

in the control and treatment of functional combinations of antibiotic therapy. But as a fixed combination, no.

The immediate commercial success of many of these antibiotic combinations was remarkable. Mysteclin-F and Panalba have been among the 200 most prescribed drugs since 1961. Signemycin was on this list in 1961, 1963, and 1964.

Senator NELSON. How would you secure your data on the most widely prescribed drugs?

Dr. LEY. Senator, we have to utilize the listings provided by industry. There are several services which provide measures in terms of number of prescriptions or number of dosage units or number of dollars involved in the sale of a particular drug over a year's period. One of the most widely known of these is the Gosselin survey, with which I am sure you and your staff are familiar.

Senator NELSON. The thought occurs to me, batch testing wouldn't give you any indication, would it?

Dr. LEY. The certification which these products undergo before they are released to the market will give you a figure for the total volume of product that has been transmitted by the manufacturer to his distribution system. They will not necessarily give you an accurate measure of the amount sold during a year.

Senator NELSON. Are you satisfied that the surveys that are done such as Gosselin that list 200 most widely prescribed drugs are reasonably accurate listings.

Dr. LEY. These surveys, Senator, are performed on the basis of an elaborate sampling procedure, and are generally dependable. As you are quite well aware, however, even such elaborate sampling services as the Gallup poll have failed to predict certain political outcomes in an election. But in general this type of sampling is very good. It is the best we can come up with.

Senator NELSON. Thank you.

Dr. LEY. Other antibiotic combinations that I haven't previously mentioned also made this "best seller" list of drugs with some frequency. For example, Pentid-Sulfa made the list six times, Ilosone-Sulfa and Tetrastatin five times each, and Declostatin four times.

The efficacy of these antibiotic combinations in practically every case was supported almost solely by in vitro studies; that is, test tube type evaluations comparing combination preparations and single entities. These tests generally showed that the combinations produced increased antibacterial activity, with organisms exposed to the combination building up resistance at a slower rate. But, in general, there was a striking lack of data from carefully controlled, critically evaluated clinical studies to test these drugs in the treatment of disease. In short, the evidence of effectiveness was inadequate in terms of today's legal requirements.

The type of "substantial evidence" now required to support efficacy claims was defined in the Kefauver-Harris drug amendments of 1962. These amendments not only provided that new drugs marketed thereafter must be proven effective, as well as safe, but also authorized a review of the efficacy of all drugs, including antibiotics, introduced from 1938 to 1962.