Both you and Dr. Beaver have addressed the question of the placebo effect, which may be based on a physiological response because of encouragement from the doctor and the fact the patient got a pill. However, in order to allow this drug to be on the market or remain on the market, does not the law require you to come up with well-controlled studies that would show that, in combination, propoxyphene and aspirin are more effective than either one alone?

The law is fairly clear. It requires the positive proof of well-controlled studies to support the introduction of a drug in the marketplace. You have been very strong in that position on the combination antibiotics, requiring proof or ordering them off the market. Are they all off now?

Commissioner KENNEDY. Almost.

Senator NELSON. So my query is: How do you justify under the statute—which requires well-controlled studies—the presence in the marketplace of a combination of active ingredients for which there appears no scientifically controlled studies that prove it is more effective?

I may be wrong. Maybe there are studies out there. But in all the literature I have looked at, I have not noticed one well-controlled study that would prove that it is more effective in combination than standing alone.

Commissioner KENNEDY. Well, clearly at the time that the combination products were introduced and at the time that we did our review, the NAS–NRC Committee and our reviewers found the evidence at that time persuasive enough to allow the marketing of these compounds.

It often happens, Mr. Chairman, that as time goes on and evidence from clinical trials on already marketed drugs accumulate, that we have to change our minds and that is why I am telling you that there is going to be a careful review of the effectiveness as well as the safety of these products and that it might very well result both in large changes or in consideration of withdrawal of those of the combination product.

You are quite right in your assertions what our policy was.

Senator NELSON. I am sure you understand very well that once a drug is in the marketplace and being used by hundreds of thousands or millions of people, all kinds of reactions that were not anticipated, due to limited, controlled studies, are disclosed almost inevitably over a period of time. And I recognize this drug was in the marketplace in combination before the efficacy amendments of 1962, is that not correct?

Commissioner KENNEDY. Some of its combinations were.

Senator NELSON. However, if a new drug application (NDA) were before you now, would you require well-controlled studies demonstrating that in combination the drug was more effective than it was as a medicine administered alone before you would permit it to go into the marketplace?

Commissioner KENNEDY. Yes, sir.

Senator NELSON. Are you aware of any well-controlled studies as of this date that would support it going into the marketplace as a combination product if the application were currently pending?