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**Do We Really Know What Makes Us Healthy? Part I
Epidemiology vs Random Controlled Studies**

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Your Life Your Health

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The September 16, 2007 *New York Times Magazine* featured an article entitled, *Unhealthy Science: Do We Really Know What Makes Us Healthy?* In this article Gary Taubes examined what the public is told about diet, lifestyle and disease. He explained the differences between an “epidemiologic study” and a “random controlled” study. Often our healthcare decisions are made upon the best information we presently have, which information is subsequently proved to be incorrect. That does not mean that we should not decide or that we should not act, but it does mean that we must constantly be learning. If we are making decisions with current “best practices,” we can be confident that we are doing the best we can. If we continue to use old, discredited information, we are not doing the best we can. The impact of this article which will be reproduced in a four-part series is to challenge us to do the best we can while at the same time, we continue to learn

“The following is taken from Tabues’ article. The entire 21-page article can be read on line. “Once upon a time, women took estrogen only to relieve the hot flashes, sweating, vaginal dryness and the other discomforting symptoms of menopause. In the late 1960s, thanks in part to the efforts of Robert Wilson, a Brooklyn gynecologist, and his 1966 best seller, *Feminine Forever*, this began to change, and estrogen therapy evolved into a long-term remedy for the chronic ills of aging. Menopause, Wilson argued, was not a natural age-related condition; it was an illness, akin to diabetes or kidney failure, and one that could be treated by taking estrogen to replace the hormones that a woman’s ovaries secreted in ever diminishing amounts. With this argument estrogen evolved into

hormone-replacement therapy, or H.R.T., as it came to be called, and became one of the most popular prescription drug treatments in America.

“By the mid-1990s, the American Heart Association, the American College of Physicians and the American College of Obstetricians and Gynecologists had all concluded that the beneficial effects of H.R.T. were sufficiently well established that it could be recommended to older women as a means of warding off heart disease and osteoporosis. By 2001, 15 million women were filling H.R.T. prescriptions annually; perhaps 5 million were older women, taking the drug solely with the expectation that it would allow them to lead a longer and healthier life. A year later, the tide would turn. In the summer of 2002, estrogen therapy was exposed as a hazard to health rather than a benefit, and its story became what Jerry Avorn, a Harvard epidemiologist, has called the “estrogen debacle” and a “case study waiting to be written” on the elusive search for truth in medicine.

“Many explanations have been offered to make sense of the here-today-gone-tomorrow nature of medical wisdom — what we are advised with confidence one year is reversed the next — but the simplest one is that it is the natural rhythm of science. An observation leads to a hypothesis. The hypothesis (last year’s advice) is tested, and it fails this year’s test, which is always the most likely outcome in any scientific endeavor. There are, after all, an infinite number of wrong hypotheses for every right one, and so the odds are always against any particular hypothesis being true, no matter how obvious or vitally important it might seem.

“In the case of H.R.T., as with most issues of diet, lifestyle and disease, the hypotheses begin their transformation into public-health recommendations only after they’ve received the requisite support from a field of research known as epidemiology. This science evolved over the last 250 years to make sense of epidemics — hence the name — and infectious diseases. Since the 1950s, it has been used to identify, or at least to try to identify, the causes of the common chronic diseases that befall us, particularly heart disease and cancer. In the process, the perception of what epidemiologic research can legitimately accomplish — by the public, the press and perhaps by many epidemiologists themselves — may have run far ahead of the reality. The case of hormone-replacement therapy for post-menopausal women is just one of the cautionary tales in the annals of epidemiology. It’s a particularly glaring example of the difficulties of trying to establish

reliable knowledge in any scientific field with research tools that themselves may be unreliable.

“What was considered true about estrogen therapy in the 1960s and is still the case today is that it is an effective treatment for menopausal symptoms. Take H.R.T. for a few menopausal years and it’s extremely unlikely that any harm will come from it. The uncertainty involves the lifelong risks and benefits should a woman choose to continue taking H.R.T. long past menopause. In 1985, the Nurses’ Health Study run out of the Harvard Medical School and the Harvard School of Public Health reported that women taking estrogen had only a third as many heart attacks as women who had never taken the drug. This appeared to confirm the belief that women were protected from heart attacks until they passed through menopause and that it was estrogen that bestowed that protection, and this became the basis of the therapeutic wisdom for the next 17 years.

“Faith in the protective powers of estrogen began to erode in 1998, when a clinical trial called HERS, for Heart and Estrogen-progestin Replacement Study, concluded that estrogen therapy increased, rather than decreased, the likelihood that women who already had heart disease would suffer a heart attack. It evaporated entirely in July 2002, when a second trial, the Women’s Health Initiative, or W.H.I., concluded that H.R.T. constituted a potential health risk for all postmenopausal women. While it might protect them against osteoporosis and perhaps colorectal cancer, these benefits would be outweighed by increased risks of heart disease, stroke, blood clots, breast cancer and perhaps even dementia. And that was the final word. Or at least it was until the June 21 issue of *The New England Journal of Medicine*. Now the idea is that hormone-replacement therapy may indeed protect women against heart disease if they begin taking it during menopause, but it is still decidedly deleterious for those women who begin later in life.

