APPENDIXES

APPENDIX I

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THE CLINICAL USE OF ANTIBIOTICS IN COMBINATION

At a recent informal meeting of a large group of internists who are leaders in the field of infectious diseases, held in connection with the Central Society for Clinical Research, unanimous concern over the increasing numbers of antibacterial agents packaged in combination for oral or intramuscular use was expressed.

The accompanying editorial was suggested at this meeting. While American physicians owe a great debt of gratitude to the drug houses of this country for the quality of their products, there can be no question that the trend toward promotion of combination preparations of this type is a dangerous one. The reasons for this are outlined in the following combined statement. It is recognized that physicians have the opportunity to use combinations of single antibiotics in any way they thing best, but availability of the scores of antibacterial products already put up in combinations decided upon by the manufacturer and not arranged for each individual patient will unquestionably lead to abuses if unchecked.

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The recent appearance on the market of preparations containing two antibiotics in the same capsule calls for an appraisel of the rationale of such therapy. Theoretical or practical reasons for administering more than one antibotic to a patient at one time are as follows:

1. A second antibiotic may delay the emergence of bacteria resistant to the first antibiotic.
2. Two antibiotics may be synergistic with one another.
3. In the initial emergency treatment of seriously ill patients where the establishment of an etiological diagnosis and appropriate antibiotic sensitivity tests may be delayed, two or more drugs may properly be used as "insurance."
4. Mixed infections caused by more than one micro-organism may be better treated by antibiotics found most effective against each one.
5. Reduction of dosage of each of two "additive" drugs may result in lowered incidence of toxic effects to each, as in the case of streptomycin-dihydrostreptomycin.

The emergence of streptomycin-resistant tubercle bacilli is delayed when aminosalicylic acid or isoniazid is given in conjunction with streptomycin. In the realm of nontuberculous bacterial infections the application of this principle is not so clear. Numerous clinical-epidemiological studies have shown that the introduction of a new antibiotic into a hospital or a community is frequently followed by an increase in staphylococci resistant to that antibiotic. An attempt to prevent the development of antibiotic-resistant staphylococci by employing a combination in the treatment of ordinary bacterial infections was carried out during the winter of 1955–1956, employing novobiocin and spiramycin. In this study the emergence of staphylococci resistant to both these anibiotics was somewhat delayed, but after a few months bacteria resistant to both of them were easily found. In any event, the strain must be originally sensitive to the individual antibiotics if the combination is to delay or depress the development of resistance to any of them when they are used together.