from The New Yorker

June 9, 1997
MEDICAL DISPATCHES

The Estrogen Question

How wrong is Dr. Susan Love?

by Malcolm Gladwell

1.

When Dr. Susan Love gives speeches, she stands informally, with her feet slightly apart and her hands in casual motion. She talks without notes, as if she were holding a conversation, and translates the complexities of medicine and women's health with clarity and wit. "I see my role as a truthteller," she told a sold-out audience of middle-aged women at the Smithsonian, in Washington, last month, and everybody roared with approval, because that's what they've come to expect of Susan Love. She was, as usual, dressed simply that day--in a blue pants suit, with no makeup and with her hair in a short perm that looked as if she had combed it with her fingers. She had no briefcase or purse or adornment of any sort, and certainly none of a surgeon's customary hauteur, since it is Love's belief that medicine has for too long condescended to women. She was there to promote her new best-seller on estrogen therapy and menopause, but she made it clear right away that she wasn't about to preach. "Don't expect to leave here tonight knowing what to do," she said. Love wanted her audience to hear the evidence but, above all, to listen to their own feelings. "You have lived in your body a long time," she told the crowd, smiling warmly and reassuringly. "You know it pretty well--you know how it reacts to things, and you can trust it."

There are at least three doctors in America who fall into the category of media-celebrity--who can reliably write a best-seller or fill a lecture hall. The first is Deepak Chopra, practitioner of quantum healing and mind-body medicine. The second is Andrew Weil, whose seventh book, "Eight Weeks to Optimum Health," has been on the best-seller lists since March. And the third is Susan Love, breast surgeon, co-founder of the National Breast Cancer Coalition, and the author of two hugely successful books: "Dr. Susan Love's Breast Book," in 1990, and this year's "Dr. Susan Love's Hormone Book."

These celebrity doctors are all, in one way or another, proponents of what is fast becoming a basic tenet of popular medicine: that the system of health care devised by doctors and drug companies and hospitals is close-minded, arrogant, and paternalistic--dismissive of the role that nontraditional remedies, and patients themselves, can play in treating illness. "Blind faith in professional medicine is not healthy," Weil states flatly in "Natural Health, Natural Medicine"--and it's a sentence that could easily have appeared in any of the books by Love or Chopra.

Of the three, though, Love's critique is the most sophisticated. She's not a hippie, like Weil, or a mystic, like Chopra. She's a respected clinician--the

former director of the Revlon-U.C.L.A. Breast Center, and an adviser to the National Institute of Health's vast Women's Health Initiative--and her criticisms have the power of the insider. Karen Stabiner writes, in "To Dance with the Devil," her brilliant, recently published account of Love's tenure at U.C.L.A.:

Love had a set of immutable rules about proper examining room behavior, all designed to even out what she saw as an impossibly inequitable relationship. She always had the patient get dressed after an exam and threatened that otherwise she would have to disrobe to even things out. She never stood with her hands folded across her chest, which would make her seem inaccessible. She tried never to stand near the door, which made the patient feel that the doctor was in a hurry. Love had been known to breeze into a room and sit on the floor, legs splayed, her notes on her lap. She often sat on the footstool the patients used to step up onto the table. It was a conscious maneuver. These women felt helpless enough without having to assume a supplicant's posture, staring up at the all-knowing physician.

In "Dr. Susan Love's Hormone Book" Love applies this skepticism to perhaps the most important topic in women's health today: whether older women should take estrogen. The medical establishment and the pharmaceutical industry, she says, have told women that they have a disease, menopause, and have then given them a cure, estrogen, even though it's not clear that the disease is a disease or that the cure is a cure. "The reason I got into this is that a lot of the books out there were 'Don't worry, dear, we'll take care of it,' " Love told me just before she took the stage at the Smithsonian. "Women were dying to get more information, literally and figuratively. They weren't hearing the voice that says, 'You can figure this out. This is your choice, this is your body, this is your life. You don't have to do what the doctor says. You can do what feels right for you.' That's the voice that was missing." It's a nearly irresistible argument, made all the more so by the way Love presents it--honestly, passionately, forthrightly. So why, after even the slightest scrutiny, does so much of what Love has to say begin to fall apart?

2.

