Wilson et al., 1985). The Nurses' Study has always had problematic aspects. It was not a randomized control study, and there was a great deal of self-selection bias built into its recruitment methodology (Hankinson et al., 2001; Rossouw, 2005; Barrett-Connor et al., 1994; 2005). Nevertheless, its original optimism regarding HT and cardiovascular protection echoed general beliefs at the time as well as the results of several other contemporary observational studies (e.g., Stampfer and Colditz, 1990). But the HERS study disputed that belief. HERS looked at the effects of estrogen/progestin on cardiovascular disease outcomes (Grady et al., 2002) and showed that there was no overall reduction in risk of coronary heart disease (CHD) events among postmenopausal women. In fact, in the hormone group, the research findings suggested a higher risk of CHD, particularly during the first year of treatment.

WHI has provided somewhat confusing evidence. In this study, subjects were randomly assigned to receive conjugated equine estrogens (0.625 mg/day) plus medroxyprogesterone acetate (2.5 mg/day) or placebo (see Chapter 3 for more information). A number of measures for CHD (e.g., total cholesterol and body weight) showed significant improvement with HT use. However, HT use also resulted in a significant increase in the risk for CHD in the first year, and no benefit overall. Participants showed a significant increased risk for nonfatal myocardial infarction with HT use, and there were no positive effects of HT use on revascularization, angina, or congestive heart failure. While the study found an improvement in cholesterol levels, the HT effects were small. Two other measures of CHD were negatively affected by HT use: triglycerides and systolic blood pressure both significantly increased. These might indicate a biological mechanism for the negative effects on health from HT use, especially among older women who might be at increased risk from stroke. In addition, the breakdown into decades from menopause, used to report study results, would not appear to be the most biologically relevant time scale.

Ovarian Cancer: The objective of another study, with subjects drawn from the Breast Cancer Detection Project (Lacey et al., 2002), was to determine whether using estrogen only or estrogen in combination with progestin would increase the risk of ovarian cancer. This study was a mammography screening program conducted

at 29 US screening centers between 1973 and 1980 by the American Cancer Society and the National Cancer Institute. A follow-up study consisted of four phases and lasted until 1998. Lacey et al. found significant associations between HT use and the incidence of ovarian cancer in the sample. In addition, risk increased significantly and consistently with increasing duration of use. Among the 44, 241 postmenopausal women who participated in this study, 329 developed ovarian cancer during follow-up. Women on estrogen-only replacement therapy, particularly for ten or more years, were at a significantly increased risk of ovarian cancer. Women who used short-term estrogen–progestin only, however, were not at increased risk by the end of the follow-up period. One quarter of the women who developed ovarian cancer reported breast or ovarian cancer in first-degree relatives. Women who were older, had a surgical menopause, or were younger at menopause were more likely to use HT. The evidence in other studies is even more impressive in establishing the HT risk for ovarian cancer and breast cancer (see Chapter 4).

Protection of Bone: The time period of several years following menopause is one of rapid metabolic and physiologic adaptation. Bone loss in women is accelerated for about the first 5 years following menopause, but then reverts to a pattern of slow loss identical to that of similarly aged men. A major benefit of HT use immediately after menopause is to delay this period of rapid bone loss. HT use after this period does not reverse this effect of menopause, although it does slow the gradual decrease in bone density that all aging persons experience. It is possible, and indeed likely, that other metabolic and physiologic adaptations besides bone mineral metabolism occur in the first years postmenopause. Attempting to return a woman's hormonal milieu to the premenopausal state after these adaptations have occurred may not have the same effects as prolonging her premenopausal state.

One fact remains constant: women on HT are less likely to experience bone fractures due to decreased bone mineral density. Indeed, even the latest studies of women on estrogen and progestin from the Women's Health Initiative have confirmed and extended this fact. In a study by Cauley et al. (2003), with over a thousand women participating, bone mass increased over 3% in those women on HT compared to placebo controls. Thus a number of investigators might and do argue that HT as a whole is beneficial to women when taking into account enhanced quality of life by the reduction of bone fractures.

1.7 Is this the Demise of Hormone Therapy?

Large population-based studies such as WHI were intended to clarify the issues surrounding HT and women's health. But many questions still linger, and the findings of increased health risks induced by HT underscore the need to address these questions (e.g., Canadian Conference on Menopause, 2006). The historical HT prescription rates over time are presented in Fig. 1.4. Prescription rates rose steadily through the late 1990s and into early 2000 and began to decline after the negative reports emerged (Hersh et al., 2004; Majumdar et al., 2004; Haas et al., 2004; Helenius

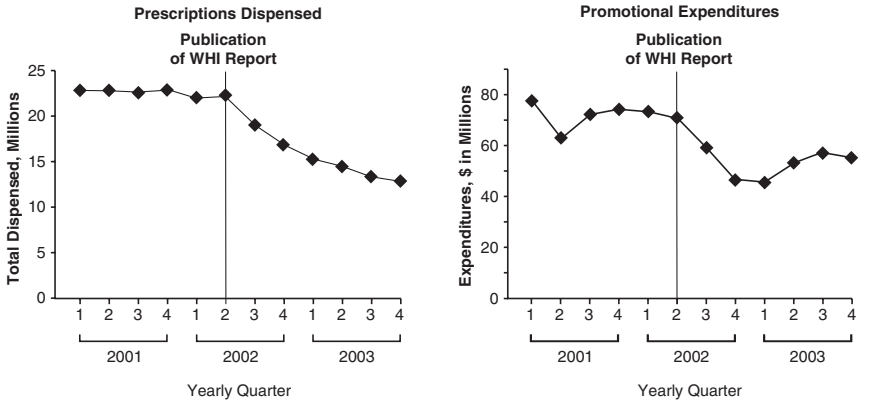

Fig. 1.4 Hormone therapy and advertising in the United States before and after WHI studies (Majumdar et al., 2004. Reproduced with permission.)

Table 1.3 HT timeline and its link to a subset of physiological/medical features

1920–1939
Searle introduced estrogen for symptoms (1928)
Estradiol synthesized (1938)
1940–1949
Premarin introduced (1942)
Albright finds the low estrogen-osteoporosis link
1950–1959
HT prescribed (but not often) for hot flashes
1960–1969
Wilsons promote HT to prevent "the tragedy of menopause"
Oral contraceptives introduced to regulate menses and prevent pregnancy
Clinical trial of estrogen and heart disease begun in men
1970–1979
Men's HT trial stopped because of early excess clotting and cardiovascular disease
Side effects of oral contraceptives recognized, especially clotting and strokes
Excess endometrial cancer risk with estrogen recognized
Progestins added to estrogen therapy in women with an intact uterus
1980–1989
Deluge of epidemiological studies suggesting that HT reduces heart disease
1990–1994
Meta-analysis suggests that heart benefit of HT would exceed possible risks
Many groups recommend that HT be offered to all women to prevent heart disease
FDA Expert Advisory Committee almost unanimously approves heart disease prevention label for unopposed HT (recommendation never activated)
PEPI trial of HT and CHD risk factors begins
Hulley obtains funding for HERS clinical trial (first participant 1993)
NIH sponsors WHI trial
Premarin is the most widely dispensed prescription drug in the United States (1990–95)

(continued)

Table 1.3 (continued)

1995–1999
PremPro, the first combination HT pill, introduced
PEPI results confirm improvements in LDL and HDL cholesterol
HERS (1998) reports early increased heart disease risk
2002–2003
WHI reports increased heart disease, stroke, and breast cancer, cognitive decline, no effect on well being, the small risks exceed smaller benefits
WHI continues unopposed estrogen arm
FDA requires black box label for all postmenopausal estrogens with or without progestin
2004–2006
WHI cancels unopposed estrogen arm

et al., 2007). Some researchers have suggested that new data indicating a decrease in the incidence of breast cancer, and a reduction in new cases of cancer overall, may correlate directly with a sharp decline in the use of HT since 2003. Many of the issues that pervade HT use have been expressed before: whether to use HT or not, the perception of the danger, the disputes over how HT is presented to physicians and their patients. The same phenomena recur, but there has been little resolution and controversy continues. To use or not use HT, that remains the question. This does not make it easy for women to decide whether to go on HT or not, or for their physicians to advise them reliably. It is therefore crucial to take a long, hard look at the decision-making process itself.

The history of HT stretches in one historical reading at least back nearly 70 years (Houck, 2002; Seaman, 2005). Table 1.3 is a partial list derived from Barrett-Connor, 2003.

Chapter 2
Demythologized Human Decision-Making

In the twentieth century many have come to accept that the great bulk of human reasoning at its best is rich in uncertainty (e.g., Dewey, 1929, 1960); yet much of medical science is focused on a search for certainty, a search reliant on statistical methods that themselves do not remove uncertainty. The issues that surround HT reflect our age, in which statistical reasoning is integrated into our decision-making. When statistics were first deployed to keep track of state business (births, deaths and so on), the methods were relegated to a second-class category of knowledge (Hacking, 1990). Statistics, while of great practical use, was not regarded as *real* science, certainly not in the class of the emerging fields of mathematical physics – the kind of science represented by Newton that awed diverse thinkers, including Voltaire.

The Enlightenment was riddled with the sense of certainty that science would provide indubitable truths. It took several centuries to demythologize the notion of scientific reason as perfect and unbiased – a science in which deductive reason would predominate, and in which inductive exemplars would be the cornerstone of the knowing process. The measure of what it meant to *know* displayed a constellation of scientific certitudes, to replace the old theological certainties. The Enlightenment was, in many instances, substituting one set of principles for another, one set of foundational anchors for another. What remained the same was the search for certainty (see Dewey, 1929, 1960).

Our conception of knowledge would change slowly in the ensuing centuries, culminating in a sense in which grappling with uncertainty would come to equate with dealing with probabilities, and defining those probabilities would become paramount. The legitimation of knowledge was to be couched, and now is couched, in terms of likelihoods. The language of statistical probability would meld into an earlier predilection, built into our brain, namely the evaluation of risk. Survival of our species depends on adaptive skills such as predicting whether it is safe to go to a water hole to drink or whether predators are likely to be present. Statistical reasoning is something we come prepared to do as a species. It is a piece of the cognitive architecture that reflects our evolutionary ascent and cognitive adaptation.

The other piece of cognitive adaptation is the ability to systematically order what we know, to organize and prioritize what is related and important. Grouping together significant or likely outcomes is a fundamental part of the knowing process; linked to our own evolution and to the evolution of the scientific process. Having a predilection

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to understand the world in terms of likely events, and having the ability to orchestrate the storehouse of knowledge in systematic ways, does not mean that we always or even usually do it well. Medical decision-making, like many other areas of life, is a grab bag of countless grey areas. This is most certainly the case with regard to HT. In this chapter I will focus on how we make decisions in a medical context, and on how we might improve that decision-making process.

2.1 Medical Education and the Culture of Scientific Decision-Making

Claude Bernard (1865, 1957), the great nineteenth century physiologist articulated the new world of experimental medicine and physiology in the middle of the nineteenth century. In his treatise, Bernard hoped that medical decision-making would be based on the new sciences of physiology. Medical students would be exposed to the sciences of the laboratory and the gathering of evidence, and science would be demythologized for practicing physicians by their exposure to the experimental methods that were then emerging.

The origins of placing medical decision-making within the culture of science were crystallized in the first part of the twentieth century with the publication of the Flexner Report (1910). The focus of Abraham Flexner's study was to reinforce that medical students, medical schools, and professors need to understand the culture of science, the laboratory state of mind, and the sense of experimentation (e.g., Peirce, 1878, 1898; Hanson, 1958; Hacking, 1990). The point was to demythologize science, to make it accessible to physicians, and bring them into the culture of discovery, science and knowledge. In other words, the goal of the Flexner Report, and of the reforms it catalogued and stimulated, was to ensure that US medical education be based in the culture of scientific research, to bring the culture of scientific fact-finding and reasoning to the practicing physician. Medical decision-making based on scientific evidence was to be the staple of medical practice and medical education.

The nudge toward rendering medical decision-making in line with scientific evidence is a cultural process (e.g., Dewey, 1916; Kuhn, 1962; Galison, 1988; Gigerenzer, 2000; Goodman, 2003). In the nineteenth century, the cultural imperative was to integrate the diversity of knowledge of physiology with medical treatment; in the twentieth and twenty-first centuries, it is about bringing the justification of medical decisions in to line with the evidence, using graded criteria to determine the value of the science. In addition, today the imperative concern is understanding the constraints on decision-making, and the biases or heuristics that permeate the decisions that individuals in most walks of life make, including physicians.

Two fields have had a significant impact on medical decision-making: one is a field that grew out of the decision sciences, the other is tied to epidemiological analysis (e.g., evidence-based guidelines, Schulkin, 2000). Decision sciences have uncovered a broad array of biases and heuristics in human decision-making, while epidemiology has evolved into what we now call evidence-based medicine (Sackett, 1994).

Table 2.1 Major differences between evidence-based medicine and medical decision-making

Issue	Evidence-based medicine	Medical decision making
What are the core problems?	Insufficient knowledge	Combining data and values consistently
	Keeping up with the literature	Judgment limitations
Solution	Critical appraisal	Decision tree
	Answerable clinical question	Sensitivity analysis
Formal models	Unimportant	Essential
Decision processing costs	Low	High
Utility assessment	Largely ignored	Core research issue
Cost-effectiveness analysis	Largely neglected	Major application
Decision psychology	Largely ignored	Core research issue

Both fields have at their foundation attempts to facilitate medical decision-making and thereby locate a decision under the rubric of bad, good or better science (Elstein, 2004; Baron, 2006). Both underlie how we will evaluate the HT experimental literature.

But there are major differences in the focus and orientation of these two disciplines (see Table 2.1, Elstein, 2004).

2.2 Decision Sciences and Medical Decision-Making

The decision sciences developed within the broader context of the cognitive sciences. Inquiry in the decision sciences is a formal and scientific approach to understanding human decision- making (e.g., Newell and Simon, 1972; Kahneman et al., 1982; Baron, 1988, 2003; Elstein, 1976). The underlying value, or utility, of a decision is determined by analyzing its consequences and the probability that a particular decision is correct or not.

A critical factor to consider in decision-making is the presence of biases. One way to understand what some call biases (Baron, 1988, 2003) and others call fast and ready heuristics (Gigerenzer, 2000) is to recognize that they are responses that we impose on our orientation and analysis of events. Thus the effort to understand biases in human decision-making requires developing an understanding of statistics, probability, and utility theory, and the recognition that human judgments are fraught with misjudgments about statistical probability (Kahneman and Tversky, 1982). Some biases can, in some contexts, be corrected by scientific evidence (probability distortions can be corrected by further evidence, for example), but other biases are more difficult to correct for (Gigerenzer and Selten, 2000; Gigerenzer, 1999). Recognition of this truth, a formal set of analytic tools, and an awareness of heuristics in guiding human decision-making enhances normatively understood human decision-making and demythologizes human problem solving. The relevance of this for understanding HT is important.

The heart of this discipline is that decision-making is fraught with inherent "framing effects," or biases in reasoning (Kahneman et al., 1982; Gilovich et al., 2002;

Gigerenzer, 2000). This is neither good nor bad in itself. Although "you are biased" is usually considered to be a pejorative statement, meaning that you see only one side of something, a more valid way to consider bias is to see that our perspective provides our orientation, the direction from which we see things (Gigerenzer, 2000).

It is important for today's clinician to be able to weigh evidence, recognize biases, and reach an informed decision; this is a central aspect of clinical reasoning. Cognitive biases can be quite persistent and therefore are unlikely to be totally eliminated (Baron, 1988, 2003; Kahneman et al., 1982). Instead, the goal should be to help physicians become sufficiently aware of the influence of cognitive biases to avoid being fooled by their own perspectives (Gigerenzer, 2000).

The decision sciences literature is rich in detail, depicting the diverse ways in which we overvalue or undervalue variables (e.g., whether HT will result in breast cancer) depending upon our orientation to events, the starting points or frames of reference from which we begin (Gilovich et al., 2002). This also holds for memory of events for which one associates rewards or hedonic value, overvaluing whether, for example, one would be happier living in California versus somewhere in the mid-west, regardless of whether the individual actually lives in California or the mid-west (Schkade and Kahneman, 1998).

It is necessarily true that we see things in relation to a background framework, that seeing is always from a particular orientation (e.g., Peirce, 1878; Hansen, 1958; Kahneman et al., 1982). The question is whether the orientation can be detected, is testable, can be criticized, challenged, experimented with, replicated and expanded. In this regard, scientific inquiry must be seen as an orientation like others. Biases permeate any endeavor and must be recognized, examined, and taken into account in decision-making. Moreover, the recognition of biases functions by what social scientists call "sensitizing concepts," that is, the biases themselves provide a context that helps us understand how we decide.

A formal part of the decision sciences is quite rigorous (e.g., decision-analytic trees and the logic of decision-making), and these tools have proved useful in some real-world contexts (Elstein, 1976, 2004). Decision science is closely tied to statistics and psychology and is an attempt to make transparent the decisions that we make (Baron, 2006). But it is misleading to think that the decision tree is anything more than a tool that assists us in the myriad ways in which we turn away from facts, not wanting to hear, see, or understand them. The decision sciences nudge us to acknowledge the biases that inhere (and that may or may not be a bad thing) and then to work to prescriptively correct them.

Consider one study: Baron, Schulkin, and Kunreuther (1990, unpublished) conducted an experiment in which subjects were exposed to several contexts wherein the likelihood of greenhouse gases might contribute to global warming. Uncertainty description was either highlighted or not. The facts were the same across groups, the emphasis on uncertainty was varied; willingness to act to alter greenhouse gases was the measure. What we found was that prior beliefs mattered for how the greenhouse emissions on global warming was understood and taken as part of their judgment. For groups in which uncertainty was emphasized, the effect was that whatever the original position one believed the data reinforced their original position; whether to act or not act. Both points of view were somewhat

justified. On the basis of costs, action might decrease future costs and harm, and on the basis of inaction, the costs of premature action might outweigh the potential costs to other human affairs. In the end, action or inaction, from viewing the same data, reflects the emphasis on uncertainty (Baron and Schulkin, 1995). This may have relevance for considerations about HT in which there is a fair amount of uncertainty. In other words, a sense of uncertainty can facilitate people sticking to the status quo, namely their original position.

There are diverse forms of biases. One of them is this same "status quo" effect: we have a tendency to stay with what we know, particularly when something is ambiguous (Baron, 1988, 2003). Another form of bias is that something is better if it is made by the body than if it is synthesized. Endogenous estrogen by nature, defined by this view, has to be better than anything we could produce in the lab, although in fact right now there is no real evidence to indicate whether this may or may not be true (NIH, 2005). Then there are a wide range of biases that reflect the frameworks that we impose, our statistical over- and underestimation, what we are able to imagine, and diverse forms of correlational confusions (Kahneman et al., 1982), to name a few kinds of inferential biases in our thinking.

A realistic way in which to understand our many intellectual predilections is to recruit them pragmatically to enhance human decision-making, including, but not only, cost benefit analysis for the decisions that we make (cf. Sunstein, 2002; Drapkin–Lyerlyt et al., 2001). One also needs a framework in which our appraisals are to be understood: the values that inhere in our judgments about events (Dewey, 1939; Neville, 1974; Moreno, 1995), one of which is how we understand, and our valuational judgments. Valuational judgments are at the heart of our appraisal systems, the cognitive capacity that reflects our interests, and the cultural milieu in which we live (Dewey, 1939). In other words, what we value underlies the decisions we make about HT, and it is important to link those values to self-corrective inquiry.

The origins of decision science are bound to statistical analysis, the determination of the utility of a decision in the likelihood of considering the outcomes (Peirce, 1898, 1992; Gigerenzer, 2000). And regardless of whether one is a physician, patient, bus driver, or rocket scientist; we are vulnerable to diverse kinds of errors in reasoning (Kahneman et al., 1982, 1998; Baron, 1988, 2003) and need to work to self-correct for them.

2.3 Physicians, Decisions, and Hormone Therapy

Because balancing tradeoffs between desirable and non-desirable effects is an everyday activity of physicians, they need a formal way to evaluate their decision-making. Experimental design, controlled variables, and predicted outcomes are the staples of modern science. Studying decision-making for medical purposes gained legitimacy in the 1970s and 1980s in a collection of studies of decision-making under uncertainty and risk, which are the conditions of everyday decisions (e.g., Kahneman et al., 1982).

The results of the decisions we make emphasize the diverse ways in which possible errors in reasoning occur. Of course the reasoning may not be the error at all, but reflection on how we reason is a prelude to self-correction. This process helps elucidate and prescribe normative goals that correct, if need be, or make clear how we reason about a particular matter (Baron, 1988, 2003). This matters in the context of HT, where errors in reasoning may in fact be commonplace, and where the decision to suggest HT and the decision to take HT might increase risk factors, have no positive effect, or simply have a negligible positive effect on a woman's general health.

In one study, titled "Physicians' Judgments about Estrogen Replacement Therapy for Menopausal Women" by Holzman et al.(1984), the goal was to examine the prescribing decisions of gynecologists and family physicians through a series of clinical vignettes and to determine how several factors could be weighed and combined in representing their decisions to prescribe or not to prescribe estrogen. Endometrial cancer risk, osteoporosis risk, and the severity of vasomotor symptoms were three of the factors. The fourth was whether or not the patient was on estrogen (current therapy), because some physicians might be reluctant to disrupt an established regimen. The two major factors determining whether a physician would suggest HT were the estimated risk of carcinoma of the endometrium and the described level of severity of vasomotor symptoms. The results indeed indicated that gynecologists were prone to perceive an increased likelihood of cancer risk in the context of HT ($P < 05$).

Interestingly, physicians' judgments of the likelihood of being sued if they prescribed estrogen and the patient developed cancer were not significantly related to their likelihood of prescribing HT. The differences among physicians in their likelihood of prescribing HT were not related to specialty, although there was a statistically significant interaction (cancer risk vs. vasomotor symptom severity) for gynecologists ($P < 05$).

Most physicians reported that they would be influenced by the patient's reporting of the severity of vasomotor symptoms and the risk of developing carcinoma of the endometrium, and, as one might expect, some physicians placed more weight on one factor than the other. Such appraisals will reflect the larger values that pervade the analytic processes (Dewey, 1939; Neville, 1974; McGee, 1999, 2003). This study shows that physicians vary widely in their use of estrogen replacement therapy during menopause, but they appear to agree that cancer risk and severity of vasomotor symptoms are the most important considerations in reaching a decision regarding a specific patient.

In the 1980s, when Gerald Holzman and his colleagues (1984) published their study, there were estimated to be about 40 million women who were postmenopausal in the United States. One feature that Holzman et al. highlighted was the legitimacy of prescribing HT for the expression and development of osteoporosis in an aging population of women. This has been a consistent phenomenon reported by numerous physician groups (Rolnick et al., 1999). They noted that almost a quarter of elderly women are vulnerable to bone fractures due to osteoporosis, and they emphasized such factors as family history, life styles, and skeletal frame as important considerations. These physicians also noted that estrogen use was associated with diverse

forms of cancer, and that this vulnerability might be minimized by keeping the dose low, periodic, and linked to progesterone.

Another study, conducted in the mid-1980s, asked physicians and their patients to evaluate a hypothetical scenario in which breast or cervical cancer is a possible, but statistically unlikely, outcome of HT (Elstein et al., 1986). Comparing the responses of the physicians with recommended actions derived from a utility model, not surprisingly, and consistent with other literature (Kahneman et al., 1982), the study suggested that the physicians had difficulty integrating competing factors into a decision that matched to recommended actions. In fact, the results suggested that physicians should reexamine carefully their practice patterns in light of their beliefs, opinions, and orientation. Withholding suggested treatment may be inconsistent with the clinician's own beliefs about the risks and benefits of estrogen therapy and may be guided by the understandable wish to avoid causing rare, but very undesirable, outcomes at the price of exposing patients to far more likely, but somewhat less undesirable, hazards.

Risk aversion regarding breast cancer is a salient issue for both women and their physicians, and despite the low probability of the event there has been enough research done to greatly reduce the prescription of HT over time (Holzman et al., 1984; Elstein et al., 1986). During the mid-1980s, obstetrician gynecologists, family doctors, and internists were less likely to prescribe HT because of the studies that suggested increased vulnerability (see Chapter 4), even if breast cancer was a low probability occurrence. In the 1980s and early 1990s, generally, physicians were less sanguine about HT because of the potential it held to increase vulnerability to cancer (Holzman et al., 1984).

A study designed to examine obstetrics and gynecology residents' judgments with regard to HT (Elstein et al., 1992) identified several strategies used in everyday clinical decision-making for HT in treating postmenopausal women. Elstein et al. investigated the effects of two risk factors, endometrial cancer and fractures because of osteoporosis, on residents' prescriptions of HT. Twelve clinical vignettes were used, depicting postmenopausal women presenting with mild menopausal symptoms: the vignettes varied by three levels of cancer risk (standard, moderate, and high) and two levels of risk of fracture due to osteoporosis (standard and high). This group of residents was more likely to adjust their prescribing behavior in response to higher levels of cancer risk than vulnerability to bone fractures ($p < .05$).

In the next decade, physicians were much more positive about HT (Baron, Holzman, and Schulkin, 1998). When a group of obstetrician–gynecologists was asked about HT in the late 1990s, about 90% reported that they believed it was the correct therapy for perimenopausal symptoms (Baron et al., 1998). The great majority of obstetrician–gynecologists recommended HT to their patients in this period. This is probably due to the fact that in the latter 1990s there had accumulated a number of studies that suggested a wide range of positive effects from taking HT, including reduction of cardiovascular disease, increases in brain/cognitive performance, and reduction of bone demineralization and vulnerability to bone fractures (see Chapters 3 – 5). Bone loss has always been the most consistent result of decreases in estrogen expression during the menopausal period (Heaney et al., 1989;

Power et al., 1999). Diverse studies have demonstrated that HT consistently increases bone mass in menopausal women (see Chapter 4). These positive results may have predisposed patients and physicians to perceive HT more positively than warranted and without enough caution.

2.4 Bias and Medical Decision-Making

Clearly, changes in information affect the decisions physicians and patients make about hormone therapy. But bias in the actual decision-making process also has an enormous effect on medical choice. When the available information is ambiguous, the methodology of our thought processes becomes especially significant. In 1998, Baron, Holzman, and Schulkin conducted a study aimed at investigating decision-making with regard to HT. They looked at four types of physician biases that might impact decisions about HT (Baron, Holzman, and Schulkin, 1998).

First, consider *omission bias* – the tendency to choose to do nothing when there is some probability of harm (e.g., Ritov and Baron, 1990). This may work against HT, because HT seems to increase the risk of breast cancer. That is, even if the increase in the risk of breast cancer resulting from action (going on HT) is smaller than the increased risk of heart diseases and other disorders resulting from inaction (not going on HT), an omission bias would incline people against HT. Thus omission bias is a tendency to choose not to do something when doing something might cause harm, and physicians would be biased against prescribing HT because of the fear of breast cancer.

A second form of bias in decision-making that is relevant to this discussion, *proportionality bias,* is a tendency to consider risk ratios when there are different risk estimates that apply to the situation. Opposition to HT may result from overvaluing the risk of breast cancer and undervaluing the prevention of endometrial cancer. So proportionality bias is a tendency to overvalue or undervalue risk, and because of it, physicians may choose not to prescribe HT for fear of breast cancer, despite the low probability of occurrence.

As noted above, *naturalness bias,* is the view that something natural must be good, while the man-made or synthetic is less good. Physicians might – as one study showed to be the case – perceive man-made estrogenic compounds less favorably than naturally occurring estrogen for HT. Women patients are also quite likely to assume that natural is better. In fact, other studies have shown that when physicians or women are asked which hormones would be less risky, the natural hormones (derived from human ovaries) are consistently preferred to pharmaceutically produced synthetic compounds, (Power et al., 2006a, b; Adams and Cannell, 2001). The results of HT derived from herbs (e.g.,soy) are conflicting (Low et al., 2003; Boothyby et al., 2004). Nevertheless, diverse forms of evidence suggest that both women patients and physicians believe natural hormones are a more valuable tool (e.g., Adams and Cannell, 2001; Geller et al., 2005; Power et al., 2006a, b).

A number of naturalistic fallacies (Moore, 1903, 1968) have been noted in human decision-making (e.g., what is better is more natural). Of course natural objects typically have significance (Dewey, 1925, 1989; Casebeer, 2003). However, it is not axiomatic that if HT is natural it is better. Perhaps studies using naturally occurring estrogens, instead of Premarin, might have produced more convincing benefits. But we do not know that is true, so it is fanciful hand waving. Again, there is as yet no real evidence that "natural molecules" are better than other forms of HT (Sapp 1999; Boothby et al., 2004), and one should note that systematic studies of diverse estrogenic compounds have just not been done.

Nonetheless, all estrogenic compounds should not be understood as being the same, and that should be part of the background discussion that physicians and patients have with regard to HT (Shoham and Kopernik, 2004). The evidence of the effects of HT have not been particularly promising with regard to so-called natural estrogenic compounds (Rasgon, 2006; Canadian Consensus Conference, 2006), though they certainly have not been tested to the same extent as something like Premarin has in the US. There are indeed diverse kinds of estrogenic compounds, and indeed they may have differential effects on some of these end-point outcomes. Thus one variant loosely knotted to a naturalistic fallacy has relevance with regard to HT: because it is natural does not mean it is necessarily right (e.g., in principle a synthetic estrogen might turn out to be quite effective).

Fourth and finally, the *ambiguity effect* is the tendency to avoid an option when information about the probabilities of its consequences is perceived to be missing. Such is the case with the effect of HT on breast cancer. Ambiguity avoidance occurs when there is a perception that the outcome is unclear. Its manifestation in the context of HT would be that both women and physicians avoid making a decision. The result is the same as omission bias – a tendency to avoid making any decision at all – but the cause, avoidance of ambiguity rather than avoidance of harm, is different.

In the Baron et al. (1998) study, in order to examine three of these forms of bias, we asked gynecologists about risk factors and queried them on their advice to patients about HT. The risks we included in this study were: increased breast-cancer risk; increased and decreased osteoporosis risks; severe and very mild symptoms of menopause; increased colon-cancer risk; and increased heart disease risk. The majority of the respondents were aware of the major benefits described in the medical literature, particularly the breast-cancer literature. Many respondents spontaneously mentioned that the findings were conflicting or that they tended to think that the risk was not serious. Many of those who mentioned endometrial cancer also noted that this risk was reduced by the addition of progesterone.

A series of hypothetical questions assessed the various biases. The following item assessed *omission bias*: "Suppose that some new form of HT is generally better than the forms currently used, so the usual choice is now between this new form and nothing. The new form affects the risk of two types of cancer, A and B, which are equally serious." A table then showed that A and B each had a risk of 5% without HT, but with treatment, cancer A's risk increased to 9% and B's risk decreased to 1%, leaving the overall rate unchanged. We pointed out the relevant effects in a table

and asked, "How would these two effects together affect your thinking about recommending this form of HT?" We asked for specific explanations.

To assess *naturalness bias*, we said, "Suppose you need to decide between two forms of HT, identical except that form N uses chemicals that occur naturally in the body, and form M uses human-made chemicals that have the same pharmacological properties."

Finally, to look for *ambiguity bias* we described a situation in which a non-ambiguous treatment had increased the risk of cancer from 5% to 6% in two studies. An ambiguous treatment had resulted in conflicting evidence: one study showed a change from 5% to 3%, another study showed a change from 5% to 9%, and experts agreed that the two studies were "equally well done and equally convincing."

The study then asked for estimates of percentage changes in lifetime risks of breast cancer, colon cancer, heart attack, and hip fracture as a result of taking HT for 10 years, and then for the lifetime prevalence (number out of 1,000) of these conditions in women over 50, and the frequency of deaths (out of 1,000) due to these conditions in women over 50, and the frequency of deaths (out of 1,000) from each cause.

Then we asked, "HT has some benefits in terms of reduced risks. If a patient asked you about alternative ways to obtain some of these benefits, what would you think of doing?" We also asked, "Do you know of any conflicting findings concerning the effects of HT on cancer? If so, what do you make of these findings?"

In the case of omission bias, 18.6% of the respondents opposed the treatment that increased one risk and decreased another equally. For proportionality bias, 20.8% opposed a treatment that doubled one risk and reduced another by a fourth, even though the increase and reduction were the same in absolute effect. For naturalness, 31.2% preferred a natural treatment, despite the fact that the hormones were identical and no evidence suggested that one produced better results than the other. For ambiguity bias, 26.8% opposed the treatment with conflicting results, even though the expectations were the same. Of course, most respondents showed no bias in each case, and some showed the opposite biases. Moreover, many of the respondents who did show bias mentioned such rational factors as the fear of lawsuits.

Respondents who showed more of these biases in general also had less favorable attitudes towards HT overall. With regard to specific biases, physicians who showed proportionality bias were less favorable toward HT generally, as were those showing naturalness bias.

All in all, the physicians who responded to the Baron et al. study clearly demonstrated biases hypothesized to cause opposition to HT – omission (18.6%), proportionality (20.8%), naturalness (31.2%), and ambiguity (26.8%) (see Fig. 2.1). The respondents who showed proportionality bias, naturalness bias, and (less clearly) omission bias were also likely to be less favorable toward HT overall. In the case of proportionality bias, this may result from over-attention to breast cancer relative to heart disease. The relative risk of breast cancer increases almost as much as the relative risk of heart diseases decreases, but heart disease is more common, so the overall change in risk may in fact be greater for coronary pathologies. In fact, in the study proportionality bias correlated with reduced willingness to recommend HT when risk of breast cancer is high.

