

evaluations of the antibiotic combinations could be implemented because of my uncertainty that the Food and Drug Administration would receive the necessary support from organized medicine, the pharmaceutical industry, and even the Congress itself where important pressure groups may have influence. The forthright stand taken by the Food and Drug Administration representatives at this meeting was a refreshing one, especially in the face of considerable predictable adversity. The other four panel chairmen and their twenty panel members were also available for opinions. The final classification of efficacy was reviewed by all the three panel chairmen concerned with antibacterial agents other than those used only for tuberculosis.

The background and current activities of the panel members and the confidence placed in them by the Policy Advisory Committee of the Drug Review Board, National Academy of Sciences, justified conservative and limited use of their personal experiences and judgment. All the panel members have contributed liberally to the published literature concerning the specific agents under review. All of them are currently active in the study and treatment of infections so their familiarity with the problems are current in scope.

The geographic areas and types of medical practice in which physicians are active is subject to wide variation. The plurality of their needs is more than equaled by the diversity of the diseases they encounter and the demands of their patients. It is essential that the value of their judgment, the validity of their experience, and the integrity of their beliefs be respected. Keeping the welfare of the patient as the focal point of medical practice, an ideal which in my belief the vast majority of physicians continue to accept, the needs of these practicing physicians was carefully considered. The consequences of the panel decisions on the effectiveness and efficiency of the delivery of health care by those physicians in their communities was also thoroughly discussed. It should be observed, however, that the prescribing habits of physicians are not necessarily valid criteria for efficacy or, indeed, even for proper usage and may poorly reflect the true state of knowledge. An extreme example of this is the indiscriminate use of chloramphenicol. Countless other less striking instances when antibiotics do more harm than good emphasize the great need for continuing physician education by the most effective possible methods. The types of contributions which practicing physicians are best able to make will be discussed subsequently.

*Combinations of antibiotics in rational treatment of infectious diseases.* The following indications have been advanced for prescribing two antibacterial drugs together:

- (1) Mixed infections.
- (2) As an attempt to control fever while investigating an obscure and/or serious illness.
- (3) To permit reduction in dose of a potentially toxic agent by the additive effect of another.
- (4) To prevent or delay the development of bacterial resistance.
- (5) To achieve antibacterial synergism, that is, an effect with two drugs which is significantly greater than might be expected from the purely additive effects of each drug alone.

The evidence for and against antibiotic combinations should be considered separately in two categories:

- (1) The validity of their use for the above indications.
- (2) The propriety of the existing formulations both in terms of the individual antibiotics in the combination and the proportions in which they exist in a fixed ratio entirely insusceptible to manipulation by the physician.

A further question which is not applicable in the present context but should be recognized concerns whether *all* fixed combinations are inherently bad; this is, I believe, a complicated issue. A review in the form of a "white paper" of the claims for the use of antibiotic combinations and the judgments of their validity will appear in the New England Journal of Medicine, 22 May, 1969. Suffice it to say that none of the first three indications are valid for the fixed combinations of antibiotics currently available. Either the specific combinations of drugs would be poor choices for the purposes suggested or when a certain combination of drugs is indicated they are not present in the commercially available combination in an acceptable and effective dosage. Several of the combinations with less than compelling theoretical basis for their usefulness, especially to prevent the development of bacterial resistance, can be discarded competely because of the advent of more active agents to which resistance occurs rarely, if ever. Tuberculosis provides the major example for the use of combination