DISCUSSION

The data presented support the thesis that antibiotic interference or antagonism can be observed in a clinical situation. The interference of one antibiotic with another may be expressed clinically in several ways, as illustrated in Table 4. As previously mentioned, Lepper and Dowling (11) observed an increased case fatality rate in patients with pneumococcal meningitis treated with penicillin plus chlortetracycline. A similar observation was made by Olsson, Kirby, and Romansky (16) in patients with the same diasease. In comparing various treatments regimens, excessive mortality was present only in the treatment group which combined penicillin and a tetracycline (16). Increased case fatality rates are not the only manifestations of antibiotic interference. Lepper, Wehrle, and Blatt (12) observed a slower response to therapy in patients with *H. influenzae* meningitis who received multiple drug therapy; in that series, penicillin was not used, although chlortetracycline was common to each treatment group. Strom (18, 19) reported apparent interference of chlortetracycline and erythromycin with the action of penicillin in streptococcal disease. Antimicrobial antagonism may occur in the treatment of infections with gram-negative enteric bacilli, as illustrated by the report of McCabe and Jackson (13). These authors (13) clearly showed a relationship between in vitro antagonism and clinical outcome, as measured by failure to eradicate bacteriuria. Bacteriological correlations are less apparent in patients with meningitis. Excepting neonates, almost all patients who die with meningitis have negative post-mortem cultures.

TABLE 4.—CLINICAL STUDIES DEMONSTRATING ANTIBIOTIC ANTAGONISM

Reference	Disease	Manifestation	Combination therapy
Lepper and Dowling (11)	Pneumococcal meningitis	Increased mortality	Penicillin+chlortetracycline.
Olsson et al. (16)	do	do	Penicillin+a tetracycline.
Lepper et al. (12)	Haemophilus influenzae meningitis.	Slower response	Chloretracycline+streptomycin+sulfisoxazole.
Strom (18)	Scarlatina	Persistence of organism	Penicillin+chlortetracylcine.
Strom (19)	do	Slower response	Penicilin+erythromycin.
McCabe and Jackson (13).	Urinary tract infection	Relapse	Various.
Present study	Bacterial meningitis	Increased mortality and residua.	Ampicillin+chloramphenicol+streptomycin.

TABLE 5.—PERSISTENCE OF VIABLE ORGANISMS IN CEREBROSPINAL FLUID AFTER 24 HOURS OF ANTIMICROBIAL THERAPY

Patient	Age	Complications	Initial therapy	Organism	Outcome
C. V.	26 yr	None	Chloramphenicol+penicillin G.	Haemophilus influenzae	Successful.
D. D.	3 yr	do	do	do	Do.
M. W.	16 months	do	do	do	Do.
D. D.	2 yr	do	do	do	Do.
T. P.	18 months	do	do	do	Do.
P. H.	7 months	Subdural	Chloramphenicol	do	Residua.
J. A.	64 yr	None	Penicillin G.	Pneumococci	Death.
J. M.	32 yr	do	do	do	Do.

What factors are responsible for the apparent antagonism in bacterial meningitis and its seeming absence in other severe infections requiring antibiotic therapy? The difference probably is due to the lack of surface phagocytosis and other host defense factors which act together with antibiotics to effect recovery (17). In meningitis, a "test-tube" situation is more nearly approximated. Wallace et al. (21) have clearly shown interference of chloramphenicol with the rapid bactericidal action of penicillin in experimental pneumococcal meningitis in dogs. That this situation may pertain in humans is suggested by the data in Table 5. The eight patients listed were observed in a previous study (15); all had viable organisms in the cerebrospinal fluid after 24 hr of antibiotic therapy. One might speculate that the host defenses in patients J.A. and J.M., who died 3 days after admission with pneumococcal meningitis, were totally inadequate because