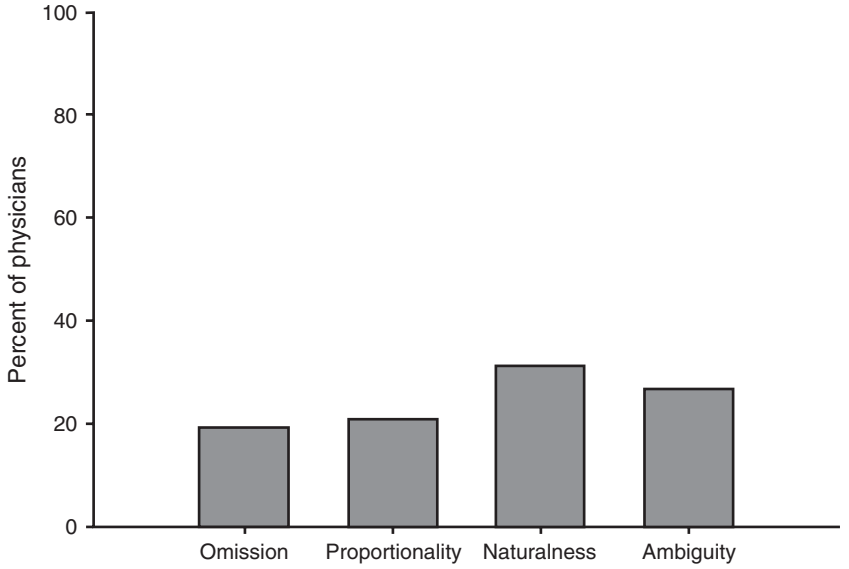

Fig. 2.1 A significant minority of physicians display a variety of biases regarding their prescribing practices for hormone replacement therapy. Data from 1995. (Adapted from Baron, Holzman and Schulkin, 1998.)

When asked about the percentage of hypothetical patients with normal symptoms of discomfort for which HT would be recommended, 75.6% of the respondents said "100%," or all patients. The last two questions, however, asked about recommendations for actual patients, and the results were quite different – the doctors were far less favorable toward HT. Only 18% said they recommended HT to 100% of their patients.

When we asked whether the physicians considered other, unspecified factors, we got 74% negative answers (i.e., no other factors were considered). The few respondents who mentioned anything said they considered the patient's personal history or family history, especially for breast cancer, or the patient's prospects for compliance with recommendations and for follow-up, such as regular breast examinations and biopsies for lumps.

Finally, in response to the open-ended question on conflicting findings about the effect of HT on cancer ("Do you know of any conflicting findings concerning the effects of HT on cancer? If so, what do you make of these findings?"), 69% mentioned the conflict about breast cancer and an additional 7% mentioned conflicting findings without naming the specific cancer. Essentially all of these respondents said that the risks were small (remember, this study was conducted in 1996) and outweighed by the benefits. Many respondents also thought that more research was needed. The reasonable heuristic that a risk factor should go against recommending HT when HT increases the same risk, and vice versa, was employed by many of the physicians. This was strongest for osteoporosis risk, heart disease, and menopausal symptoms (not a risk, but a certainty). It was weakest for colon cancer, and moderately strong for breast cancer.

We examined the relationships between responses to questions about the effects of risk factors on prescribing and beliefs about effects of HT on risks. We might expect that colon cancer risk, for example, would increase the tendency to recommend HT in respondents who believed that HT reduced that risk, i.e., a negative correlation. We found this pattern to be true in the case of colon cancer.

In general, the respondents in 1996 were knowledgeable about the literature and in general favored HT (Baron et al., 1998). They were sensitive to individual differences in risks. They showed the biases of interest – omission, proportionality, naturalness, and ambiguity – and their attitudes toward HT were particularly related to two of these biases, proportionality and naturalness. Of course, the naturalness bias may not be a bias in either direction, because it may turn out that natural estrogen is the one we should use or that a synthetic one we make is much better for what we intended to use HT for. These are empirical issues. The sense of heart disease vs. breast cancer evokes different responses, and therefore judgments about HT decision-making have to be understood within that context (Holzman et al., 1984; Holmes et al., 1987; Lyerly et al., 2001).

In contrast to studies done in the early 1980s that had found that a majority of respondents were opposed to HT for most patients, a majority of the subjects in our study recommended it in all cases. When asked about the benefits of HT, reduction of cardiovascular pathology ranked highest (Baron et al., 1998) (see Fig. 2.2).

These studies suggest that decision-making about HT is vulnerable to diverse forms of decision-making biases (e.g., omission, ambiguity).

2.5 Evidence-Based Medicine and Medical Decision-Making

Evidence-based medicine (EBM) arose from epidemiology, which deals with the logic of research design, the clarification of studies, and the broad assessment of data and the story they tell. EBM has influenced many areas of medicine, and most

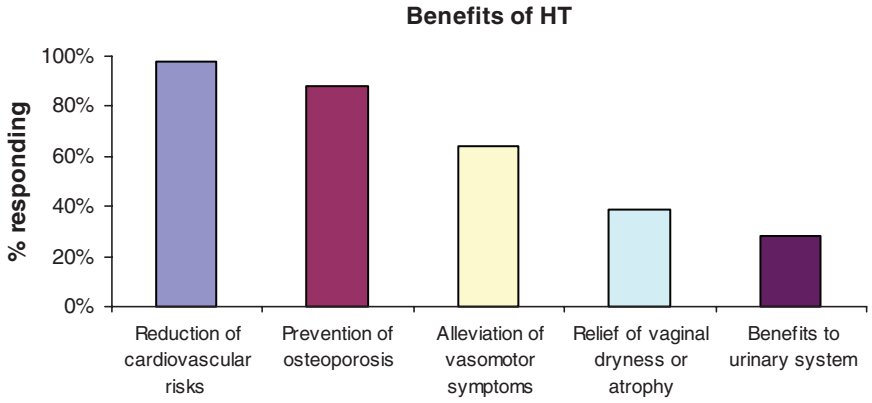

Fig. 2.2 Physicians orientations towards HT. (Adapted from Baron, Holzman and Schulkin, 1998.)

medical specialty societies have used an EBM approach in reorganizing their practice guidelines. Many books prepared for medical professionals have appeared that emphasize evidence-based medicine, but the field still only accounts for a subset of clinical decision-making (e.g., Chalmers, 1988; Guyatt and Rennie, 2002; Sackett et al., 1997; *Evidence-Based Obstetrics*, Jones et al., 2003). In a real sense, the term "evidence-based" is a term that signifies scientific legitimation. The idea that experts would grade information, make it available, and then back it up by whether it meets criteria harkens back to many attempts to legitimate inquiry and place it on a firm footing.

Evidence-based medicine is a more recent attempt to give a scientific foundation to medical decision-making. Its legitimacy derives from scientific rigor in research and the use of research findings. EBM is part of the larger culture of evaluating the glut of information that is available and turning that information into informed choice (e.g., Sackett et al., 1997; Cook et al., 1997). Information is parsed and made manageable. Teams of experts evaluate information to decide how well studies are designed and how strong the evidence is.

The founders of medical epidemiology and EBM sought to find rigorous scientific grounding for medical decision-making by having the decision strictly follow the science (Chalmers et al., 2002). Of course, ultimately the patient makes the decision, but it is the role of the physician in EBM to know the latest science and to communicate those facts to the patient. The key issue, normatively, was to tie the practicing physician to research findings, and the primary measure of validity was to be the randomized control trial and the gradation of evidence with regard to this ideal experiment (Sackett and Brian, 1995; Haugh et al., 1996).

Evidence-based material provides physicians with the ability to understand the findings of diverse randomized control trials. One well-known version of EBM is the Cochrane Library, which evolved to provide health care decisions based on sound logical footing and good science (Cochrane, 1972; Jadad and Haynes, 1998). The Cochrane Collaboration was the brainchild of the British epidemiologist, Archie Cochrane. He and his colleagues wanted to produce, and indeed did produce, documents devoted to evaluating the scientific and medical literatures. The goal, again, was to systematically review the scientific evidence, codified in terms of level of support. The Cochrane approach relied on principles that included collaboration, reduction of bias, keeping current on the literature, access to information, and inclusiveness and goodwill of those involved (Sackett, 1994); Within a relatively short period of time, several centers both within and outside the UK (Daly, 2005).

Following quickly on Cochrane's work, many professional societies throughout the world developed committees that produced evidence-based documents on a wide variety of medical issues. Medical decision making is now systematically linked, normatively, to evidence, and again to degrees of evidence. These documents were based on the highest and most valid form of evidence: the *randomized control clinical trial*. In this research design, groups are defined and randomized in advance of the study hypotheses. In other words, groups of women who chose to participate in the study are either given HT or not based on random assignment. All factors that

potentially confound the study are controlled for. A weaker version of this design is the *intervention study*, in which the groups are not defined by random assignment, which introduces a level of bias that can confound the results. For the intervention studies, both randomized and not, one example would be the vulnerability to develop cognitive benefits as a result of HT (see Chapter 5). Of course, if the results indicate that one group did less well on pretesting, it cannot be determined that the treatment (or absence of treatment) caused the difference in test results. While valuable for generating hypotheses, *observational studies* provide less convincing evidence than do randomized clinical trials, but valid approaches in this category are cohort and case controlled-studies. The *cohort studies*, for example, reflect being exposed to HT or not, while *case controlled studies* often reflect retrospective analysis. The cohort studies often reflect a particular vulnerability or disease condition. One example is investigating the existence of increased risk in women who have a particular cancer (e.g., endometrial cancer), and then following the impact of having been exposed or not to HT. *Case reports* and *expert opinions* represent the lowest form of evidence. But the use of this analysis, it is important to remember, is not to dictate to the patient her choice, what is to be her medical decision, but to provide the best and clearest presentation of the evidence.

2.6 Evidence-Based Medicine, Practice Guidelines, and Hormone Therapy

Guidelines for treatment can grow out of EBM. A series of evidence-based studies was designed to assess the risk for Venous Thromboembolism (VTE) with post-menopausal estrogen replacement. VTE involves clots forming in the cardiovascular system. Estrogen levels are known to equate with risk for VTE. In order to assemble and assess evidence, the following databases were searched: MEDLINE (from 1966 through 2000), Health STAR (from 1975 through December 2000), and the Cochrane Controlled Trials Register. The analysis included estrogen replacement, thromboembolism, thrombophlebitis, pulmonary embolism, blood clot, thrombosis, blood coagulation disorders, homeostasis, hypercoagulation, fibrinogen, fibrinolysis, anticoagulants, and thrombolytic therapy. The study uses this material to argue that the use of postmenopausal estrogen is linked with more than a two-fold increased risk for VTE. The risk of fatality was greater in studies that included women with coronary artery disease. Importantly, later onset of menopause was also tied to an increased risk of thromboembolism. A number of Cochrane evidence-based analyses such as this have been integrated into the HT literature to facilitate and enhance medical decision-making (e.g., Grabiel-Sanchez et al., 2005; Hogervost et al., 2003; Maclenan et al., 2004; Lethaby et al., 2003).

Consider another evidence-based study on breast cancer and HT (Pritchard, et al., 2002). The main goal of guidelines that came out of this study was to provide HT information and recommendations to women with a previous diagnosis of breast

cancer and their physicians. This was particularly important since the growth of breast cancer is estrogen-dependent, and thus HT presents the potential for an increased risk. The evidence-based analysis was grounded on a systematic review of the English language literature published from January 1990 to July 2001. Medical subject headings used in the search were "breast," "breast neoplasms," "estrogen replacement therapy," "estrogens", and "hormone replacement therapy." For the purposes of these guidelines, HT was considered a replacement as estrogen alone, or estrogen plus progesterone (diverse forms and diverse forms of delivery). The conclusions from this study were that the use of HT (either estrogen alone or estrogen plus progesterone) is not recommended for women who have had breast cancer. Indeed, women who have had breast cancer are at a greater risk of breast cancer in the absence of HT, and HT increases their risk beyond that of a similar woman without a history of breast cancer. Given the increased risk of breast cancer linked with HT in women without a diagnosis of breast cancer, it is possible that the risk of recurrence and contralateral breast cancer associated with HT in women with breast cancer could be of a similar magnitude.

One primary factor in EBM is the value of the randomized control trial, and the grounding of physician suggestions to the patient in the best kind of evidence (Grimes, 1995). The primary argument for developing the guidelines was to reduce harmful biases, to make the evidence more transparent, and to place decision-making in the context of self-corrective processes. Physician practices are evolving towards a sensibility that makes space for EBM (Olatunbosum and Eduard, 1998). The evaluation and grading of the evidence has shifted from individual, semi-autonomous decision-making to a more collective professional body of authority.

In one study, for example, we found that physicians rated the evidence-based material as very helpful to their practices (Farquhar et al., 2002). But we know that there is still wide variation and inconsistency in the implementation of practice guidelines, and in their effectiveness in promoting better decision-making (e.g., Morgan et al., 2005). And we know, at least in the context of obstetricians and gynecologists in the United States, that the evidence-based practice guidelines are perceived as significant and in some cases implemented (Morgan et al., 2005), but keeping track of actual physician behavior is not easy (Elstein et al., 1999). Practice guidelines serve an important advisory role for physician suggestions to their patients but they are not a moral substitute (Mahowald, 2006). We also know that if they read the evidence-based documents, obstetrician gynecologists tend to perform better on self-reported knowledge and practice questions (Morgan et al., 2005).

A number of investigators have raised concerns about what they perceived as EBM's rigidity (e.g., Naylor, 1995; Maynard, 1997; Tonelli, 1998). Moreover, the guidelines themselves are not always based on the best scientific evidence (e.g., Chauhan et al., 2006). If followed blindly, no doubt EBM has potential pitfalls. As an approach it is still incomplete, perhaps immature. And like any method it is imperfect and continually requires scrutiny and development (Farquhar and Vail, 2006). But as one approach to bolstering, controlling, and bringing greater legitimacy and scientific accuracy to medical decisions, it is a valuable tool (Cook et al., 1997; Goodman, 2003).

The Cochrane studies are the paradigmatic example of evidence-based analysis that facilitates medical decision-making. Clinical guidelines informed by these and other forms of evidence-based analyses have their origins in the mid-1960s, and are one way to nudge physicians, where possible, towards practice more consistent with the science that makes the most sense, and, while not a silver bullet, evidence-based guidelines are important in the development of physicians' knowledge of the science. Such guidelines have grown dramatically in specialty societies, such as the American College of Obstetricians and Gynecologists (Zinberg, 1997; Farquhar et al., 2002). This is one way in which the often over-whelming amount of information can be transformed into manageable forms for the physicians. The guidelines are defined as having the goal, "…. To assist practitioner and patient decisions about appropriate health care for specific clinical circumstances…." Evidence-based medicine, as indicated above, helps ensure that professional knowledge and decision-making are anchored to sound science, and used to enhance health care. Congress recognized the need for such guidelines and in 1990 the Institute of Medicine (1993) was approached by the Agency for Health Care Policy and Research for how to develop evidence-based guidelines in an assessment of the WHI and HT.

The background for understanding HT, from the point of the view of the physician who needs to convey information to the patient and assist her choice, can be understood in part by looking at the guidelines that specialty societies (e.g., American College of Obstetricians and Gynecologists, American College of Physicians, American College of Cardiology) disseminate to the practicing physicians. Obstetrician–gynecologists have been very positive towards HT when compared to other physician groups (e.g., Brett et al., 2005) and their practices have changed with the changing science that has emerged (Holzman et al., 1984; Baron et al., 1998; Power et al., 2006; Chapter 6). In the United States, over 90% of obstetrician–gynecologists are fellows of the American College of Obstetricians and Gynecologists (ACOG). There are well over 40,000 fellows, and guidelines in numerous forms that cover a wide range of relevant topics are distributed to the members (Zinberg, 1997; Farquhar et al., 2002). The guidelines have evolved from authoritative documents to a concerned attempt to render evidence-based assessment of the scientific literature understandable. The physicians look to the guidelines for recommendations on practice methods.

In an evidenced-based document titled "Hormone Therapy" (ACOG, 2004), the most comprehensive document that the American College of Obstetricians and Gynecologists has produced to date on this topic, ACOG set out practice guidelines for HT. HT is recommended for short-term relief but cautioned for long-term use. This evidence-based analysis was consistent with those of many of the other groups that sat together to analyze the results (e.g., Nelson et al., 2003; National Institute of Health, 2005; Canadian Consensus Conference on Menopause, 2006; Ettinger et al., 2006; North American Menopause Society, 2007). The point is to facilitate the understanding of the science for the physician, who can then communicate this information to the patient. The guidelines are themselves imperfect documents, but then so is the science surrounding HT.

2.7 Integration of Decision Sciences and Evidence-Based Medicine

The decision sciences and EBM are now taught in postgraduate continuing education courses for physicians. There are sections (particularly evidence-based approaches, Elstein, 2004) of academic medical teaching devoted to both approaches (Kleijen and Chalmers, 1997), just as, for example, philosophy departments teach critical thinking (e.g., Peirce, 1898, 1992; Hacking, 1990; Glymour, 1992). The evaluation of evidence is never easy, partly because it is not uniform and the quality varies with the subject matter (Chalmers, 1988; Cook et al., 1997). Even after evidence is evaluated, decision-making is hedged by biases or orientations that the clinician must account for and recognize. Thus, both disciplines are important supports in formulating the best advice for the patient to make an informed medical decision. The decision sciences appear more technical and academic, EBM more clinical and applied, but it would be a mistake to undertake EBM without understanding and applying decision sciences to discern biases and heuristics (Kahneman et al., 1982; Baron, 1988, 2003; Gigerenzer, 2000). Relevance to HT is but one example, among many others.

When groups of researchers evaluate the data potentially applicable to a particular decision, the researchers ought to examine their own decision-making during the evaluation as carefully as they examine the data, and also determine the effects of the evidence-based document on physician performance. In other words, one should determine outcome measures as a result of the diverse documents. Again, evidence-based medicine is a tool among other tools, and has to be contextualized to be rendered useful (Timmermans and Mauck, 2005), not mythologized as the only mark of legitimacy (Feinstein, 1983; Feinstein and Horwitz, 1997; Charlton, 1996). When possible peer review of the committee that put together the evidence-based document, self-correction, determination of the questions, awareness of the biases – and even consideration of the rules for grading the evidence, including the logic of considering the randomized controlled trial as the most highly valued form of medical research – should be built into the process and translated into health-related policy decisions (Muir–Gray, 1997; Doak, 2006). One criticism of the design of the randomized control study of the WHI, for instance, is the subject pool embedded in the design; the participants were on average 63 years. Women who are well past menopause present different risk profiles and pathological issues than women who have recently undergone the climacteric, and the WHI analysis of results does not fully allow for that factor. Attention to the rubrics of EBM and the decision sciences help researchers remember that, without accounting for biases, even a perfect formal study does not necessarily mean the results are going to answer the question or understand the phenomenon one set out to understand (e.g., Doak, 2006; Harman, 2005; Grimes and Lobo, 2002).

Decision science directs our attention to recognizing and accounting for possible bias in decision-making, and evidence-based medicine rests on collective choice

(asking physicians to accept their colleagues' evidence-based judgments). In the end, any theory and practice of decision-making has to take into account both individual choice and collective consensus. It is important that physicians learn the proper application of these disciplines, but also that they begin to link them together as they and others work continuously to improve medical decision-making. While these two traditions spawned modern methods to support medical decision-making, they are only tools in our arsenal. We still need intellectual vigilance, an experimental spirit, a continuing sense of being educated, and endless self-correction (see also Chapter 6). And this is what we need in the context of understanding the dilemmas that surround HT, the basic science, the medical practices, and the seductive ploys of advertisers, for allowing the patient to make the best possible decision.

2.8 Patient Rights and Informed Consent

An evolving sensibility in medical decision-making has taken place, leading to greater awareness of human rights (e.g., Dworkin, 1971; Warner, 1980; Veatch, 2000), patient rights (Macklin, 1993), and women's rights (e.g., Sherwin, 1996; Tong, 1996; Wolf, 1996). That sensibility has affected physician considerations about HT (Macklin, 1999; Lyerly et al., 2001; Watkins, 2002; Houck, 2006). One view of human rights and their expansion is tied to the right to know what something is, what its dangers are for the subject, and that participation and access to information are at the heart of human choice (Sarokin and Schulkin, 1991) (see Fig. 2.3). The development of patient package insertions for information about products, including that of HT, reflects the larger issue surrounding the right to know (Watkins, 2002; Houck, 2006).

Again, the knowing process, normatively understood, is itself, in part, about self-correction (Dewey, 1916): getting a sense of the evidence, and also gaining some sense of fallibility (Peirce, 1878) as to biases/orientations that figure importantly in decision-making (Kahneman et al., 1982; Gigerenzer, 2000; Baron, 2003). More generally and historically, a growing sense of rights knotted to autonomy and choice (e.g., Kant, 1788), in addition to social connectedness and social cohesion (e.g., Dewey, 1935; Rawls, 1971), is a normative goal. The modern concept of rights is tied to inquiry (Schulkin, 1991) and has culturally evolved in a liberal, participatory democracy (Dewey, 1935; May, 2001).

The issue of rights emerged from our culture's evolution towards a dual focus on independent thought and an ability to empathize with others. The concepts of independence and dependence are melded in an environment where communities thrive when comprised of individuals who are responsible for their own decisions and are capable of reason and inquiry. In other words: two key categories are knotted to our conception of rights: choice and participation (Schulkin, 1991). The notion of rights is itself tied to a shared sense of humanity that transcends national boundaries. Our modern conception of rights is tied to the Enlightenment period, and since then, there has been a proliferation of our sense of what constitutes a human right. In the context of this book about hormone therapy, it is about the patients' decision-making being

Coevolution of Women's Rights with the Women's Health Initiative

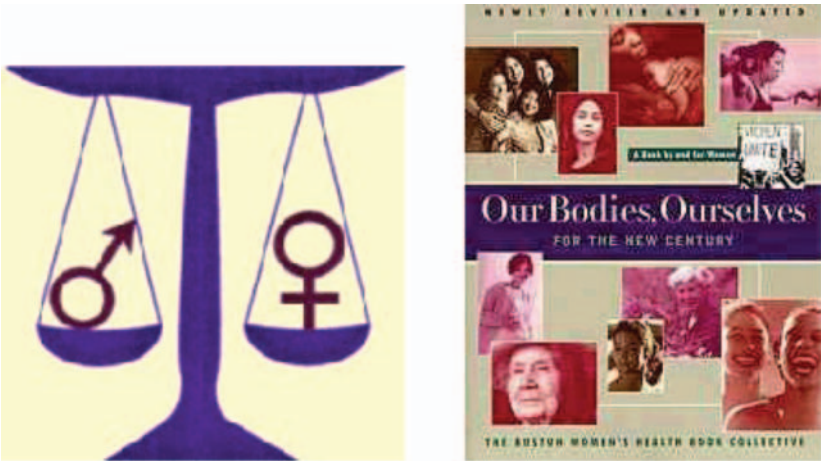

Fig. 2.3 Gender Equity (Anderson and Schulkin, unpublished)

central. The dignity of the individual is emphasized in this process, along with a conception of inquiry.

The evolving sense of human rights as something all too easily trampled has resulted in a heightened vigilance, and even suspicion, of medical authority. This can be seen in the development of codified patient rights. Such principles have evolved, in part, for the protection of human subjects in human experimentation (e.g., The Nuremberg Codes, Declaration of Helsinki, President's Commission on Ethical Issues in Medicine, see e.g., Veatch, 1989, 1997, 1999; Faden and Beauchamp, 1986; Baker et al., 1999). The goal of these codifications is the protection of the human subject, ensuring that when patients undergo a treatment they are maximally informed of what is involved, of the potential consequences and risks, and that they are competent to understand them. Informed consent is now a fundamental feature of biomedical ethics (Katz, 1984; Faden and Beauchamp, 1986; Berg et al., 2001). Rendering the information about HT to the patient as completely and transparently as one can is a moral medical imperative in Western medicine; to be informed is to know something about what one is consenting to, so that when the patient makes her choice with regard to HT she is in the best possible position to do so. Unfortunately, too much of the information that has been available to women promoted HT as the wonder hormone, and a climate of unrealistic medical expectations was established.

Depicted in Fig. 2.4 are some, although far from all, the significant events that underlie the evolution of patient rights (see also Veatch, 2000; Baker et al., 1999; Brody et al., 2000; Getz and Borfiz, 2000).

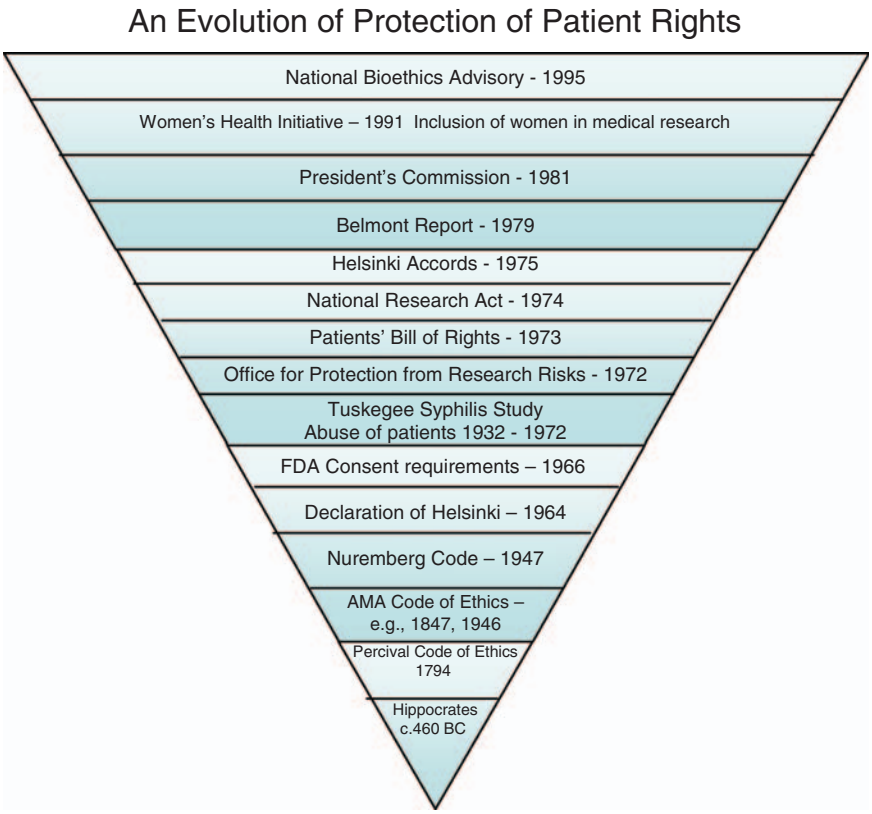

Fig. 2.4 Partial sketch of the cultural evolution of major events in patient protection and patient rights with regard to informed consent (Coleman and Schulkin, unpublished)

Amid this sense of medical marvels was the moral imperative of promoting a cultural value of moving away from a narrow authority-driven expression. A respect and promotion of patient participation and patient responsibility combined with an understanding of the social milieu and the cultural biases were understood as important factors in medical decision-making (cf. Katz, 1984; Faden and Beauchamp, 1986; Beauchamp and Childress, 1994; Gert et al., 1997, 2006; Wear, 1993; Wolf, 1996). The promotion of patients being thoroughly informed before they choose, and the respect for this endeavor of making the information as transparent as possible to inform choice, while also benefiting and respecting the patient (Pellegrino and Thomasma, 1988), is a goal of the culturally reinforced covenant or contract between the physician and the patient (Veatch, 1981). Of course in the real world, "thoroughly informed," like "perfect rationality," is perhaps more myth than reality.

Informed consent takes place in a context of disclosure, assessment, and understanding (Beauchamp, 1989, 1997; Berg et al., 2001). One feature is the attempt to make transparent not only what is known, but also the biases that

underlie diverse treatments, the orientation of the physician herself and possible conflicts of interest (Moore et al., 2005). In the end, the physician has a moral responsibility to respect the individual and her right to self-determination (e.g., Warner, 1980; Veatch, 1981).

Thus, with regard to HT, the physician ought to (Epstein et al., 2004): (1) understand the patient's experience and expectations; (2) build trust and participation; (3) provide evidence-based material with a discussion of uncertainties; (4) expose biases in the data and orientation; and (5) continuously check for understanding on both sides (Moore et al., 2005; Gert et al., 1997, 2006; Jecker et al., 1997).

Many studies show the influence of physicians on their patients' HT use (Schneider et al., 2000; Sarrell, 1999). Diverse studies also show that women's physicians, media, and friends were the dominant source of information about HT, and that women who noted that their physicians gave them information about HT were more likely to report its use (e.g., Schneider et al., 2000; Power et al., 2006).

Decision Aids: A variety of aids are available to facilitate informed decisions with regard to HT (e.g., Legare et al., 2003; O'Connor et al., 2003). These decision aids are designed to: (1) provide information tailored to the patient's health status; (2) clarify values; (3) provide examples of others' related medical experiences; and (4) provide guidance in shared decision-making. Ideally, decision aids will improve patients' knowledge of the options with regard to HT, create realistic perceptions on risks and harms, enhance participation in decision-making, and reduce decisional conflict about best course of action. The decision aids are credible in so far as they are: (1) recent and up-to-date; (2) evidence-based; (3) without conflict of interest; (4) balanced; and (5) effective. Of course this is easy to pontificate about and hard to realize. Nonetheless, these are normative goals of patient/physician decision-making. Decision aids are not easy to construct, nor is it easy to determine what the actual impacts are, as they can be influenced by many different factors (Ubel et al., 2001). Developing methods to improve physician responsiveness to evidence-based guidelines, for example, is an ongoing affair (Frankel et al., 1999). An evidenced-based, Cochrane-style systematic review of the literature suggests that decision aids expand and improve upon both patient and physician knowledge of medical decisions (including HT) and increase the important sense of patient participation in decision-making (O'Connor et al., 2005).

Nothing takes the place of humane and informed discourse. It is an essential feature of the physician–patient relationship, and it bears directly on HT in communicating evidence and fostering a sense of participation in the decision-making (Epstein et al., 2004). There are many ways in which information is communicated to patients, including conceptual understandings of risks and benefits, numerical translation of clinical evidence, word choice/phrasing, graphical representation of quantitative data, and decision aid programs. There is no "best practice" in the communication of health information to help patients make an informed decision.

The relationship between the physician and the patient is obviously important for the communication of health care issues. Moreover, in the perception of risk, the patient's individual experience – not just aggregated representations or utility

functions computed for risk – needs to be taken into account. A recognition of her individual experience and the context of her decisions matters in the health-related assessment (Lyerly et al., 2001).

In the case of HT, informed choice is a fluid concept, changing with circumstances and in a context of conflicting information and time constraints. The decision analytic tools become useful in the patient's care in making that conflict transparent (Elwyn et al., 2001). There are several meanings of "informed consent," but cognitive competence, voluntary choice, and an understanding of the information from the point of the view of the patient are essential. For the physician, the imperative is to present the information clearly, and to expose bias and conflicts (Beauchamp and Childress, 1994; Gert et al., 1997; Berg et al., 2001).

Both physician and patient biases undermine this process, and one important point is to make them transparent (Baron, 1988, 2003, 2006). A physician's overly positive orientation towards a treatment for which the data is underdetermined obviously is a problem, because the physician is not in a position to best detail the known risks and benefits of the particular treatment (Holzman et al., 1984). An evaluation of what is perceived as threatening may differ between the physician and the patient. The prospect of vulnerability to breast cancer with HT, as unlikely in statistical terms as it is relative to potential benefits (e.g., reducing the risk of bone fractures), is understood differently by physicians and patients (Holzman et al., 1984; Holmes et al., 1987). The risk of breast cancer from HT may be considered by a physician to be acceptable (Peterson et al., 2004), but a patient's fear of it may impact her decision to go on HT (Armstrong et al., 2000). There is nothing abstract or statistical about the prospect of loss of a breast to a woman, and for many even the slightest risk matters (Macklin, 1994; Lyerly et al., 2001).

Trust, transparency, and communicative discourse are essential ingredients in the relationship between physician and patient (e.g., Katz, 1984; Jackson, 2001; Kuhse and Singer, 2006). The assessment of the risks of a treatment amidst the benefits, and who informs the patient and the physician, is an evolving medical affair with regard to HT (e.g., Hendrix, 2003). Valuable studies that provide good information may have unintended consequences. Both physicians and patients have expressed the desire to participate in randomized control trials with regard to HT for some time (Wilkes and Meade, 1991). But in the aftermath of the Women's Health Initiative (WHI) studies on HT, not only did the number of women on HT decrease, but some patient groups reported less trust of the information from physicians than before regarding suggestions about HT (Schonberg et al., 2005).

2.9 Conclusion: The Importance of Being Earnest about Evidence

Understanding HT means taking into account the way we evaluate – or should evaluate – evidence. Once we acknowledge the diverse ways we are prone to error, decision-making is proportioned down to size from its Herculean mythology

(e.g., Dewey, 1916, 1929, 1968). But recognition of fallibility does not leave us without a foothold. That is provided by the many ways in which the heuristics or biases provide an orientation to the problems that need resolution (Kahneman et al., 1982; Baron, 1988, 2003; Gigerenzer, 2000). In other words, once human problem solving is demythologized, then we can actually understand how we go about medical decision-making, and what is reasonable to expect. Herbert Simon (1969, 1982, 1997) a psychologist who received the Nobel Prize in economics, introduced the concept of "bounded reason." For Simon, reason, or rather problem-solving, is bounded by context and circumstance, imperfect starting points and limitations of knowledge and knowledge processing. It is a world of epistemological adaptation, not of purity, but of real life problem solving, not an imposed idealization (Gigerenzer and Selton, 2001). The "Enlightenment" perspective of the super-rational person is sized down to human proportions in this view (Dewey, 1916; Gigerenzer, 2000).

"Bounded reason" is about good enough reason amidst all the noise one has to cope with in making decisions about HT and, really, about most things that matter. The sense of knowledge is that of "tool boxes," rough and ready problem solving devices (Dewey, 1916; Gigerenzer and Selten, 2001). This holds for issues in HT, and, in general, the bioethical decisions that underlie our goals and expectations (Dewey, 1939; Moreno, 1995). What underlie the literature surrounding HT are diverse competing interests amongst diverse groups; providing some context, or public context, for deciding together is an important normative goal (Moreno, 1995, 2003).

The origins of evidence-based medicine in its modern form are knotted to the Cochrane Studies. The intellectual roots, however, are much older (e.g., the 1910 Flexner Report) and can be found in the systematic integration of scientific knowledge; the link is the evaluation of the scientific evidence in the context of facilitating medical decisions (Schulkin, 2000; Elstein, 2004). Knowledge is to be evaluated, and ranked in terms of scientific significance and strength. We look for reasonable expectations (e.g., Elster, 1989), not perfect mythologized reason.

