

DISCUSSION

The patients with *H. influenzae* meningitis in this study comprised a group similar to series previously reported (Haggerty and Zial, 1964). 90% of the patients were between two months and four years old. This age distribution followed the characteristic pattern which, as shown by Fothergill and Wright (1933), reflects inversely the age prevalence of bactericidal serum antibody. Three per cent (two cases) were young adults, a proportion similar to the 2.7% of patients more than 20 years of age recorded in Dolphin and Popham's (1951) review of 915 cases. There was the expected male predominance.

Analysis of the results of therapy with ampicillin and chloramphenicol in these two comparable groups of patients failed to elicit any clear-cut differences. General clinical criteria such as mortality, neurological sequelae, duration of fever, subdural effusions, sterilization of the C.S.F. rates of reduction in the number of cells, per cent polys and protein content in C.S.F. and rise in C.S.F. sugar, were similar in both groups. The C.S.F. cell counts and sugar levels showed no differences on the first and the third days after admission, or afterwards. Among small numbers of observations on the second day, the larger variation in values for the ampicillin patients resulted in differences in distributions of values about the medians for that single day of bordering significance (Figs. 1 and 2). However, in view of the data for the days prior to, and following, this second day of treatment, it is doubtful that these differences were meaningful.

Although all nine ampicillin patients less than one year of age manifested at least some deficiency in response to therapy, nine of 19 controls in this age group had satisfactory responses (Table V). A trend toward fewer unsatisfactory responses with ampicillin than chloramphenicol was observed in patients two or more years of age. As stated previously, neither therapeutic group was weighted with disproportionate numbers of severely ill or moderately ill patients at any age. Disregarding age, the proportion of satisfactory responses in both therapeutic groups was almost identical. The apparent minor differences in response to ampicillin and chloramphenicol by age group would probably disappear if more patients were tested. Consideration of these data emphasizes the difficulty of being certain that every important variable is known in any clinical study.

The one patient in the ampicillin group who died and the two who survived with major residua were all severely ill on admission. Nevertheless the clinical findings in these two survivors were of interest in that C.S.F. pleocytosis with polymorphonuclear predominance persisted in one, and both developed subdural effusions and hydrocephalus eventually requiring neurosurgical correction. None of the patients in the control group required neurosurgery, although it should be noted that four deaths occurred in this group.

Several studies have demonstrated the *in vitro* effectiveness of ampicillin against *H. influenzae* (Rolinson and Stevens, 1961; Klein and Finland, 1963) including type B strains isolated from C.S.F. in our hospital (Ivler *et al.*, 1963). Although ampicillin displayed significantly more activity *in vitro* than penicillin G against C.S.F. *H. influenzae* isolates, the differences were small and of questionable clinical significance (Ivler *et al.*, 1963). Nevertheless, the overall response of patients with *H. influenzae* meningitis treated with ampicillin was comparable to the results observed with chloramphenicol. These favourable results with ampicillin stand in contrast to the reported experience with penicillin G even when patients treated with the latter drug had meningitis due to *H. influenzae* strains sensitive to penicillin G, and C.S.F. penicillin G levels were maintained by intrathecal therapy (Drysdale, McIntosh and Brodie, 1946; Zinnemann, 1946; Thomson, Bruce and Green, 1947). Perhaps qualitative differences in the activity of ampicillin and penicillin G against *H. influenzae* account for the more effective results with ampicillin.

Ampicillin levels in the C.S.F. samples studied to date have been variable, ranging from 0.1 to 1.0 $\mu\text{g./ml.}$ with average C.S.F.-to-serum ratios of 20 to 30%. These C.S.F. levels seem rather low in view of the overall satisfactory clinical response to ampicillin. Indeed, C.S.F. levels of 0.1 to 1.0 $\mu\text{g./ml.}$ barely approximate the *in vitro* minimum bactericidal concentrations (Ivler *et al.*, 1963) and clinical responses have not correlated well with C.S.F. levels. For example, a C.S.F. sample from an eight month old patient who developed subdural effusion and hydrocephalus contained more than 7.0 $\mu\text{g./ml.}$ of ampicillin, one of the highest levels found in any patient.

The peripheral blood differential count of 15% neutrophils noted in a three month old in the ampicillin group on the seventh day of therapy could not be