an antidiarrhea mixture containing sulfaguanidine, the earliest of the nonabsorbable sulfonamides. (1) The mixture was prescribed by the patient's father, a physician. Some years earlier a lecturer, who had discussed the uses and abuses of antibiotics, was approached by a physician from the audience for advice about his four-year-old daughter; she had become totally deaf as a result of repeated administration of Combiotic, a combination of procaine penicillin and dihydrostreptomycin, by a pediatrician colleague for impetigo that kept recurring in spite of several courses of this agent.

These are not uncommon examples of serious untoward effects that are totally unnecessary and directly attributable to a component of a fixed drug combination that was not making any therapeutic contributions. They are all the more impressive for having involved the immediate families of physicians. The protection of the public, and also of practicing physicians against just such improper therapy, was one of the main reasons for the concerted but frustrated efforts over many years, by most of the leading clinical experts, teachers and research workers in the field of infectious diseases, to discourage manufacturers from marketing and physicians from prescribing antimicrobial agents in fixed combinations. Now the 1962 Kefauver-Harris New Drug Amendments to the Food Drug and Cosmetics Act of 1938 and the regulations promulgated by the Food and Drug Administration under authority of those laws are being invoked to achieve this purpose.

The Kefauver-Harris Amendments introduced new and in some respects radical concepts. Most important was the requirement that new drugs must be effective as well as safe before they can be marketed. The manufacturer is required to provide proof that the drug has all the effects that it is claimed to have in the "labeling" (which includes the "package insert" and all advertising material) for the purposes and under the conditions of use for which it is recommended. Safety—that is, freedom from serious toxic effects—may also be taken into account in the evaluation of efficacy in that a toxic drug may not be acceptable if safer and more effective drugs are available for the same indications. "Substantial evidence," consisting of adequate and well controlled investigations by qualified experts, must be presented in support of each claim before it is accepted. When drugs are marketed in fixed combinations, the law and regulations require that each active ingredient must be shown to have not only the effect claimed for it as a single drug, but must also contribute to the efficacy with respect to each separate claim made for the combination in the dosage ratio present in the combination.

Soon after Dr. James L. Goddard became commissioner of the Food and Drug Administration he decided that the provisions of the Kefauver-Harris Amendments relating to efficacy should apply to all drugs marketed under new-drug applications that had been "approved for safety" since the passage of the Food Drug and Cosmetics Act of 1938. (2) This required a review of all claims for an estimated 4000 drugs and about 7000 formulations, a task far beyond the capabilities of the FDA. To accomplish this Herculean task expeditiously, Goddard succeeded in enlisting the co-operation of the National Academy of Sciences-National Research Council Division of Medical Sciences, under its chairman Dr. R. Keith Cannan, and the Drug Research Board, under the chairmanship of Dr. William S. Middleton, to gather up and organize the experts and provide leadership and guidance for this task. Some 30 panels were eventually enrolled, each consisting of a chairman and five members, most of them recommended by the major national professional and biomedical societies. Some additional experts were consulted on an ad hoc basis when special advice and experience was needed.

The guidelines of the Drug Efficacy Study were set up with the help of a Policy Advisory Committee, after joint consultations with the FDA, representatives of industry and the chairmen of the panels. The staff work was done by Mr. Duke C. Trexler (who already had experience as executive secretary to the Commission on Drug Safety) and a group of physicians and staff members of the FDA specifically assigned to the Drug Efficacy Study to assist the panels and expedite their work. The entire task from inception to its expected completion next June, when all the last reports are submitted to the FDA, will have taken more than three years.

As anticipated, many new problems requiring decisions arose in the course of the review; these were considered by the panels with the help of the Policy Advisory Committee headed first by Dr. Middleton and later by Dr. Alfred Gil-

NOTE.—Numbered references at end of article, p. 5269.