APPENDIX VIII

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ANTIBIOTIC ANTAGONISM IN BACTERIAL MENINGITIS

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In vitro studies have shown that certain antibiotics used in combination may be antagonistic. Few studies have shown this phenomenon in patients. Lepper and Dowling observed an increased case fatality rate in patients with pneumococcal meningitis treated with penicillin and chlortetracycline in comparison to those treated with penicillin alone. From 1 July 1965 through 4 July 1966, 264 patients ≥2 months of age were assigned by chart number to treatment with either a single drug (ampicillin, 150 mg/kg daily) or a combination of drugs [ampicillin, 150 mg/kg daily; chloramphenicol, 100 mg/kg daily to a maximum of 4 g/day; and streptomycin, 40 mg/kg to a maximum of 2 g/day (48 hr only)] for acute bacterial meningitis. The groups were comparable in respect to age, severity of disease, and etiology of disease. Of 140 patients treated with the single drug regimen, 6 expired, giving a case fatality rate of 4.3%. There were 13 deaths among 124 patients receiving multiple antibiotic therapy, or a case fatality rate of 10.5%. A similar increased rate of neurological residua was observed in patients treated with multiple drugs. These differences were observed in those patients who were severely ill on admission; however, they were not restricted to one age group or etiological category. Antibiotic antagonism may explain the observed differences in case fatality rates and in rates of neurological residua.

With the development of each new antibiotic, researchers have investigated whether its spectrum of activity could be broadened or enhanced by combination with an existing drug. Although combinations of antimicrobials have proven beneficial in a few instances, the undesirable effects of antibiotic antagonism have also been observed. Antagonism has been observed in vitro in many test situations, leading Jawetz et al. (9) to perform a series of studies which partially systematized the relationships of antimicrobial interaction. Jawetz et al. (9) noted that bacteriostatic antibiotics, such as chloramphenicol and tetracycline, may act antagonistically with those that are bactericidal, such as penicillin, streptomycin, bacitracin, and neomycin. They categorized the former as group II drugs and the latter as group I drugs. This grouping according to in vitro activity, with bactericidal action used as an end point of antimicrobial potency, has been confirmed by other investigators with only minor revisions (6, 14). The antimicrobial agents introduced since the original reports of Jawetz et al. can be categorized similarly, with the Jawetz formula in general holding true (4).

Experimental demonstrations of the phenomenon of antibiotic antagonism have not been limited to in vitro situations. Jawetz et al. (10) found that mice infected experimentally with *Streptococcus pyogenes* had a higher case fatality rate when treated with a single does of penicillin plus chloramphenicol than with penicillin alone. Ahern, Burnell, and Kirby (1) confirmed these results; however, the same authors (1) found that no interference in antibiotic action could be demonstrated when the same antibiotics, administered for 2 to 3 days, were substituted for the single-dose regimen. Dowling, Lepper, and Jackson (5) studied pneumococcal infections in mice treated with combinations of chlortetracycline and penicillin. By varying the doses of penicillin, they were able to confirm the observations of both Jawetz et al. (10) and Ahren, Burnell, and Kirby (1), and they concluded that the discrepancy between these authors' observations was apparently due to the "comparative dosages of antibiotics used and not to maintenance of antibiotic blood levels for two or three days." The fact that one study could confirm two opposite viewpoints supported the concept held by many physicians that antibiotic antagonism was a laboratory phenomenon which had no relevance to clinical medicine.

At the same time the original in vitro studies (9) were reported, Lepper and Dowling (11) observed that a group of patients with pneumococcal meningitis who received penicillin plus chlortetracycline had a much higher case fatality

NOTE.—Numbered references at end or article.