Medical decision-making for the physician is subject to self-corrective inquiry, which is why it is part of the sciences. And just as importantly, the physician is fostering the sense in which women are making decisions with regard to HT; the physician conveys the information and the patient makes the decision. The emphasis is on a shared sense of responsibility (e.g., Macklin, 1999; Neville, 1974; Tauber, 2005) and respect for the patient's goals as an individual (Richman, 2004). Of course that is no easy chore.

The view presented is an obvious one: patients need to be active in their medical decision-making. In the end they make the decision to accept or reject a treatment like HT. Staying informed and understanding the value of the randomized control trials in assessing benefits and risks is an imperative. Demythologizing science and medicine, putting them into a context, makes them more accessible and better understood (Brody, 2004; Goodman, 2003). To put decision analysis and evidence-based medicine themselves in a real world context, let's turn to the clinical research findings on HT.

Chapter 3
Autonomic Regulation, Heart, and Strokes

3.1 Introduction

A favorite chestnut of college professors tells us that "one should never assume, because it makes an ass out of you and me." For years, many physicians and researchers assumed that HT would most likely positively affect women's susceptibility to heart disease, stroke, and thrombosis after menopause. The assumption made a great deal of sense, but the reality has turned out to be somewhat different.

Estrogen plays a fundamental role in the regulation of autonomic function, normal cardiovascular function and central states of the brain. Declining estrogen levels during the perimenopausal period result in a number of changes related to autonomic regulation. The autonomic nervous system regulates key functions of the body, including the heart muscle, the digestive tract, and the glands. Estrogen also promotes growth factors in diverse end organ tissue, and that growth in turn is important in the maintenance of organ function. Growth factors are vital chemical transduction mechanisms, sustaining many different tissues (Turgeon et al., 2004; Mendelsohn and Karas, 2005; McEwen, 2001, 2002). For instance, estrogen stabilizes endocrine-affected tissues (heart, bone, etc.) by the induction of gene products. In the brain they are often called neurotrophic factors, and in the periphery they are often simply called growth factors (Schulkin, 1999). Estrogen tends to increase metabolic and regulatory activity; progesterone tends to have the opposite effect (Hapgood et al., 2004; Schumacher and Robert, 2002). These events underlie basic regulatory and vegetative functions that are essential to medical health.

Women frequently report discomfort related to autonomic changes during the early phases of estrogen decrements. These autonomic changes, the best known being hot flashes, are a major factor for women considering hormone replacement therapy. A study by Rovner et al.(1990), for example, examined how women weigh and combine risk/benefit information when making a decision about HT. The women in the study were between the ages of 45 and 55 years with an intact uterus, and not on HT. More than fifty percent of the women were still having regular menstrual periods; 25% had had a period within the previous year; and 21.4% had had no period for at least 1 year. More than half of the women indicated they were experiencing hot flashes. The study participants were asked to consider tradeoffs related

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to HT. The results suggested that the decision of women to consider HT was linked to the severity of hot flashes. The women used the information related to both hot flashes and the risk of fracture due to osteoporosis when rendering their decisions about HT use. While these women had concerns about cancer with the estrogen-only therapy, they were less concerned about cancer with the combined estrogen/progestin therapy. But the women in the study were consistently influenced by information regarding severity of hot flashes, and were somewhat influenced by information regarding osteoporosis risk. This result is consistent with other research (e.g., Power et al., 2006b). Both the expectations and the threat and experience of hot flashes are an important factor in women's decision to undergo HT.

In this chapter, I describe autonomic changes during the perimenopausal and early menopausal period. I then consider heart, stroke and thrombosis and related comorbid disorders as they relate to both the normal aging process and to hormone replacement therapy. Historically, clinical trials of heart disease and stroke have always exhibited gender bias, and the desire to correct that bias was part of the impetus for the formation of the WHI study. So the WHI is both a significant study and an important historical event, tied to gender equity with regard to research, a greater participation of women in the culture of research and the kinds of research that occur (Institute of Medicine, 1993; Macklin, 1994).

3.2 Menopause and Autonomic Changes

The menopausal period begins, on average, at about 52 years of age. It can last as long as 10 years or be as brief as several months. Independent of its duration, menopause itself is quite variable in symptoms. The clearest indication of menopause is the decline and end of menstruation, with concomitant decreases in estrogen and progesterone (see Table 3.1, Rannevik et al., 1995).

Elevated levels of follicle stimulating hormone (FSH) are an indication of the transition into menopause and menopause itself (Santoro, 2005). There is also decline in other hormones bound to reproduction (Sherman, 2005) (see Table.3.2).

While menopause appears to be experienced differently by women in different cultures (Avis, 2005) and different lifestyles (Gold et al., 2004), there are many studies, including double-blind controlled studies and observational studies (MacClenan et al., 2004; National Institute of Health Report, 2005; Canadian Consensus, 2006), that have consistently documented relief with HT from the various symptoms associated with menopause and perimenopause.

Nearly half of the women in Western countries report some form of night sweats and hot flashes during menopause (Wood and Mitchell, 2005). This is a condition of rapid heat flashes of great intensity in bouts of short duration (5–10 minutes), causing a sudden and uncomfortable sense of warmth and often profuse sweating. Many women find these symptoms not only uncomfortable but distressing and embarrassing.

The symptoms associated with the beginning of menopause are well known and have a long history of being described in a medical context (Pinkertson and Zion,

Table 3.1 Levels of estrogen pre- and post-menopause

	Estradiol	
Months Pre/Post Menopause	N	Pmol/l
Premenopause		
73–84	31	461±356
61–72	49	435±262
49–60	75	487±371
37–48	94	513±427
31–36	107	515±358
25–30	127	478±415
19–24	136	481±433
13–18	146	477±428
7–12	152	410±362
1–6	154	383±363
Postmenopause		
1–6	145	182±163
7–12	119	171±151
13–24	158	151±134
25–36	157	117±92
37–48	157	102±50
49–60	152	93±48
61–72	146	87±49
73–84	135	80±29
85–96	112	74±23
97–108	85	72±18

2006). One such historical description traces the vasomotor symptoms in medical terms to the early part of the nineteenth century (see Table 3.3).

Another core feature of menopause is dryness in the vaginal wall. Vaginal dryness increases during the perimenopausal period and can continue for a long period of time or indefinitely. Vaginal dryness is associated with more aversive sexual experiences; intercourse is more painful and therefore a woman experiences lessened desire for it (MacClenan et al., 2004). In general, sexual arousal decreases independent of vaginal wall dryness, and is generally linked to declining levels of estradiol (Dennerstein et al., 1980; MacClenan et al., 2004).

Effects of HT treatment on autonomic symptoms: Diverse forms of hormone therapy can offer quite dramatic relief from symptoms associated with the early menopausal and perimenopausal periods (MacLennan et al., 2004). In a Cochrane evidence-based review by MacLennan et al., (2004), the results indicated a 77% reduction in hot flashes in randomized controlled trials of HT. Other symptoms associated with this period, e.g., sleep disturbances, breast tenderness, and vaginal dryness, were also relieved (but see also Nelson, 2005; Col et al., 2004; Greendale et al., 1999).

While low doses of estrogenic compounds in short duration are effective in ameliorating many of the aversive symptoms (e.g., MacLennan et al., 2004; Parsey et al., 2000; National Institutes of Health Report, 2005; Canadian Consensus Conference,

Table 3.2 Menstruation and FSH in the Reproductive, Perimenopausal and Postmenopausal Phases (adapted from Santoro, 2005)

	Reproductive			Perimenopause		Postmenopause		
Phase	Early	Peak	Late	Early	Late	Early		Late
Length of Phase	Variable			Variable		1 year	4 years	Lasts to end of life
Menstrual Cycles	Variable to Regular	Regular	Regular with a length of ~2 days shorter	Varying length of cycles (more than 7 days different than normal	Two cycles have been skipped and a period of amenorrhea	1 full year of amenorrhea	None	
Endocrinology	Normal FSH		FSH elevated	FSH elevated		FSH elevated		

Table 3.3 Early medical history of menopausal symptoms

Year	Event
1837	Earliest mention of menopausal symptoms in medical literature
↓	
1887	First link of thermo-regulatory imbalance and VMS
↓	
1895	Psychological symptoms of menopause associated with vascular and blood flow mechanisms
↓	
1910	HT proposed for menopausal symptoms

2006), little, if anything, is known about the long-term implications of the use of HT (National Institutes of Health Report, 2005). The issue now is whether women should continue on HT after experiencing relief from short-term symptoms.

The depiction of menopausal discomfort as a disease, as opposed to a normal physiological change, exposes the impact of the larger cultural milieu on issues relating to women's health (Hubbard et al., 1982; Lock, 1994; Avis et al., 1993). Early representations about the medical effects of the loss of estrogen were associated as much with stereotypic value judgments about women's age and appearance as they were about women's actual state of health, and the medical profession made a much-needed correction when it began to recognize that concern about estrogen loss was something that needed to be thought about more deeply, that could be presented in a misleading and offensive manner, and was in itself a reflection of a specific cognitive orientation towards women and their bodies (Murtagh and Hepworth, 2003).

Variations in menopausal symptoms: The effects of menopause vary widely across and within cultures (Lock, 1993, 2005; see also Avis et al., 1993, 2005; Punyahorta and Street, 1998; Haines et al., 2005), just as there is variation in the doctor–patient relationship across cultures (Fox and Swazey, 1984; Macklin, 1999, 2006).

One study reported by Lock (1993, 2005) is depicted in Table 3.4.

Japanese women consistently report fewer hot flashes and night sweats than do women in Canada and the US, although the reasons for this divergence, and indeed the real nature of the divergence itself, are not clear. Do Japanese women simply have a less extreme physiological response to the autonomic changes of menopause, or does their reduced reporting of hot flashes and night sweats have more to do with their expectations and perceptions of them as aging women?

In addition, women within any culture experience menopause in quite different ways. If you were to get on a bus in any metropolitan area and ask every middle-aged women who got on the bus about their menopausal symptoms (and were they all to answer you), you would collect an enormous range of responses. Some women have almost no detectable symptoms; other women are severely hampered by their discomfort. Again, it isn't clear how much of this variation is due to physical differences, and how much is due to perceptions and expectations. The results from Avis et al. (1993) are presented in Table 3.5.

Table 3.4 Cross-cultural variation in menopausal severity

Menopausal Status	Japan	Manitoba	Massachusetts
Hot Flashes			
Premenopause	6.4	13.8	17.9
Perimenopause	13.5	39.7	38.1
Postmenopause	15.2	41.5	43.9
Total (100%)	1,104	1,039	5,505
	X^2=15.77	x^2=84.17	x^2=269.510
Night Sweats			
Premenopause	4.1	10.6	5.5
Perimenopause	4	27.6	11.7
Postmenopause	3	22.2	11.3
Total (100%)	1,104	1,039	5,484
	X^2=0.772	x^2=33.71	x^2=31.335

Table 3.5 Cross-cultural variation in menopausal severity

	Study		
Symptom	Japan	Canada	USA
Diarrhea/constipation	24.5	12.8	21.4
Persistent cough	4.2	5.2	10.1
Upset stomach	6.3	12.9	16.1
Shortness of breath	3.1	8.2	51.6
Sore throat	10.5	9.1	10.7
Backaches	24.2	26.8	29.6
Headaches	27.5	33.8	37.2
Aches/stiffness in joints	14.5	31.4	38.6
Dizzy spells	7.1	12.3	11.1
Lack of energy	6	12.3	38.1
Irritability	11.5	39.8	29.9
Feeling blue/depressed	10.3	17.1	35.9
Trouble sleeping	11.7	23.4	30.6
Lack of appetite	4.6	30.4	5.4
Hot flushes	12.3	4	34.8
Cold or night sweats	3.8	19.8	11.4
Hot flushes/sweats (combined)	14.7	36.1	38
Total (100%)	1225	1307	7802

The cultural variation should force one to focus on this issue and what it might mean. For example, Mary Mahowald (2006, p. 194) cites perhaps a common conception from a linguist colleague that many women perhaps experience in our culture:

> While reading sections on menstruation, pregnancy, and menopause, she noticed that the definitions of all three related the condition to women's reproductive capacity. Menstruation was defined in positive terms, as entailing the ability to become pregnant, which was also described in positive terms; in contrast, menopause was defined negatively, as failure in

ovarian function, cessation of menses, and loss of reproductive capacity. To Emma, the negative definitions were consistent with what she had recently read in the popular press about the distress and discomfort associated with menopause, but they were at odds with her mother's account of the experience, as a relief or "liberation" from having to worry about menses and pregnancy.

So there are at least two facts here: one is variation in response to the hormonal change, and the other is the larger cultural milieu and how it is understood. Both are nontrivial facts, laden with valuational appraisals, a pervasive perfume in the HT air. And both need to be part of our considerations with regard to the social/medical issues that surround HT.

3.3 Heart Disease and Women

The autonomic changes associated with aging also affect the risk of heart disease, stroke, and thrombosis. Women are drastically impacted by heart disease following menopause and it is an all too common, yet still underestimated, cause of fatality in women (see Fig. 3.1) (Harman, 2005; Mendelsohn and Karas, 2005).

It has been abundantly clear for a long time that when women go through menopause and their estrogen levels drop, their susceptibility to heart disease rises, although the precise nature of the link is not entirely understood. Heart disease is not a unidimensional phenomenon. But estrogen is, importantly, linked to cardiovascular regulation. Perhaps, the drop in estrogen and the decreased regulation

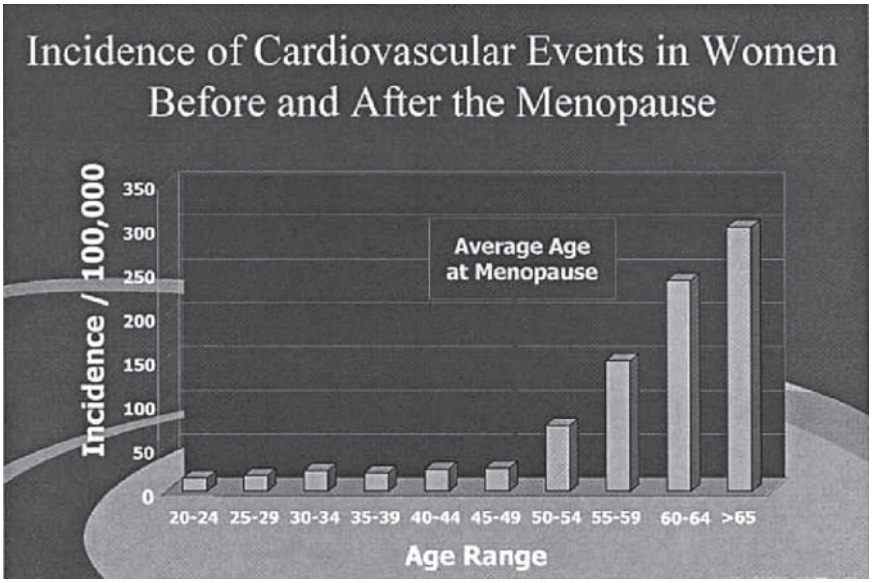

Fig. 3.1 Incidence of Cardiovascular Events in Women Before and After the Menopause

of extracellular fluid volume associated with menopause compromises the heart. Estrogen, after all, contributes to fluid balance, which is fundamental for cardiovascular regulation (Denton, 1982; Fitzsimons, 1998). Estrogen, by regulating proteins (e.g., statins, angiotensin, etc.) underlies both fluid volume and heart-related health matters.

So it's not surprising that researchers and physicians prior to the WHI generally assumed that HT would be good for women's hearts (see Rossouw, 2005). In fact it was a very dominant point of view, despite the fact that periodically evidence appeared that suggested that HT might not be protective, and indeed might be harmful under some conditions.

Varying evidence: The problem was, the evidence varied. Many of the observational and case control studies found significant effects of cardiovascular protection for women on HT (see reviews by Stampfer and Colditz, 1990; Institute of Medicine, 1993) and lower mortality rates for coronary heart disease (CHD), e.g., Grodstein et al., 1997. These results were no doubt part of the reason that many were initially very optimistic about the WHI studies with regard to cardiovascular diseases (Rossouw et al., 1995; Rossouw, 1996). However, like a drumbeat in the distance, studies kept cropping up that had found no protection or an increased risk of cardiovascular pathology in women on HT (Rossouw, 2005; Canadian Consensus Conference, 2006).

For example, one prospective analysis, the Nurses' Health Study (Grodstein et al., 2001) found increased risk in a subset of women. Among those women who were postmenopausal, there was a substantial increase in risk for CHD associated with both short-term and longer-term HT use. There was a 25% increase for coronary heart disease in women with HT use of less than 1 year, although longer-term hormone users demonstrated a decrease in risk for a second major coronary event compared with never-users. There was no strong suggestion that risk was linked specifically to treatment with estrogen alone or in combination with a progestin.

Again, in-double blind trials, neither estrogen alone nor progesterone combined with estrogen appeared to decrease coronary artery atherosclerosis in women over 65 years of age (e.g., Hodis et al., 2001, 2003). In fact, the studies together only provide a negative prediction of risk, despite the strong expectation that some form of coronary-protective result would emerge. And the evidence that HT is associated with risk for CHD continued to mount. The HERS study, which was randomized and double blind over a 4-year period, found a significant risk of CHD-related events. Follow-up studies of these women did not reveal any beneficial effects in the years following cessation of the study (Rossouw, 2005). Another randomized blind control trial found that women given both estrogen and progestin when compared to a placebo control group over a number of years did not have a lower risk of heart-related diseases (Hulley et al., 1998; Grady et al., 2000, 2002).

The results suggested that HT is not beneficial towards CHD, although there is much debate that remains about the studies (e.g., Lobo, 2005; Harman et al., 2005; Barrett-Connor et al., 2000). What then explains the positive results from the observational studies? There are several potential explanations, which are depicted in Table 3.6.

Table 3.6 (Adapted from Rossouw, 2005.) Sources of systematic bias in observational studies of hormone use and coronary heart disease

Healthy User Selection Bias	Women who choose hormones are healthier to start with
Confounding by Indication	Physicians are less likely to prescribe hormones to women at high risk of CHD
Compliance Bias	Women who continue hormones are good compliers with other healthful behaviors
Prevention Bias	Hormone users are under medical surveillance, more likely to have early detection and treatment of risk factors
Prevalence-Incidence Bias	Primary prevention cohort studies may not link CHD events to hormone use in the first year or two after initiation of hormones
Survivor Bias	Women who stop hormone therapy may do so because of inter-current illness

Table 3.7 (Adapted from Rossouw et al., 1995.)

Component	Primary Outcome(s)	Secondary Outcomes
Hormone Replacement Therapy	Coronary Heart Disease	Combined fractures
Dietary Modification	Breast cancer Colorectal cancer	Coronary heart disease
Calcium and Vitamin D	Hip fracture	Combined fractures Colorectal cancer
Observational Study	Various	Various

The WHI studies: Reconciling the divergent research findings and finally nailing the issue of whether HT is beneficial for heart disease was one of the major goals of the WHI studies (see Fig. 3.2) (Rossouw et al., 1995, 2002). There was a considerable amount of optimism about the results; HT should work. That is, HT should decrease a woman's vulnerability to cardiovascular-related disease. Coronary heart disease and prevention was the place in which to evaluate either estrogen or the combination of both hormones. Nearly 63,000 women between the ages of 50–79 years old were enrolled in the WHI studies (Rossouw et al., 2002).

Bernadine Healy, who was to become the first and only female Director of the National Institutes of Health in 1991, helped initiate an Institute oriented towards women's health (Mastrioanni et al., 1994). Many if not most previous studies tended to treat males as the normative gender, excluding women as participants. The plan for WHI was to undertake large studies devoted to aspects of women's health that had been neglected. Part of the importance of this initiative was to provide a context for medical gender equity (Institute of Medicine, 1993; Sherwin, 1996; Merton, 1996; Macklin, 1994). The orientation of WHI HT studies were in relation to cardiovascular-related diseases, diverse forms of cancer, fractures and bone metabolism and other issues previously tied to HT. The studies on heart and heart-related topics were just one amongst others. Informed consent, knowing the possibilities of the study and the larger issues being tested that could benefit potential subjects were major components. Some of the others are listed in Table 3.7.

The WHI, as I indicated earlier in the text, is a massive study. For the estrogen and progestin vs. placebo study a total of 16,608 randomized women ages 50–79 years old with an intact uterus at baseline were enrolled between 1993 and 1998 into one of 40 US clinical centers. Women were randomized to receive either 0.625 mg/d of Premarin (conjugated equine estrogen, CEE) or placebo. The average duration of follow-up was 5.2 years. Of that number, 8,506 received 1 pill of 0.625 mg/d CEE plus 2.5 mg/d MPA. 8,102 received placebo (Rossouw et al., 2002; Manson et al., 2003). A woman was considered to be postmenopausal if she had no vaginal bleeding for 6 months (or had a hysterectomy) and levels of hormones were markedly decreased.

When the data consistently revealed an increased risk for cardiovascular disease (including stroke and venous thromboembolic diseases, see below), the trial was terminated approximately 1 year early. Interestingly, in postmenopausal women with a prior hysterectomy in the estrogen alone trials, risk for stroke, but not heart disease or breast cancer, was increased (Anderson et al., 2004). Coronary heart disease showed no overall pattern, although the risk in years 6–8 of follow-up was lower for women in the CEE group (Hsia et al., 2006). But the results, when taken together, clearly suggested that HT cannot be recommended as a primary tool for the prevention of cardiovascular disease, and perhaps can result in a small increase in stroke and pulmonary embolism risk (e.g., Rossouw, 2005; Barrett-Connor et al., 2005; Canadian Consensus, 2005) (see Fig. 3.2).

Problems with WHI: The WHI study had a number of problems. In the first place, it was oversold as a study to end all studies. It also had an imperfect design when one looks closely at it; one dose of horse urine does not make this study's findings the final word on the topic. Better to have been more modest, to have used several doses, tried other estrogenic compounds, and expanded the study across different age groups. One the other hand, it is a full study, with many subjects. The overselling occurred not just at the hands of the pharmaceutical companies, but also from the WHI itself. The expectations were unrealistic. The pharmaceuticals and the researchers were confident that HT would reduce CHD, and the results were a rather horrible surprise for all concerned.

The age range of the sample in the WHI study has been a subject of criticism. Participants were between the ages of 50–79 years; the average age for the estrogen and progesterone or the estrogen arms of the study was 63, with an average of about 6 years on HT. Some have argued that the results therefore are only applicable to older women (Speroff, 2004; Lobo, 2005; Harman et al., 2005). Interestingly CHD seemed to be somewhat reduced in the 50–59 age group (younger group, Hsia et al., 2006; Rossouw et al., 2007; Manson et al., 2007). However, during 7 years of use, CEE did not provide overall protection against myocardial infarction or coronary death in generally healthy postmenopausal women.

Finally, while evidence-based analysis from many groups have only reinforced the view of either no benefit or increased risk for cardiovascular pathology (Mosca et al., 2004; Trevisan, 2003) there continue to be some studies finding evidence of protection, such as the prospective observational study (Grodstein, 2000; Grodstein et al., 2001). However, the randomized control studies in older women argue against

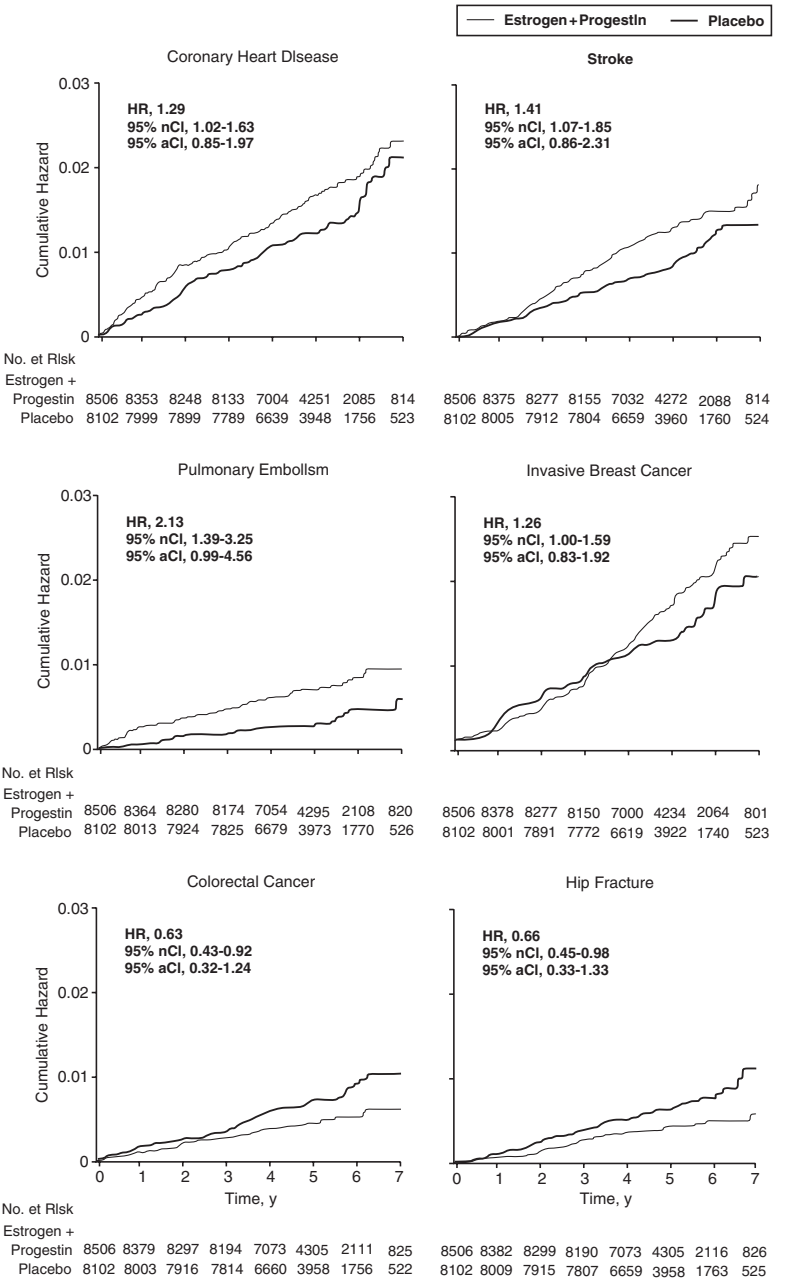

Fig. 3.2 Kaplan-Meier estimates of cumulative hazards for selected clinical outcomes

any protection against cardiovascular pathology as a function of HT. Thus, in one randomized blind and control trial, women given both estrogen and progestin when compared to placebo over a number of years did not experience a reduction in their risk of heart-related diseases (Grady et al., 2002). As a result, evidence-based guidelines from groups such as the American Heart Association do not recommend HT in the prevention of cardiovascular disease, nor does the American College of Obstetrician and Gynecologists (Mosca et al., 2004).

A partial summary of the randomized control trials both within and outside the United States is depicted in Table 3.8 (Cherry et al., 2002).

Thus, HT does not appear to offer protection against heart-related disease across a number of controlled studies – and not just WHI (National Institute of Health Report, 2005; Canadian Report, 2006). Nonetheless, the continued search for pharmacological solutions and studies on the basic biology of heart disease and estrogen remain an active field of research.

The selling of the WHI study: The issue of the "overselling" of this clinical study remains. Modesty as a normative goal should have been more operative. But that would have made the study less "sexy," less sellable (Houck, 2006). HT is a commodity, and for a variety of motives, some laudable and some less so, researchers, physicians, and pharmaceuticals needed to sell it. As a result, within a short period of time the media was reporting the results of the WHI, and both physician and patient behavior rapidly altered with regard to HT (McIntosh and Blalock, 2005; Ena and Rozenberg, 2003; Schneider, 2002; Power et al., 2006a, b, see Chapter 6). Media-saturated confusion permeates the information pathways with regard to HT. The subtleties of the studies were not broadcast, but the major effects were: no protection conferred, even a slight risk for heart-related pathology.

In the medical scientific community, the talk has turned to the continued development of the selective estrogenic compounds (SERMS). But thus far, results for raloxifene have been mixed with regard to protection against cardiovascular pathology (see Barrett-Connor and Laughlin, 2005). In one study, for example, raloxifene did not significantly reduce the overall vulnerability to cardiovascular pathology; however, in one select group who was at high risk it did (Barrett-Connor et al., 2002). Raloxifene does seem to reduce serum lipids (NIH, 2005).

Complicating factors: Before finalizing judgment on HT and heart disease, we need to understand several additional relevant physiological facts; estrogenic compounds regulate glucose metabolism, and can affect body weight, cholesterol, triglycerides, and lipoproteins, all of which impact cardiovascular-related health and diseases. One study that examined the effects of HT on this system (Shlipak et al., 2000) found that 0.625 mg/day of CEE and 2.5 mg/day of MPA reduced lipoprotein levels. This pattern may not apply to other domains. However, Hodis et al. (2003) did not find this relationship held for the progression of atherosclerosis in postmenopausal women.

Any number of risk factors (ethnicity, degree of exercise, and diabetes; Vittinghoff et al., 2003) can contribute to heart disease. There is evidence that HT impacts physiological signaling systems that contribute to metabolic and cardiovascular disorders, in a randomized control trial, women on estrogen and

Table 3.8 Cardiovascular disease and hormone replacement: Randomized controlled clinical trials of postmenopausal hormone therapy (Adapted from ACOG 2004.)

Trial	Length	Early harm	CHD benefit	Dosage
Healthy Subjects				
Postmenopausal Estrogen/Progestin Interventions (PEPI)	3 years	Not reported	No	0.625 mg/day CEE vs. 0.625 mg/day CEE plus cyclic MPA (10 mg/day for 12 days/month), vs. 0.625 mg/day CEE plus continuous 2.5 mg/day MPA, vs. 0.625 mg/day CEE plus cyclic micronized progesterone (200 mg/day for 12 days/ month)
Postmenopausal Hormonal Replacement on progression of atherosclerosis (PHOREA) 2001	48 weeks	Not reported	No	17 Beta-E2 1 mg/day plus 0.025 mg cyclic gestodene (12 days/month or 12 days every 3rd month vs. placebo
Estrogen in the Prevention of Atherosclerosis Trial (EPAT) 2001	2 years	Not reported	No	1 mg/day 17 Beta-E2 or placebo
Women's Health Initiative Estrogen plus Progestin 2002	5.2 years	Yes	No	0.625 mg/day CEE plus 2.5 mg/day MPA vs. placebo
WHI- Estrogen only 2004	6.8 years	Yes	No	0.625 mg/day CEE
Subjects with known heart disease				
Coronary Drug Project 1973	56 months	Not reported	No	2.5 mg/day CEE vs. 5.0 mg/day CEE vs. placebo
Heart and Estrogen/progestin Replacement Study (HERS) 1998	4.1 years	Yes	No	0.625 mg/day CEE plus 2.5 mg/day MPA vs. placebo
Women's Angiographic Vitamin and Estrogen (WAVE) 2002	2.8 years	No	No	0.625 mg/day CEE vs. 0.625 mg/day CEE plus 2.5 mg MPA vs. placebo
Estrogen Replacement and Atherosclerosis (ERA) 2000	3.2 years	Not reported	No	0.625 mg/day CEE vs. 0.625 mg/day CEE plus 2.5 mg/day MPA vs. placebo
Schulman et al. 2002	21 days	Not reported	No	1.25 mg intravenous CEE followed by either 1.25 mg/day oral CEE or 1.25 mg/day plus 2.5 mg/day of MPA or placebo for 21 days

(continued)

Table 3.8 (continued)

Trial	Length	Early harm	CHD benefit	Dosage
Estrogen in the prevention of reinfarction trial (ESPRIT) 2002	2 years	Not reported	No	2 mg/day oral E2 valerate or placebo daily
Papworth HRT Atherosclerosis Study (PHASE) 2002	30.8 months	Not reported	No	80 mg/day of 17 Beta E2 (if posthysterectomy) or 120 mg/day or 17 Beta E2 (if no hysterectomy) vs. placebo
Women's Estrogen-progestin Lipid Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) 2003	3.3 years	Not reported	1. No 2. No	1 mg/day oral 17 Beta E2 with or without sequentially administered MPA (5 mg/day for 12 consecutive days/month)
Women's Estrogen for Stoke Trial (WEST) 2001	2.8 years	Not reported	No	1 mg/day oral 17 Beta E2 vs. placebo

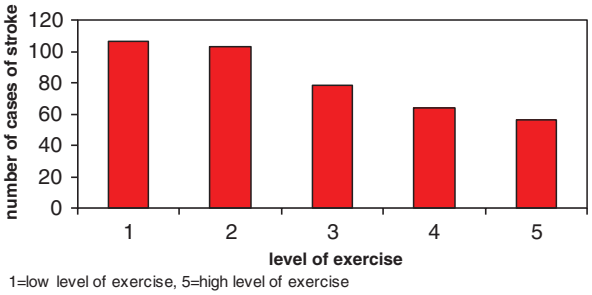

Fig. 3.3 Number of Cases of Stroke and Level of Exercise

progestin with coronary heart disease were actually less likely to have TYPE II adult onset diabetes (Kanaya et al., 2003). Moreover, diet, life style, exercise, and smoking status are linked to a reduction in cardiovascular-related deaths (Hu et al., 2000; Canadian Consensus Conference, 2006). Both walking and more vigorous forms of exercise are known to reduce the vulnerability to cardiovascular pathology (see Fig. 3.3) (Manson et al., 2002). Future HT studies in regard to CDH will need and indeed will take these many factors into account (see Table 3.9).

3.4 Strokes and Thrombosis

Stroke is one of the leading causes of mortality for both women and men, especially African–Americans. When separated from cardiovascular pathology, strokes are the third leading cause of death. On average, at least one person has a stroke every 45 seconds in the United States, and there are about three-quarters of a million new cases of stroke per year. Various medical treatments have been used to reduce the likelihood (or perhaps severity) of strokes, many of which are targeted at comorbid contributing factors such as hypertension and diabetes, and thrombotic contributing factors such as platelets (Canadian Consensus, 2006 and NIH, 2005).

