Antibiotic Penetration of the Brain
A Comparative Study

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This paper is concerned with antibiotic penetration of the brain in patients having non-infamed meninges. It establishes the amount of antibiotic penetration of actual extravascular cerebral tissue. Such information may be useful in the antibiotic prophylaxis of basilar fractures, prophylaxis in routine craniotomy, or in the management of open cranial-cerebral wounds. Such data might also be pertinent to the therapy of established brain parenchymal infection in which the meninges are not necessarily involved, in particular, brain abscesses.

There are many studies in the literature on cerebral spinal fluid levels of antibiotics in the non-infected central nervous system following systemic injection. Most antibiotics are recovered in the cerebrospinal fluid in little, or very small, amounts after the usual, or even increased, systemic doses. In the most carefully done studies, it has been concluded that the blood-brain barrier and cerebrospinal fluid barrier are not the same. It can then be expected that actual drug penetration of the cerebrospinal fluid would differ from drug penetration of the extravascular cerebral tissue. With particular reference to antibiotics, it should be noted that the single other study on antibiotic penetration of cerebral tissue, which was conducted in 1954, attempted to correlate brain levels and cerebrospinal fluid levels and found this discrepancy in penetration of the two media.

Five antibiotics were chosen for this study: 1) chloramphenicol, 2) cephalothin, 3) ampicillin, 4) penicillin, and 5) cephaloridine. Chloramphenicol is a well-established drug and penetrates many tissues with ease. Therapeutic levels have been recovered from the cerebrospinal fluid of patients with non-infamed meninges. Spinal fluid levels have approximated one-fourth of the blood levels. Cephalothin, a newer broad spectrum antibiotic, has had particular success against penicillin-resistant staphylococci. Its use, to date, in the management of central nervous system inflammatory disease has been limited. In non-infamed meninges, it diffuses poorly into the cerebrospinal fluid. Ampicillin, also a newer broad spectrum antibiotic, was early recognized as an effective drug in the management of meningitis. Since then, it has become the antibiotic of choice in many centers for the initial therapy of meningitis. It readily passes into the cerebrospinal fluid when the meninges are inflamed. However, like cephalothin, the amount found in the CSF in normal individuals is insignificant. Penicillin is a well established antibiotic in the management of infection due to penicillin-sensitive, gram-positive pathogens. Cephalexin is a recently released, broad spectrum, bactericidal antibiotic chemically related to cephalothin.

Materials and Methods

Human brain tissue was analyzed for the five antibiotics. In all cases, the analyzed tissue had been removed as part of the usual surgical treatment of the basic disease or lesion. By necessity, then, most cases selected were either those with brain tumor or those requiring temporal lobectomy following trauma. In each case, effort was made to select as near normal tissue as possible, away from the primary lesion. Only one antibiotic could be given each patient and this was administered prior to surgery. The dosage of four antibiotics was the same, namely, 2 gm. The dose of penicillin calculated to be equal to 2 gm was 3.2 million units. Chlor-
amphenicol was given intramuscularly, while ampicillin, cephalothin, penicillin, and cephaloridine were given intravenously. The times of drug administration and specimens obtained were noted. Paired blood samples were taken at the time of each specimen, when possible. Aseptic handling of tissue was required as antibiotic levels were determined by biological assay. The brain samples varied from 50 to 300 mg. Each was frozen, ground into an emulsion, and a known amount of buffer solution added. Assay for all five antibiotics was by the modified cup-plate method using *Sarcina lutea* as the test organism. Since the primary interest was in the actual amount of antibiotic in brain tissue itself, and since the specimens were necessarily contaminated with their own blood volume, as well as free blood, each sample was corrected for blood content. This was accomplished by spectrophotometric analysis of the homogenates for their hemoglobin content. The blood-antibiotic contamination could then be calculated and subtracted from the specimen concentrations to obtain the amount of antibiotic per gram of extravascular brain tissue.

**Results**

Measurable antibiotic levels were found in the brain for all five antibiotics assayed. Corrections for blood contamination in the

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**Fig. 1.** Blood concentrations of chloramphenicol.

**Fig. 2.** Brain concentrations of chloramphenicol before and after correction for blood-antibiotic contamination.

**Fig. 3.** Blood concentrations of cephalothin.