components or in which the fixed combination is not the treatment of choice;

2. Exposed the patient to the increased toxicity inherent in a combination without increasing the benefit;

3. Denied flexibility of the dosage of the components;

4. Ignored the marked changes in the pattern of bacterial susceptibility in recent years and the development of new and better antimicrobial agents; and

5. Ignored the availability of penicillin and streptomycin individually for combined use at the discretion of the physician.

These considerations and the limited indications for these combinations have rendered fixed-dosage forms of penicillin and streptomycin of little value in therapeutics. Accordingly, the Panels seriously question whether they still belong in the therapeutic armamentarium. It is the judgment of these two Panels that the use of these fixed combinations should no longer be recommended and that the physician should continue to use the individual components according to his best clinical laboratory information.

You can summarize all of that by saying in one word that they are "obsolete."

Finally this last paragraph—I would like to leave a little disclaimer here—there may be special instances where fixed combinations are of value—and this is what I alluded to before. They include the combined use of isoniazid and thiacetazone in the treatment of tuberculosis because of great convenience.

Senator NELSON. In this country?

Dr. KUNIN. No. I don't believe that these drugs are used in this country at this time—but if evidence were to be provided that would be satisfactory to an expert panel, or to the Food and Drug Administration, that there was an advantage to this particular combination, then I think the Food and Drug Administration, for the benefit of the American public, should accept evidence of that kind. That is why I am leaving this door open. I mentioned that such combinations are particularly useful in underdeveloped nations where it is much more preferable to give a single dose each day. In addition, evidence is accumulating—and here is the second example—that antimicrobial synergy—that is the effectiveness of the combination is greater than the sum of the individual activities of the ingredients exists when a drug called trimethoprin is combined with a sulfonamide.

This particular combination is undergoing extensive evaluation in the United Kingdom and other parts of the world. Actually it is licensed in the United Kingdom, and it is being used fairly widely.

Senator NELSON. What is the drug?

Dr. KUNIN. It is a combination of trimethoprim, which blocks the synthesis of a particular metabolite at one site, and sulfonamide blocks the same pathway at another site, so that the two together appear to have synergy or an effect greater than the sum of the two. It looks very promising.

Now, "promising" doesn't mean necessarily that it should be approved or accepted by our Food and Drug Administration. Nevertheless, there has been a fair amount of work with this, and it has been released in the United Kingdom. We will just have to look at the data and the evidence for this particular combination.