Estrogen, Or Premarin (the trade name under which it is principally sold), is the most widely used prescription drug in the Untied States. Taken in the short term, during the onset of menopause, it offers relief from hot flushes and other symptoms. Taken over the long term, as part of a regime of hormone-replacement therapy (H.R.T.), it has been shown to reduce the risk of hip and spinal fractures in older women by as much as half, to lower the risk of heart disease by somewhere between forty and fifty per cent, and even--in recent and very preliminary work--to either forestall or modify the ravages of Alzheimer's disease and osteoarthritis. H.R.T. has two potential side effects, however. It raises the risk of uterine cancer, and that's why many women who take Premarin add a dose of the hormone progestin, which blocks the action of estrogen in the uterus. Long-term H.R.T. may also lead to higher rates of breast cancer.

It is the last fact that Love considers the most important. She has spent almost all her professional career fighting breast cancer, and was one of the earliest and most vocal opponents of radical mastectomies. Through the National Breast Cancer Coalition, she helped lead the fight to increase government funding for breast-cancer research, and it's hardly an exaggeration to say that her first book,

"Dr. Susan Love's Breast Book," is to women's health what Benjamin Spock's "Baby and Child Care" was to parenting. Love is concerned about breast cancer above all else: she's worried about anything that might increase the risk of such an implacable disease. What's more, she believes that the benefits of estrogen are vastly exaggerated. Women humped over with osteoporosis are, according to Love, "far more common in Premarin ads than in everyday life," and she says that, since serious bone loss doesn't occur until very late in life, taking estrogen over the long term is unnecessary. On the question of heart disease, she says that the studies purporting to show estrogen's benefits are critically flawed. In any case, she points out, there are ways women can cut their risk of heart attack which don't involve taking drugs--such as eating right and exercising. So why take the chance? "It's only very recently that we've started talking about using drugs for prevention, and that's O.K. when we talk about high cholesterol or high blood pressure," she told me. "Those are people who have something wrong. But when you talk about H.R.T. for postmenopausal women, you're talking about women who have nothing wrong, who are normal, who may never get these diseases, and who are not necessarily at high risk. There is no drug that is a free lunch. There are always side effects, so why would we put women on a drug that has the side effect of a potentially life-threatening disease?"

What Love has done is recalculate the risk/benefit equation for estrogen which is fine, except that she consistently overstates the risks and understates the benefits. In the case of osteoporosis, for example, it is true that most women don't experience the effects of bone loss until their seventies. But some--about ten to fifteen per cent of women--do, with quite serious consequences. It's also the case that the maximum protection against hip fractures comes only after ten years of H.R.T., which, considering how debilitating hip fractures are to the well-being of the elderly, is a strong argument for long-term estrogen use. Or consider how Love deals with the question of heart disease. All the major studies from which conclusions have been drawn are what are called observational studies: epidemiologists have found a large group of women who were taking estrogen, followed them for a number of years, and then determined that those women had about half the number of heart attacks that women who weren't taking estrogen had. The problem with this kind of study, of course, is that it doesn't tell you whether estrogen lowers the risk of heart disease or whether the kind of women who have the lower risk of heart disease are the kind of women who take estrogen. Love suspects that it's the latter. In all the studies, she points in her new book, "the women who took estrogen were of higher socioeconomic status, better educated, thinner, more likely to be non-smokers . . . more likely to go to doctors . . . and therefore more likely to have had overall preventative care, such as having their blood pressure checked and their cholesterol monitored."

What Love doesn't point out, though, is that over the past decade estrogen researchers have been scrupulously attempting to account for this problem, by breaking down the data in order to match up the estrogen users more closely with the nonusers. Women on hormones who smoke, have a college degree, and have high blood pressure, say, are matched up with women who smoke, have a college degree and high blood pressure, and don't take hormones. It's an imperfect way of breaking down the data, since the resulting samples are not always large

enough to be statistically significant. But it gives you some idea of how real the effect of estrogen is, and when researchers have done this kind of reanalysis they've found that estrogen cuts heart attacks by about forty per cent, which is a lower figure than before the reanalysis but still awfully impressive.

With breast cancer, Love takes the opposite approach--taking a relatively weak piece of evidence and making it appear more robust than it is. Her logic goes something like this. We know that hysterectomies, regular exercise, and early pregnancy--all things that lower a woman's exposure to her own estrogen--reduce the risk of breast cancer. We also know that having one's first period before the age of twelve, having children late or never having children, reaching menopause late, drinking a lot of alcohol, or being overweight--things that raise a woman's exposure to her own estrogen--increase the risk of breast cancer. "Since your body's own hormones can cause breast cancer," Love writes, "it makes sense to conclude that hormones taken as drugs will also increase your risk."