Central thrombosis is the leading cause of ischemic central damage (e.g., Stam, 2005). There are striking ethnic/racial differences in vulnerability to strokes. For example, African American women are at increased risk. Other potential risk factors are diet, hypertension, diabetes, smoking, lipids, etc. (Johnson and Fulp, 2002; Eyre et al., 2004; CDC, 2002).

Observational studies and randomized trials – as well as meta-analyses – converge on an increased risk for stroke in women on HT. Moreover, the risk increased as women grow older (Miller et al., 2002; Anderson et al., 2004; Prentice et al., 2005).

Table 3.9 (Hu et al., 2000)

	Total Physical Activity Levels, MET Quintiles					
	1- Low	2	3	4	5- High	p-value
METs, h/wk						
Range	0–2.0	2.1–4.6	4.7–10.4	10.5–21.7	>21.7	
Median	0.8	3.2	7.7	15.4	35.4	
Total stroke						
No of cases	106	103	78	64	56	
No of person–years	106,368	116,243	112,876	111,058	113,542	
Age adjusted RR (95% CI)	1.00	0.87 (0.67– 1.15)	0.68 (0.51– 0.92)	0.57 (0.42– 0.78)	0.49 (0.35–0.67)	<0.001
Multivariate RR (99% CI)	1.00	0.98 (0.75–1.29)	0.82 (0.61–1.1)	0.74 (0.54–1.01)	0.66 (0.44–0.91)	0.005
Ischemic Stroke						
No of cases	71	61	53	44	29	
Age adjusted RR (95% CI)	1.00	0.77 (0.55–1.08)	0.69 (0.48–0.99)	0.58 (0.4–0.85)	0.37 (0.24–0.57)	<0.001
Multivariate RR (99% CI)	1.00	0.87 (0.62–1.23)	0.83 (0.58–1.19)	0.76 (0.52–1.11)	0.52 (0.33–0.8)	.003
Total Hemorrhagic Stroke						
No of cases	26	24	21	15	23	
Age adjusted RR (95% CI)	1.00	0.84 (0.48–1.46)	0.76 (0.43–1.35)	0.55 (0.29–1.04)	0.83 (0.47–1.45)	.6
Multivariate RR (99% CI)	1.00	0.92 (0.53–1.61)	0.89 (0.5–1.59)	0.69 (0.36–1.32)	1.02 (0.58–1.82)	.88

Another risk factor that increases with HT, in women with coronary artery disease, is biliary tract surgery (Simon et al., 2001).

Among healthy women, the WHI found an increase in the risk of stroke in women on HT in both the estrogen and progesterone and the estrogen alone studies (Wasserheil –Smoller et al., 2001, 2003; Rossouw et al., 2002; Rossouw, 2002; Anderson et al., 2004; Rossouw, 2005). Among women with central cardiovascular pathology, HT increased risk even further (Lemaitre et al., 2002). However, in women closer to menopause it may reduce strokes and cardiovascular pathology (Rossouw et al., 2007; Manson and Bassuk, 2007; Barrett-Connor, 2007).

A potentially fatal vulnerability arises in deep veins in the legs, where an embolism can be devastating. There is evidence that HT increases the risk of this venous thromboembolic pathology. For example, in the HERS study, among women on HT (estrogen and progestin) in a follow-up after 4 years on HT, there was an increased risk of thromboembolic disease (Grady et al., 2000).A randomized study with women on HT for about 6.8 years (Hulley et al., 2002; HERS study) demonstrated a two- to three-fold increase in incidence of both deep vein thrombosis and pulmonary embolism in the hormone group. But interestingly, Hulley at al reported that the longer follow-up available in HERS II suggests that the relative risk for venous thromboembolic events may decrease after the second year of HT. However, the study also indicated an increased risk for biliary tract surgery in the HT group compared with the placebo group (see also Hunninghake et al., 2001; Simon et al., 2001). Other randomized control trials have also shown increased risk of venous thrombosis (Cushman et al., 2004).

Unlike heart disease, experts were aware of the potential increased risk of stroke and thrombosis for women on HT early on, and any vulnerability to stroke has always been considered counterindicative for hormone replacement therapy. Study results have served to reinforce that position.

3.5 Urinary Incontinence

Other health issues present less clear evidence: urinary incontinence is one. We know that urinary incontinence can be a feature of the aging autonomic system; the older one is the greater incidence. One Cochrane review (Moehrer et al., 2005) suggested an improvement in urinary incontinence following HT, though it stated that more data was needed. However, in the WHI study, women who received progestin with estrogen showed either an increased risk of this urinary discomfort in women who had not previously reported it, or worsened urinary incontinence after 1 year in women who had previously experienced it (Hendrix et al., 2005; but cf. Palacios et al., 2005; MacLennan et al., 2004; Cardozo et al., 2005; Moehrer et al., 2005; Steinauer et al., 2005). The relationship between HT therapy, urinary incontinence, and menopause is just not clear, however, and more study is needed.

3.6 Conclusion

The debate about HT and heart disease is not over yet (Harman et al., 2005). The promise of reduced mortality and better quality of life associated with HT (Ettinger et al., 1996; Paganini–Hill et al., 2006) has not been fulfilled, but it has not been completely banished either. While menopausal symptoms are not uniform across ethnic groups (Avis, 2005; Lock, 1994, 2005), vasomotor and other symptoms related to the onset of menopause and with decreases in estrogen are clearly ameliorated with HT. Hot flashes and night sweats are a genuine misery for many women, so much so that some patients on HT would like to continue the therapy despite knowing about the elevated risks.

A major focus of current research is on the size of the dose that is given and the time at which HT is administered (NIH, 2005; Canadian Consensus, 2006; Palacios et al., 2005). In addition, the closer to the onset of menopause HT is begun, the more likely there will be an effect on cardiovascular-related illness (e.g., reduction of the progression of arteriosclerosis) and thrombosis-related diseases. Diverse forms of estrogenic compounds can ameliorate the symptoms of autonomic change during the period of transition into menopause, when discomfort is usually at its highest pitch (Nelson, 2004; Col et al., 2004; Ettinger et al., 2001; Utian et al., 2001). But we also know that symptoms may reappear following termination of HT (NIH, 2005; Canadian Consensus, 2006). Nevertheless, forms of autonomic relief are apparent from the use of HT (and apparently in low doses) in the reduction of symptoms associated with menopause.

The best approach, theoretically, is probably low dose, short term HT, perhaps given intermittently. One common view is that since HT exacerbates risk among women vulnerable to heart pathology and strokes in middle age, prevention perhaps could begin in younger adults (Rossouw, 2005; Barrett-Connor et al., 2005). The evidence is quite good that HT does not prevent heart disease in women in which there is some form of progression, and in fact HT exacerbates their problems. But among the large majority of women treated with HT the absolute risk of heart disease is still not high (although high enough to terminate the WHI studies). So the timing of HT may be essential (Mendelsohn and Karas, 2005; Grodstein et al., 2006). The theory is that the beneficial effects of HT with regard to atherosclerosis, for example, can provide protection before the onset of the disease, but exacerbate symptoms once the disease has set in (Mendelsohn and Karas, 2005). There are known positive relationships between estrogenic compounds and lipid and inflammatory signals in women on HT (Zegura et al., 2003) which can result in a reduction of coronary atherosclerosis (Akhrass et al., 2003; Barrett-Connor and Laughlin, 2005), if dose and timing are managed properly.

Lifestyle is also an important contributing factor as far as vulnerability to heart disease and stroke (Hu et al., 2000). Physicians and patients probably need to begin with managing the comorbid factors, especially physical activity and diet, which contribute to these ailments. Depression is another comorbid factor linked to cardiovascular pathology (Cizza et al., 2001), and racial disparities in diabetes contribute

to different rates of heart disease and strokes in different groups (Johnson and Fulp, 2002; CDC, 2002; Col et al., 2004; Eyre et al., 2004).Ultimately, menopause needs to be understood in both a physiological and larger social context. The medicalization of menopause is something to be thought about, not just assumed. We will not be able to understand the phenomenon until the stakeholders interested in it are able to discuss it in some common context.

Chapter 4
Bad News–Good News: Cancers and Bone

4.1 Introduction

In this chapter, unlike the classic joke structure, I begin with the bad news, and work my way to the good news. The bad news is that women on HT do seem to be at increased risk for breast cancer. The good news is that HT does not appear to increase a woman's risk of getting endometrial or ovarian cancer and may reduce the incidence of colorectal cancer, and – best news of all – has a positive effect on the health of women's bones, teeth, and possibly also skin. The challenge, for women and their doctors, lies in weighing the benefits and deficits. This chapter presents readers with crucial information about the effects of HT on cancers and bone, and uses the tools of evidence-based medicine and an informed decision making process to demonstrate how patients and physicians can come to informed decisions about the use of HT.

Why begin with the bad news? Well, clearly, this is no joke and we are not comedians. But any good stand-up artists will tell you that it's important to first address what seems to be the most obvious concern before delivering the surprise follow-up; and there's no doubt that women's fear of breast cancer has been enormously important in their decisions regarding HT in recent years. Media coverage of the studies showing a relationship between HT and breast cancer incidence has been intensive, causing women to leave off HT in record numbers. Indeed, one recent study attributes a statistically significant drop in the number of new breast cancer diagnoses to the number of women abandoning HT or not initiating hormone therapy (Ravdin et al., 2007).

However, just as initial euphoria about HT was probably a mistake, physicians and patients need to consider all the evidence about HT's relationship to cancers and bone health from as many angles as possible.

4.2 Breast Cancer

The connection between breast cancer and HT, in terms of statistical likelihood, is disputed by some and embraced by others (compare Canadian Consensus, 2006, and Belisle et al., 2006). We know from the research that, no matter how well-informed

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we are, we tend to over- or under-inflate statistical probabilities relative to a background framework (Kahneman et al., 1982). A recent study has shown that women, for example those who are at high risk for breast cancer, underestimate the risk, while another group of women at moderate risk of breast cancer overestimate the risk (Haas et al., 2005). The mere idea of breast cancer or breast removal is devastating to women, and regardless of whether HT increases the risk for breast cancer by a large or a small degree, the elevated risk tends to dominate decision making. This was true even prior to the WHI, when the risk-benefit calculation was more favorable for HT than it is now (Holzman et al., 1984). Given the emotional trauma associated with breast cancer, no calculation matters; we cannot axiomatically maximize cost/benefit analysis. But we do need to try to put the risk in context (Mahowlad, 2000).

Estrogen binds to specific receptors in breast and ovarian tissue. While we now know that estrogen, like other steroids, has both genomic and membrane related effects on diverse body tissue, long-term effects are primarily genomic (e.g., lead to changes in gene products, McEwen, 2002). Therefore, estrogen levels and breast cancer are linked, (Belisle et al., 2006; NIH Report, 2005), and since HT increases estrogen levels, it is not entirely surprising that it increases the incidence of breast cancer, perhaps because it increases estrogen levels at a physiological stage in which lower estrogen levels are normal in aging women. In addition, the longer the duration on HT, the greater the likelihood of breast cancer. This has been observed in both observational studies and in randomized control trials (NIH report, 2005; Canadian Report, 2006). The issue of informed consent with regard to HT is thus of great importance for women. Let's review the studies which exposed the relationship between HT and breast cancer.

Million Women Study in Britain: Prescription of HT is a worldwide phenomenon, though it is much greater in Western Europe and the United States than elsewhere. In a study in Britain, Wilkes and Meade (1991) found that prior to the beginning of a one million subjects' recruitment study in Britain, 98% of physicians in general or gynecologists specifically reported prescribing HT at one time or another (see Fig. 4.1). Over half of those who prescribed HT used a combination of estrogen and progestin. Half of the doctors thought HT use for 6 months to 3 years was appropriate. For the prevention of osteoporosis, a number of physicians (27%) thought that 6–10 years was an appropriate length for HT.

Wilkes and Meade also investigated the physicians' views on the risks and benefits of HT. Most then considered HT prescription for the prevention of cardiovascular disease (57%) and osteoporosis (62%). Most physicians also felt that any risk of cancer precluded prescribing HT as a preventative heart and bone loss measure (64%), with fewer than half stating that they would not prescribe HT in those contexts, and about a quarter of physicians being undecided. For most of the physicians, the primary reason for the prescription of HT was to relieve menopausal symptoms, though the doctors would consider prescription for preventative measures as well. Almost half of the physicians said they would definitely or probably enter patients into a randomized control trial to better understand the risks and benefits of hormone therapy either opposed or unopposed and with and without a uterus.

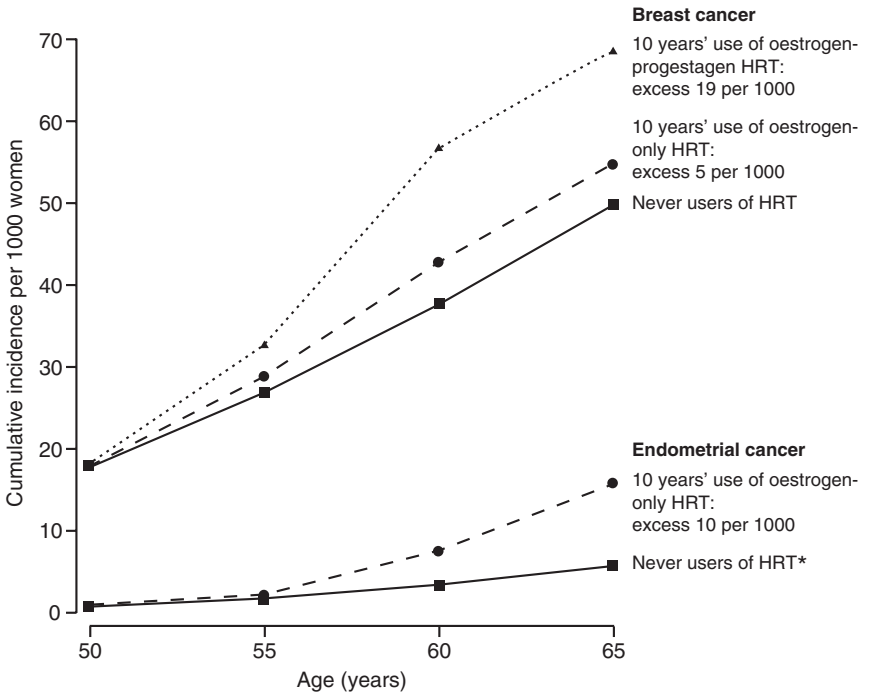


Fig. 4.1 Incidents of breast cancer following HT in the One Million Women British study (Permission granted for Beral et al., 2003.)

Table 4.1 Numbers of women flagged on the NHS Central Registers number (%) who ever used HRT, and numbers of incident invasive and fatal breast cancers (Banks et al., 2002)

	Women flagged on NHS Central Registers (n)	Ever users of HRT (n[%])	Incident breast cancer (n)	Breast cancer deaths
Menopausal status at baseline				
Premenopausal	63,153	6023 (10%)	645	26
Perimenopausal	77,833	11,356 (15%)	597	38
Postmenopausal	828,923	436,166 (53%)	7,140	517
<5 years since menopause	237,639	127,022 (53%)	1,953	141
5–9 years since menopause	295,168	175,700 (60%)	2,724	185
10 or more years since menopause	296,116	133,444 (45%)	2,463	191
Unknown	114,201	96,627 (85%)	982	56
Age 50–52 years and hysterectomy before menopause	45,968	30,873 (67%)	380	33
Age 50–52 years and HRT before menopause	60,606	60,606 (100%)	544	18
Information on menopause missing	7627	5,143 (67%)	58	5
Total	1,084,110	550,172 (50%)	9,364	637

However, many were still wary of the risks over the benefits. Cancer – and particularly breast cancer – was an issue, and an unresolved one. Age, dose, and duration of use remained, and indeed still remain, a nagging empirical set of undetermined issues (Panay, 2004; Belisle et al., 2006).

In this context of unresolved questions regarding the risk for breast cancer, a major study in Great Britain was initiated. Called the Million Women Study (Beral et al., 2002), more than a million women aged 50 – 64 were recruited between 1996 and 2001. On average, participants used HT for 5.8 years. HT use was highest in the age group of 50–54 (twice as high as any other age group). Groups were defined with regard to HT use and menopausal status: premenopausal women were defined as those who still had regular periods; perimenopausal woman as those with irregular periods, and postmenopausal women as those with no period at all, naturally. A fourth group encompassed those who had undergone bilateral oophorectomy. HT use varied greatly with regard to gynecological, medical, and surgical history (Banks et al., 2002) (see Table 4.1).

In one analysis that included an astounding 828,923 postmenopausal women, the study found that there was a significantly greater risk of breast cancer in women on HT than women who had never been on HT. Women who had been on HT in the past were not at greater risk than women who had never been on HT, but contemporary HT use did render women more vulnerable to breast cancer. Women were at greater risk with combination estrogen–progestin than with estrogen alone. Moreover, the greater the duration of HT use the greater the risk for breast cancer. However, the diverse forms of these compounds as well as the various forms of administration were unrelated to the amount of relative risk.

The prospect of increased incidence of breast cancer resulted in the termination of other studies. For example, a large study called "WISDOM", conducted in the United States, was terminated by the principal investigators because of the perceived danger (Vickers et al., 2002). Also, the HABITS trial, a study of HT use in breast cancer survivors, was also terminated after the risk was deemed unacceptable.

Moreover, many other noted studies, both observational and cohort, found increases in risk for breast cancer from HT, notably the Nurses' study. The Nurses' study found that both estrogen alone and the combination of estrogen and progestin increased the risk of breast cancer (Colditz et al., 1995; Hulley et al., 2002). Other studies also found that there was an increase in breast cancer with women on HT (e.g., Nelson et al., 2002; Schairer et al., 2000; Col et al., 2001). However, the type of progestin that has been used has not been considered enough, in terms of its contribution (Hapgood et al., 2004; Koubovec et al., 2005; NAAMS, 2003).

And then the results of the WHI study appeared, which only substantiated earlier fears about breast cancer and HT, although the results were more nuanced. For the estrogen and progestin group, the WHI study showed that the risks of HT outweighed the benefits, and was associated with an increased risk of breast cancer (Chlebowski et al., 2003). However, the estrogen alone group demonstrated no significant effect on breast cancer – in fact there was, surprisingly, somewhat of a decrease (Anderson et al., 2004; Stefanick et al., 2006).

A number of critics have challenged the structure of some study groups, and have noted variations in the duration of use of HT across studies (e.g., Shapiro, 2004). Others have noted that, statistically, the actual risk increase is small (Bush et al., 2001). Nevertheless, the evidence-based material taken together appears to have established an increased risk for breast cancer resulting from HT (e.g., Col et al., 2001). The kind of HT and the manner in which HT is given appears to interact with the risk of breast cancer HT (Armstrong et al., 2000, 2004). Some of the findings with regard to selective estrogen receptor modulators (SERMS) may be promising in here. That is, raloxifene [a SERM] has been shown to decrease breast cancer risk in women who are postmenopausal (e.g., Cummings et al., 1999).

Putting Breast Cancer Risk in Context: Breast cancer, or vulnerability to it, is linked not to just the medical treatment that the patient chooses, but the social milieu in which it is couched and the psychology in which it is understood and experienced (Lyerly et al., 2001; Macklin, 1994). Context and human contact underlie the medical/social issues.

Women live longer, and women are also more health conscious than men. Women have reinforced and kindled a perspective on patient health, that it should be equitable and fairly distributed (e.g., one of the reasons for the WHI studies). Consider, for a moment, osteoporosis; Women are more likely to suffer the arching back, the brittle and broken bones of aging than men. Osteoporosis is characterized by bone fragility such that fractures can occur under conditions of minimal trauma, including the normal stresses of living. Osteoporosis is generally a disease of older adults because the cumulative effect of bone mineral loss takes time to deplete the skeleton. The dramatic increase in elderly populations worldwide, and the expected continuation of this population increase, means that an epidemic of disease related to bone fragility may be in the future. Treatment of established osteoporosis is difficult, and the public health emphasis has therefore been placed on prevention (Heaney et al., 1989; Institute of Medicine, 1997). Since HT is linked to reduced bone loss (see below), the risk of breast cancer has to be weighed against the benefits of preventing osteoporosis.

Doctors and patients weigh the risk differently, however. Holmes et al. (1987) interviewed physicians and perimenopausal women to assess their utility calculations for the various health outcomes of estrogen replacement treatments. For all health outcomes, physicians rated illness episodes followed by recovery as being closer to perfect health than did perimenopausal women. Physicians estimated the importance of an outcome resulting in relief of symptoms above fracture prevention, whereas women rated fracture prevention above symptom relief.

In the majority of instances, physicians rated intermediately severe outcomes showing some degree of disability as being closer to the most preferred outcome than did perimenopausal women. The worst fracture outcome, premature perioperative death at age 65, showed the reverse pattern; physicians rated this outcome as less preferred than did perimenopausal women. Both physicians and perimenopausal women considered cancer the most significant negative outcome. However, women reported that fracture was more important than vasomotor symptoms, while physicians indicated that women would value symptom relief more than reduction of the risk of fracture. In general, for the physicians, the most preferred outcome was a fracture

that is surgically repaired and cancer that does not recur. For women, on the other hand, fracture reduction was the most important desired result. This perhaps is not surprising since the idea of being immobile, of losing physical activity, is a large psychobiological loss (see Fig. 4.2). And of course it is women who should be making this decision.

Another factor in the HT/breast cancer risk/benefit calculation is the ethical issues surrounding physician/pharmaceutical interactions (Ruff et al., 2005; Dana and Loewenstein, 2003; Angell, 2004). Pharmaceutical companies themselves often have extensive websites about HT (e.g., Wyeth, Merck), which in effect advertise directly to women as well as physicians. In both Britain and the US there has been, and continues to be, much debate about the legitimacy of this practice, especially as direct consumer advertising is uneven with regard to accuracy (Goodman, 2003).

At the same time as the debate on HT, breast cancer, and osteoporosis has evolved, the Internet has developed into the primary form of access to information about possible medical choices. The Internet has been both praised and excoriated for the range of accuracy of the information conveyed in enhancing medical decision making (see Fig. 4.3) (Diaz et al., 2002). The population, not surprisingly, that uses the Internet for medical information tends to be well educated and white; and women's health is one of the most sought after kinds of information (e.g., Diaz et al., 2002). Diverse forms of Internet-based access to information have evolved, including social support groups (Bresnahan and Murray-Johnson, 2002).

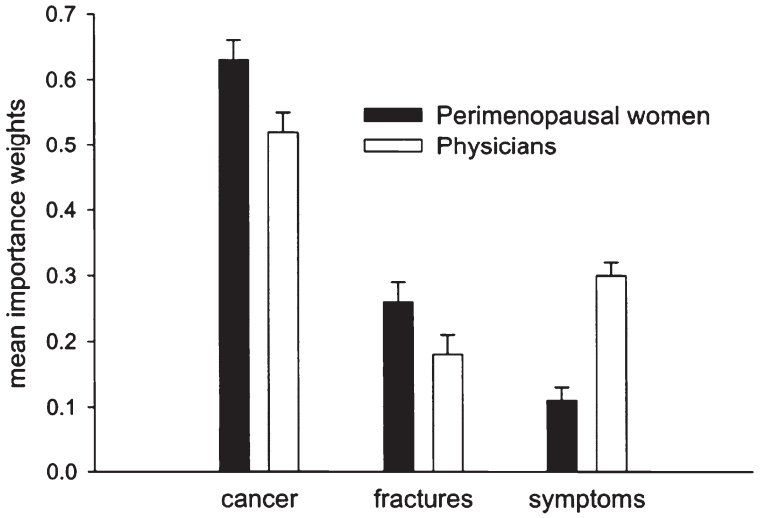


Fig. 4.2 Responses to questions by physicians and patients with regard to HT (Adapted from Holmes et al., 1987.)

One reason behind the importance of the Internet and direct advertising to women's health choices is that women are often dissatisfied with their communications with their physicians. This is particularly apparent when it comes to discussions about menopause and HT (Wathen, 2006). Greater communicative competence and interpersonal contact and patient satisfaction is attributed to female physicians, including the reported length of time of the visit (Emmons et al., 2006). When it comes to issues that can impact vulnerability to a cancer, communicative skills bear a great burden in adjudicating the assessment of the risks and benefits of HT. Physicians, as they know they should, need to recognize the variable responses of the patient (Walter et al., 2004; Legare et al., 2002a, b), and must facilitate a participatory environment (Epstein et al., 2004). Dialogue and context matter, as does a recognition of the individual (Drapkin-Lyerly et al., 2001).

Women considering the risks and benefits of HT are open to using many information sources (see Fig. 4.4). Interestingly, women have often reported that a fundamental source of information about HT is from women's magazines (e.g., Griffiths, 1995; Clinkingbeard et al., 1999; Power et al., 2006b). In one study more than 76% of respondents reported that they received information from women's magazines, followed by 68% from health care providers. However, in that same study, almost 50% of the women reported that their questions about menopause and HT were not answered.

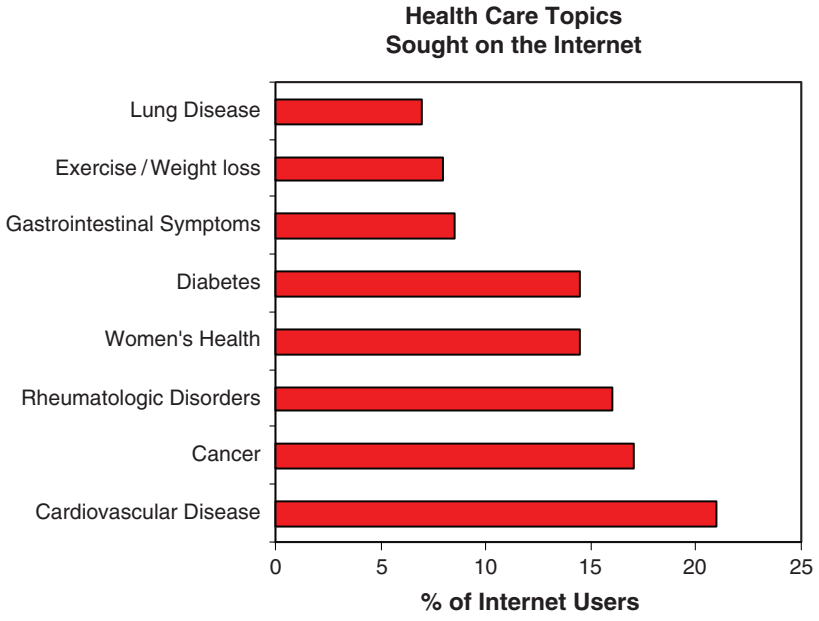
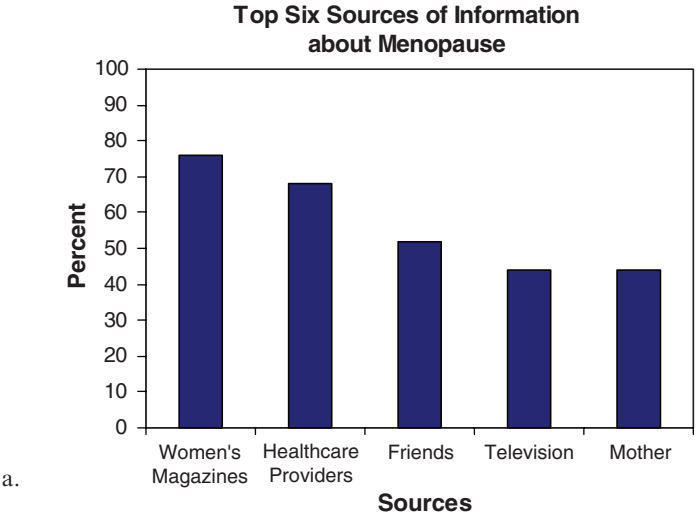


Fig. 4.3 Health care topics looked at the internet (Adapted from Diaz et al., 2002.)



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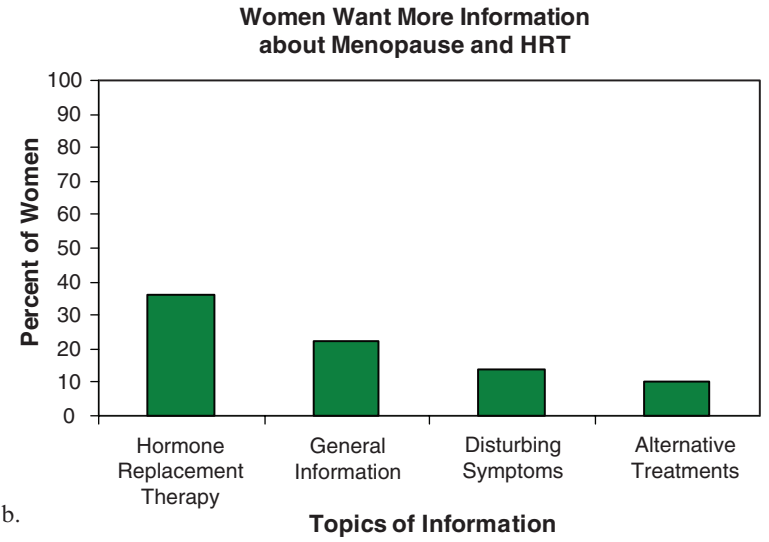


b.

Fig. 4.4 Sources of information for women about menopause and hormone therapy (Adapted from Clinkingbeard et al., 1999.)

Only through good communication can doctors and patients put the risk of breast cancer in context. For instance, some data suggests that lack of exercise and excessive body weight gain can produce a greater incidence of breast cancer than HT use (Belisle et al., 2006). It can be difficult for anyone to access and assess that sort of information working on their own with a computer or a magazine; they need a physician as a partner in correlating the risks generally, and in assessing their own particular risks (see Table 4.2).

Table 4.2 Risk factors for breast cancer

Factor	Baseline Breast Cancers* per 1000 women	Additional Cancers per 1000 women	Total Cancers per 1000 women
No HT use (baseline)	45	0	45
5 years HT	45	2	47
10 years HT use	45	6	51
15 years HT use	45	12	57
Alcohol consumption (2 drinks/day)	45	27	72
Lack of regular exercise (hour/week)	45	27	72
Late menopause (10-year delay)	45	13	58
Body mass index (10 kg/m^2 increase)	45	14	59
Weight gain after menopause (≥20 kg)	45	45	90
Late childbearing and reduced breast-feeding	45	45	90

*Baseline or basic risk applies to all women and is due to factors that cannot be controlled (such as aging and gender). Increases are estimates based on published data indicating risk associated with lifestyle choices. Modified by Belisle et al., 2006.

4.3 Ovarian, Endometrial, and Colorectal Cancer

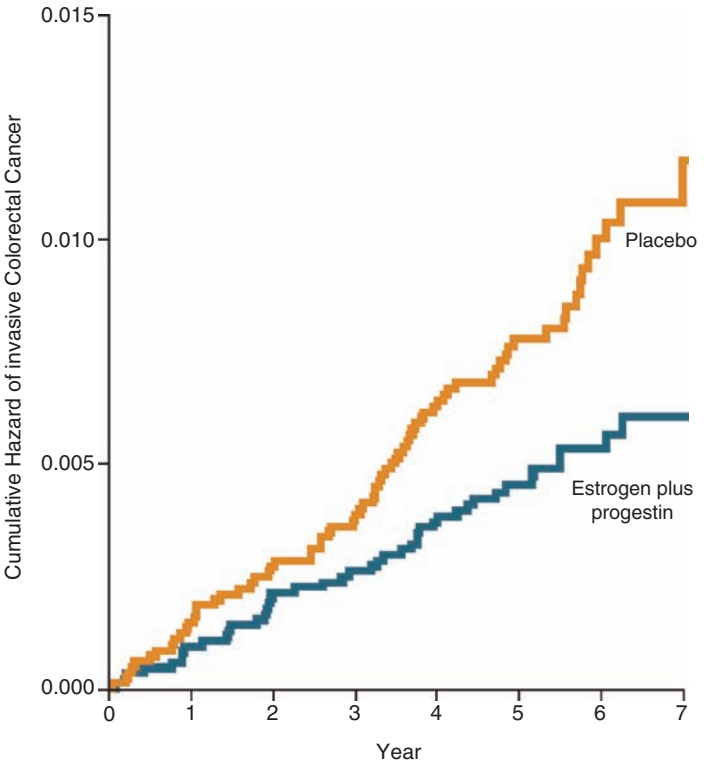
Ovarian cancer, endometrial cancer, and colorectal cancer are major causes of death among women in the United States. There is a genetic link for these cancers (American Cancer Society, 2003), as there is for breast cancer, and obviously both ovarian and endometrial cancers involve reproductive systems sensitive to hormones such as estrogen. Given the considerable evidence linking HT to increased risk for breast cancer, might there not also be a negative relationship between HT and other cancers? Here's where the news begins to improve. With regard to ovarian cancer a number of observational, retrospective, and case controlled studies have found few statistical effects of HT use on increased vulnerability to ovarian cancer (see Coughlin et al., 2000; Garg et al., 1998; Anderson et al., 2004; though see also Glud et al., 2004; Belisle et al., 2006). One major caveat is the WHI study (Lacey et al., 2002). This study examined a group of women who had ovarian cancer, and found that unopposed estrogen did result in increased rates of ovarian cancer. Duration of use was particularly associated with increased rates of ovarian cancer. This finding also applied to women with a prior hysterectomy. Short-term use of estrogen and progestin, however, was not associated with an increased risk for ovarian cancer.

Turning to endometrial cancer, the relationship between risk and use of HT is less clear. For one thing, the risk is potentiated by other comorbidity factors such as obesity, hypertension, and diabetes (Belisle et al., 2006). Analyses of data from a large number of studies has consistently identified increased risk in women on estrogen alone, while other analyses of HT use in which the estrogen was combined with progestin both did and did not reveal this trend in vulnerability to endometrial cancer (cf. Grady et al., 2002a; PEPI trials, 1996). The results from the WHI with

estrogen and progesterone, however, found no statistical relationship or increased risk in women on both the estrogen and progestin (Rossouw et al., 2002).

