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To Whom It May Concern,

I am writing regarding the meeting to be held on October 7, 2003 by the Endocrinologic and Metabolic Drugs Advisory Committee which will discuss the Women's Health Initiative Study Results: Implications for the use of hormone therapy with estrogen/progestin, as a second-line drug, in the prevention and treatment of postmenopausal osteoporosis in women.

As a result of the WHI, hormone therapy is recommended for menopausal symptom control on a short term basis. But the definition of "short term" is subjective, and for many women, taking them off hormone therapy causes their symptoms to recur, prompting a return to the therapy. As a result, many women take hormone therapy for several years postmenopausally. It is well known that the health impact of the menopause goes beyond short term vasomotor symptoms; the published findings to date of the WHI are not sufficient to preclude consideration of hormone therapy for long term health benefits.

The hormonal RCT component of the WHI was designed to answer two specific questions:

1. Does hormone therapy increase breast cancer risk in postmenopausal women?

2. Does hormone therapy serve as a mode of primary prevention for cardiovascular disease in postmenopausal women?

It has, to date, answered neither of these questions. For starters, the average age of participants in the WHI trial was 63 years. These women already had an increased risk of breast cancer due to their age alone. The internal test statistic or z-score used to terminate the trial early was predetermined by the authors of the study. The t-scores were NOT statistically significant whether one looks at the nominal or adjusted confidence intervals as they either crossed or included the value of 1.0. The follow-up time was short, as reflected in the total number of breast cancer cases. While there was an increase in cases among the treatment group for years 4 and 5, there is a plausible biological explanation for this: stimulation of as yet undetected preclinical cancers. This is

plausible given that the average time for single cell cancerous transformation to become clinically detectable for breast cancer is, on average, 10 years. Additionally, there were breast cancer cases detected in year one- clearly there was a subset of women in both groups with undetected malignancies at the outset of the trial.

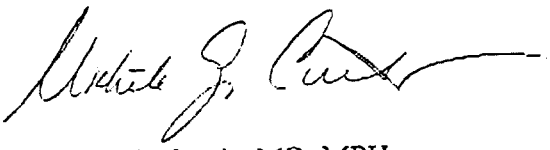
As for the cardiovascular (CV) impact that was so widely touted- a slight change in the number of cases in either group would have significantly altered the results. In addition, one of the diagnostic categories used to determine if a CV event occurred was silent MI, based on EKG changes. The EKG is recognized as an insensitive and non-specific test for the diagnosis of silent MI. If a large number of the CV events that "occurred" were based on the diagnosis of silent MI, the absolute certainly with which the authors can be sure an actual CV event took place is markedly diminished. Unfortunately, as far as I am aware, this information (how many CV events were based on the diagnosis of silent MI) is not available. The discrepancy between the local adjudicators and the national adjudicators was quite high with concordance only being reached 86% of the time. The entire validity of using the variable of CVD, as defined in the WHI, is questionable. Coupled with the elderly nature of the population- which precludes and defies the ability of anyone to call the trial a study of the primary prevention of CVD- and the lack of follow-up on statin use between the groups over time, clearly demonstrates that the WHI fell far short of even beginning to address the issue of CV prevention.

If, despite all of these flaws, the WHI is going to be held up as the gold standard by which hormone therapy is to be judged, until specific analysis of data regarding hormone therapy and osteoporosis gathered by the WHI trial is released assessing the validity of hormone therapy as a second line therapy for osteoporosis is inappropriate. It is my understanding that this data should be available very soon.

There is sufficient data to conclude, with great certainty, the benefits offered by hormone therapy in the prevention of osteoporosis for menopausal women. Even in light of the WHI, there is insufficient evidence to argue that any other risks associated with hormone therapy offset these benefits. Hormone therapy should retain its status of a good second line preventive agent for osteoporosis.

If you have any questions or would like to discuss this with me further, please feel free to call 713-906-6202 at your convenience.

Sincerely,



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