That sounds persuasive. But where's the clinical evidence to support it? "I just reviewed the hormone/breast-cancer research from the last five years," Trudy Bush, an epidemiologist at the University of Maryland, told me. "I found one report, from the Nurses' Health Study, showing a forty-percent increase in breast- cancer risk. I found four reports--two very large and well done--showing no effect, and I found another study showing that estrogen gave women significant protection against breast cancer. They're all over the place."

The problem is that measuring the link between estrogen and breast-cancer risk is tricky. The Nurses' Health Study, for example, which showed that women on H.R.T. had a forty-per-cent greater chance of getting breast cancer, is the study that has received the most media attention and the one that preoccupies Love: it is among the largest and best of the studies, and its conclusions are worrying. But it has some of the same selection-bias problems as the heart-disease studies. The estrogen users in the study, for example, had fewer pregnancies, got their periods earlier, and have other differences with the control group which would lead you to believe that they might have had a higher risk of breast cancer anyway.

There is another possible complication: estrogen does such a good job of fighting heart disease that most women who are on H.R.T. live substantially longer than women who aren't. In a recent computer analysis, Nananda Col, who teaches at the Tufts School of Medicine, and her colleagues there took the most conservative possible estimates--the highest available estimate for breast- cancer risk and the lowest one for heart-disease benefit--and devised an H.R.T. risk/benefit table, from which any woman can figure out on the basis of her own risk factors what her expected benefit would be. It shows that a woman who smokes, has relatively high cholesterol, high blood pressure, and moderate breast-cancer risk can expect to live two and a half years longer if she takes estrogen. That's two and a half years in which she has a chance to develop another disease of old age--for example, breast cancer. In other words, you'd expect to see more breast cancer in women who are on estrogen than in women who aren't, even if estrogen has nothing whatever to do with cancer, for the simple reason that women on estrogen live so much longer that they have a greater chance of getting the disease naturally.

Most experts agree that, in the end, H.R.T. is probably

linked to some increased breast-cancer risk. What all the questions suggest, though, is that the effect is probably not huge and is certainly nowhere close to cancelling out the benefits of estrogen in fighting heart disease. Col, in her computer analysis, estimates that only about one per cent of women--those with the very highest risk of breast cancer and only a slight heart-disease risk--can expect no gain, or even a loss, in life expectancy from H.R.T. Everybody else--even those who have a close relative with breast cancer--is likely to benefit from the drug, and for some women taking estrogen is as good a way of living longer as quitting smoking. It is, unfortunately, very hard to convince most women of this fact. As few as a quarter of those who begin H.R.T. stay on the treatment for more than two years, and much of that has to do with the persistent inclination of many women to overestimate their risks of getting breast cancer and underestimate their risks of developing heart disease. In one recent study of several hundred educated middle-aged women, almost three-quarters of those polled thought that their risk of developing heart disease by age seventy was less than one per cent--when, in fact, statistically, it's more like twenty per cent. In making her argument the way she does, then, Love is not "truthtelling"; she's simply furthering an existing--and dangerous--myth. "You can understand where she's coming from," Trudy Bush says. "Fourteen hours a day, six days a week, she sees women with breast cancer, and that's all she sees. Your world becomes very narrowly defined. It happens with everyone who is a breast surgeon. But I also think that there is a perception on the part of some women who are activists that there is a conspiracy to force women to buy these hormones and force doctors to prescribe them. Instead of the military-industrial complex, it would be the A.M.A.-pharmaceutical complex. But things aren't so simple. In my opinion, we're all struggling here, trying to tease this out. We can only look at the data."

In March, Love published an Op-Ed piece in the Times, in which she directly addressed the question of the relative risks facing women. "Pharmaceutical companies defend their products by pointing out that one in three women dies of heart disease, while one in eight women gets breast cancer," she wrote. "Although this is true, it is important to note that in women younger than age 75 there are actually three times as many deaths from breast cancer as there are form heart disease."