But there is one form of cancer that has consistently been shown to be *reduced* in HT patients: colorectal cancer (see Fig. 4.5) (Grodstein et al., 1999). As with other forms of cancer, obesity, diet, and activity contribute towards the expression of this pathology (NIH Report, 2005; Canadian Conference, 2006). Nevertheless, in various observational studies, HT has been associated both with a reduction of colorectal cancer and a reduced risk of fatality from this disease. In a meta-analysis of studies of the effects of HT on risk for colorectal cancer, a 20% reduction in colorectal cancer was found for women who were on HT at one time. Among women who were currently on HT, there was a 34% reduction in incidence of colorectal cancer when compared to women who had been on HT or who had never been on HT. This reduced risk held for both women who had been on HT for a short time as well as those who had been on HT for 10 years or more.

The WHI trials of estrogen combined with progestin showed a decrease in colorectal cancers associated with HT (Chlebowski et al., 2004). For example, of the 115



No. at Risk

Estrogen plus progestin	8506	8402	8334	8260	8051	5872	3096	1358
Placebo	8102	8014	7937	7856	7656	5495	2740	990

Fig. 4.5 Colorectal cancer (Permission granted from Chlebowski et al., 2004.)

cases of invasive colorectal cancers, 43 were linked to HT, as compared with 72 cases in the control group.

The results in the estrogen-alone trials were less promising and did not appear to produce such a beneficial effect (Anderson et al., 2004).

While the evidence on colorectal cancer and HT is somewhat positive, and the relationship between ovarian and endometrial cancer and HT use is not entirely rosy, it does seem that patients on a short course of combined estrogen and progesterone are not at greatly elevated risk for ovarian and endometrial cancers. Patients with genetic or other medical history indicating a predisposition to these cancers and/or breast cancer have a complicated task ahead of them. How does one calculate the benefits vs. the costs for a woman with, say, a family history of breast cancer, colorectal cancer, *and* osteoporosis?

The first place to start is to look more closely at HT and bone health.

4.4 Bone

The facts about bone health and aging: More than 99% of the calcium in the human body is found in the bones and teeth, and calcium, the major mineral in bone, is a primary determinant of bone density. Childbirth is generally associated with a decrease in bone density in most women, particularly during lactation. But in most women, bone mass returns to its former levels after lactation has ended. By contrast, the decrease in bone density that occurs during menopause is associated with decreased levels of estrogen, and does not return to "normal." There is abundant evidence for a relationship between decrease in bone structure and decreased levels of estrogen during menopause (Heaney et al., 1989; Hutchinson et al., 1979).

The increased morbidity and mortality associated with osteoporosis is related to fractures (see Fig. 4.6). The increased incidence of fractures in the elderly population

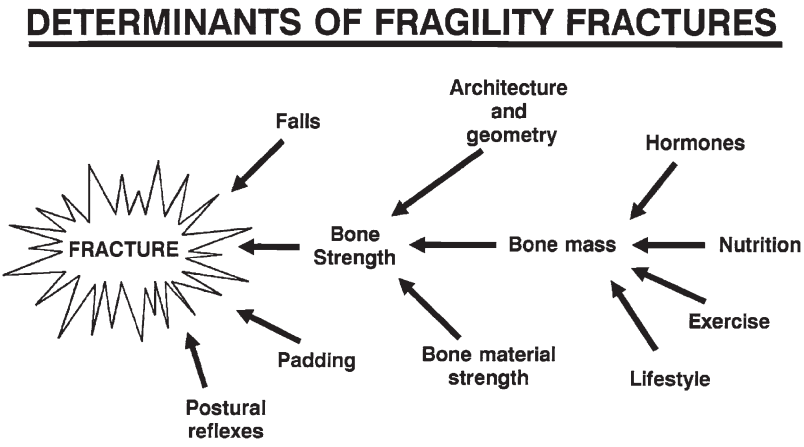


Fig. 4.6 Factors that contribute to fractures (Adapted from, Heaney, 1996.)

arises from a number of different factors, but skeletal fragility is certainly important. Bone strength can be negatively affected by reduced bone mass, poor bone architecture (e.g., reduced trabecular connectivity), and accumulating fatigue damage (Heaney, 1996).

Bone is continually being remodeled.Vitamin D, a steroid hormone induced in the skin by ultraviolet light, is essential in bone and calcium metabolism (DeLuca, 1988; Holick, 1994). In the mature adult, bone formation often does not replace 100% of the reabsorbed bone. This imbalance in bone formation is dependent on age, hormones, and calcium intake (Institute of Medicine, 1997; National Institute of Health, 2005; Canadian Conference, 2006). For example, the number of osteoblasts decreases with age, whereas low estrogen level and low dietary calcium intake both increase osteoblast formation. Low estrogen concentration also increases the depth of the bone cavity. This latter type of bone loss is irreversible and has serious negative consequences for bone strength (Power et al., 1999).

There are many factors that contribute to the susceptibility of the older adult to negative calcium balance. Both intake and absorption decline, excretion increases, and bone reabsorption becomes greater than bone formation. The body's ability to adapt to different calcium intakes through the calciotropic hormone systems decreases with age until it is essentially nonexistent at an age of about 80 years. The active calcium transport system is Vitamin D dependent and involves synthesis of a calcium-binding protein (DeLuca, 1988; Holick, 1994).

In women there is a dramatic increase in bone loss during the 5 years immediately following menopause (Kovacs and Kronenberg, 1998, see Fig. 4.7). This high rate of bone loss is only minimally affected by calcium supplementation (Prentice, 1994). Hormone replacement therapy can prevent this loss, especially if combined with calcium and Vitamin D supplementation (Heaney et al., 1989; Heaney, 1996; Institute of Medicine, 1997).

More than five years after menopause the rate of bone loss decreases. It is at this time that calcium supplementation has been shown to be effective at reducing bone loss, especially in conjunction with Vitamin D supplementation (Institute of Medicine, 1997; Canadian Consensus Conference, 2006). Bisphosphonates have also been shown to reduce bone loss. Combination therapies that include calcium, Vitamin D and, for women, hormone replacement therapy or HT, all help to reduce bone loss in older adults (Heaney, 1992, 1996; Recker et al., 1999), although the magnitudes of the effects are in question (Jackson et al., 2006).

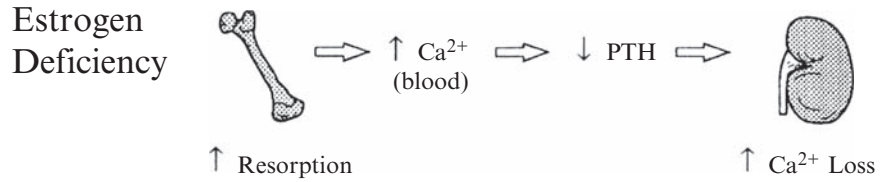


Fig. 4.7 Estrogen deciency (Adapted from Kovacs and Kronenberg, 1998.)

Bone health and HT: The WHI studies have only reconfirmed what was learned from a number of studies about bone loss and bone stabilization in women on HT. In one study, for example, the risk of hip fracture increased with both age and number of years from menopause for both HT and placebo groups (Cauley et al., 2003) (see Fig. 4.8). Women randomly assigned to HT, however, had significantly fewer fractures across age and years from menopause than did the placebo control group. Interestingly, this effect was most pronounced among women with high calcium supplementation (Cauley et al., 2003). Women with calcium intakes below 1,200 mg/d showed little benefit from HT; women on placebo showed little (or even a negative) benefit from having calcium intakes over 1,200 mg/d. So, at low calcium intake there was essentially no difference between HT and placebo, and women on placebo appeared to have a higher risk of fracture with high calcium intakes than they did with low calcium intakes. But with high calcium intake, HT clearly lowered the risk of fracture.

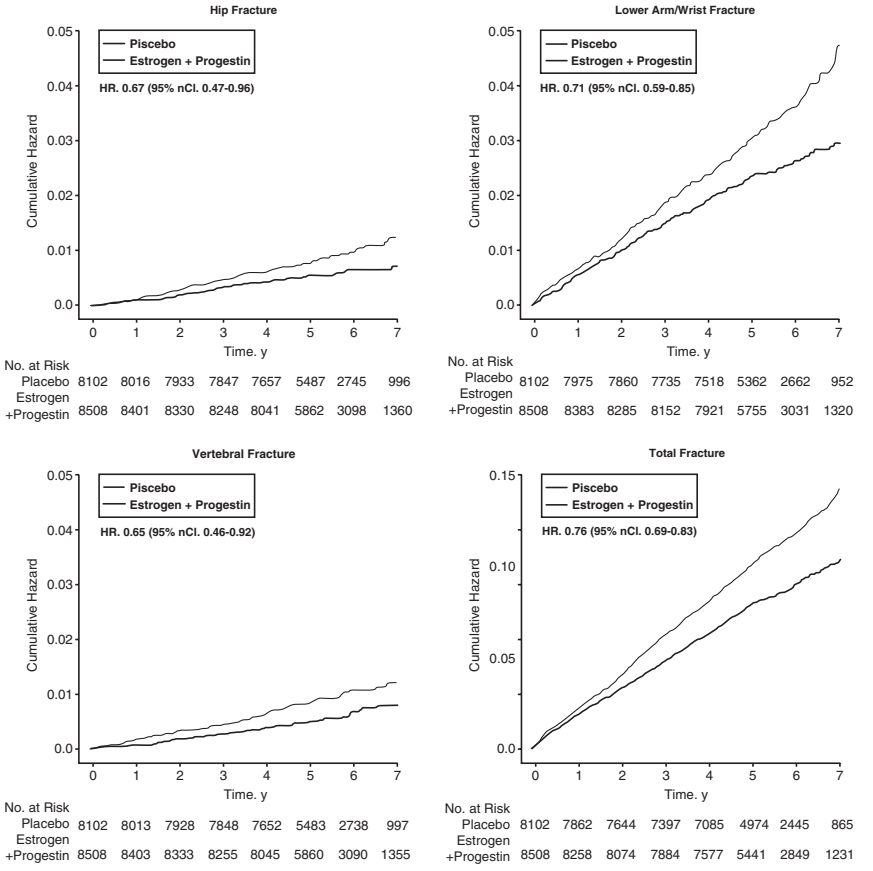


Fig. 4.8 Reduction of bone fractures with HT (Permission granted, Cauley et al., 2003.)

High initial bone mass index, or BMI, was generally protective against hip fracture risk for both groups, but women with high BMI already appeared to gain no particular benefit from HT regarding hip fracture risk. The study did show a benefit from HT for risk of all fractures for all BMI generally, however, and HT clearly increased bone mineral density for women in the study HT involving both estrogen and progestin, and estrogen only, decreased hip fractures (Cauley et al., 2003; Anderson et al., 2004).

A number of epidemiological studies (e.g., Banks et al., 2004) have confirmed these observations, many of which have saturated the literature (Hutchinson et al., 1979; Canadian Conference, 2006). Banks et al. illustrates a palpable truism: fractures increase with age, but diverse forms of HT can provide protection from bone fracture, and that protection stops with the discontinuation of HT (see Table 4.3). Thus HT confers no long-term protective effects; bone mass protection is only observed among those women who stay on HT. Importantly, the time that HT is taken may be an important factor. The closer to the onset of menopause that HT begins, the fewer fractures reported. The strength of the Banks et al., study is that it included 138,000 women in the US; the weakness is that it relied on self-reporting.

Importantly, other forms of bone sustaining compounds, such as bisphosphonates (Institute of Medicine, 1997; Canadian Consensus, 2006), also decrease fractures. There are clearly alternatives to the bone sustaining effects of HT. For example, in a double blind study involving nearly 300 women, ibandrontate reduced vertebral fractures by over 60% (Heaney et al., 1989; Heaney, 1996). The pathogenesis of bone loss is clearly linked to decreases in estrogen (Seeman, 2002), but numerous factors such as early vs. late menopausal expression (Bainbridge et al., 2002), physical activity, calcium intake, and body weight (Gerdhem et al., 2003) also impact bone metabolism. Moreover, despite the reduction of bone fractures there are still an elevated number of bone fractions among older women who are currently on or have been on HT (Nelson et al., 2002).

In addition, randomized control trials with alternative non-estrogenic compounds – selective estrogen receptor modulators or SERMS – have shown a decrease in bone loss and cholesterol levels (Delmas et al., 1997). SERMS are a class of molecules that do not promote mammillary growth factors (Canadian Consensus, 2006). In one study of ralixofene, for example, for women 45–60 years old bone mineral density was significantly increased in spine, hip and neck (Delmas et al., 1997). This study included women who had been on the raloxifene for 24

Table 4.3 (Greendale et al., 1999)

Generic Name	Regimen
Conjugated equine estrogens (Premarin)	0.625 mg oral daily
Estropipate (ogen)	0.625 mg oral daily
Micronised 17-Beta estradiol valerate (Climaval)	2.0 mg oral daily
17-Beta estradiol transdermal patch (Estraderm)	0.05 mg four times daily
17-Beta estradiol implant (Riselle)	25 mg every 6 months
17-Beta estradiol percutaneous gel (Estrogel; Divigel/Sandrena)	1.0 mg topically daily

*Doses are the lowest estrogen doses that prevent bone loss in randomized trials

Table 4.4 New vertebral fracture in 6,828 postmenopausal women receiving placebo or raloxifene hydrochloride therapy for osteoporosis (Ettinger et al., 1999)

	Placebo	Raloxifene 60 mg/d	Raloxifene 120 mg/d
Study group 1			
No. of women	1522	1490	512
Women with ≥ vertebral fracture, No. (%)	68 (4.5)	35 (2.3)	42 (2.8)
Study group 2			
No. of women	770	769	765
Women with ≥ vertebral fracture, No. (%)	63 (21.2)	113 (14.7)	82 (10.7)

Table 4.5 Risk factors that identify who should be assessed for osteoporosis

Major Risk Factors	Minor Risk Factors
Age 65 years	Rheumatoid arthritis
Vertebral compression fracture hyperthyroidism	Past history of clinical
Fragility fracture after age 40	Chronic anticonvulsant therapy
Family history of osteoporotic fracture	Low dietary calcium intake
Systemic glucocorticoid therapy 3 months	Smoker
Malabsorption syndrome	Excessive alcohol intake
Primary hyperparathyroidism	Excessive caffeine intake
Propensity to fall	Weight 57 kg
Osteopenia apparent on X-ray film age 25	Weight loss 10% of weight at Chronic heparin therapy
Hypogonadism	
Early menopause (before age 45)	

(From Canadian Consensus Conference on Osteoporosis, 2006.)

months. In another randomized control study with raloxifene, among women taking the drug for 3 years there was both increased bone mass and reduced vertebral fractures (Ettinger et al., 1999) (see Table 4.4).

To summarize, although all older people lose bone mass and strength and are thus at increased risk for serious bone fractures, HT in women clearly helps maintain bone mineral density, and reduces the risk of fracture. Moreover, risk factors for osteoporosis should be made transparent (see Table 4.5).

4.5 Teeth and Skin

Teeth: Positive results from studies of HT and bone fractures have been easily extended to teeth. In one study, the subjects were 488 women ages 72–95, surveyed on the 23rd cycle of the Framingham Heart Study (Krall et al., 1997). Data was collected on the history of HT use, duration of HT use, number of teeth and overall tooth retention, as well as smoking status, alcohol use, weight, and education level.

The findings indicated that specific teeth are more likely to be retained in any event. Canines, incisors, and premolars seem to be retained regardless of estrogen

use, although overall, women who use estrogen are more likely to retain these teeth than women who are not on HT. Duration of estrogen use also increased the total number of teeth present in the study population. Women who reported use of HT for more than 8 years retained significantly more teeth than women reporting estrogen use from 1–4 years and 5–8 years. Further, the percentage of women with complete loss of teeth decreased among women who had ever taken estrogen replacement.

In another study, women who were part of the Leisure World Cohort (Paganini-Hill, 1995 see also Krak et al., 1997) were asked about number of teeth, use of dentures, HT use and duration, and dentist visits. The average age of the population was 81 years, with cohorts beginning at age 70 and ending with those women over 90 years. Tooth count decreased significantly with age, but in all but the youngest age group, it was higher in the estrogen group than among non-users. HT users were less likely to have complete tooth loss than non- HT users, and, as with tooth count, the proportion of edentulated women decreased as duration of HT use increased. Denture use was less prominent among HT users than non-users, and current ERT users did not differ from past HT users in having dentures. Clearly, HT use reduces the risk of tooth loss.

Effects of HT on Skin: Physical beauty as it is associated with femininity has always been one of the primary allures of HT, and in a culture in which sexual appeal is a vehicle of both power and submission HT is knotted to the larger social milieu (Houck, 2006). The effects of HT on skin are advertised regularly (Whittaker, 1998), and feature prominently in anecdotal accounts amongst women as to the benefits of HT.

As with teeth, menopause takes its toll on the skin. Aging generally produces dryness of skin tissue. Two randomized control trials conducted to date have both indicated that skin is affected by HT use (Maheux et al., 2000; Pierard-Franchimont et al., 1999). Both sets of findings suggest a positive impact of HT use on skin tissue (Sator et al., 2001) (see Table 4.6 here).

Table 4.6 Two randomized controlled clinical trials (adapted from ACOG, 2004)

Authors	Design	Key Findings	Conclusions
Maheux et al. 1994	Double-blind, randomized, placebo controlled, n=30 per group treated with 0.625 mg CEE or placebo for 12 months; skin biopsy	Increase in dermis thickness at 12 months by biopsy; increase in skin thickness at 12 months by ultrasonography	Estrogens may reduce skin aging changes
Sauerbronn et al. 2000	Double blind, randomized, placebo controlled, n=21 E2 valerate + CPA; n=20 placebo for 6 months; skin biopsy	Increase in collagen fibers with HT; no differences in skin thickness or elastic fiber content	HT results in significant increase in collagen fibers.

CEE= conjugate equine estrogen; E2 estradiol; CPA= cyproterone; HT= hormone therapy

4.6 Conclusion

The risk of breast cancer associated with HT is palpable and real, but the answer to the question of whether the risk outweighs the benefits is not transparent. Recent reports have suggested a decline in breast cancer with a drop in HT use (McNeil, 2007; Anderson et al., 2007). In 2003 alone, there was a 7% decrease in the incidence rate for breast cancer, which was seen both for in situ cancers (5.5%) and malignant cancers (7.3%; Ravdin et al., 2007). The decline in 2003 was most evident in patients older than 50, and was posited to have occurred largely because of a decrease in the incidence of estrogen receptor positive breast cancer. Interestingly, women ages 50–69 saw a dramatic 12% decrease in incidence. While there is clearly an increased risk of breast cancer, enhancement of bone health is a clear-cut gain. The risk of breast removal is perhaps considered to be more menacing than the risk of bone loss to younger women at the beginning of menopause than that of older women later on. The process of estimating that risk may result in different perceptions of the extent and nature of potential danger by patients, doctors, and even experts (e.g., Harman et al., 2005; Grimes and Lobo, 2002; Walter et al., 2004).

One important point is to maximize patient choice and patient knowledge with an enhanced communicative ethic between the physician and the patient (Smith, 1996). There is wide variation for the reasons to either stay on HT, discontinue its use, or to never go on it in the first place (Bosworth et al., 2005; Taylor et al., 2006; Faulkner et al., 1998; Wathen, 2006). Informational sources for patients are of course physicians and other health care professionals, in addition to friends and family, magazines, Internet sites, and other sources of the media (Wathen, 2006).

There is great need to develop further interventions that promote the health-related literacy of patient/physician interactions and the knowledge bases of both (Schillinger et al., 2002; Detmar et al., 2002) while demythologizing the context of what to expect from a medical intervention such as HT. One wants the patient to be empowered by choice; HT may be a particularly good area in which to promote the cultural evolution of patient rights, patient knowledge and patient choice.

Estrogen and progesterone are fundamental hormones that play a large role in the regulation of the internal milieu. They are not simply tied to reproduction. The clinical studies that have been reviewed have identified some conditions in which HT has protective properties, and other conditions in which HT does not. The WHI studies identified significant increases in risk for invasive breast cancer in the estrogen plus progestin group, results that are consistent with the Million Women Study in Great Britain. Endometrial and ovarian cancer incidence was not greatly affected (nor was lung cancer incidence or total cancer incidence); and colorectal cancer incidence may even be reduced by HT. Other studies have found that hormone replacement therapy improves bone, tooth, and skin health. Given the dangers of osteoporosis in an aging population, this is no small advantage.

Within this confusion of bad news and good news lies another important fact; administering replacement hormones is not as simple as replacing insulin to repair a diabetic. In other words, it's not just a matter of replacing a missing substance. The aging body is a changing body, and the natural loss of hormones over time is part of that process of change. The physiological complexity of these fundamental hormones must be understood and set in the context of a therapeutic idea that transcends the relative simplicity of the insulin/diabetes model (Turgen et al., 2005; Nilsen and Brinton, 2003).

A number of investigators argue that many of the effects of HT may be age-dependent (Rossouw, 2005; Harman, 2005; Canadian Consensus, 2006; North American Menopause Society, 2007), and perhaps they are right. Others have suggested that risk is dose-dependent. Low dose is often construed as the safest approach (Brynhildsen and Hammar, 2002). Results from observational studies linked to the WHI and other studies (e.g., Ettinger et al., 2001; Prestwood et al., 2003; Nilsson and Heimer, 1994) suggest that lower doses (e.g., 0.25 mg/d of 17B-estradoil) of HT can be effective and, indeed, current research efforts are oriented to use minimal doses of estrogen and progestin intermittently in HT. Further, a primary focus of current research examines the use of lower doses for younger women (Barrett-Connor et al., 2005).

There is little question that bone loss is reduced in women on HT. Estrogen combined with progestin reduced the observed hip and clinical vertebral fracture rates by one third compared with placebo (Cauley et al., 2003; Banks et al., 2004). But there is variation in bone loss in women (Wells et al., 2000), and there are diverse alternative methods to retard bone loss (Institute of Medicine, 1997; Canadian Consensus, 2006). Women's decisions about HT need to take those factors into account (Papaioannou et al., 1998; Gass and Taylor, 2001; Canadian Consensus, 2006). Women and their physicians also need to know about alternatives to HT, and right now the extent of that knowledge is quite variable (Power et al, 2006; Wathen, 2006; Geller et al., 2003; Ma et al., 2006).

The two major trials, the WHI here in the States and the Million Woman study in Great Britain, were stopped due to preliminary findings of increased risk for cancer. There are arguments on both sides as to whether or not this should have occurred (Speroff, 2004; Beral et al., 2002; MacLennan and Sturdee, 2002), but it did. Risk analysis is contingent upon the background baseline of disease and vulnerability (Col et al., 2001, 2003; Eyre et al., 2004; Peterson et al., 2004; Kanis and McCloskey, 1998). The issue remains whether the use of HT during earlier and at intermittent lower doses might prove therapeutic (Speroff. 2004; Grimes and Lobo, 2002; Barrrett-Connor et al., 2005; Rossouw, 2005). Bad news, good news: physicians and patients need to know about and consider all factors as they apply to individuals before making a truly informed decision.

Chapter 5
Brain, Mood, and Cognition

5.1 Introduction

A philosophical mind-experiment asks, if a mad scientist kidnapped you and your best friend, and translated your brains into each other's bodies – where would YOU be? Almost any modern person would immediately answer, "Where my brain is." It's unlikely that any scientist, mad or otherwise, will be performing that experiment any time soon, so we don't have an empirical answer. But the immediacy of our response, our confidence as to where our self is located, reveals a strong bias in Western culture towards the mind as our source of identity, and the brain, intelligence, and memory as its means of expression. Any process that impedes our cognitive function is a source of real concern. It means not only loss of function, but a loss of self.

Estrogen, as it happens, impacts cognitive performance, as is shown in diverse animal studies (McEwen et al., 1997; Gould and McEwen, 1993). Estrogen and other hormones are tied to much more than reproduction. They are knotted to brain activity, neuronal protection and perhaps memory (see Fig. 5.1). As a result, prior to WHI studies, most researchers believed that HT most likely had preventive properties with regard to cognitive decline (Yaffe et al., 1998), and many physicians prescribed HT with this aim in mind (Rolnick et al., 1999). Results of WHI studies have tempered this belief, but physicians and patients still have fears and hopes regarding the effects of HT on mental function.

But hormones have a global impact across the body, and steroid hormones such as estrogen and testosterone impact a wide range of functions, including metabolism, immunological functions, cell growth and differentiation and behavior (McEwen, 2001). Studying the effects of these hormones in isolation can be very misleading. With this in mind, in this chapter, I describe some of the basic science behind the effects of estrogen on brain and behavior, before discussing the question of whether HT affects mood/mental health, the possible effects of HT on memory and cognitive function, and the relationship between HT and the expression of Alzheimer's disease. Women considering HT, and the doctors advising them, need to consider these issues as part of their overall decision making process.

J. Schulkin, *Medical Decisions, Estrogen and Aging.*

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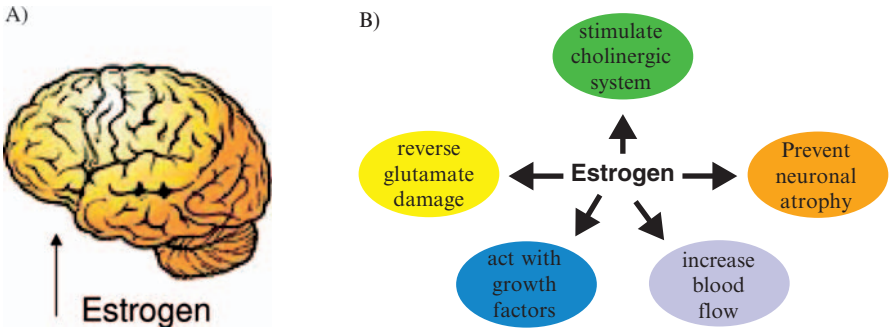

Fig. 5.1 Diverse effects of estrogen on brain

5.2 Estrogen and the Brain

Behavior and brain function: Estrogen receptors are present in many parts of the brain. The most recent data indicate the presence of both the alpha and beta forms of estrogen receptors. Estrogen receptors have been localized in the cerebral cortex, hypothalamus, pituitary, brainstem, the limbic system – including the hippocampus – and the frontal, cingulated, and primary olfactory cortices (Pfaff, 1980, 1999). Many of these regions play important roles in cognition, memory and mood. In addition, estrogen's effects on neuronal growth and development are well known. Exposure of the brain to estrogens profoundly affects both its morphology and its function during critical periods of neonatal development (Goy and McEwen, 1980). Extensive aromatization, which converts testosterone to estradiol, occurs within the brain.

Later in life, following the menarche, there is evidence that changes in neuronal structure and function occur as estrogen levels fluctuate during the female estrous cycle, as can be seen in the rat model. Estrogen fluctuations influence, for example, spatial learning (e.g., Hampson, 1990; Hampson and Kimura, 1988), effects which are mediated by neuronal changes in the brain. The effects can be rapid or delayed, membrane-related or genomic (McEwen et al., 2001). From an evolutionary point of view, one function of estrogen is the arousal of behavior, increased attention and locomotion. Estrogen increases the behaviors linked to environmental adaptation, and by increasing the expression of diverse neuropeptides and neurotransmitters, ensures the behavioral expression essential for adapting to changing environments (Pfaff, 1999; McEwen and Norton, 2005).

Brain and Behavioral Activity: In animal studies, estrogen and progesterone combined are known to increase oxytocin receptors and to facilitate the onset of female reproductive behaviors, particularly by their actions within hypothalamic tissue (Pfaff, 1980, 1999). They influence energy levels and appetite in addition to sexual arousal. These hormones are important to the female body and brain, beyond obvious reproductive functions. Several studies have identified changes in how the level of estrogen influences behavioral activity and metabolic turnover.

Curt Richter (1934), the psychobiologist at Johns Hopkins, long ago noted that rats deprived of estrogen have decreased levels of running behavior. One known important effect of estrogen's central neurotransmitter gene expression is to increase the expression of dopamine and serotonin and other neurotransmitters (Pfaff, 1999). Central dopamine is fundamentally tied to the organization of action and the prediction of reward (e.g., Schultz, 2002; Berridge and Robinson, 1998). The induction of central dopamine by estrogen mobilizes the organization of behavior – in the case of running behavior, searching for a reward, solving problems, etc.

Elevated levels of estrogen are associated with greater arousal in animal studies (e.g., Richter; 1934; Pfaff, 1999; Morgan et al., 2004), as well as with greater alertness to sensory signals, increased motor activity, and increased reactivity (Morgan and Pfaff, 2001; Morgan et al., 2004). Estrogen levels, in animal studies, are linked to (1) enhanced alertness to sensory information, (2) more motor activity, (3) more emotional responses and (4) better performance on diverse cognitive tasks. The effects of estrogen on systems in the brain are multidimensional.

Neural Function: Estrogen has also been implicated in the promotion of neurogenesis in animals, particularly in regions of the brain such as the hippocampus, a region that is important for memory (Gould and McEwen, 1993; Abrous et al., 2005). For example, intra-hippocampal estradiol implants facilitate spatial memory by activating cholinergic expression in the brain (Packard et al., 1992). Moreover, evidence suggests that regions of the hippocampus demonstrate changes in syntaptic density that correlates with levels of estrogen (see Fig. 5.2) (Woolley and McEwen, 1993; Woolley et al., 1997).

Estrogen also seems to promote neuroprotection from brain damage by the regulation of diverse gene products (Garcia-Segura et al., 2001). In fact, many genes that underlie behavioral and physiological adaptation are regulated by estrogen, including endorphins, growth and neurotrophic factors, etc. (Pfaff, 1999). Thus estrogen's effects on diverse systems, including the rebuilding of bone are derived from its regulation of genomic systems in the brain. Some of estrogen's more outstanding effects include the rebuilding of neural tissue, and the regulation of neurotransmitters such as cholinergic neurons (Toran-Allerand et al., 1992; Packard et al., 1996; Rapp et al., 2003). The effects of estrogen on the hippocampus also impact cognitive performance and problem solving, such as memory tasks (Gibbs, 2006).

These study results hold implications for many cognitive functions across the life span, which have enhanced the arguments for prescribing HT as a means of controlling age-related loss of cognitive function, and have perhaps encouraged unrealistic expectations about estrogen-related therapies.

We can be confident about the structural and functional consequences of elevated levels of estrogen; they are profound. As estrogen levels fluctuate naturally, they expand and then deflate hippocampal neurons (Woolley et al., 1997). It is well known that the natural variation in hormone levels influences diverse cognitive functions in women (see Fig. 5.3) (Kimura, 1995, 1999). Enhanced verbal acuity and memory are features frequently linked to elevated levels of estrogen, either occurring naturally across the estrous cycle (Hampson and Kimura, 1988), or through estrogen treatment (Estabrooke et al., 2002).

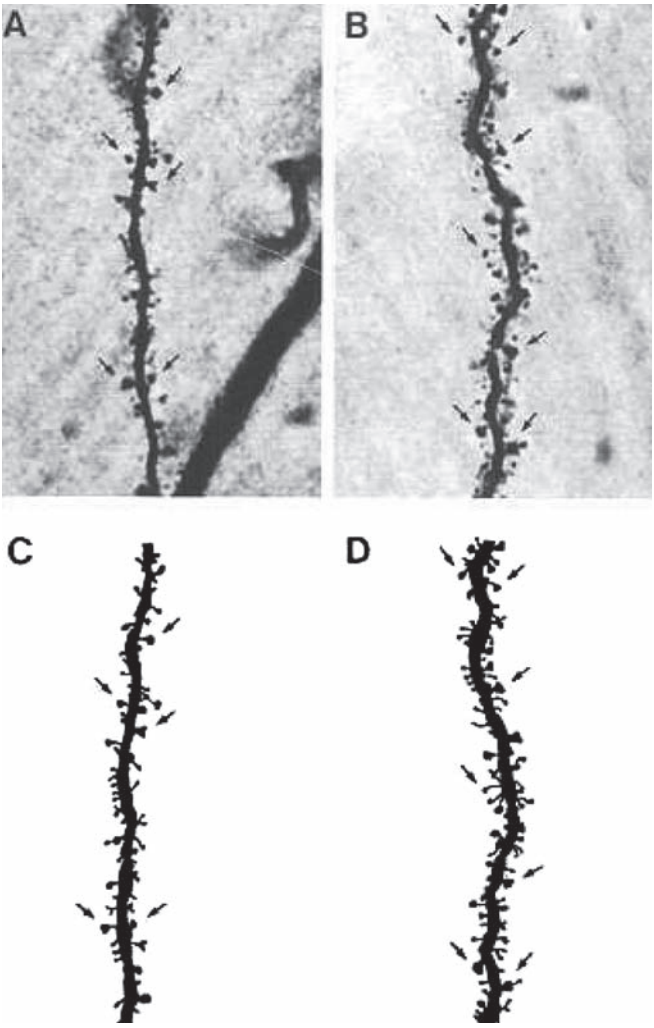

Fig. 5.2 Increases in neuronal dendrites in estrogen (B, D) treated rats in the hippocampus as compared to controls (A, C) (Adapted from, Wooley et al., 1997.)

