drugs for this purpose but none of the fixed antibiotic combinations are applicable. The use of more than one drug to enhance antibacterial action is the most valid of the five indications. Clinical situations when this principle is applicable, however, are not frequently encountered, are usually serious diseases for which facilities for specific diagnoses are hopefully available, and for which antibiotic dosage requires specific tailoring. The administration of the appropriate combinations in the dosage indicated for these situations would be impossible with any of the fixed combinations commercially available.

The claims for most of the commercially available antibiotic combinations are exaggerated usually by implications related to the above poorly supported indications. Emphasis is placed on the concept that rational treatment based upon sophisticated laboratory methods is fine for urban practice *and* a medical center but more than a clinical diagnosis may be difficult in a less luxurious setting. Faced with this problem "broad-spectrum" coverage is desirable and the antibiotic combinations provide this. In actual fact, a reasonably accurate clinical diagnosis sufficient to decide the antibiotic of choice is usually possible and most of these combinations are employed for purposes which do not require combinations at all. Such examples are antibiotic coverage in surgical operations to prevent infection when this may be entirely unnecessary or an attempt at "shotgun treatment" of diseases of unknown nature which may or may not be infectious in origin. In several of the combinations, such as those containing one antibiotic combined with streptomycin or novobiocin, patients are subjected to unnecessary adverse effects from these agents because they add nothing to the therapeutic effect of the primary agent with which they are combined.

It was for these reasons that the panels unanimously stated that:

(1) Fixed combinations of antibiotics now available lead to the inappropriate use of these drugs for the treatment of disease states in which the combination is no more effective than one of the components or when the fixed combination does not even contain the individual antibiotics of choice.

(2) Patients have been exposed to increased toxicity inherent in the combination without increasing therapeutic efficiency.

(3) Fixed combinations deny flexibility with respect to the dosage of the individual components of the combination.

(4) Fixed combinations now available ignore developments which have occurred in the pattern of bacterial susceptibility and the appearance of new and better antibacterial agents.

(5) The agents in fixed combinations are readily available individually for combined use at the physician's discretion as to the choice of agents and their proper dosage.

Finally, 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 the 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 relatively early. Many laboratory investigations and clinical reports of series of infections treated with the penicillin/streptomycin combination appeared to document the favorable response of patients to the combination. Subsequent carefully controlled studies, increased insight into the importance of mixed bacterial flora and the significance in these infections of individual components of that flora, as well as the advances in chemotherapy with the discovery of new antibiotics have all operated to alter appreciably the logic behind this particular antibiotic combination.

The next portent of things to come and the initial departure from sound principles of chemotherapy appeared under the advocacy of Dr. Henry Welch, then Director of the Division of Antibiotics of the Food and Drug Administration. This was first documented in his opening remarks at the Fourth Symposium on Antibiotics and later published in *Antibiotics Annual*.[1] By this time over

[1] Welch, Henry, opening remarks, *Antibiotics Annual*, 1956–7, 1–2, Medical Encyclopedia, Inc., New York, 1957.