This statistic is central to Love's argument. She is saying that it makes no sense to avoid something that will kill you tomorrow if it increases your chances of dying of something else today. Incredibly, however, Love has her numbers backward: in women younger than seventy-five, there are actually more than three times as many deaths from heart disease as from breast cancer. (In 1993, about ninety-six thousand women between thirty-five and seventy-four died of heart disease, while twenty-eight thousand died of breast cancer.) Even the general idea behind this argument--that heart disease is more of a problem for older women and breast cancer is more of a problem for younger women--is wrong. In every menopausal and post menopausal age category, more women die of heart attacks than die of breast cancer. For women between the ages of forty-five and fifty-four, death rates for heart disease are roughly 1.4 times those for breast cancer. For women between the ages of fifty-five and sixty-four, it's nearly three times the problem; for women between the ages of sixty-five and seventy-four, it's five and a half times the problem; and for women

seventy-five and older it's almost twenty times the problem.

It's hard to know what to make of this kind of error. The Harvard epidemiologist Meir Stampfer was so dismayed by it that he wrote a letter to the editor of the Times, which was published a week after Love's article appeared. But he didn't think that her mistake was deliberate. He thought that she had just looked at the government's mortality tables and confused the heart-disease category with the breast-cancer category. "Somebody told me that they heard her on the radio or TV giving those wrong numbers, and I was pretty astonished," Stampfer told me. "And then, when I saw it in print, I flipped my lid a little bit. I'm assuming that it's just an unwitting transposition of the numbers."

That, at least, is the charitable explanation. When I met with Love, a month or so after Stampfer's letter appeared, I asked her about the relative risks of breast cancer and heart disease. We were sitting together in a booth at a hotel coffee shop in downtown Washington. It was the kind of situation, you'd think, where she might have felt free to admit to embarrassment or to offer some kind of candid explanation for what went wrong. But that's not what happened. "One of the problems with that comparison is that they act like these diseases are all at the same time," she answered. "Most women at fifty know someone who has died of breast cancer. Most women at fifty don't know someone who has had heart disease." Her eyes locked reassuringly on mine. "That's because under seventy-five there are three times as many deaths from breast cancer as from heart disease."

3.

There is an even more striking problem with the anti-estrogen movement, and that is the way that it ignores the next generation of H.R.T., the compounds known as serms (for "selective estrogen-receptor modulators"). For many years, it was thought that estrogen was a kind of blunt instrument, that if a woman took the hormone it would affect her bones and her breasts and her heart and her uterus in the same way. In other words, it was thought that a woman's body had one kind of molecular switch that would be turned on all over the body whenever she took the hormone. But when scientists were testing the drug Tamoxifen on women with breast cancer several years ago, they found out something unexpected. Tamoxifen was supposed to turn off the estrogen switch, so someone with breast cancer would take it on the theory that starving breast tissue of natural estrogen would help shrink or prevent tumors. "Everyone expected that the bone quality in these women on Tamoxifen would not be good." Donald McDonnell., a pharmacologist at Duke University, told me, explaining that people had assumed that if there was no estrogen going to the breasts there would be none going to the bones, either. In fact, though, the women's bones were fine. Somehow, Tamoxifen was turning off the estrogen switch in the breasts by acting just like estrogen in the bones. "What that suggested for the first time was that maybe estrogen doesn't work the same way in every cell and maybe we could use this information to build better compounds that would be tissue-selective. " McDonnell said.

What researchers now believe is that there many kinds of estrogen switches in the body, and that whether they turn on or off is highly dependent on the type of the estrogen like compound that they are presented with. Tamoxifen, by purest chance, happens to be a compound that turns the

switch on in the bones and off in the breasts. Unfortunately, it also turns the switch on in the uterus, raising the risk of uterine cancer. But a second generation of serms is now in development; these act like estrogen in the heart and the bones but block the harmful effects of estrogen in the breasts and the uterus. McDonnell has one such compound that is about to go into clinical trials. The Indianapolis-based drug firm Eli Lilly has another--Raloxifene--that is much further along and could be on the market within a year or so. Before very long, in short, women worried about raising their breast-cancer risk will have the option of taking a different kind of hormone that doesn't affect their breasts at all --or that may even protect against breast cancer.

"In the past, what you were looking at was a risk/benefit game," John D. Termine, a vice-president at Lilly's research laboratories, told me. "There was estrogen with all these terrific properties, but at the same time there was this downside, that women were afraid of breast cancer. Now Raloxifene and the other serms come along, and we're going to have alternatives. Now the risks and benefits are much different, because we have something else. . . . One of the physicians on our advisory board said that it's like when beta-blockers were introduced for heart diseases. It changed the game completely."