These exciting research findings hold promise for understanding why HT is potentially important for maintaining hormone levels outside of the reproductive years. There is a broad set of evidence demonstrating the importance of estrogen on hippocampal synapse formation (Kretz et al., 2004), prefrontal cortex formation (Hao et al., 2006) and showing that high levels of estrogen promote a number of

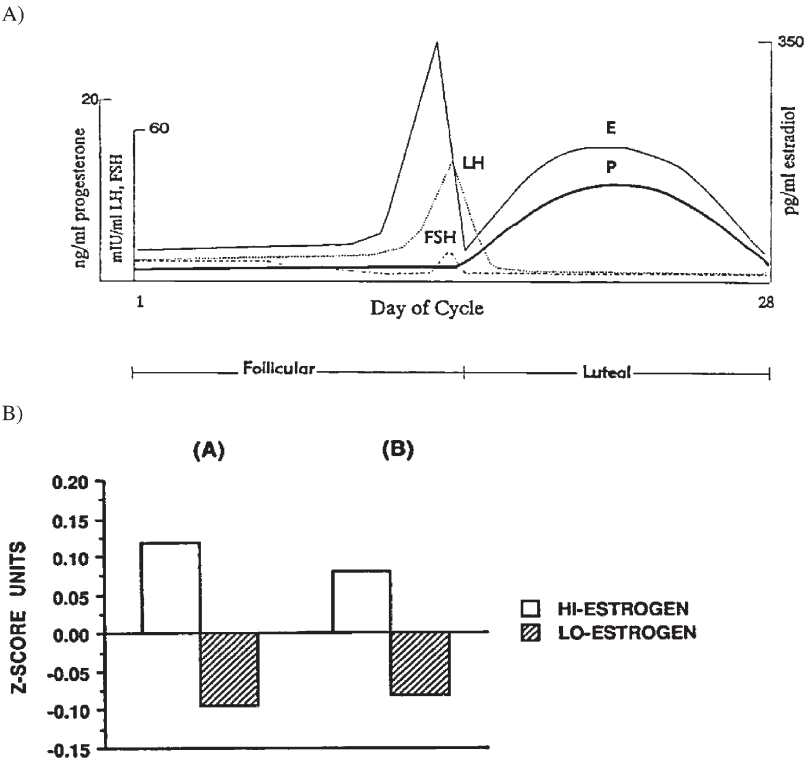

Fig. 5.3 (A) Levels of hormones (B) Women's performance on two cognitive measures (articulatory word speed and accuracy) with either high or low levels of estrogen (Permission granted for Hampson and Kimura, 1990.)

behavioral functions, including memory formation (Leuner et al., 2004; Luine et al., 2003). The presence of estrogen receptors throughout most areas of the brain highlights the potentially ubiquitous role of this class of steroid hormones. In particular, animal experiments indicate a role for estrogens in memory and mood through the induction of neuropeptide gene expression in the brain (McEwen, 2002). These are the endocrine factors that set the conditions for hot flashes, mood changes, and cognitive performance and decrements in cognitive functioning, to which we now turn.

But our conception of brain activity is continuous with the larger culture in which we live, in the respect that we afford older people, and the way in which we participate with one another towards an evolving sense of how we age. Concepts of human dignity and the importance of quality of life reflect the larger values through which we understand our activities. The normative issue, in other words, is simply

to be living to be older (Callahan, 1990, 2003; Caplan, 1989, 1997), but the way in which we live as older adults, and the relative autonomy with which we can control our actions. It is with these values in mind that we turn to the effect of HT on mental health, cognitive function, and age-related disease processes.

5.3 Hormone Therapy, Mood, and Mental Health

Just as physiological changes occur around menopause and are linked to levels of estrogen, so too must women experience some psychological response; most notably many women experience a variation in sexual interest and other motivated behaviors (Dennerstein et al., 1980; Castelo-Branco et al., 1998; Kovalevsky, 2005). But sexual and other mood-related responses always take place in the context of the larger cultural milieu in which we find ourselves, the expectations that are imposed on women by society, and the empowerment of the individual (e.g., Kaufert and McKinlay, 1985; Houck, 2006). To offset these social influences on choosing HT, many women's health care sites are designed normatively to empower women and to enhance the range of options and choices that they can make (see Fig. 5.4) (Wathen, 2006). The relationship between menopause, mood, and HT is not a simple one of supplying a missing substance, and women deciding whether to undertake HT need to capture all those nuances.

There is a widespread belief that depressive disorders become more prevalent around the menopause, which suggests a role for estrogen in mood states. A major problem in assessing this relationship is the fact that depression affects 10 –20% of adult women in North America. This high prevalence is demonstrated by the widespread use of antidepressants. Fluoxetine (Prozac) is one of the top five most prescribed drugs in the United States – conjugated estrogen (Premarin) is another. A number of women who were never depressed become depressed during the perimenopausal period, and in general there is a reported increase in clinical depression at menopause (Rubinow et al., 2002; Schmidt et al., 2000; Schmidt, 2005). But it is important to keep in mind that the vast majority of women do not become severely depressed during the menopausal period (Schmidt, 2005).

After all, menopause usually coincides with a time when many external life changes occur, such as children leaving home, changes in employment status or job responsibilities, increased responsibility for elderly parents, and losses through the death of friends and loved ones. Both men and women thus are at risk for developing a lowering of mood in midlife. Most people are able to cope with these life changes, especially when confronted with only one or a few in a given year, but the stress can lead to mild forms of depression. For about 10% of women, this depression is severe enough to require pharmacological intervention (Schmidt, 2005). It is possible that the level of physical discomfort that women face at menopause, such as hot flashes and vaginal dryness (Schmidt, 2005; Grigoriadis and Sherwin, 2006), as well as emotional and cultural factors such as fear of aging (Lock, 1993, 2005; Bell, 1987; Houck, 2006), precipitate changes in mood and depression in themselves, apart from the direct effects of a drop in estrogen levels. In one randomized double blind control

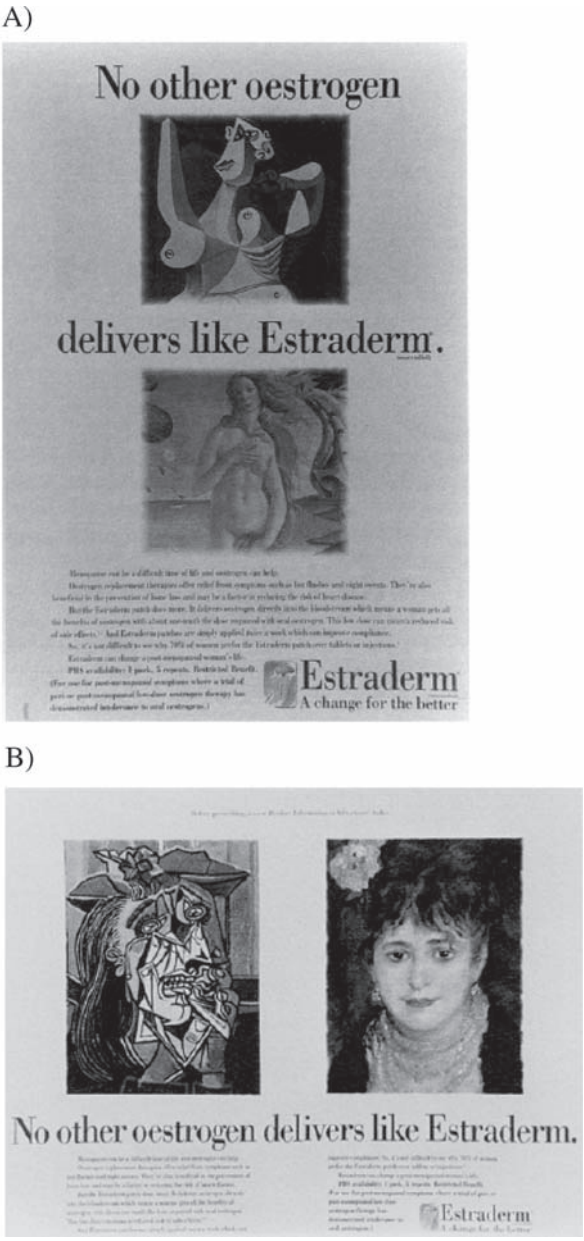

Fig. 5.4 Advertisement for an estrogenic compound (Permission granted from Whittaker, 1998.)

study from HERS, investigating the effects of HT on quality of life issues, the greater the experience of physical and emotional discomfort due to menopausal symptoms, the greater the improvement in quality of life that women on HT experienced (Hlatky et al., 2002).

But there is also some evidence to support a direct relationship between hormone levels and mood. Going back to the 1930's, there have been attempts to link estrogen treatment to amelioration of altered and dysphoric mood states (Rubinow et al., 2002; Schmidt, 2005). Sherwin and her colleagues, for example, studied healthy menopausal women, randomly assigning them to one of four HT regimens in order to examine the effect of estrogen–progestin hormone replacement therapy; conjugated equine estrogens were used. Increased levels of estrogen correlated with higher mood scores. There have also been several placebo-controlled studies, which have included measurements of quality of life, which have found estrogen treatment to have significant effects in ameliorating depression (Schmidt et al., 1998; Soares et al., 2001).

However, it is important to note that, while estrogen may produce statistically improved mood scores in some of these studies (Rubinow et al., 2002; Grigoriadis and Sherwin, 2006; Schmidt, 2005), the distribution of scores were primarily in a clinically normal range even prior to treatment. That is to say, patients were not clinically depressed at baseline, being within the range of normal mood both before and after therapy. Under these conditions, subjects may have been unable to notice any difference in how they felt. Alternatively, they actually did notice, and the question is whether anyone should be concerned enough about subclinical levels of depression to consider using a drug regimen to modify them. Most women just do not seem to undergo hormonal changes so severe that they result in true depressive disorders during the menopausal transition period and during menopause. Medicating for mood during menopause may be an over-medicalization of the problem.

Other studies have found that HT, both with and without progestin, may influence a number of aspects of quality of life that are related to mood, but the effects are not terribly pronounced. In a massive randomized double blind study from the WHI (Hays et al., 2003) that examined sexual function, sleep, physical activity, energy, and other mental health measures, there was a marginal effect on these functions in older women (mean age 62) who were being treated with estrogen and progestin as compared with those on a placebo. In another study from the WHI (Brunner et al., 2005) that examined women who had had a hysterectomy and who were treated with estrogen alone, there were very similar mild improvements in their health-related quality of life.

To complicate matters, some women develop depression while they are taking estrogen supplements. There is some evidence that the differential effects of various estrogens and the way they are administered should be considered (Canadian Consensus Conference, 2006).

So while HT can, in some instances, improve mood state and sense of well being, its effects have not proved to be extensive. Women and their doctors might first want to consider changes in physical activity and nutrition, which can profoundly influence motivational states, including sexual motivation (Purdie et al., 1995; Greendale et al., 1996). Studies of selective serotonin re-uptake inhibitors (SSRIs) in lieu of estrogen have shown effectiveness in alleviating symptoms of anxiety and insomnia, but not irritability and hot flashes (Rubinow et al., 2002).

One model that is evolving in view of this evidence links estrogen with serotonin (Rubinow et al., 2002; Schmidt, 2005). The loss of estrogen input is believed to challenge the serotonergic system and may even result in clinical depression.

On the whole, the data do not support HT alone as a therapy against depression (Morrison et al., 2004; Schmidt, 2005), though there short-term estradiol may reduce some depressive symptoms (Schiff et al., 2005). Further, HT should not be considered a hormone treatment like insulin, which is used to alleviate a particular symptom for which death may result without remediation. HT is more like a contributing factor, one factor amongst others, in the treatment of mood and mental health.

5.4 HT's Effects on Memory and Cognition

Memory is not a uniform, one-dimensional phenomenon. There is no one system that underlies memory; rather, there are multiple memory systems (e.g., James, 1890, 1952; Squire, 1987; Schacter, 1996). Dimensions of memory include working and reference memory (or long term memory), declarative and procedural memory, and also specific kinds of memory linked to different cognitive/neural systems. Memory in humans depends on a complex interplay of discrete inputs, including vision, hearing and other sensory and expression paths. A decline in memory often parallels aging, with a broad range of decline recognized. This age-linked decline is currently thought to be independent of any specific hormonal effect, though some researchers challenge this assumption. Specific manifestations of age-related loss of memory include poorer performance on tests of recall and recognition of lists of words or word-pairs, and poorer memory of short paragraphs and verbal or visual stimuli. By contrast, memory tasks that do not require short-term storage and retrieval of material show little, if any, change with age. Similarly, memories of events in the remote past remain fairly intact (James, 1890, 1952; Schacter, 1996).

Estrogen is well known to promote and facilitate diverse forms of learning in animals, and to generate neural growth and to sustain neural transmitter function (McEwen et al., 2001). Many studies have provided evidence for positive links between HT use and cognitive capacity (Grigoriadis and Sherwin, 2006). Others have shown no effect, and yet others have shown clearly negative effects (Yaffe et al., 2003). Evaluating the evidence is difficult, and factors such as type of cognitive skill and age of participant must be considered.

Perhaps the most consistent finding of an effect of estrogen on memory revolves around verbal and working memory. In one study, women with an average age of around 50 who were on HT (estrogen alone or estrogen and progesterone) for at least a month were administered memory tests. The results indicate that their performance on verbal tasks was enhanced by HT (Duff and Hampson, 2000). However, not all studies duplicate these results, in particular not in older women. And there may be other critical variables that this test did not account for: route of action of HT; other naturally occurring processes that diminish with menopause and are not restored by hormone replacement; the type of hormone (including class

of estrogen, and combination with progesterone or not); and perhaps even dosage levels (Sherwin, 2005; Gleason et al., 2005).

Brain imaging studies, in which estrogen was given to postmenopausal women, shows that estrogen does activate brain regions, and enhances performance on working memory tasks (Shaywitz et al., 1997) perhaps via central cholinergic neurotransmitter regulation (Van Amelsvoort et al., 2003). In addition, one study, for example, has found that in healthy women HT is associated with a decline of muscarinic receptor binding and better verbal memory (Norbury et al., 2007). Another possible mechanism, for which there is supporting data, is the estrogenic promotion of central dopamine activation (Craig et al., 2004), the promotion of diverse forms of other neurotransmitters, and neuropeptide gene expression that includes serotonin and oxytocin (Pfaff, 1999).

In prospective studies, which included double blind placebo-controlled studies, positive effects were found in women on HT compared to those that were not. One study by Sherwin (1988) demonstrated enhanced performance on four cognitive tests (paragraph recall, clerical speed and accuracy, and abstract reasoning) in women on HT compared to placebo controls. In an earlier study, Fedor-Freyberg (1977) found enhanced performance on five cognitive tests: Stroop test, reaction time test, visual search task, and two attention tasks.

Estradiol has been reported to enhance visual memory in a number of studies. For example, Kimura (1995) measured the performance of menopausal women on cognitive (visual memory) tests and found that, in all tests, women in the HT group performed at a better rate than women in the placebo group. In another test, Kampen and Sherwin (1994) found that women on HT performed better on memory tasks for recall of written paragraphs than women on placebo. Resnick et al. (1998) found that visual/spatial function is enhanced in women on HT.

Elevated levels of estrogen can facilitate performance on numerous different tasks (Hampson and Kimura, 1988; Hampson, 1990; Kimura, 1999; Sherwin, 2005). There are even reports that such effects are relatively rapid following initiation of HT. Women who had been on HT for as few as two to three weeks, have been reported to demonstrate enhanced responses on cognitive tasks (Wolf et al., 1999; Duka et al., 2000). On the other hand, a randomized control study (Schiff et al., 2005) found that mood was elevated in women on HT, but it did not alter cognitive functions.

Population-based studies have also yielded somewhat conflicting results. Analyses of women enrolled in the Rancho Bernardo (Barrett-Connor et al., 1999) study identified no difference in performance on a variety of neuropsychological tests between current estrogen replacement therapy users, past-users, and women who had never been treated. The hypothesis that estrogen deficiency is associated with a decline in cognitive function in postmenopausal women was not supported, though test performance did worsen with age. But older women with high endogenous estrogen levels performed significantly worse than younger women on two of three cognitive function tests.

On the other hand, a number of studies have demonstrated that HT is associated with improved performance in such specific areas of functional testing as higher paragraph recall, recall of proper names, verbal abilities, memory and cognitive

abilities. However, other studies failed to confirm these findings and, overall, studies continue to produce mixed results (see review by Low and Anstey, 2005). These inconsistencies may be the result of the varying study populations, different study designs, the psychometric tools used, the type of estrogen preparations in use, and other confounding variables. On the whole, however, the observational data do suggest some positive effects of estrogens on specific areas of memory and cognitive function, and indicate that HT may lead to improvements in memory, reaction time and attention.

Sherwin and her colleagues (1988a, b, 1990; 2005; Philips and Sherwin, 1992a, b; Sherwin and Tulandi, 1996) examined the differences between pre- and postoperative scores on several psychometric scales in premenopausal women undergoing total abdominal hysterectomy and bilateral salpingo-oophorectomy for benign disease. Following surgery, subjects were allocated to one of four conditions: placebo; estrogen alone; androgen alone; and estrogen/androgen. The findings indicated that all of the women who received any of the hormone preparations maintained their scores, while the placebo control group showed significantly decreased scores. The cognitive domains that responded favorably to hormonal therapy included short and long-term verbal memory, perceptual speed and accuracy, and abstract reasoning.

However, the WHI double-blind study yielded no positive effects of HT on memory tasks (e.g., spatial and temporal memory tasks, immediate and delayed recall of events, abstract reasoning, demands on following directions, sentence and writing constructions, etc Rapp et al., 2003), and found that HT perhaps even exacerbated cognitive decline in a subset of women (Espeland et al., 2004). This study included thousands of women tested for diverse kinds of cognitive performances. Of course, these were women over 65 years of age, for whom the beneficial cognitive effects of HT may simply be too late.

Studies with SERMS have thus far been inconsistent as well. One study in postmenopausal women treated with raloxifene for 3 years found no overall beneficial effect (Yaffe et al., 2001), while another study using a higher dose of raloxifene (120 mg/kg per day) seemed to have some beneficial effects in reducing cognitive impairment in a subset of women (Yaffe et al., 2005).

Despite the contradictory evidence from the many different studies of cognitive functioning, one recurrent theme is that the effects of HT appear to be more consistently positive in younger women (Canadian Consensus, 2006). In fact, some data on memory functions specifically support this claim (Henderson, 2005). For instance, in one study, women were observed over different periods of time (from 5 to 15 years) after terminating HT treatment. These women were all treated for a short duration, but had only entered menopause six months prior to the study. They were on HT for 2 years and then tested in diverse cognitive tests that tested for memory at age 65. Those that were treated with HT during the earlier phases of menopause did significantly better on memory tasks than the other groups not similarly treated. All trials used 1–3 mg of 17 Beta estradiol combined with progestogen, except one when women received 75–1.5 mg of piperazine estrone sulfate (Bagger et al., 2004, see also Phillips and Sherwin, 1992; Sherwin and Tulandi, 1996).

Gross clinical alterations of memory and cognition are generally apparent to the observer (Toran-Allerand, 2004, 2005), but to detect more subtle changes, one must use complex and specific psychometric tools. It is critical to remember this distinction. Gross alterations in memory and cognition represent recognizable disease processes. Minimal changes, which can be detected through precise scales, may ultimately affect the quality of life or high-level performance of an individual, but oftentimes go undetected or don't relate to recognizable diseases or disease processes. While HT does seem to have some positive effect on cognitive function, does that benefit outweigh any contraindications? Doctors and patients have to consider relative levels of risk and benefit when deciding whether hormone replacement therapy is appropriate.

5.5 HT and Alzheimer's Disease

Watching someone you love become a victim of Alzheimer's Disease (AD) is one of life's saddest events. The incidence of dementia rises with age, and Alzheimer's is becoming increasingly prevalent in a population of aging individuals, of which many more are women, most likely because they live longer than men (see Fig. 5.5). Perhaps nearly half of nonagenarians have AD (see Fig. 5.6) (Plouffe and Schulkin, 1998; Grigoriadis and Sherwin, 2006).

Losing one's own self may be an even more frightening prospect than losing a loved one, and loss of a core self, of course, is dramatically expressed in AD, a degenerative disease of the nervous system (e.g., Goedert and Spillantini, 2006; Robertson and Mucke, 2006). Besides personal loss, Alzheimer's is a great expense both societally and monetarily. So it is important to understand what roles estrogen and estrogen replacement therapy may play in the incidence and course of AD (see Table 5.1).

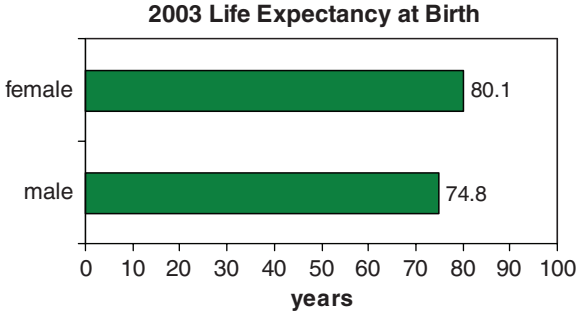

Fig. 5.5 Years lived by men and women in the United States

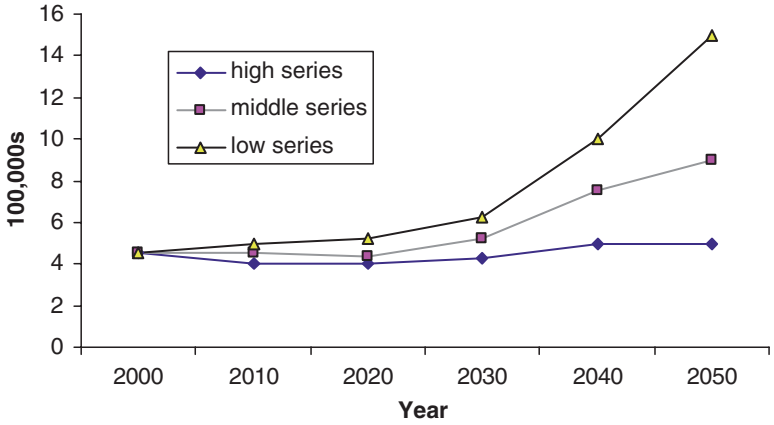

Fig. 5.6 Prediction of Alzheimer rates (Adapted from, Hebert, 2001.)

Table 5.1 Diagnostic criteria for Alzheimer's disease (from Henderson 2000)

Clinically ascertained Alzheimer's disease ('probable Alzheimer's disease')

(1) Dementia
  (a) Cognitive deterioration affecting
    (i) Episodic memory, plus
    (ii) At least one other area of cognitive functioning
  (b) Cognitive deterioration severe enough to interfere substantially with daily activities
(2) Dementia symptoms beginning in middle age or later
(3) Cognitive deficits not solely attributable to clouding of consciousness
(4) Gradual onset and progression of cognitive deficits
(5) Based on a thorough medical evaluation – one that includes neurological assessment, mental status testing, and appropriate laboratory tests – no other illness that could account for the patient's dementia

Pathologically verified Alzheimer's disease ('definite Alzheimer's disease')

(1) Dementia
(2) Neuropathological verification of numerous neuritic plaques in hippocampal and neocortical regions, usually accompanied by widespread neurofibrillary tangle formation in hippocampus and neocortex

Prevention: The most pronounced reduction in neuron numbers in AD brains is in the CA1 region of the hippocampus, and this loss is not replicated in age-matched controls (West et al., 1994). While many individuals can be expected to show the histopathological changes of AD, only about half of these women will ever display clinical symptoms of AD. Therefore, the degenerative process probably precedes by many years clinically evident "aging" of the brain. If this is so, estrogen administration after menopause will not necessarily decrease the risk of AD in elderly women. HT may be beneficial, however, if it is administered before there is deterioration of neural tissue. That is, the timing of HT might be crucial in preventing the development

of AD, and indeed some evidence suggests that early HT administration reduces some of the cognitive impairments that may occur late in life (Bagger et al., 2004). Animal studies reinforce the view that the timing of the HT is critical with less sensitivity with aging (Adams et al., 2001, 2002)

Treatment: Suppositions regarding estrogen's benefits in treating AD stem from studies that generally confer on estrogen a role in protecting neurological function (McEwen, 2002). A few clinical reports are available on the use of exogenous estrogen in women with AD. One such study demonstrated that three of seven women who received 2 mg/day micronized estradiol had improved scores on the Mini Mental State Examination (a rather demoralizing title) and on the Randt Memory Test (Fillet et al., 1986) after 6 weeks of treatment, while the others showed no change. A small study by the Japanese National Institute of Mental Health found improvement over 6 weeks on the New Screening Test for Dementia in six of seven women with AD, all of whom were treated with 1.25 mg/day of conjugated estrogens (Sano et al., 1996).

Taken together, these early small-scale studies suggest that estrogen is beneficial in the treatment of AD. One meta-analysis of relevant studies confirms a consistent trend suggesting that estrogens may improve cognition, reduce the risk of dementia, and improve the outlook for patients with AD (Yaffe et al., 1998). However, they did not recommend the routine use of estrogen replacement therapy for the sole purpose of prevention or treatment of AD until appropriate clinical trials were performed.

One study on treatment with high-dose estradiol found improved cognition in women with AD (Asthana et al., 2001). Using a double-blind, parallel-group design, subjects were randomly assigned to receive either 0.10 mg/day of 17β-estradiol or a placebo by a skin patch for eight weeks. After the week eight evaluation, treatment was discontinued and subjects were followed for an additional eight weeks. A comprehensive battery of neuropsychological tests was administered to each subject at baseline, at weeks three, five, and eight on treatment, and at week 16, off treatment. The battery targeted the cognitive domains of attention and memory that characteristically are impaired in subjects with AD. Estrogen-treated subjects demonstrated improved performance over baseline on a test of selective attention relative to subjects who received a placebo. Women who received estrogen demonstrated improved performance over baseline on verbal and visual recent memory, compared with women randomized to the placebo group. With respect to verbal memory, subjects in the estrogen group outperformed placebo subjects on total recall of the Buschke Selective Reminding test during the two-month treatment period. Women who received estrogen were able to name a greater number of pictures on the Boston Naming Test than were women who received only a placebo during the two- month treatment period. The findings of this study suggest that short-term administration of a high dose of estrogen is associated with significant improvement in verbal memory, visual memory, and attention for postmenopausal women with AD.

The WHI study: Unfortunately, one the WHI studies looking at HT effects on memory or dementia (Shumaker et al., 2003) yielded bad news. Shumaker et al. conducted a randomized, double-blind, placebo-controlled clinical trial that included 4,532 postmenopausal women free of probable dementia, aged 65 years or older.

Estrogen plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older. In other words, estrogen plus progestin therapy did not prevent mild cognitive impairment in these women, but, in fact, worsened it. On the other hand, this study is based on one dose of HT, these were older women, and the cognitive tests were not exhaustive or rich.

Other evidence from the WHI is also not positive. In another study, Shumaker et al. (2004) followed a subset of the WHI population, testing for dementia and mild cognitive impairment (MCI). This study found numerically equivalent increased risk of dementia for women on estrogen alone and for women on estrogen plus progestin, as compared with women on placebo, though only the combined HT result was statistically significant. The pooled data indicated a significantly greater risk of dementia and/or MCI in women using HT as compared with women on placebo. Over the course of the study, 310 women displayed symptoms of either dementia or MCI, out of approximately 10,000 women enrolled (178 on HT; 132 on placebo).

The number of events is small, but the data show no protective effect of HT, and actually indicate an increased risk of cognitive impairment. Thus, the WHI study provides no evidence to support giving HT to prevent dementia or MCI. Again, however, the women in the study were all over 65, and it is possible that HT given to women at the time of perimenopause/menopause might have different – and beneficial – effects. The authors suggest that HT might have negative effects on vascular health in the brain. This may reflect the fact that the women were all over 65 – and that there may be a reason to believe the stage of AD interacts with effects of estrogen.

Another study from the WHI (Espeland et al., 2004) looked at approximately 2,800 women assigned to either estrogen alone or placebo. The population is the same as for the estrogen alone results in the Shumaker et al. (2004) study above (age 65 + and dementia-free). This study analyzed the data on global cognitive function as assessed annually by the Modified Mini-Mental State Examination (3MSE). The study found that performance on the test improved over the first 2 years in both women receiving estrogen and the placebo group, but that the rise was smaller for the estrogen group. The estrogen groups showed no further rise after 2 years, and indeed may have declined, while the placebo group continued to show increasing scores for several more years. The reasons for their improved performance are not clear. It is possible that the increased performance in the placebo group was due to a repeat-test taking effect. The results were similar to those found for women on combined HT therapy. The decline in performance was most evident among women with low baseline scores. Among women with above average scores, there was no difference between HT and placebo.

Again, these women are all over 65, and the authors again raise the issue that HT may have exacerbated underlying vascular disease in the brain. The authors caution that the cognitive tests that were used do not capture performance on individual domains of cognition, which may explain why these results differ from previous studies that found a benefit from HT. Those studies found it to enhance verbal memory specifically, as compared with general cognitive performance. And finally, the authors point out that in laboratory animal models, giving estrogen sooner rather than later

after ovariectomy can make a big difference in cognitive performance. Thus, HT use at menopause may still result in enhanced cognitive abilities 20 years later, but giving HT to women 20 years after menopause may have no beneficial effects, and indeed may be harmful.

The suggestion that HT may accelerate cognitive decline due to underlying neural vascular disease continues to be investigated. And clearly, the results of the WHI trials do not definitively prove that estrogen has no beneficial effects on cognition. Yaffe et al. (2005), in a solid review of the literature, concluded, as many have, that recommending HT for Alzheimer's is ultimately unwarranted and perhaps dangerous. Subsequent studies have borne this position out. While early treatment may be effective, once the disease has crept in, hormone therapy may have no effect, and it might even make matters worse. Since Alzheimer's appears to take root long before its clinical symptoms appear, and since the only means of reliably diagnosing AD right now is via brain autopsy, figuring out who may benefit from preventive treatment is a difficult proposition (Henderson, 2004).

5.6 Conclusion

Prior to the WHI, there was a sense that HT could help avert cognitive decline (Yaffe et al., 1998). Evidence-based reviews suggested that cognitive functions possibly affected by the decline of estrogen were ameliorated in some cases by HT (MacLennan et al., 2004), although conflicting data clouded the impact of HT on the functions of mood and clinically-related health and cognitive performance.

But the WHI studies found either no effect of HT on cognitive performance, or found decrements in performance and an enhanced vulnerability to dementia. Moreover, one can reasonably suggest that under the many different conditions in which it is now administered, HT is not a prevention for Alzheimer's disease, nor are symptoms associated with early menopause such as hot flashes nor estrogen therapy necessarily impact cognitive capacity (LeBlanc, et al., 2007). While the WHI studies are easily criticizable for the age at which the subjects were tested and the kind of estrogenic compound that was used, nevertheless, the sheer size of the WHI population alone means its results cannot be ignored.

The result, right now, is a status quo effect. People are entrenched in their views with no resolution in sight. What we can say is that a window of opportunity may have been missed with the WHI studies. More modesty in predicting the impact of the study might have allowed researchers to take a more nuanced view of the effects of HT on mood and cognition, rather than "taking sides" as if this were a battleground rather than an enlightened inquiry into a complex situation. From the earliest studies, it was clear that estrogen therapy was not some sort of simple replacement regime like insulin for diabetics, but that many interactive systems and dynamic processes were involved. As more research is done, experts need to keep that in mind if they are to tease out precisely how HT may affect cognitive function and mental health.

It still seems possible that some HT cocktail, periodically administered, would be effective if begun early in the perimenopausal period. A number of investigators have noted that there is very little data, really, for the perimenopausal periods (e.g., Grigoriadis and Sherwin, 2006), and one recent double blind randomized study suggests that HT shows some protective effects on cognitive functioning in recently menopausal women (Dunkin et al., 2005). Hormone therapy should not be considered out of the question with regard to cognitive functioning, since surely the animal research continues to show diverse protective effects of estrogen on cognition.

In addition to investigating the impact of administering HT at different times, researchers also need to expand the range of estrogenic compounds studied by creating new ones and using diverse sources of compounds. Most of the studies in the United States have used Premarin. Results with other compounds have thus far been underwhelming (Krebs et al., 2004; Grady et al., 2004), but given the positive effects in the animal research (e.g., Brinton, 2002; Brinton et al., 2006; Gibbs, 2006; Rasgon, 2006), testing of additional estrogenic compounds could be crucial. We define ourselves by our minds, and attribute much of our quality of life to our mental capacity. Given our aging population, no stone should remain unturned in our quest to discover the effects of HT on cognition and mood.

Chapter 6
Physicians' and Women's Responses to HT Findings: Implications for Continuous Learning and Self-Corrective Inquiry for Physicians

6.1 Introduction

John Dewey in his book *Experience and Education* famously said "that all human experience is ultimately social, that it involves contact and communication" (p. 38) and ultimately requires development and change; but his words apply to any field of intellectual inquiry, and they certainly have relevance in the field of medical decision making.

Learning is a lifelong process, not something that just happens in school. Physicians are especially aware that medicine is a continuously evolving field in which new and often contradictory evidence must be regularly evaluated and re-evaluated. But how we apply continuous learning, the lens through which we evaluate it, and the extent to which we are aware of specific biases and strive to correct for them in our decision making processes – the process of self-corrective inquiry – is perhaps less often addressed.

Hormone replacement therapy is not a unique vehicle for examining how physician and patient learning and decision making evolves with access to new information – revelatory information about cardiac stents, for instance, or the treatment of diabetes, have provided some of the same dramatic conditions leading to major rethinking in treatment regimes. What the HT story does uniquely provide, however, is a wide range of evidence over time about how doctors and women have radically reassessed, or failed to reassess, or partially reassessed the values and dangers of a specific therapy, a therapy that is also tied to many cultural and social perceptions about femininity and the aging process. In that way it is a useful template for looking at the medical decision-making process, how it works and doesn't work, and how it might be improved.

In this chapter, we will first look at the imperatives facing obstetrician–gynecologists as a group, before examining how both doctors and women were affected by the evidence of the WHI studies. Then we'll look at the process of continuous medical education (CME) and the implications that the recent HT findings hold for it.

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6.2 Learning and the Physician

The goals of continuous learning and self-corrective inquiry are perhaps more imperative for those physician groups that deal with a broad array of conditions and medical illnesses, such as obstetrician–gynecologists. Hormone replacement therapy represents a major challenge in that it involves so many bodily systems, has received so much media attention, is the subject of direct consumer advertising and remains unresolved medically, socially and scientifically. With such unbounded confusion and conflict in the field, some sense of intellectual resolution, coupled to inquiry and humility in the process of that inquiry, is an important objective.

It was not so long ago that obstetrician–gynecologists understood their profession as almost totally oriented toward reproduction: successfully delivering babies and managing pregnancies. That began to change, though, as women began to demand attention to their total health as distinct from the medical needs of males; and with that change in clinical focus, so changed their sense of the profession. What has emerged is an expanded medical practice, participating in a wide range of issues that affects women's health (Grimes, 1995; Gabbe, 1996). These issues include adolescent gynecology, infectious diseases both during and outside of pregnancy, mental health issues, social problems such as domestic violence and birth control, issues of gynecological cancers, and menopausal issues in older women.

