

THE CASE FOR AND AGAINST SYNERGISM

Penicillin and streptomycin have a synergistic effect against enterococcus and probably against penicillin-sensitive viridans *Streptococcus* as well. Also, laboratory evidence of synergism of various combinations of drugs against individual strains of several microbial species has been published, but much remains to be done before these studies can be applied at the clinical level. Furthermore, different combinations would seem to be synergistic against different species or even against different strains within the same species.

There is some clinical evidence that tetracycline derivatives or tetracycline in combination of with streptomycin result in a lower relapse rate in the treatment of brucellosis than occurs with either drug alone. If the treatment period with a tetracycline is greatly prolonged, however, a similar low relapse rate will be achieved.

THE "INSURANCE" PRINCIPLE

In the treatment of serious staphylococcal and other infections the life of a patient may be jeopardized by withholding treatment until a satisfactory etiological diagnosis can be obtained or until antibiotic sensitivity tests are completed. In such situations the employment of more than one antibiotic is frequently justified, but these should be used in full doses.

DIMINISHED TOXIC EFFECTS

When equal amounts of streptomycin and dihydrostreptomycin are administered, an additive therapeutic effect is obtained. The toxic effect of streptomycin is chiefly upon the vestibular portion of the eighth cranial nerve, whereas dihydrostreptomycin affects the auditory portion. When a 50-50 combination is used, diminished toxicity results without loss to therapeutic efficacy.

The question may be asked: "Why not use combinations since they do no harm?" Possible harmful effects are five in number. First, the use of fixed combinations of antibiotics tends to encourage inadequate therapy. Though sub-optimal doses of each of two antibiotics may occasionally provide a synergistic action against certain strains of bacteria, it certainly cannot be assumed that more can ordinarily be accomplished by suboptimal than by optimal amounts of therapy. Nor is there any evidence that the spectrum of activity will be broadened beyond that provided by the type and amount of individual antibiotics actually administered. Hypersensitivity and toxicity may be expected to increase when two drugs are used instead of one; furthermore, when a physician encounters a toxic effect, such as a rash, he will not know which of the drugs was responsible. A third harmful effect is the probable development of bacteria resistant to either or both of the drugs used in the combination. And the fourth, a direct corollary of the second, is the accumulation of antibiotic-resistant microbes within hospitals or other semiclosed communities. The fifth is that if this trend is not checked now, the practicing physician will soon be confronted with such a bewildering array of antibiotic combinations supported by multicolored promotional material piling up daily upon his desk that rational chemotherapy will give way to chaos.

The indications for the use of combined antibiotics all apply to clinical situations which at the present time demand selection of specific doses for individual cases. The one exception is the streptomycin-dihydrostreptomycin combination. There are no data or experience which would justify the employment of any fixed combination of two antibiotics in a single ampule or a single tablet or capsule for systemic use. It is our firm conviction that the promotion and sale of such combinations should be discouraged until and unless adequate data from controlled clinical investigation justify this practice, and then only with respect to definite combinations for specific purposes.

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