Readers Respond

The following two letters were written in response to a recent editorial ("From the Editor") by *Menopause Management* Editor-in-Chief Wulf H. Utian, MD, PhD (September/October 2006;15:6).

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Menopause Management *invites readers' responses to all of Dr. Utian's editorials. Please forward your responses to jkenny@menopausemgmt.com.*

Is Evidence-Based Medicine a Pipe Dream? But of course!

Geoffrey C. Kincaid, MD

"Is evidence-based medicine a pipe dream? It's your call!"[1]

So concludes Dr. Wulf H. Utian's excellent "From the Editor" article, published in the September/October 2006 issue of *Menopause Management*. In the editorial, Dr. Utian recounts the dilemmas spawned by "evidence-based medicine" (henceforth EBM) that we clinicians have been struggling to resolve—or at least to find some means of reaching an accommodation with—since the publication of the Women's Health Initiative (WHI) just over 4 years ago.[2]

The unequivocal answer to Dr. Utian's query is an emphatic: "But of course!" A "pipe dream," according to the original meaning of the phrase, is an opium-induced hallucination. EBM, as the term has been used since the early 1990s (the claim that evidence is hierarchical, with randomized controlled trials at the apex, etc.), could hardly be given a more fitting description.

EBM's fundamental error, perfectly exemplified by WHI—and, in particular, by the statement, "The results indicate that this regimen should not be initiated or continued for primary prevention of coronary heart disease" (CHD)[2]—is that of "context-dropping." That is, by generalizing from their findings while simultaneously ignoring contradictory evidence derived from observations other than from randomized controlled trials—and thereby severing data from context—the WHI researchers succeeded in invalidating their own conclusions.

The operative epistemologic principle is best explained by Leonard Peikoff in *Objectivism: The Philosophy of Ayn Rand.*[3] He states: "'Context' means 'the sum of cognitive elements conditioning an item of knowledge.' This sum is what enables us to reach the new conclusion, to prove it, to interpret it, to apply it. This sum, in short, is what sets the item's relationship to reality and thus the item's meaning and proper use."

Peikoff goes on to state (emphasis added): "Out-of-context claims or proposals, like out-of-context quotations or concepts, are by their nature invalidated. *Whenever one treats a conclusion as an atom unrelated to the rest of cognition, one thereby detaches the conclusion, along with the thought process involving it, from reality.*"

The concept "context" recognizes the fact that we live in a causal universe, and that all entities and events within such a universe are ultimately interconnected. One cannot speak of any one such entity or event without implicitly invoking, and contrasting it with, every other entity and event. The concept "healthy" has no meaning except by way of contrast with its opposites ("unhealthy" or "sick" or "diseased") and in relation to the entity being described (newborn versus young

adult versus septuagenarian). The traditional history and physical, in which are recorded such disparate items as age, dietary habits, recent travels, states of health of near and distant relatives, color and shape of the fingernails, the nature of sundry faint sounds issuing from the chest and abdomen, etc., provides tacit testimony to the interconnectedness of all things.

Clinical research is no exception. WHI was not conceived in a vacuum. The conviction that hormone therapy (HT) is, in fact, an effective agent for the primary prevention of CHD rests on a firm foundation. The natural history of coronary disease in men versus women, the increased incidence of CHD following uncompensated oophorectomy in premenopausal women, the numerous observational studies involving women treated with conjugated estrogens for vasomotor symptoms, studies of oophorectomized primates, studies of carotid intimal thickness, and the known biochemical effects of estrogen with regard to lipid metabolism, endothelial function, and plaque formation: all these and more support such a conclusion, and provide the context within which WHI must, if it is to serve a valid cognitive purpose, be construed.

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> *– Geoffrey C. Kincaid, MD*

Nevertheless, when it came to interpreting their findings with regard to CHD, the WHI writing group completely ignored this entire context. The best they could offer by way of corroboration, given their commitment to EBM's "gold standard," was the Heart and Estrogen/progestin Replacement Study (HERS).[4] But do WHI and HERS logically necessitate the official conclusion that "this regimen should not be initiated or continued"? Would it not have been both proper and prudent to consider an alternative—one consistent not only with WHI and HERS, but also with the considerable body of knowledge already existing? Why could the writing group not have concluded thusly: *Our findings, considered within the context of existing knowledge, allow us to refine the applicability of that knowledge to clinical practice as follows: in order to optimize its cardioprotective effects, HT must be initiated at or near menopause, before the development of significant plaque, and while endothelial estrogen-receptor activity remains high.* Why, indeed, if not for the intellectual blindness or, one might say, if not for the narcotic stupor engendered by EBM?

Science, including traditional (pre-EBM) scientific medicine, demands the noncontradictory integration of all the evidence. EBM preaches disintegration: ignorance on principle. Far from encouraging the application of data to clinical practice, EBM does precisely the opposite. By promulgating a "gold standard," it devalues the supporting evidence upon which the value of that gold depends. A profession-wide opium-smoking binge could hardly have been more destructive.

WHI was a disaster, and EBM is what made it so. We must, for the sake of our profession and for the sake of those we serve, put down the pipe, spend some time in detox, and get back to reality.

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Evidence-Based Medicine: A Casualty of the Women's Health Initiative

Howard N. Hodis, MD

Although one could look at the results from the Women's Heath Initiative (WHI) trials and conclude that the concept of evidence-based medicine is the culprit for post-WHI woes, it is, in itself, also a casualty of the WHI.

The WHI trials simply missed the boat, as did all of the other randomized controlled trials in the same genre. At the time these randomized controlled trials were designed, no one realized that the selected cohorts of women were inappropriate because they were not the same as those cohorts studied in observational studies from which the estrogen cardioprotective hypothesis was derived. Simply stated, elderly postmenopausal women remote from menopause have been predominantly studied in clinical trials, whereas young, recently menopausal women were studied in the observational studies.

Complicating the WHI trial results has been the pressure to make conclusions with finality, perhaps a result of the high costs of these studies for the American taxpayer. Although the WHI observational study is totally in line with the 20 or so observational studies that preceded it, the completely opposite results of the WHI observational study versus the WHI randomized controlled trials results remain, by and large, unacknowledged. Drawing conclusions not supported by the trial results has resulted in overgeneralization of the data. WHI trial results are being applied to all women regardless of whether they are of the appropriate age or time from menopause. It's like forcing the proverbial round peg into a square hole.

Regardless, the WHI trials provide excellent evidence-based medical information. Hormone therapy (HT)—conjugated equine estrogens (CEE) alone and CEE + medroxyprogesterone therapy—has a null effect on cardiovascular disease in elderly postmenopausal women remote from menopause, as well as a reduction in cardiovascular disease in relatively younger postmenopausal women closer to menopause. The latter finding of beneficial effects in younger postmenopausal women closer to menopause is totally predictable from the 20 or so observational studies, including the WHI observational study. Perhaps it is difficult to accept two seemingly opposing evidence-based conclusions from the same trial testing a single agent.

In the end, the concept of evidence-based medicine is alive and well, even in the WHI. What has given evidence-based medicine a bad name with respect to the WHI and similar trials was the incomplete understanding of how to apply the existing data to randomized controlled studies at the time of origination of trial design, compounded by resistance to accepting this unfortunate oversight at the conclusion of these trials. The WHI and other trials of the same genre have taught us this fact. We need to admit it, learn from it, move on, and conduct appropriate trials to specifically test the estrogen cardioprotective hypothesis in the appropriate population of women. This is what science is all about—and the process upon which the best evidence-based medicine is derived!

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