In all such circumstances, however, the drugs should be given by the parenteral route. These drugs, oral sulfonamide and penicillin in question are not injectible, and, therefore, would not be very helpful in the very serious infections.

Senator NELSON. Are any of the combinations injectible?

Dr. KUNIN. Yes. The combination pencillin and streptomycin is injectible. But we will get to that and tell you all the reasons why we don't think this combination is rational either.

Senator NELSON. But most of them are administered orally.

Dr. KUNIN. Most of them are administered orally.

The market of course is always greater for oral preparations than for injectible preparations.

In addition to the use of the other fixed mixtures which have been shown to be much more effective than single drugs—let me put it this way.

If you have to treat with multiple agents, one would rarely use sulfonamide and penicillin, there are so many other mixtures given individually that would be much more effective.

Now, the only area that there is some discussion concerning the use of penicillin-sulfonamide seems to be a common occurrence in pediatrics, that is the running ear or earache. Here there are three organisms that are important. Some of these ears are infected with pneumococcus, and some with streptococcus, and some with an organism called *Hemophilus influenzae*. Pneumococci and streptococci are quite sensitive to penicillin. *Hemophilus influenzae* is not sensitive and requires a different kind of drug. We have two alternative drugs. We have Ampicillin and tetracycline for this particular organism.

One of the major claims is that the sulfonamide component of the penicillin-sulfonamide mixture might have some advantage for this particular organism. We point out, however, that this particular organism is almost only seen in children less than 3 or 4 years of age, and actually in the literature it has been very difficult to demonstrate any superiority of the combination of penicillin and sulfonamide over penicillin alone in this particular condition. This is probably because most of these infections are not due to bacteria, but to virus infections of the ear where no antibiotic would be of any value.

Then we discuss the question of exposure to multiple drugs. This is probably one of the key objections in this area. The sulfonamide and penicillins are potentially dangerous drugs. Reactions are common. They can be severe and even fatal. The use of both drugs simultaneously therefore increases the risk to the patient, and is to be avoided for this reason. Other troublesome aspects of this problem is the difficulty in detecting the drug causing the reaction when multiple drugs are used.

Senator NELSON. Under the law now, in order to get an NDA approved, there has to be proof of safety. That became the law in 1938, and safety and efficacy became the law in 1962. Your panels have been reviewing this problem from the standpoint of efficacy. If I understand you correctly, what you are saying is that in combinations there is also a serious safety problem.

Dr. KUNIN. Yes; because you are adding on another drug. The problem of safety is that no drug is safe. All drugs are dangerous.