

bination of two antimicrobial agents, the degree of antibacterial activity is generally quite unpredictable and under other circumstances antimicrobial effectiveness may be decreased by combination therapy.

Furthermore, in the case of several of the available combinations (such as Panalba, Albamycin T, Signemycin, erythromycin-sulfa, et cetera), the dosage formulation is such that in some instances, if the manufacturer's recommendations are followed, the patient would receive too little of both drugs for maximal effectiveness, in other instances, too little of one of the two drugs in the combination, and in the case of some erythromycin-sulfa combinations, if the physician wishes to administer even moderately large doses of erythromycin, the patient will receive an excessive and potentially dangerous amount of sulfonamides.

Let me comment next on possible enhancement of antibacterial activity by two drugs. It is true that in three unusual circumstances combinations of drugs are more effective than single drugs alone. The best example is perhaps tuberculosis; bacterial and endocarditis due to group D streptococci and occasional endocarditis due to streptococcus viridans are treated more effectively by a combination than by single drugs. However, it must be emphasized that these are rare and very serious infections where dosage of each drug is usually individually adjusted on the basis of many considerations.

Senator NELSON. When you state on page 2 that it is true that in three unusual circumstances, combinations of drugs are more effective than single drugs alone, you, I take it, still are not recommending that a fixed combination be used in the treatment.

Dr. EICHENWALD. No, I am not.

In general, laboratory testing of combinations has given variable results, depending on the concentration of drug employed, the specific laboratory conditions, the nature and susceptibility of the organism, et cetera. The effects of combination may be antagonistic (which means that activity is less than the sum of the separate activities). There may be synergism (enhancement of antibacterial activities beyond the additive effects of the two drugs) and, finally, there may be addition (activity equal to the additive effect of the two drugs). None of the in vitro data, the test tube data, have consistent clinical correlations. There is no way of using in vitro tests to identify instances in which fixed combinations will be advantageous or disadvantageous.

Despite the fact that many of the drug combinations have been on the market for a decade or more, no controlled studies have appeared in the literature which would indicate that the enhancement of clinical activity claimed for these combinations exists. During the National Drug Study, each pharmaceutical firm marketing a combination was given the opportunity to provide to the panel supporting data for their claims; none were forthcoming. The data in the literature purporting to demonstrate clinical efficacy for these combinations are uncontrolled, and mostly consist of a few patients treated with variable results. In general, the results obtained were no better than those one would expect had a single agent been used.

The third theoretical argument for combinations is that they permit more ready treatment of infections before etiology is known and are useful in instances where it is impossible to determine etiology.