

came here. And actually essentially all the important information on the toxicity of novobiocin was published in a monograph by Dr. Finland in 1956. And to my knowledge, although there may have been some refinement of statistics, there really is no significant new information which was not adequately described by that time in, I should say, about a 350- or 400-page monograph on the subject.

Mr. GORDON. Why did the FDA wait until last week to change its label?

Dr. HEWITT. That is a question—

Dr. KUNIN. I would like to comment on that, to be fair to the Food and Drug Administration. Remember that every drug has toxicity, and it is a matter of relative toxicity in terms of the advantages or disadvantages of the drug. Novobiocin at that particular point in time was one of the potentially good drugs for staphylococcus infection. We did not have the new semisynthetic penicillins. So it was not unreasonable to use novobiocin fairly liberally at that time. Therefore the FDA really had no reason to act prior to that time. The development of the new semisynthetic penicillins is quite recent, actually.

Mr. GORDON. How long ago?

Dr. KUNIN. I would say the really good oral semisynthetics have been in the market about 2 years now.

Dr. HEWITT. Longer than that, about 4 years.

Dr. KUNIN. Four years.

And with that the utilization of novobiocin alone is—I think there is hardly any market for it. I don't think anybody uses it, or very rarely.

Dr. HEWITT. I have some figures on that. Maybe I should allude to those figures, however, which will clearly, I think, establish the fact that novobiocin is not used actually alone to any extent at all, in fact it probably alone is one of the least used of the antibiotics at the present time.

Senator NELSON. But it is used in a fixed combination?

Dr. HEWITT. Yes; to a very considerable extent.

Now, because I guess I may be the oldest gentleman here, and because I was involved with the early penicillin streptomycin program under Dr. Kiefer at the time when Cal Kunin was a house officer in the Boston City Hospital—

Dr. KUNIN. I wasn't even a medical student then.

Dr. HEWITT. I would like to sketch briefly in historical perspective the introduction, development, and current position of antibiotic combinations which may assist in making clear a scientific, sound, and reasonable approach to this problem. By curious coincidence the first two antibiotic agents of great medical importance were penicillin and streptomycin, the former coming into wide use in the middle 1940's and the latter in the early 1950's. Penicillin was primarily active against one of two large groups of bacteria known as gram-positive organisms and streptomycin was primarily active against the other large group of bacteria known as gram-negative organisms. Both classes of these bacteria may be present in a variety of infections, especially those in areas communicating with our environment and, therefore, particularly those in the respiratory, genitourinary, and gastrointestinal tracts. The logic of "broad-spectrum activity" and the use of multiple drugs in the treatment of such infections appeared