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NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL DRUG EFFICACY EVALUATIONS AND ANTIBIOTIC COMBINATIONS

The purpose of this report is to describe the scientific basis of the judgments reflected in the evaluation of individual products by the Drug Efficacy Study Panels of the National Academy of Sciences—National Research Council and my view of the place of combinations of antibiotics in the rational therapy of infectious diseases. The discussion will consist of the organization of my panel and the characteristics of its membership, the categorical areas which provided evidence as a basis for the evaluations of drug efficacy, and an historical perspective upon the introduction, development, and present usefulness of antiobiotic combinations. Some conclusions will be stated which appear justified in the present state of our knowledge as to the present position which the combinations should occupy.

Organization of the panel. I am a Professor of Medicine at the University of California Medical School, Los Angeles, in charge of the Division of Infectious Diseases. I have the responsibility for teaching medical students and young House Staff physicians who for the most part will leave the University Medical Center environment well trained for private practice. The major portion of this teaching is performed at the bedside of sick patients. I also manage a clinical research and training program oriented toward infectious diseases. Lest there be any misunderstanding I would like to emphasize that I am not an ivory tower basic scientist. By training and experience as well as in my research I have been concerned with the study of disease and the methods for its treatment. I have had a practice of my own for twenty years and even to the present rely upon this type of activity for one-third of the income I derive from professional activities. The majority of patients I see results from the requests of medical colleagues who apparently regard me as sufficiently practical and competent to help them with both common as well as unusual or difficult problems of sick people and do not classify me as an isolated scientist pronouncing without benefit of experience. All of these qualifications were the basis for my selection as chairman, as well as the others, of Drug Efficacy Panels dealing with antibacterial agents used for the treatment of infections.

The five members of my panel consisted both of internists concerned with adult medicine and a pediatrician, particularly appropriate since a large volume of antibiotic combinations is prescribed for children. These gentlemen, likewise, were not sitting in libraries writing textbooks and giving lectures to medical students but rather were daily seeing sick patients and caring for their medical and emotional needs. All of us participate liberally in local and national societies, the membership of which consists largely of "general physicians" concerned with both general and specialized medical problems.

The panels were concerned primarily with evaluation of efficacy which to my knowledge was not rigidly defined in the Drug Amendments of 1962 to the Federal Food, Drug, and Cosmetic Act of 1938. This should not, however, present formidable problems if one takes a simplistic view with the welfare of the patient as the central focus. In order for a drug to be effective there should be "substantial evidence"* that it has a beneficial effect in the treatment of human disease and that these are the effects it is purported to have. It is obvious that some drugs will be better than others for an identical purpose but this rightfully was not a concern of the panels and should properly be relegated to avenues for physician education where it may receive adequate discussion and dissemination and be periodically updated on the basis of new scientific evidence. None of these drugs can be administered without some risk of ill effects and this must obviously have some bearing on efficacy. A drug should clearly have more benefit than harm. Thus, although penicillin would, strictly speaking, be effective for the treatment of streptococcal sore throat in a patient with a previous history of anaphylactic

*As defined in the 1962 Drug Amendments, "the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."