You might think that this development would be of enormous significance to Love, answering, as it does, her great worry about the potential side effects of H.R.T. In fact, she mentions serms just twice in her book and, each item, only briefly. It's a bit as if someone had written a book about computers in 1984 and

Scientists are hoping to use some of this new information to design the perfect hormone: one that will protect the uterus and breast from cancer, stop hot flushes, and prevent osteoporosis and heart disease. It would be lovely--could it do housework too?--but I'm skeptical,. It would still be a drug. And I have yet to see a drug that doesn't have some side effects.

This is an extraordinary passage. It would still be a drug? What form does a successful medical intervention have to take before Love finds it acceptable? And, for that matter, since when does the possibility of side effects negate the usefulness of a drug? Drugs have side effects, but we take them anyway, because in most cases the side effects are a lot less significant than the main effects. (That's why they're called side effects.) At one point in her speech in Washington, Love spoke of her daily breakfast of soy milk and flax-seed granola, and boasted jokingly that it was so rich in natural plant estrogens that "one bowl is as good as a Premarin pill." Now it turns out that one bowl is not as good as a Premarin pill, because plant estrogens as much weaker than animal estrogens. Nor are plant estrogens exactly "natural," because plant estrogens are, technically, nonsteroidal while Premarin--like the estrogen a woman makes herself--is a steroid. But Love wasn't really intending to enter into a discussion of estrogen chemistry. She was simply expressing her skepticism of modern medicine--of the idea that medical salvation can come in the form of a pill. Her objection is not to Premarin itself so much as it is to the idea that postmenopausal women should rely on any sort of drug at all.

This is where, sooner or later, you end up when you start down the path of people like Andrew Weil and Deepak Chopra and Susan Love. To read the health books on the best-seller lists right now is to be left with

the impression that exercise and a good diet are all that matter--that medicine is too ineffectual to help us if we do not first help ourselves. That's one of the reasons these books are so successful: they take the language of emotional and spiritual fulfillment and apply it to medicine, prompting people to find and follow their own instincts about health in the same way they have been taught to find and follow their own instincts in relationships, say. When Love told me in Washington that "this is your choice, this is your body, this is your life," that's what she meant--that the medical was the personal. This kind of talk may inspire people to shape up, which is all to the good. But it does not begin to reflect how sophisticated and powerful medicine has become. In the introduction to his 1990 book "Natural Health, Natural Medicine" Weil claims that "professional medicine" is "bad" at treating, among other diseases, cancer and viral infections. Yet today, just a few years after he wrote those words, not only are we on the verge of getting a new class of anti-influenza drugs but a combination therapy for H.I.V. appears to have dramatically extended the lives of aids patients, and over the next several years the biotechnology industry is likely to get approval for almost two dozen new cancer drugs, representing second generation of treatments, to replace chemotherapy and radiation. The list of things that traditional medicine is bad at gets shorter all the time.

Earlier this year, a study appeared in the Journal of the American Medical Association that put many of these changes in perspective. The study, conducted by a team from Harvard University's School of Public Health, attempted to figure out why the mortality rate from coronary heart disease dropped so dramatically in the nineteen-eighties. In that decade, the decline averaged 3.4 per cent a year, which means that in 1990 there were about a hundred and thirty thousand fewer deaths from heart disease in America than there would have been if the mortality rate had been the same as it was in 1980. Most people, I think, would credit this extraordinary achievement to our getting more exercise in the nineteen-eighties and losing weight. But we didn't, much. Smoking, which is obviously a major risk factor for heart disease, was down, but not by a lot: the Harvard group estimated that declines in smoking probably account for about six per cent of the decrease. People did eat better as the decade progressed, but better diet probably accounts for only about a quarter of the difference. Most of the drop--about seventy per cent of the total--happened because of the increased use of procedures like angioplasty and coronary bypass and, more important, the advent of a new class of powerful clot-dissolving drugs, like streptokinase and tissue-plasminogen activator.

This does not, of course, change the fact that people should exercise and eat properly and take charge of their lives., We should all listen to our bodies and make our own choices. But there are times when what we can find out about our bodies and do for ourselves pales in comparison to what we do not know and cannot do--when we have to rely on doctors and medicine to do things for us. There is more to medicine than can be explained by the language of personal fulfillment.

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