Moreover, the field itself has changed with regard to who the practitioners are. Obstetrics–gynecology went from being a field predominated by men to what is projected, within several years, to be a field predominated by women in the United States (Cain et al., 2001; Emmons et al., 2006). The communicative skills that women perhaps bring with them to this field matter a great deal, given that the field has been especially affected by revolutions in women's rights, their control of and knowledge about their own bodies, and also the patient rights and patient choice movements.

How have obstetrician–gynecologists responded to these changes in their field of practice? A study of how they suggest treatments for depression within their practices may be illustrative of how they balance their broad general knowledge of a range of topics with the need for specialist consults. Our study found that obstetrician–gynecologists are willing to treat mild depression and willing to prescribe in the same manner as typical psychiatrists, namely, prescribing the right doses of a selective serotonin reuptake inhibitor [SSRI] if the patient decides to take this course of action. If the depression is severe, the obstetrician–gynecologist will direct the patient to a specialist. The strategy appears to be to self-manage the disorder under conditions in which the severity is within the bounds of their self-perceived medical competence (Schmidt et al., 1997; Dietrich et al., 2003), and to seek consultation with a specialist when the issue is beyond their expertise. In other words, they are willing to assist the patient as long as the depression is not too severe and beyond their sense of competence. Applying this principle to other areas, vulnerability to breast cancer through mutations of BRCA1/2 genes (Armstrong et al., 2004) with regard to prescribing HT would be a situation in which the primary care

gynecologist should seek consultation with a specialist. What helps guide and orient obstetrician–gynecologists in their providing evidence for patient decisions with regard to treatment is to consult or refer to evidence-based documents that specialty societies produce (Zinberg, 1997; Grimes, 1995; Farquhar et al., 2002).

It is within this context of an expanded practice that HT has become an issue for many obstetrician–gynecologists and their patients. The physician is required to help elucidate the pros and cons of a treatment, comprehend what the expectations of the patients are, and clarify the physician's own orientation. That means continuously being educated about topics and conditions on which they may be consulted, and this is perhaps particularly apparent with regard to HT, where new data are continuously throwing old beliefs into doubt, where there is still room for disagreement, where the risks are challenged by some and embraced by others, and where cultural values associated with femininity and aging underlie decision-making, not always at a conscious level (e.g., Bell, 1987; McCrea and Markle, 1984; Houck, 2006; Watkins, 2002).

But it is the patient who makes the decision, and women have consistently reported wanting more information about hormonal and non-hormonal treatments for menopausal transition (Theroux and Taylor, 2003). The WHI trials have perhaps highlighted this issue even further. We know from studies conducted to facilitate patient and joint patient–physician decision-making (Masse and Legare, 2001) that women experience greater conflict when not given some control over treatment choices. Hormone therapy is a quintessential example of the importance of patient/physician interactions in decision making (Mort, 1996, 2001) as physicians and their patients discuss the diverse forms and approaches to HT (Shoam and Kopernik, 2004). Patient-centered decision- making (Eckman, 2001) looks to provide more contexts in which physicians inform their patients about the pros and cons, to explain the ambiguities in the research, to elucidate medical issues and to continue to revise their practices, in this case with regard to HT. Of course, this is no easy task for the physician, amidst the pressure of time, knowledge, practice and lawsuits.

6.3 Placed in Context: Physicians' Beliefs about HT and Responses to the WHI

The results of the WHI studies dramatically affected the prescription of HT and have impacted physician beliefs, attitudes and practices (cf. Bestul et al., 2004; Ettinger, 2003; Ena and Rozenberg, 2003; Hillman et al., 2004; Haas et al., 2004; Hess et al., 2005; Schonberg et al., 2005; Heitmann et al., 2005). The conclusions regarding just how physicians have responded to the WHI, presented in this section, are largely based on two recent studies. The first (Power, Zinberg and Schulkin 2006a) was initiated soon after the estrogen and progesterone arm of the WHI was terminated; the second was conducted at the end of 2004 and the beginning of 2005, following the suspension of the WHI estrogen-only arm of the WHI study (Power, Schulkin and Rossouw 2007). The overall design of the two studies was very similar, and

both were intended to understand something about the beliefs, practices and responses of physicians to the HT findings. Within this time period the major results of the WHI studies had appeared in peer reviewed journals.

Major findings from the WHI studies: There is still heated debate about the significance of some of these results, especially regarding the age at time of testing of the participants and the kind of hormonal treatment used. It is clear that the debate continues, and that debate is quite passionate with regard to HT. Nonetheless, this is where it stands now with regard to the WHI, as most physicians understand it (see Table 6.1):

In the context of the above results, we asked obstetrician–gynecologists if they were aware of the WHI findings. Virtually all of the obstetrician–gynecologists in the 2003 study were aware of the findings of the WHI, and nearly all knew that the trial was stopped due to the preliminary results regarding increased risk for breast cancer, heart attacks, and strokes. In the second study, while the vast majority of obstetrician–gynecologists reported being aware of the termination of the estrogen and progestin arm of the study, only three-quarters knew that the estrogen arm of the trials had been terminated as well.

Decision to stop the trials: Though aware of the increased disease risk found in the WHI, almost half of the respondents (47%) disagreed with the decision to stop the trial, and almost half (48%) did not find the research reports convincing (see Fig. 6.1).

Those physicians who have taken HT or had an immediate family member take HT were less convinced by the research, although this result disappeared after controlling for year of residency and thus may be related to older people being more likely to have taken HT or to have a family member who did so (see Fig. 6.2). Current knowledge regarding HT was also found to be a significant factor, with a majority of those who rated current knowledge as comprehensive not being convinced by the evidence. Perhaps related to knowledge, physicians with a favorable view of alternative therapies to HT were more likely to accept the evidence of the WHI. This may be a reflection of these physicians' beliefs that there are credible alternatives.

The length of time respondents had been in practice was a factor in whether or not they agreed with the decision to end the trial. Those who had completed their

Table 6.1 The effects of combined treatments or estrogen only

Risk or benefit	CEE + MPA [2,5]	CEE [3,5]
Heart attack	↑	No change
Stroke	↑	↑
Venous thrombosis	↑	↑
Breast cancer	↑	No change
Colorectal cancer	↓	No change
Hip fractures	↓	↓
Dementia	↑	↑

CEE = conjugated equine estrogens 0.625 mg daily; MPA = medroxyprogesterone acetate 2.5 mg daily

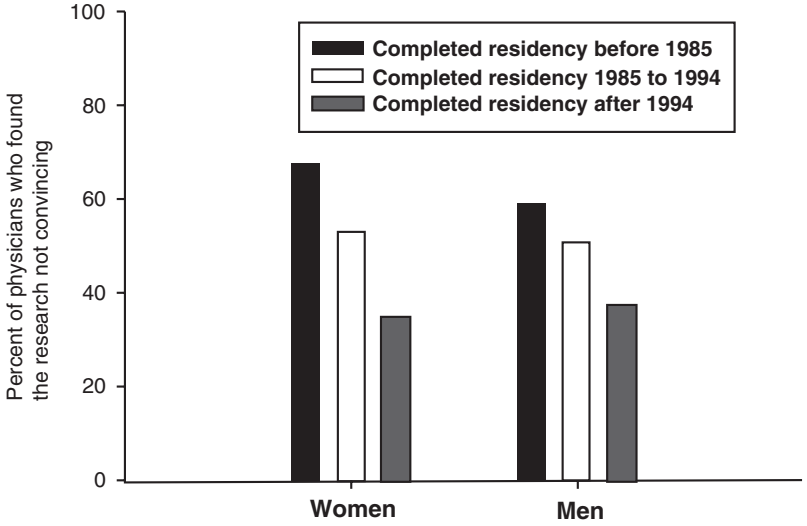

Fig. 6.1 Percent of physicians who did not find the WHI results convincing (Adapted from Power et al., 2006a.)

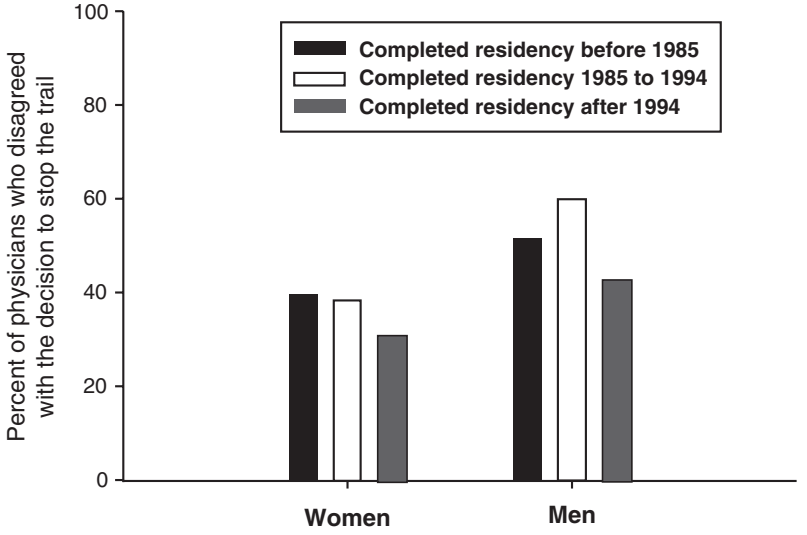

Fig. 6.2 Percent of physicians who did not agree to end the clinical WHI trials (Adapted from Power et al., 2007.)

residency prior to 1995 were less convinced by the research and disagreed with the decision to end the trial. These clinicians were also more confident in their ability to counsel patients and to interpret the scientific literature compared with those who completed their residency in 1995 or after.

A slight majority of physicians (54%) thought it possible to continue to enroll subjects in more randomized controls. Male physicians were significantly more committed to the trial not being terminated than were female physicians. Women obstetrician–gynecologists generally report less skepticism with regard to the results of the WHI studies than men (Power et al., 2006a).

Nearly half of the physician respondents suggested that additional clinical trials are necessary, specifically trials at different dosages, and that more trials need to be conducted with estrogen-alone. In addition to believing there is a need for examining the effects of different dosages, clinicians believe that such studies need to put greater effort into matching subjects on relevant variables. As a group, they were optimistic that more patients could be enrolled in randomized trials.

Prescribing patterns: Almost half of the respondents reported that they had prescribed HT to fewer than half their eligible patients in the last 6 months. The pattern of prescribing tended to be consistent with the physicians' individual opinions regarding the efficacy and safety of HT. Those physicians who regularly recommended prescribing replacement estrogen for their perimenopausal patients continued to think that there were greater benefits than risks from the treatment.

A minority (15.4%) of respondents prescribed HT only if the patient requested it. Among this group, nearly half responded that the risks of HT exceed the benefits for *postmenopausal* women, and two-thirds responded that the benefits of HT outweigh the risks for half or fewer of *perimenopausal* women. In contrast, among the nearly half of physicians who reported prescribing HT to more than half of eligible patients, two-thirds responded that the risks of HT were less than the benefits for *postmenopausal* women, and more than three-quarters reported that the benefits outweigh the risks for a majority of *perimenopausal* women. Somewhat more than half of responding physicians reported that their prescribing practices regarding HT were unlikely to change in the near future; however, four of ten reported that they were likely to prescribe HT less often (29.6% somewhat less likely, 8.5% dramatically less likely). This is consistent with the findings that prescriptions for HT had been reduced by 32% 9 months after publication of the WHI findings on combined HT (estrogen+progestin) within the physician population generally (Majumdar et al., 2004).

Calculating risk and benefit: With regard to the perception of risk factors, three-quarters or more of respondents indicated that a family history of breast cancer or of clotting disorders would influence them to not prescribe HT for a patient. Most respondents indicated that they would also be influenced by a patient's family history of colon cancer or osteoporosis, if the patient complained of sexual dysfunction, or if the patient complained of mood swings, in deciding whether or not to prescribe HT.

Most of the physicians who responded to the study thought that the *positive effects* of HT on menopausal symptoms include reducing hot flashes; reducing vaginal dryness and increasing sexual desire and satisfaction; reducing the incidence of bone fractures and increasing bone mineral density; reducing sleep disturbances; reducing urinary incontinence; reducing the incidence of colon cancer; and increasing the overall quality of life, including decreasing the incidence of depression. Respondents to the second study were less sanguine about the beneficial effects on

mental health than in our previous study; for example fewer subjects thought that HT was beneficial in the treatment of depression (see Table 6.2).

Most respondents also reported that the *negative effects* of HT on phenomena that have not been found to be associated with menopause, but have been found to result from HT, include increasing the incidence of clotting disorders, stroke, breast cancer, and cardiovascular disease. In general, physicians who had completed their residency more recently were less optimistic about the benefits of HT and more negative about the risks (see Fig. 6.3).

When one compares the earlier study (1995, published in Baron et al., 1998) with regard to the benefits of HT with the later one (2003, 2004, published in Power et al., 2006a, 2007) the change is in perspective with cardiovascular disease.

Alternative Therapies: Responding physicians were generally neutral or positive about alternative therapies to HT, with only 6.7% indicating that such therapies are harmful. Over a quarter of respondents considered alternative therapies to be viable treatment options, and an equal number responded that such treatments probably do more harm than good. A third considered alternative therapies to be at best

Table 6.2 The percentage of responding physicians that answered that HT was a viable treatment option for each of the following conditions (Data from Power et al., 2006a)

Hot flashes	97.2%
Vaginal atrophy	93.5%
Osteoporosis	75.3%
Loss of libido	61.6%
Depression	37.7%
Dementia	7.8%
Cardiovascular disease	2.6%

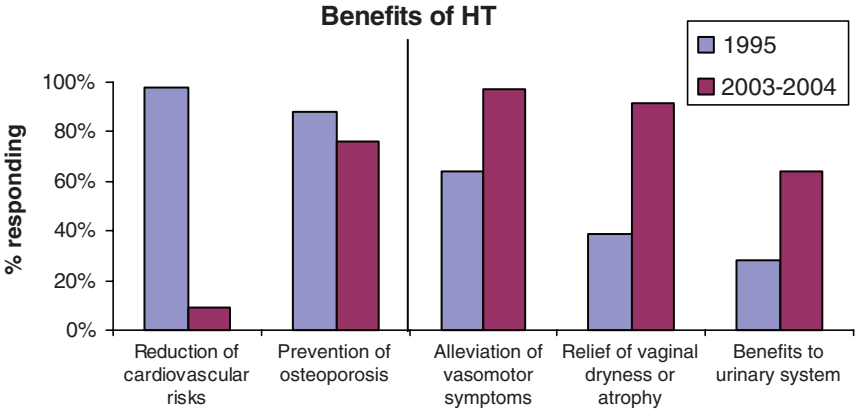

Fig. 6.3 Perceived benefits from physicians in two studies (Adapted from Baron et al., 1998; Power et al., 2006a.)

Table 6.3 Physicians' Application of Recent HT Research

"Given the results of the recent studies, what other factors would you consider when you decide how to apply them in practice?"	
Your own experience with patients, concerning benefits and short-term symptoms	76.3%
Results of case-control and other population studies (without random assignment but with attempts to match subjects on relevant features).	73.9%
Your own experience with patients, concerning possible long-term risks such as breast cancer or heart disease.	56.9%
Your knowledge of the basic science of how hormones work.	50.4%
Other evidence, such as sex differences in heart disease as a function of age.	39.6%
Animal studies.	14.5%
No other evidence when studies using random assignment are available.	8.8%

a placebo. Female physicians were more likely than males to consider alternative therapies to be viable treatment options, and older respondents were more committed to HT than were younger respondents.

Effects of the WHI Study on Physician Thinking and Practice: Knowledge about the WHI studies on HT was widespread amongst physicians, and all were affected in some way by that knowledge in terms of how they evaluated HT and in their prescribing practices. But some interesting patterns emerged. Women physicians and younger physicians (or at any rate those physicians who had more recently completed residency) tended to give far more credence to the WHI findings and to change their prescribing practices accordingly. Age/length of practice and sex also affected openness to alternative therapies. And doctors who had previously been committed to HT were more likely to be skeptical of the WHI findings, and to continue prescribing HT, than doctors who had used it less often (Power et al., 2006 Power et al., 2007; Power, Baron and Schulkin, 2008).

None of these patterns is particularly surprising and we could venture many reasons for all of them. But their importance here is what they imply about how physicians absorb and use new information, and how they correct, or fail to correct, biases in their decision making processes.

Table 6.3 outlines what other evidence obstetrician–gynecologists would consider important when deciding how to apply the results of recent studies to practice.

6.4 Women's Beliefs about HT and Their Responses to the WHI

Women's information about HT: Women often decide about HT after getting their information from a variety of sources (see Fig. 6.4) (Wathen, 2006).

Not surprisingly, one study (Haas et al., 2005) found that the percentage of newspaper articles reporting on hormone therapy across the country increased after

the HERS and the WHI studies. Along with this increase was a greater discussion of the harms and benefits of hormone therapy in these articles over time (see Fig. 6.5) (see Table 6.4).

The goal of one study conducted in the US by Breslau et al. (2003), was to understand women's knowledge of the new scientific data and their responses to the WHI and ovarian cancer study findings. The questionnaire asked about various health conditions, current menopause and ovary function, HT use and intentions regarding HT use, awareness of the HT studies and responses to the findings, health information sources, and satisfaction with information seeking. The women were

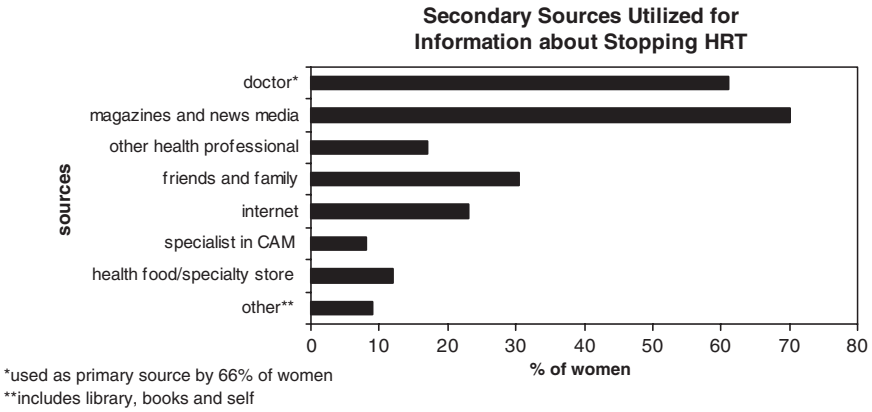

Fig. 6.4 Sources of information for discontinuation of HT (Adapted from, Wathen, 2006.)

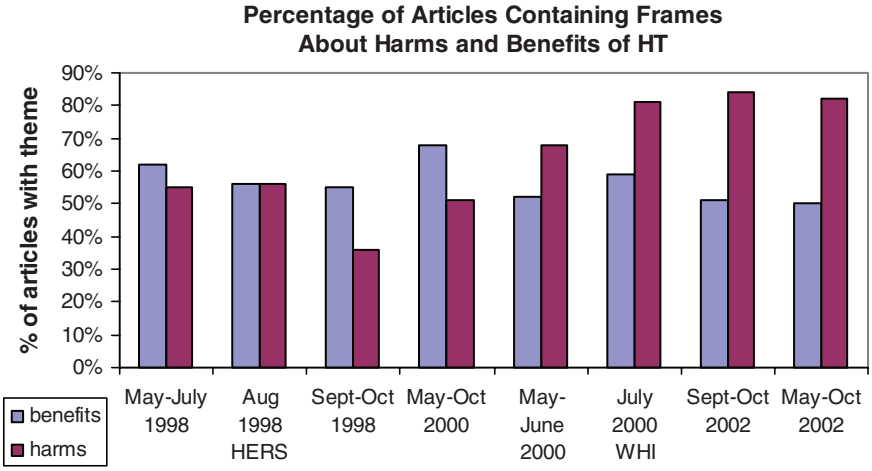

Fig. 6.5 Harms and benefits articles in the popular press in the US (Adapted from Haas et al., 2005.)

Table 6.4 Distribution of articles by location of local newspapers and by national newspapers that report an HT story (n=663)

Local newspaper sites	% of articles
Denver, CO	7.2
New Hampshire	0.6
New Mexico	3.8
North Carolina	13.1
San Francisco Bay area	10.8
Seattle, WA	10.9
Vermont	1.1
Subtotal local newspapers	47.5
Regional and national papers	
Boston Globe	4.5
Los Angeles Times	7.2
New York Times	14.5
Wall Street Journal	5.7
Washington Post	14.3
USA Today	6.3
Subtotal national and regional newspapers	52.5
Total	100

queried about whether they had cardiovascular disease (heart disease, stroke, or blood clots), cancer (breast, ovarian, or colorectal), or osteoporosis. The results suggested that the majority of women (64%) knew about the recent HT study findings. Not surprisingly, the greater their education level the more aware they were of the findings. Three-quarters reported not knowing what to do next. Only one-quarter of the respondents sought additional information. Those who planned to obtain or had obtained additional health information specified multiple sources: health care professionals, print media, Internet, social networks, and broadcast media. Premenopausal women had a lower rate of information seeking than did postmenopausal and perimenopausal women. Similar results from studies elsewhere were reported in a study in Great Britain (Welton et al., 2004) and in Germany (Hietmann et al., 2005) following the publication of the WHI and the WISDOM studies.

Power et al. (2006b) found that media reports regarding the WHI influenced patients' information-seeking behavior in the context of their visits to gynecologists. Physicians reported that, over the previous year, their patients had been asking more questions about HT and were also less likely to request HT. Patients were also more likely to discontinue using HT, more frequently sought information regarding alternatives to HT from their gynecologists, appeared to be more generally apprehensive about HT, and appeared to be better informed about the treatment. Physicians also reported that, overall, they were spending more time counseling patients about HT.

In yet another study, patients' responses to the news from both the WHI and the HERS were assessed (Power et al., 2006b). In this study, we compared groups of women based on age: One-fifth of participants were 40 years or younger, 27.3% were between 41 and 50 years, and half were over 50 years About a third of the responding

patients (36.7%) reported that they were postmenopausal, 18.8% reported they were currently undergoing menopause (perimenopausal), and 38.2% reported they were premenopausal (6.3% did not answer this question). Among respondents over 50 years, only 10.2% classified themselves as premenopausal. Almost one-quarter of respondents (23.3%) reported they had had a hysterectomy; this proportion increased to 37.3% among women reporting they were postmenopausal. Among peri- and postmenopausal patients, approximately equal proportions reported that they are currently using HT (33.0%), have stopped using HT (31.1%), or have never used HT (30.2%).

As expected, age, education, and whether a woman classified herself as pre-, peri-, or postmenopausal were all significant factors. For example, the proportion of women who considered themselves to be informed of the risks and benefits of HT increased with both age and menopausal stage. Fully 72.7% of women over 50 years considered themselves "well informed," compared with only 27.7% of women 40 and younger. Slightly less than half (48.5%) were aware of the findings from the HERS or the WHI. Women over 50 years were also more likely than younger women to respond that they know enough to make a decision regarding using HT based on current evidence (21.9% versus 8.7%). Among women over 50 years, the level of education she had attained was a significant factor in whether she was aware of the findings from HERS or WHI, but not in whether she considered herself informed regarding the risks and benefits of HT. Educational level also affected the extent to which these older women had considered the risks and benefits for themselves.

Patterns in HT use before and after WHI: Before the WHI studies, HT use was high, but women did not typically take replacement hormones for a long period of time (e.g., Saver et al., 1999; Roumie et al., 2004; Haas et al., 2004; Buist et al., 2004).

In the US, even before WHI, a great majority of women stopped using HT within a year or so. However, a subset did continue on HT to avoid a recurrence of symptoms such as hot flashes (Brett and Reuben, 2003), and many women continued with HT in order to avoid potentially aversive withdrawal symptoms (Grady et al., 2003). Following the news from the large-scale clinical trials, a report from Northern California noted that 50% of the women studied decided to not continue on HT after WHI results in 2002 (Ettinger et al., 2003). However, the women reported that they were not well informed about the WHI study, and many of them did not choose to discontinue until as much as 8 months after these results came out.

In another study of almost 170,000 women between the ages of 46–80, a dramatic decline in HT use was reported in over 40% of the women during the 4 months following the WHI major findings (Buist et al., 2004). Other studies found similar declines following the WHI reports (cf. Roumie et al., 2004; Hillman et al., 2004; Rolnick et al., 2005). For example, one major study reported that within 9 months after the WHI initial results from HT there was a 32% decrease in prescription patterns.

A study at the University of Florida (Levens and Williams, 2004) conducted in the aftermath of the WHI findings looked at women's decision making with regard to HT. Levens and Williams found that women were not inclined to terminate HT when it was used for the relief of discomfort associated with menopausal transition.

Most (70%) reported use for short-term relief of symptoms. Among the others, 16% reported that they were on HT for protection against osteoporosis, 10% for protection against heart disease, and 4% for protection against Alzheimer's disease. Women were aware of an increased risk of, for example, breast and heart disease, but they did not estimate the actual risk as it was reported in the WHI studies.

Another study (Rolnick et al., 2005), using a random sample from a data base from a pharmacy in Minnesota in 2002, looked at women's HT use and concerns just prior to the publication of the WHI, but following the HERS trial. Women reported modifying their HT use. The majority (63%) reported termination of use, and this was particularly true of older women. Forty-six percent of women reported using HT for bone protection, followed by cardiac protection (31%).

Calculating Risks and Benefits: In the Power at al. (2006b) study, respondents over 50 years were equally divided among those who reported currently using HT, those who reported terminating use of HT, and those who reported never having taken HT. Among these women, opinions were also about equally divided as to whether HT use after menopause would be helpful, harmful, or they did not know. More highly educated women were less likely than others to answer "don't know", but the women were still about equally divided between helpful and harmful.

Among women currently using HT, three-quarters reported that it would probably help them, while fewer than 4% believed it would harm them. Among women who had stopped using HT, two-fifths believed that HT use would be harmful to them. Among women who had never used HT, most (60%) reported that they did not know if HT would be helpful or harmful, although more believed it would harm them (24%) than believed it would help them (16.4%).

When asked about what factors made it difficult for them to evaluate the risks and benefits of HT, the most frequently endorsed option was individual preferences and lifestyle of the woman (43.1%), followed by the conflicting results of scientific studies (31.1%), the belief that the risks and benefits are very close (16%), and the belief that not enough studies have been conducted (13.5%). Seven percent reported believing that such studies cannot be trusted because of conflicts of interest.

Opinions were fairly evenly divided regarding the risks and benefits of HT. Women over 50 years of age or who reported they were postmenopausal regardless of age were more informed (i.e., more likely to be aware of the HERS or WHI findings), and more likely to have made a decision regarding whether HT would be helpful or harmful to them. These results are consistent with the results of a telephone survey of women conducted in 2002 (Breslau et al., 2003) that found that both older women and college-educated women were better informed regarding HT. In the Power et al., (2006b) study, women's decisions regarding HT were consistent; those who were currently using HT believed it would be helpful to them, and those who had stopped using HT were more likely to believe that it would harm them (see Fig. 6.6).

Alternative Therapies: Among all respondents in the Power et al. study (2006b), about a third thought alternative therapies do more good than harm, 30% thought they neither helped nor harmed, and relatively few felt that these therapies were harmful (8.4%). And in another study such alternatives are not well known to diverse health care providers (Geller et al., 2005). However, a large proportion

(26%) did not answer this question. Among those women who did answer, women under 50 years of age had a more favorable opinion of alternative therapies as compared with women over 50 years of age. About a fifth of respondents in this group reported that they had used an alternative therapy to HT, and the most frequently utilized alternatives were soy products and black cohosh. Interestingly, it appears that women often seek information on alternative treatment methods from pharmacists. (Rolnick et al. 2005).

The Quandary for Women Patients: About equal numbers of women (45% for both, in the Power et al. 2006b study) agree that scientists and physicians are sufficiently knowledgeable about HT to give appropriate advice, or agree that these groups do *not* yet know enough about the risks and benefits of HT to give appropriate advice. What are women to do? Relying on their own knowledge doesn't seem to be an entirely satisfactory answer. Although a majority of women in the studies cited consider themselves well-informed about HT, there is little consensus among patients of obstetrician–gynecologists regarding the risks and benefits of HT. Our evidence suggests that women are divided because of the conflicting findings, just as their physicians are divided over the course of medical action they should take. So how do physicians provide women with the information and advice they need – and, perhaps more importantly, how do they provide a sense of confidence and control amidst all the confusion?

A primary recourse may be for physicians to stay updated, and reinforce their decision making skills, through continuing medical education courses, to which I now

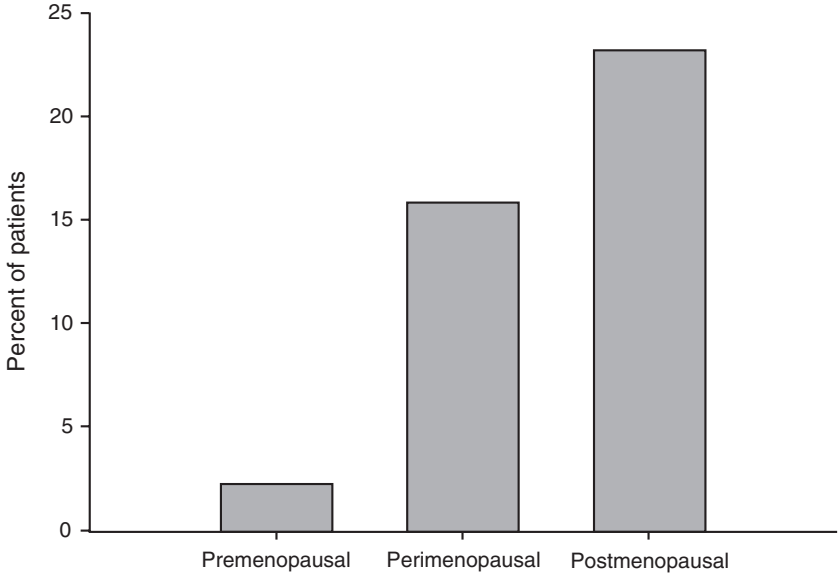

Fig. 6.6 Among women with the highest level of education (postgraduate) opinion was generally divided between HT being helpful or not. Premenopausal women leaned toward harmful and postmenopausal women leaned toward helpful. (Adapted from, Power et al., 2006b.)

turn. For it is within this context, that the physician can sustain the learning and self-corrective inquiry essential for knowledge, practice and relationships with their patients and ultimately for facilitating patient decision-making with regard to HT.

6.5 Hormone Therapy and Continuing Medical Education

For physicians to be credible, particularly in a litigious world, they must be continuously educated, finding out the latest features of medicine relevant to their practice (Montgomery, 2006). Continuing medical education (CME) underlies the endeavor to stay informed and is essential to the practice of medicine. For the physician, CME lies at the heart of the evolving medical decision making process.

One feature of CME is, obviously, helping physicians keep up with new medical findings and technologies that potentially impact practice. Physician organizations have long mandated this type of CME and there is nothing new or controversial about it. What I am suggesting is something a little different: using the CME framework to help improve, not just physicians' medical expertise, but their methods of analysis and decision making.

Findings of significant variations in practice behaviors have brought renewed emphasis to the need to achieve, through CME, use of standardized clinical protocols, guidelines, and other quality-assurance mechanisms (Lewis, 1998; Davis, 1994). For this to happen, new learning methods and approaches must be devised and new standards of accountability put into place. Such practices are particularly relevant for HT, since there is no one form of treatment, no textbook recipe axiomatically applied.

In an earlier paper, several colleagues, many of whom had worked in the field of CME for a number of years, outlined its core features (Abrahamson et al., 1999).

(1) CME planning and program development should be based on needs assessment, including outcome data.
(2) The goals of CME should include the development of skills necessary for lifelong learning, the exercise of clinical reasoning, an understanding of the decision-making process, and specific content acquisition.
(3) The multiple goals of CME should be reinforced by the appropriate choice of learning methods.
(4) Incorporation of new instructional technologies for CME should be based on their intrinsic strengths as learning tools after thorough evaluation.
(5) Faculty development is important within CME and should include exposure to new learning methods (theory and application), enabling faculty to translate their content expertise into formats more appropriate to learners' needs.
(6) Educational activities should be supportive of and coordinated with the transition to evidence-based medicine.
(7) Professional and, whenever possible, interdisciplinary interaction should be given priority in CME programming.
(8) Outcomes-based measures of CME effectiveness and research should be introduced into the determinants of physicians' practice behaviors.

Perhaps most importantly, the goals of CME should include the development of skills necessary for and reinforcing of lifelong learning, the exercise of clinical reasoning, patient interaction, and understanding of the decision making process, as well as specific content acquisition. The traditional function of CME is to address the education and training needs of doctors following residency and through to retirement. However, CME often concentrates on expanding a physician's knowledge without instructing him or her about how to use that knowledge to solve clinical problems. True leaning demands that the acquisition and retention of information be accompanied by the development of reasoning skills, so that knowledge can be applied effectively in clinical settings. Self-assessment, problem solving, and evidence-based analysis are three educational techniques that may serve as routes to achieving these skills.

A central objective should be to help the learner recognize what he or she still needs to know. This self-assessment function encourages critical thinking and reinforces the goal of lifelong learning. Physicians would benefit from developing techniques that enhance their capacity to evaluate critically their own knowledge and skills – and to fill in the gaps where necessary. Decision analysis is an important tool in enhancing physicians' self-reflection about biases and orientations to events. Decision analysis entails, in part a formal, scientific approach to decision making in which the value or utility of each of the decision's possible consequences is multiplied by the probability of the consequence, thus arriving at a score for each outcome (Baron, 2006).

Physicians who are exposed to this sort of self-directed, self-reflective learning tend to continue in that mode and to keep up-do-date later in practice (Davis and Thompson, 1996). So decision analysis could be an important cognitive adaptation with regard to following new practice guidelines and research. Indeed, in one sense, self-corrective inquiry is at the heart of scientific legitimacy and, by extension, medical decision making.

