years of clinical experience or, for that matter, different than the natural hormone, estradiol, which circulates in the blood. In other words, we have no data that they are more dangerous than the native hormones at comparable levels of potency. They may be proven to be more hazardous, but there just isn't any evidence for this as yet. Even natural estrogens are toxic to laboratory animals when given in excessive dosage. Then the important thing is the relative amount that is given to the patient and how it is given.

Information on the amount of hormone produced in the normal cycle indicates levels of 50 to 200 micrograms of estradiol per day. The oral contraceptive medications contain a dose on a potency basis some four to five times the peak levels of the cycle, clearly providing amounts outside the physiological range. I think the current recommendations to lower the estrogen dosage and indications that complications are fewer with less estrogen would be in keeping with sound pharmacological principles. It is obvious that we need more studies with the lower level medication in terms of their efficacy in preventing pregnancy as well as in the production of side effects. But I would clearly make a plea for studying the possibility of using drugs with lower estrogen in them.

Now, so much, then, for the estrogen. I could summarize it by saying we have had 30 years of experience and there is not much that has come out with the newer preparations that we have not seen already, that has not been known and has not been written about at one time or another. It might be related to dose potency, but there is no other information of unique character of the estrogens used in the pill.

When you come to the progestational agent used in these oral medications, they are different from the estrogens. There are more marked qualitative and quantitative variations in biological effects and we don't have the same number of years of clinical usage. Rather than 30 years of experience, it is closer to 15 years with these agents. Experience with some of these progestins is longer than with others and the dosage has varied some tenfold since the first pills were introduced. It is not fair to talk about the side effects produced with the higher dose medication today, because the higher dose medication is usually not used. It is, therefore, not possible to bring to bear the same clinical experience as with the estrogens, and there is even less certainty about equating biological properties within this class of compounds. Clearly more information is required for current dose levels and types of hormone. With a given side effect, we still may not know whether it is the estrogen or progestin component or both which are responsible. For instance, we have some thoughts on this, but we do not have enough information as yet—again a plea for more research in this area.

Now, the synthetic estrogens have been used with the progestin because the two together can usually prevent pregnancy more effectively and provide a more natural artificial cycle at a lower dosage level than either alone. That is why they are used together, either in the combined pill or sequentially, one followed by the other.

Now, the combination of estrogen with progestin, unfortunately, produces effects which are different than the sum of their individual