Q: What is the essence of your presentation?

A: Nearly all physiology is context-dependent. That means that one size doesn’t fill all, that no medication is good for everybody, that no level of any biological factor, in and of itself, really tells you anything about physiology. This is particularly applicable when we are talking about the effects of hormones on the brain and on behavior, because under certain circumstances the same hormone can actually precipitate an adverse effect or it can treat it.

In the context of the menstrual cycle, in people who have depressions during the luteal phase, one can see that the syndrome is actually precipitated by increases in reproductive hormones. You can eliminate the syndrome by simply suppressing ovarian function and eliminating the steroid secretion. Conversely, in the context of the perimenopause, the same hormone can actually be used to treat depression in women who do develop depression during the perimenopause. The subsidiary point is that if ALL women don’t become depressed during the perimenopause, that doesn’t mean that perimenopause is irrelevant to affective function. That was a conclusion, albeit erroneous, that was created in the 60s and the 70s when investigators looked at depression in association with perimenopause.

So, again, our goal should be one of individualized medicine, our goal should be one of stratifying populations, segmenting them on the basis of their risk factors, on the basis of those factors that will allow us to predict what will be helpful and what will be harmful.

Q: If that is the goal, then where do we start to get to that place?

A: I think we have to start with a change in our conceptions; we are always looking for an answer for very large problems, rather than recognizing that it’s the variances, the differences between people that will be most informative. In our studies, then, we need to be somewhat more agnostic, not assume that we know what the relevant factors are. We need to cast a wider net, embrace that variance and allow it to tell us what the relevant profiles are; but again conceptually, we need to recognize that there are, for example, some women who will absolutely benefit from estrogen replacement in the context of the perimenopause. There are other women for whom it wouldn’t be indicated including women who are post-menopausal as it would be deleterious to their health.
Q: Talk about estrodial deficiency and its role in CVD and depression.

A: We don’t yet adequately understand the role of estrodial replacement in context of heart disease or in the context of susceptibility to affective dysregulation; largely as a consequence of the Women’s Health Initiative. That study was designed to answer questions that were suggested by epidemiologic data of the time, but it was really the wrong question. The animal literature had demonstrated that the administration of estrodial in the context of a delay between the cessation of ovarian activity and actual administration produces very different effects from those that are produced when estrodial is given close to cessation of ovarian activity. Specifically, one can see in animals that the proximate administration of estrodial is protective in the brain and is protective in the cardiovascular system and that the delayed administration is not protective in the brain and with additional age intervening, is actually associated with immune stimulation that can have very adverse effects on the brain. The same findings are observed in the cardiovascular system. With age you see a response to estrodial that is more what would be called “pro-inflammatory”, as opposed to the anti-inflammatory effects that are seen when estrodial is administered proximate to cessation of ovarian activity. So the bottom line is, we don’t really know what the role is. We have lots of evidence to suggest that there is a beneficial effect, but that beneficial effect again is context-dependent. That is what our job is—to determine the risk profiles of individuals with sufficiently comprehensive information on the factors that may influence the response to estrogen so we can administer it when people are susceptible and will benefit and avoid its use in individuals who are at high risk.