“This latest variation does come with a caveat, however, which could have been made at any point in this history. While it is easy to find authority figures in medicine and public health who will argue that today’s version of H.R.T. wisdom is assuredly the correct one, it’s equally easy to find authorities who will say that surely we don’t know. The one thing on which they will all agree is that the kind of experimental trial necessary to determine the truth would be excessively expensive and time-consuming and so will almost assuredly never happen. Meanwhile, the question of how many women may have died prematurely or suffered strokes or breast cancer because they were taking a pill that their

physicians had prescribed to protect them against heart disease lingers unanswered. A reasonable estimate would be tens of thousands.

“The Flip-Flop Rhythm of Science

“At the center of the H.R.T. story is the science of epidemiology itself and, in particular, a kind of study known as a prospective or cohort study, of which the Nurses’ Health Study is among the most renowned. In these studies, the investigators monitor disease rates and lifestyle factors (diet, physical activity, prescription drug use, exposure to pollutants, etc.) in or between large populations (the 122,000 nurses of the Nurses’ study, for example). They then try to infer conclusions — i.e., hypotheses — about what caused the disease variations observed. Because these studies can generate an enormous number of speculations about the causes or prevention of chronic diseases, they provide the fodder for much of the health news that appears in the media — from the potential benefits of fish oil, fruits and vegetables to the supposed dangers of sedentary lives, trans fats and electromagnetic fields. Because these studies often provide the only available evidence outside the laboratory on critical issues of our well-being, they have come to play a significant role in generating public-health recommendations as well.

“The dangerous game being played here, as David Sackett, a retired Oxford University epidemiologist, has observed, is in the presumption of preventive medicine. The goal of the endeavor is to tell those of us who are otherwise in fine health how to remain healthy longer. But this advice comes with the expectation that any prescription given — whether diet or drug or a change in lifestyle — will indeed prevent disease rather than be the agent of our disability or untimely death. With that presumption, how unambiguous does the evidence have to be before any advice is offered?

“The catch with observational studies like the Nurses’ Health Study, no matter how well designed and how many tens of thousands of subjects they might include, is that they have a fundamental limitation. They can distinguish associations between two events — that women who take H.R.T. have less heart disease, for instance, than women who don’t. But they cannot inherently determine causation — the conclusion that one event causes the other; that H.R.T. protects against heart disease. As a result, observational studies can only provide what researchers call hypothesis-generating evidence — what a defense attorney would call circumstantial evidence.

“Testing these hypotheses in any definitive way requires a randomized-controlled trial — an experiment, not an observational study — and these clinical trials typically provide the

flop to the flip-flop rhythm of medical wisdom. Until August 1998, the faith that H.R.T. prevented heart disease was based primarily on observational evidence, from the Nurses' Health Study most prominently. Since then, the conventional wisdom has been based on clinical trials — first HERS, which tested H.R.T. against a placebo in 2,700 women with heart disease, and then the Women's Health Initiative, which tested the therapy against a placebo in 16,500 healthy women. When the Women's Health Initiative concluded in 2002 that H.R.T. caused far more harm than good, the lesson to be learned, wrote Sackett in *The Canadian Medical Association Journal*, was about the “disastrous inadequacy of lesser evidence” for shaping medical and public-health policy. The contentious wisdom circa mid-2007 — that estrogen benefits women who begin taking it around the time of menopause but not women who begin substantially later — is an attempt to reconcile the discordance between the observational studies and the experimental ones. And it may be right. It may not. The only way to tell for sure would be to do yet another randomized trial, one that now focused exclusively on women given H.R.T. when they begin their menopause.

“A Poor Track Record of Prevention

“No one questions the value of these epidemiologic studies when they're used to identify the unexpected side effects of prescription drugs or to study the progression of diseases or their distribution between and within populations. One reason researchers believe that heart disease and many cancers can be prevented is because of observational evidence that the incidence of these diseases differ greatly in different populations and in the same populations over time. Breast cancer is not the scourge among Japanese women that it is among American women, but it takes only two generations in the United States before Japanese-Americans have the same breast cancer rates as any other ethnic group. This tells us that something about the American lifestyle or diet is a cause of breast cancer. Over the last 20 years, some two dozen large studies, the Nurses' Health Study included, have so far failed to identify what that factor is. They may be inherently incapable of doing so. Nonetheless, we know that such a carcinogenic factor of diet or lifestyle exists, waiting to be identified.

“These studies have also been invaluable for identifying predictors of disease — risk factors — and this information can then guide physicians in weighing the risks and benefits of putting a particular patient on a particular drug. The studies have repeatedly confirmed that high blood pressure is associated with an increased risk of heart disease

and that obesity is associated with an increased risk of most of our common chronic diseases, but they have not told us what it is that raises blood pressure or causes obesity. Indeed, if you ask the more skeptical epidemiologists in the field what diet and lifestyle factors have been convincingly established as causes of common chronic diseases based on observational studies without clinical trials, you'll get a very short list: smoking as a cause of lung cancer and cardiovascular disease, sun exposure for skin cancer, sexual activity to spread the papilloma virus that causes cervical cancer and perhaps alcohol for a few different cancers as well.

“Richard Peto, professor of medical statistics and epidemiology at Oxford University, phrases the nature of the conflict this way: “Epidemiology is so beautiful and provides such an important perspective on human life and death, but an incredible amount of rubbish is published,” by which he means the results of observational studies that appear daily in the news media and often become the basis of public-health recommendations about what we should or should not do to promote our continued good health.”

Dr. Holly's closing comment: Medicine knows a great deal but we don't know everything. The reality is that personal health is still the responsibility of each person. After all, it is your life and it is your health.