While a good deal of self-directed learning may be independent learning, not all of it should be undertaken that way; an approach rooted in problems and problem solving is needed (Dewey, 1916, 1929, 1960). CME appears most likely to affect outcomes when program content is discussed and reinforced in a group. Problem-based learning (PBL) holds several advantages as a CME method, in that it encourages self-directed learning within the context of a group or team exercising a case-management approach. Incidentally, the dilemmas that pervade HT provide an ideal context for PBL. PBL also nurtures and exercises an assortment of skills that go beyond knowledge acquisition, yet are essential to learning and clinical proficiency, such as self-assessment, information management, the exercise of clinical reasoning, and a collaborative, team-management approach (Schmidt, 1993; Lewis, 1998).

Educational activities should be supportive of and coordinated with the transition to evidence-based medicine and evidence-based outcomes and the linking of theory to evidence-based approach. Understanding entails both theory and practical outcomes. Continuing medical education courses that encourage and provide a map of data in the context of evidence-based assessment as it relates to clinical management provide an important educational vehicle for busy physicians (e.g., Henderson, 2004).

Continuing medical education courses have, for some time, been offered to assess the risk and the evidence regarding use of HT for women with a history of breast cancer (e.g., Pritchard, 2002), and the utility of short duration and low doses of HT for relief of symptoms associated with menopause (Col et al., 2004). Variations in practice behaviors have been documented, and these have led to an emphasis on the need to achieve outcomes and develop standards for quality of care that are evidence-based, both nationally and within large delivery organizations. Typically, efforts to promote such changes (i.e., development of standardized clinical protocols, guidelines, and other quality-assurance mechanisms) also signal the need for CME. Therefore, CME planning should be undertaken in concert with the development and implementation of evidence-based clinical standards and guidelines such as the one for HT, and CME program content and formats should complement these goals.

Much of the variation in physicians' practice styles may depend on medical culture, and to be effective within such a context, CME would have to have more to do with changing the habits and attitudes of physicians and altering cultural expectations than with providing information. Information alone would be unlikely to have an effect, and might even be discounted if it were not consistent with physicians' preexisting beliefs; the study results noted above, about physicians' responses to the WHI study, show how significantly prior beliefs, practices, and training affect how physicians evaluate and use new information. Additional research should be undertaken to explore this hypothesis, and to determine the motivating factors behind physicians' behaviors and practice styles: their gender, personal experiences and age, all which impact their readiness to prescribe HT, as well as their responses to other changing medical information (Power et al., 2006a; Biglia et al., 2004).

In other words, knowledge alone does not change physicians' behaviors. Practice styles tend to be steeped within an internal milieu, and to emerge within a community of physicians. Instructing physicians in the process of decision making itself is important because the ability to weigh evidence, to recognize biases, and to reach an informed decision are crucial in the exercise of clinical judgment (Henderson, 2004).

Decision analysis teaches that there tend to be three obstacles standing in the way of effective decision-making (Baron, 1988, 2003, 2006). These are: bad data (or lack of data); ignorance of decision-making concepts; and intuitions or biases that serve to impede effective decision-making. It is important to recognize the biases that pervade decision- making. For example, previous research has suggested that perhaps an *omission bias* is operative in medical decisions with regard to HT, and indeed we found just that in our research (Baron et al., 1998). Apparently, physicians are more likely to discontinue a possibly harmful treatment than to begin a helpful one, when the difference between the two is held constant (Aberegg et al., 2005). They appear more worried about harm than help. Perhaps in a cultural climate of lawsuits causing no harm has an even higher premium in influencing physician behavior. When physicians were asked about a concern with regard to HT in 2003 there was a strong tendency towards omission bias, correlated with how convinced they reported they

were about the evidence (Power, Baron, and Schulkin, 2008). Physicians need to be aware of these biases or orientations that permeate their medical decision-making, and CME is an excellent venue for doing so.

In an age of significant physician burnout from longer hours and less control, an ever expanding body of information to tackle, and, most importantly, increased lawsuits and insurance costs, physicians, at least in obstetrics and gynecology, have been leaving their profession in record numbers (see e.g., Williams and Skinner, 2003; Mello et al., 2003). Increased external pressures from various sources (e.g., the impact of managed care on loss of individual authority, increased law suits, higher insurance premiums) have led to decreased levels of satisfaction with being in the medical profession. Indeed, liability insurance has been reported to be the most significant factor for leaving the field of obstetrics and gynecology, in addition to other fields of medicine (Bettes et al., 2004). On the other hand, increased perception of liability is thought to facilitate better-informed consent practices of physicians (Braddock et al., 2002). When physicians act less like doctors, patients suffer. Physician burnout serves no one's interests.

In the Bettes et al. (2004) study physicians were concerned about managed care and burdened by professional liability. The first reflects their loss of control over patient care and the second their vulnerability to financial burden. Both significantly contributed to physicians being worried about burnout and the termination of their career in medicine. One saving grace, it appears, is that they reported CME's as being a significant factor in ameliorating physician burn out. In the study by Bettes et al. (2004) the greater the interest in CME and, presumably, continuous learning, the greater the decrease in reported physician burnout. So the interests of the physician, at least of the obstetrician–gynecologist, are embodied in self-corrective inquiry – or, at a minimum, they view CME's in a positive light. Amidst the diverse conflicts and limitations that make the practice of medicine exceedingly difficult, and one should acknowledge that, one important source of comfort is a good dose of education through CME's.

Ideally, instruction in decision-making principles should be introduced at the level of medical schools and residency and then reinforced in the CME setting. For older practitioners, decision analysis perhaps can serve as a useful tool for integrating current knowledge and making the transition to evidence-based practice. The convergence of the decision sciences and evidence-based medicine (Kleinjen and Chalmers, 1997) in teaching is a unique accomplishment with potentially enormous impacts on decision making about HT and, just as importantly, about informed decisions generally.

6.6 Conclusion

Hormone therapy ranks high on the list of obstetrician–gynecologists' concerns for their patients (Wilkins-Haug et al., 2000). Since obstetrician–gynecologists have come to define themselves as physicians for women over the whole life cycle,

perhaps it is not surprising that in physician groups, obstetrician–gynecologists were nearly two times more likely to prescribe HT than other primary care physicians. Obstetrician-gynecologists were by far the physician group most involved with patients regarding HT (Hersh et al., 2004). Women actively seeking information about whether or not HT is right for them need their doctors' best efforts. Studies of women's response to the WHI studies indicate that women are disturbed by the evidence, asking their doctors' help more than ever. Yet studies of doctors' responses to the same information show that physician culture, gender, age, and prescription history can affect their analysis of this new information counterproductively.

CME may be the best vehicle for helping physicians respond most effectively to new and complex information. For physicians in practice today CME already represents the primary strategy for coping with dramatically expanding medical knowledge, new technology, and new and evolving aspects of clinical practice. Adding decision analysis to the CME curriculum would integrate learning methodology into the educational process and provide physicians and their patients with more rapid and effective use of new medical knowledge, including HT research results.

Medical decision-making is an evolving set of circumstances. HT is just one example among many. The dilemmas surrounding HT point to the continuous role of CME's in the professional life of the physician. Issues range from what they and their patients do and do not know about HT and the latest findings to how to coherently convey information amidst vague and often misleading sets of data. There is no recipe in the abstract for this; it is highly contextual. But the approach should always be the empirical approach; what is the best evidence from the point of view of the physician and clearly conveying it to the patient who is making the decision with regard to her health.

There is another factor specific to the evolution of our medical decision-making, namely to enhance patient responsibility for choice, to expand the sense of physician/patient interaction amidst the recognition of the conflicting biomedical and bioethical points of view (e.g., Engelhardt, 1986, 1996, 2000; Montgomery, 2006). In the case of women and HT, women play a substantial role in medical decision-making; they still might defer to the medical opinion of their trusted doctor, once they have been listened to, but they are the final decision makers. A number of studies, including those regarding HT (Roumie et al., 2004), continually demonstrate the importance of patient/provider communication in relaying new health information with regard to HT.

We need to understand the history of HT (e.g., Houck, 2003, 2006; Watkins, 2001, 2002) to address the diverse cultural biases that underlie the packaging of HT by diverse interest groups, and in demythologizing the expectations of the science and in understanding the science. Importantly, an evolving and expanding sense of the language of rights has emboldened individuals in medical contexts (Macklin, 1999; Mackenzie and Stoljar, 2000; Brody et al., 2000). Thus, if a physician's recommendations are inflexible and not in line with a patient's perceived choices, the patient always has the power to select a different doctor.

Education in human experience, as Dewey noted in Experience and Education, is a “moving force” (p. 38) and physician acquisition of the tools of decision analysis would allow them to change their practices more effectively and efficiently in response to new findings. They will not, of course, achieve perfection, but they may move nearer to it.

Conclusion: Hormones and Reasonable Expectations of Aging

Introduction

The degree and extent to which women pass through menopause and reach old age is a modern phenomenon in our evolutionary history (Austad, 1994; Hawkes, 2003). Ours is the first extended period in history in which the majority of women live an appreciable part of their adult lives without menstruation and the hormones that stimulate it. Most features about aging do not look particularly good. Adaptive arguments, in general, are not compelling with regard to aging (Caplan, 2004), though arguments about grandmothers contributing to the success of their related offspring has some adaptive plausibility (see Hawkes, 2003, 2004), and the adaptive features of having elders in a culture is argued very persuasively in the paleo-anthropological literature (see Mithen, 2006). Nor are our troubled health care systems an endless repository for coping with an aging population (Callahan, 1990, 2003). The decline in reproductive hormones is part of more general decline in hormonal systems and end organ systems and function tied to aging.

Hormone therapy is not, thus far, a simple panacea providing "femininity forever," however we choose to define that. Moreover, a fundamental question many HT analyses avoid is, how much do we want to medicalize menopause? There has been a tendency to do just that for many reasons, some justified (e.g., a woman in severe discomfort from hot flashes). An appreciation of biology is not the same as a quick and easy pharmacological fix. How we respond to such issues reflects the valuational judgments that we make about aging in general and menopause in particular, judgments that permeate our decision-making (e.g., Dewey, 1939; McGee, 1999, 2003). Amidst the conflict that permeates the HT literature, a stable context for discussion is essential to meet some form of consensus (Krieger et al., 2006). Getting clear about the issues is an important step for setting a context for a rational discussion. One such depiction is in the next table (see Table C.1).

The valuational conflicts that surround HT are also an opportune time to search for piecemeal self-corrective solutions (Dewey, 1939; Moreno, 1995). Bioethical discourse in a liberal culture requires a sense of inquiry knotted to social action and the search for common ground, consensus (Dewey, 1935, 1963; Moreno, 1995;

Table C. 1 Key issues relevant to debates over use of HRT from different disciplinary perspectives: history, women's health advocates, epidemiology, biology, and clinical medicine (Krieger et al., 2006.)

Discipline	Key Issues
History	1. Disciplinary boundaries affecting understanding and awareness of risk 2. Definition, production, and use of pharmaceutical substances 3. Definition and practice of medical subspecialties 4. Comparative histories of medical practice
Women's Health Advocates	1. "Expose the abuse, critique the science, light the fire": critical role of women's health advocates 2. Political clout of pharmaceutical industry and manipulation of "consumer" fears and desires as "choice" 3. Contrast between "curative" and "risk management" treatments 4. Role of medical–industrial complex in manufacturing and marketing drugs for profit. 5. Debates on drugs rarely linked to debates over structure of health care system.
Epidemiology	1. Inadequate use of appropriate study design (RCT), over-reliance on observational data, disregard for RCT's not favorable to HRT, and poor interpretation of epidemiological studies 2. Disregard of socially patterned confounding, vis a vis who does and who does not take HRT 3. Disregard for risk in relation to age (risk of breast cancer greater than coronary heart disease among women in their 40s and 50s), and discounting of adverse risk of breast cancer relative to risk of risk reduction for cardiovascular disease. 4. Disregard for distinctions between absolute and relative risk 5. Impact of pharmaceutical industry on epidemiological research, including emphasis on alleged benefits over risks and revised view of "acceptable risks" for healthy populations
Biology	1. Hormones by definition are global signalers in the body, such that "side effects" of hormonal therapies are inevitable. 2. Steroid hormones affect more than the reproductive system and are involved in cell growth and differentiation, as well as immunity, metabolism, and behavior. 3. Endogenous and exogenous hormones, including xenoestrogens, are typically studied in systems that show only a small portion of their biological activity 4. Ignorance vastly exceeds knowledge about the full range of biological functions of endogenous hormones and exogenous hormone-like agents. 5. The complexity of biological systems precludes accurate quantitative "risk assessment" and is not compatible with non precautionary "command and control" approaches to regulating and licensing safe levels of individual chemicals.
Clinical Medicine	1. Among the wealthier countries in which pharmaceutical companies have their principal markets, the pharmaceutical industry increasingly underwrites conferences and research, plus offsets journal costs through extensive advertising.

(continued)

Table C. 1 (continued)

Discipline	Key Issues
	2. In these same countries, the "best selling" drugs currently are "risk reducing" drugs, consonant with an increasing trend to focus on eliminating individual risk. 3. Limited time, low reimbursement for counseling (cognitive services), and defensive medicine shape medical practice, increasing medical conformity and encouraging physicians to prescribe "risk reducing" drugs. 4. Clinical guidelines encourage physicians to prescribe treatments even if there is not conclusive evidence that drugs are the best way to approach risk reduction. 5. Until recently, physicians in the USA were encouraged at least to counsel women about the use of HRT as a standard care for women during and after menopause, but have now been discouraged from routinely prescribing it.

May, 2002). We are in "this" together, as uttered and reiterated by the different conflicted stake-holders on HT.

Insulin, Diabetes, and Aging: One core medical-related set of values is to work to achieve a balanced integration of lifestyle and cognitive adaptation amidst the decline of end organ systems as we age (Institute of Medicine, 1997; NIH Report, 2005; Canadian Consensus, 2006). Clearly aging is a fundamental feature of living organisms (Rose, 1991), and most end organ systems begin to show decline over time. Certainly it is not only the reproductive organs that evidence a decline. But menopause, in addition to many changes in our life, is affected by lifestyle choices (e.g., choosing exercise, the foods eaten, etc. Eyre et al., 2005; Canadian Conference, 2006).

At the outset of this book I drew attention to the fact that the deficiency model of insulin in the normal pancreatic diabetes that emerges in children is misleading when it comes to HT. Insulin is essential for life, for the child or for the adult. I'd like to return to that problem of the deficiency model, this time focusing on adult onset diabetes, or what is often called Type II diabetes with regard to HT and the quality of life.

Insulin secretion is essential for normal glucose regulation, but living longer and eating certain kinds of foods over a lifetime begins to wear and tear on normal insulin secretion for the utilization and integration of food sources (Schwartz and Porte, 2005). Of course insulin secretion does not occur in a vacuum; it is tied to the normal functioning of other physiological regulatory systems (e.g., secretion of cortisol, Dallman et al., 2000). Most hormonal systems, particularly in the context of whole body physiological viability, are inextricably connected to other physiological systems (McEwen, 1999, 2002; Schulkin, 2003).

Then, of course, there is the life history of the individual, and the dietary habits an individual acquires throughout life. We live in a society where vulnerability to morbid obesity is a fact about our culture of cuisine and nutritional expression.

Type II diabetes is a phenomenon on the rise. It reflects two facts, one of which is that aging is tied to decline in insulin secretion and the utilization of glucose in diverse end organ systems, and more and more people are living to an age at which insulin production and expression is naturally depressed. The other is our life style choices – what we eat as it impacts our vulnerability to Type II diabetes. A history of eating foods that are taxing on regulatory systems can result in the breakdown of those systems, including glucose regulation by insulin (Dallman et al., 2000; Porte, 2001; Schwartz and Porte, 2005). Of course there is the added factor of genetic vulnerability (individuals more likely to express age-related decline in insulin secretion) and other vulnerabilities unrelated to how we eat (including diabetes related to pregnancy). Decision-making about lifestyle and food choice, with a recognition of vulnerabilities, is knotted to rational decision-making with regard to warding off age-related diabetes.

Cognitive Function: Consider another example about aging: brain tissue declines over time (Sapolsky et al., 1986; McEwen and Stellar, 1993; Sapolsky, 1992). Neural patterns vary with genetics and lifestyle, but some decline in cognitive function is one feature of the neural degeneration brought on by normal aging. Alzheimer's disease reflects the deterioration of the brain. Clearly some individuals are more vulnerable to Alzheimer's disease than others, but this is exacerbated by many things, including life style and life experiences (McEwen and Stellar, 1993). And, again, the increase in the prevalence of Alzheimer's and other forms of senescent dementia is related to our expanded life spans.

Thus, for example, cortisol, a steroid hormone fundamental for metabolic regulation and involved in most aspects of physiological regulation including stress, is known, when elevated for long periods of time, to exacerbate the aging process of the central nervous system and facilitates the onset of Alzheimer's by degenerating diverse physiological and end organ systems.

Cortisol is essential for all aspects of energy metabolism (Dallman et al., 2000; Sapolsky et al., 1986; Schulkin, 1999). And levels of cortisol linked to lifestyle and genetics are protective of tissue in the short run, but facilitate the aging process of tissue in the long run (Sapolsky et al., 1986) and brain tissue, particularly those regions of the brain linked to memory (e.g., hippocampus, Sapolsky, 1992; McEwen, 2002).

Cortisol is involved in bodily functions for many reasons. It is important for fighting off diseases, coping with stress, eating foods that require glucose regulation and many other domains of physiological functioning. Fighting off diseases (and so elevating cortisol) only increases vulnerability to organ system degradation. For instance, we know that the induction of diabetes in animals induces changes in hippocampal structure (Magarinos and McEwen, 2000). Thus warding off diabetes – the kind we have some control over by regulating our diet – is interrelated to the issue of elevated cortisol.

Long periods of elevated cortisol are detrimental to the body. Life experiences, temperament and circumstances, which do not facilitate the turning down of cortisol, degrade end organ systems because of the metabolic strain of high cortisol, which is the hormone of glucose metabolism is required by each cell. It is no

surprise that high levels of cortisol are also a predictive factor for the vulnerability to bone fractures (Greendale et al., 1999; Cizza et al., 2001).

But all systems decline with age. Intelligent aging is warding off what we can by the lives that we live, by what we eat and how we interact with other people, and of course *Fortuna*, the genetics and the sheer luck that might come our way (e.g., thyroid function, Cizza et al., 1996). Good medical decision-making entails knowing what we can do and what we cannot, and engaging the ambiguous intellectual space where it is not clear what to do.

Thus, while we now know that tissue, even the nervous system, has regenerative potential (McEwen, 2001) under some conditions, in some systems there is little doubt that living things (except viruses and certain cell lines) naturally decline and succumb to inevitable mortality. The question in the medical context is how to sustain function by adapting to decrements in end organ systems (Pew and Van Hemel, 2005). Physical activity is good for the bones, heart and circulatory system in general (Hu et al., 2000; Engelke et al., 2006; Lock et al., 2006), and for warding off osteoporosis, as well as sustaining mental health and cognitive functioning (see Fig. C.1) (Kramer et al., 1999; Larson et al., 2006).

But how far does the concept of "replacement" go? There is obviously no one answer. In this great age of biology we continue to replace natural tissue with organ transplants, replacement endocrine, and so on. Perhaps even more exciting is the limitless possibility of stem cell research. But aging is a part of the life cycle, and pursuing some lines of research decreases possibilities in others. Normative notions of aging should be aimed towards a quality of life that is meaningful, as pain-free as possible, and not simply the amount of time lived, but the quality of life lived (Callahan, 2003; Caplan, 2004). This is where the physician and the patient working together balance possibilities with reasonable expectations.

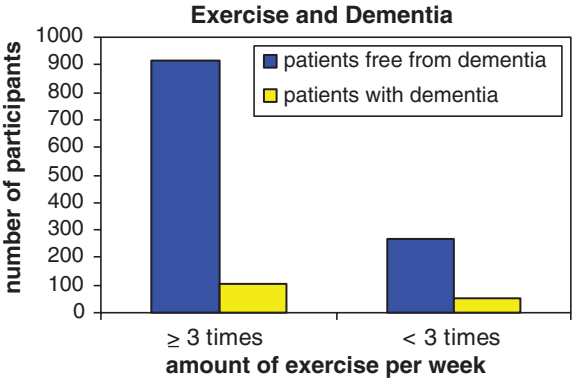

Fig. C.1 Exercise and cognitive decline (Adapted from, Larson et al., 2006.)

As I have indicated, valuational judgments are not something outside decision-making, but are endemic to it (e.g., Dewey, 1939; Neville, 1974; Putnam, 1981; Moreno, 1995); they certainly pervade the decisions that are made about a particular medical approach to one's health. This is especially apparent with regard to decisions about HT. What is the value of HT in the context of a woman's sense of her overall health and approach to medical treatments, the extent to which she wants medical treatment, and the way she wants the physician to treat her in a medical context with regard to aging? For an educated patient, taking hold of the decisions is the normative goal amidst the expansion of medical knowledge and medically available therapeutics. One normative goal is to expand patient choice and responsibility (Schulkin and Neville, 1983).

This phenomenon of expanding and translating biological findings into medical practice and patient decision-making pervades the cultural landscape. Key insights into the molecular foundations of life are common at this time, and they continuously push towards the eternal conception of continued youth (Guarante, 2003 ; Schuiling, 2005). The genes that control the development and maintenance of cells and end organs systems are a focus that has reached the translational stage. The promise of molecular medicine still looms as an imminent possibility. The idea of injecting, for example, a healthy gene into a virus that then travels to an end organ system that is malfunctioning and replaces the defective genes with healthy ones to promote growth of normal tissue is still just a promissory note right now, but its fulfillment is genuinely in view.

In this regard, the continued development of alternative estrogenic compounds pervades the research on HT (e.g., Brinton and Zhao, 2006). The search for estrogenic compounds that increase and sustain heart and brain tissue but do not activate cell proliferation in the breasts of women is still a thread of ongoing research. Thus, women who are vulnerable to malignancy in breast tissue could be made to be less vulnerable by estrogenic compounds that avoid these tissues, while preserving estrogen's function in other tissue (e.g., bone and brain). Placing this work in the context of scientific advances while moving away from the unrealistic myth of doing away with aging is placing the science in the larger context of what we can expect and should expect.

Humans as Social Animals: Scientific advances and medical practice are also tied to the larger social milieu (Dewey, 1929, 1960). We are social animals (see Aristotle for the classic argument on this), and the ethics of social cooperation is at the heart of our evolution. In other words, we need each other. A rather large piece of our biology is knotted to social attachments. We evolved in social cooperation as well as in competitive groups (Darwin, 1872, 1965; Humphrey, 1976). One important human end, goal and value are the human bonds that sustain human meaning (Jaspers, 1913, 1997) and that ameliorate some of the heartaches that life imposes just by living, thereby helping to reduce the toils of aging.

The advances to retard aging ought to be placed in the context of fostering human social contact. Our biology is embedded within the larger milieu of social meaning. For example, the greater the social contact, the greater the sleep quality in older women (see Fig. C.2) (Friedman et al., 2005), and sleep quality, in turn, is related to

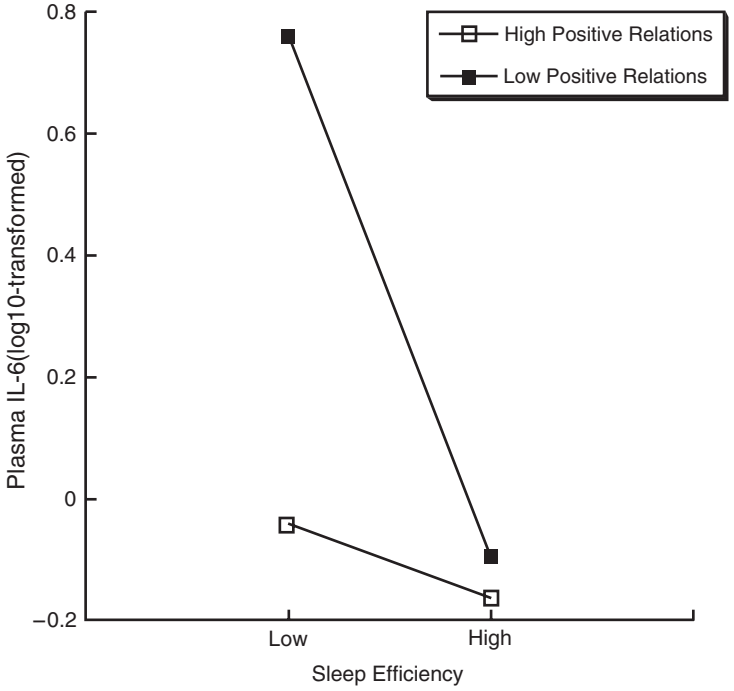

Fig. C.2 Sleep efficiency and plasma levels of IL-6 in individuals with high or low rated positive relations (Permission granted from Friedman et al., 2005.)

sustained physiological functioning. This is not just an obscure finding; there is a large literature on the social regulation of the internal milieu (e.g., Steptoe et al., 2004).

An important element that emerged with bioethics was a perspective that highlighted social contact (Murtagh and Hepworth, 2003). Bioethical considerations under this perspective emphasize social contact, communication amongst individuals including patient/physician interactions, context and diversity of expression, and less of a focus on uniformity (Sherwin, 1996; Tong, 1996; Mahowald, 1996, 2000; Smith, 1996).

Here is a valuational consideration: social contact matters, and while human social contact cannot eliminate the hard decisions and the challenges of aging, it helps, and it contributes to the larger meaning in which medical and other decisions are couched and understood. With friendship such an important ingredient in human life, human contact and meaningful relationships (see Fig. C.3) (Jaspers, 1913, 1997) help mitigate the hard knocks of aging. The aging process increases our vulnerabilities, our dependence on others, but these are small, and perhaps ephemeral, when compared to the important human bonds. A 70-year friendship won't necessarily protect against broken bones, degraded cardiovascular functioning and decreased memory capacity, but it is an absolutely crucial factor in getting one through life.

Fig. C.3 Long-term friends (Rosalind Schulkin (on right) and Lea Siegelman.

We ought not to be focused on the indefinite preservation and extension of life without consideration of the quality of life, the vulnerabilities of individuals, and the resources available (Callahan, 1990, 2003; Caplan, 2004). What we want, normatively understood, is to enhance the quality of our increasingly longer lives, and place medical decision-making and medical advances into lifestyles of action worthy of the human endeavor. Normative expectations run through medical decision-making that is a life long event (Thomasma and Kushner, 1996; Steinbock et al., 2003). Such normative expectations are ancient and run through bioethical considerations (Kuczewski and Polansky, 2000). How to age? What are wise expectations? How far to extend life? These are the questions, ancient and contemporary, and weighty amidst considerations about HT. Of course the other question, or seduction, is the fountain of youth – how to stay young and attractive, fertile, etc. These questions reflect valuational judgments and ought to be knotted to self-corrective inquiry (e.g., Dewey, 1939, 1972 ; Putnam, 1981; Moreno, 1995); these questions are filled with normative expectations about health and of our evolving (or devolving) culture (Caplan, 1997, 2004).

The question we can reasonably ask about HT is not whether it is good for staving off aging, but whether it can improve the quality of life of its inevitably aging recipients. HT considerations must be placed in a context of what is right for the patient; and it is the patient's choice, informed by the physician's knowledge and advice. The effects of HT are quite varied and complex. There is no simple relationship between HT and many of the outcome measures (e.g., cognitive performance). Hormone therapy is no magic bullet as our knowledge now stands, and it should never have been treated as such.

Medical Decisions, Warranted Assertions, and HT

The practice of medicine has changed dramatically since the rise of large-scale science and studies supported by the National Institutes of Health (Feinstein, 2003). In this context one is reminded that inquiry is social, the results are always imperfect (Dewey, 1925, 1989), and that inquiry does not end but is always ongoing; this is particularly true with regard to medical decision-making (e.g., Moreno, 1995). Dewey (1938) suggested that decision-making should result in practices that make the most sense, that benefit one in diverse ways, amidst the recognition of their limitations. "Warranted assertions," a term of Dewey's (by which he meant well supported reasons given the context, circumstance and issue), is also, perhaps, what Herbert Simon, a Nobel Prize winner in economics and one of the originators of the decision sciences, meant by a word he coined, "satisficing" (Simon, 1982). Satisficing refers to what might be called "good enough reasoning," similar to "good enough parenting." Part of what is meant by all these metaphors about decision-making is the need to move down from the Promethean heights towards slogging it out in the slough of the real world (Putnam, 2006).

Of course we all know that the pedestal of rational self-interest is a lofty goal that is severely comprised in everyday practice (Kahneman et al., 1982; Dana and Loewenstein, 2003). What we are not, as human decision makers on an everday basis, are maximizers of rational self-interest, as envisioned by classical economics (Simon, 1982; Camerer and Fehr, 2006). Self-interest can easily turn to self-deception and ultimately undermine good biomedical decision-making.

On the other hand, the fall from a conception of perfect rationality is not a descent into irrationality, but just a more realistic sense of who we are as agents making decisions, as doctors or patients. The goal is to look at what we are and then cope with it, make it better, and not proselytize from afar and from something far from actual human experience. Having normative goals and being clear about them is one thing. It is quite another thing to confuse them with actual performance (Dewey, 1939, 1972; Baron, 1988, 2003).

Perhaps the issue of HT is a reminder that the perfection that we strive for is rare in medical decision-making and elsewhere. This realization is perhaps part of growing up. Of course the other part of growing up is recognizing the seduction of internal desires and external factors.

Conflicting evidence has been the epistemological wellspring of the HT literature (Bush et al., 1983; Grodstein et al., 1997; Stefanick et al., 2006). Preclinical research has most often legitimated the use of HT to protect against forms of bodily pathology (Hammond et al., 2001). Pharmaceutical advertising exploits the desire for agelessness (Watkins, 2002; Katz, 2003; Houck, 2006), and it can influence physician attitudes with regard to HT (Hess et al., 2005). The endless advertising of youth, the glorification of youth, is something that should be coupled with wisdom of knowing what really counts, of keeping the larger goals and ends that permeate a participatory democracy where well informed citizens contribute to the overall enhancement of the culture, themselves and their progeny and close loved ones.

Decision analytic steps are burdensome. Flow charts of decision-making are not the sort of thing most physicians or patients are likely to engage with, but for both physician and patient the combined sense of decision-making is a normative goal of medical decision making. But in fact the goal is for the patient to be the bearer of responsibility for her health as she decides what is best for her given the options available to her and her valuational assessment of what is best. The uncovering of information (Rothbert et al., 1990), the discussion of HT between physician and patient, is an ongoing and evolving medical affair (Schneider et al., 2000; Kim and Kwok, 2003; O'Connor et al., 2003) and is inextricably tied to better-informed individual choice by the patient (Braddock et al., 2002) and an ethical discourse that seeks to maximize physician/patient interactions.

The assessment of risk and cost-effectiveness has been inherent in decision making about HT for sometime (e.g., Weinstein, 1980; Weinstein and Schiff, 1983), but has to be understood in the larger context of valuational judgments, judgments that are continuous with the science but not identical to it (e.g., Dewey, 1939; Putnam, 1981; Neville, 1974; McGee, 1999, 2003). In the end, informed individuals – when there is choice and where the context allows for it – are in a position to have more freedom of choice, and that is one normative goal in a liberal society (e.g., Sidgwick, 1902; Rawls, 1971).

Ambiguity and Self-Corrective Inquiry

It is never easy to deal with ambiguity, and ambiguity permeates the literature on HT. As we have seen, decision analysis shows that ambiguity increases bias in decision making, and physicians need to assemble a modicum of self-correction to counteract that ambiguity. What can we expect from physicians? And what should they expect of themselves? What we expect is a clear assessment of the risks and options to enhance patient decision-making. This is simply not easy on all sides. The media coverage of HT, and advertising campaigns associated with HT, both tend to give patients an inappropriate view of HT as either a wonder drug or a dastardly danger, when it is really neither.

There are no easy answers to the real dilemmas that surround HT. We are witnessing a changing perspective with regard to HT that amounts to a paradigm shift. What I have tried to do in this book is to suggest a blueprint for a continued self-corrective approach that the physician should have toward medical knowledge in general, and HT in particular. The patient is caught in a confusing medical space; her primary care physician should understand something about the richness of the basic sciences, amidst the confusion of the clinical literature surrounding HT, and communicate it in the best possible way to the patient for her to make the decision. What should pervade the medical communication process is a sense of continuous self-corrective inquiry with regard to medical decisions, using the tools of decision analysis and evidence-based medicine, in conjunction with the latest research.

Core findings and risk analyses are still not clear in HT, so diverse strategies need to be implemented in patient/physician decision making. While recent media

coverage of HT studies stress the risk (Haas et al., 2006), there is nevertheless broad consensus that a number of symptoms associated with menopause are ameliorated by HT (Kim and Kwok, 2003; Peterson et al., 2004; Grimes and Lobo, 2002). And there is both speculation and some evidence that short- term low dose HT use in the early stages of the perimenopausal and menopausal period may be protective (Rossouw, 2005; Harman et al., 2005; Manson & Bassuk, 2007; Barrett-Connor, 2007).

If there is little dispute with regard to the short-term use of HT as a treatment for menopausal symptoms, there is much dispute about long-term use in delaying the aging process. There continues to be an array of new scientific studies. Noted individuals such as Phyllis Greenberger, Chief Executive Officer of the Society for Women's Health Research, was quoted in the *Washington Post* (Tuesday, October 20, 2005) as saying that, despite the findings from the WHI, "she has no plans to stop taking the hormones she started at age 50" (but see Clark, 2003). Of course, many women discontinued HT following the results of the WHI studies, and physician groups returned to a moderate orientation toward HT, stressing short-term relief rather than longer-term amelioration of disease-related states (e.g., heart).

The most sensible course at present is to employ short-term use of HT as the best medical prescription. Nonetheless, there are a number of very positive findings associated with HT during long-term use which still warrant further consideration, including testing with different kinds of HT, natural and other forms of hormone used, different doses, and, of course, the timing of the therapy. So much hangs on the few dosages of HT that have actually been tested. Thus, the scientific book is not closed with regard to HT, and it probably never will be. Physicians and women patients together must accept this ambiguity and sort through the options in a spirit of corrective self-inquiry.

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