

## CHAPTER 4

### RESULTS

#### I. Studies of Cerebrospinal Fluid and Serum Concentrations of Antituberculous Drugs at Various Intervals During Hospitalization

##### 1. Concentrations of Antituberculous Drugs in CSF and Serum

Concentrations of isoniazid, pyrazinamide, rifampin and streptomycin in CSF and serum after 3-hour administration of drugs at various intervals of all patients were summarized in Table 1,2,3,4,5, 6,7 and 8. The mean concentrations of these four drugs at various intervals were also shown in the Tables and were plotted upon the weeks of treatment as shown in Figure 1,2,3,4. Most concentrations of streptomycin were expressed in the value of zero(0) due to no inhibition zone diameter was observed.

##### 2. Correlation between CSF and Serum Concentrations of Antituberculous Drugs

When plotted between CSF and serum concentrations of pyrazinamide in every patient, the correlation coefficient (r) was 0.8922 as shown in Figure 5. The statistical analysis, by Pearson's correlation, exhibited significant correlation between CSF and serum concentrations of pyrazinamide ( $p < 0.05$ ). The correlation coefficients between CSF and serum concentrations of isoniazid, rifampin and streptomycin as demonstrated in Figure 6,7 and 8 were 0.1654, -0.4223 and 0.2934 respectively. The correlation between CSF and serum concentrations of

rifampin was statistically significant with  $p < 0.05$  as pyrazinamide but the correlation was inverse. There was no statistically significant correlation between CSF and serum concentrations of isoniazid ( $p > 0.05$ ). In the study, correlation between CSF and serum concentrations of streptomycin was not statistically significant ( $p > 0.05$ ).

### 3. Comparison of the Mean Concentrations of Antituberculous Drugs at Various Intervals.

The mean serum and CSF concentrations at days 1-7 were compared with days 8-14, days 15-21, days 22-28, days 29-35, days 36-42 and days 43-49 by using analysis of variance techniques. Though the mean concentrations in CSF and serum of isoniazid, pyrazinamide, rifampin, and streptomycin at various intervals were different as illustrated in Table 1,2,3,4,5,6, 7 and 8, the differences were not statistically significant ( $p > 0.05$ ).

### 4. Comparison of the Mean CSF/serum Ratios of Antituberculous Drugs at Various Intervals

The ratios of CSF and simultaneous serum concentrations of each antituberculous drug in every case were calculated as illustrated in Table 9,10,11 and 12. The mean CSF/serum ratios at various intervals were also demonstrated in the Tables. Statistical analysis revealed no significant difference between the mean CSF/serum ratios of isoniazid, pyrazinamide, rifampin and streptomycin at various intervals by ANOVA for one-way classification ( $p > 0.05$ ). The average percent penetration into CSF of isoniazid, pyrazinamide, rifampin and streptomycin were about 89.08, 91.23, 5.09 and 20.79, respectively which were summarized in Table 13 including the overall mean concentrations of the drugs.

5. Comparison of Concentrations in CSF and Serum of Antituberculous Drugs with MIC against M. tuberculosis

Concentrations of isoniazid in CSF in all cases and the mean concentrations of the drug were above the minimal inhibitory concentration (MIC) of the drug against Mycobacterium tuberculosis as shown in Figure 1. The same as isoniazid, the overall mean concentration of pyrazinamide in CSF was above the MIC as illustrated in Figure 2. Since the MICs of rifampin against M. tuberculosis were different in many textbooks (11,14,75), the mean MIC of 0.2342 mcg/ml was calculated from the average of the above MICs. Though the overall mean concentration of rifampin in CSF (0.29 mcg/ml) was above the mean MIC (0.23 mcg/ml) of the drug against M. tuberculosis, the mean concentrations of the drug as shown in Figure 3 fluctuated from the MIC. However, with continuing administration of rifampin, the therapeutic level of it in CSF was not attained. Only 22 out of 46 concentrations of streptomycin in CSF were above the MIC of it against M. tuberculosis and the overall mean concentration in CSF (3.78 mcg/ml) was only little higher than the MIC (3.5 mcg/ml) against M. tuberculosis. Figure 4 showed that the levels of the drug were lower than the MIC at the beginning of treatment and tended to increase afterwards. The overall mean concentration in CSF of these four antituberculous drugs and the MICs and the mean of them against M. tuberculosis were expressed in Table 14.

Table 1 CSF INH Concentrations after 3-hr Administration at Various Intervals in Patients with Tuberculous Meningitis

| Patients                       | Sex | Age | CSF INH concentrations (mcg/ml) after 3-hr administration at |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |
|--------------------------------|-----|-----|--|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|
|                                |     |     | days 1-7   |     | days 8-14              |     | days 15-21             |     | days 22-28             |     | days 29-35             |     | days 36-42             |     | days 45-49             |     |
|                                |     |     | conc   | day | conc                   | day | conc                   | day | conc                   | day | conc                   | day | conc                   | day | conc                   | day |
| Group I                        |     |     |  |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |
| 1. IT                          | M   | 25  | -  |     | 5.72                   | 11  | 3.41                   | 18  | -                      |     | -                      |     | -                      |     | -                      |     |
| 2. SP                          | F   | 20  | 1.00   | 4   | 1.50                   | 8   | -                      |     | 1.95                   | 25  | -                      |     | -                      |     | -                      |     |
|                                |     |     | -  |     | 3.35                   | 10  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | -  |     | 3.45                   | 11  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 3. CT                          | M   | 24  | -  |     | -                      |     | 1.99                   | 15  | -                      |     | -                      |     | -                      |     | -                      |     |
| 4. SSR                         | M   | 22  | -  |     | 1.54                   | 14  | -                      |     | -                      |     | -                      |     | 2.24                   | 39  | -                      |     |
| 5. PV                          | F   | 19  | 2.60   | 4   | 4.69                   | 10  | 2.16                   | 19  | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | 2.92   | 6   | 3.65                   | 13  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 6. PT                          | M   | 35  | 1.27   | 4   | 1.91                   | 9   | 1.94                   | 15  | -                      |     | -                      |     | -                      |     | -                      |     |
| 7. SM                          | F   | 23  | -  |     | 2.50                   | 10  | 2.60                   | 15  | -                      |     | -                      |     | -                      |     | -                      |     |
| $\bar{x}_I \pm SD_I$           |     |     | 1.95 <sup>±</sup> 0.95                                       |     | 3.15 <sup>±</sup> 1.44 |     | 2.42 <sup>±</sup> 0.61 |     | 1.95 <sup>±</sup> 1.40 |     | -                      |     | 2.24 <sup>±</sup> 1.50 |     | -                      |     |
| Group II                       |     |     |  |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |
| 8. SG                          | M   | 70  | 2.05   | 2   | -                      |     | 1.10                   | 16  | 2.76                   | 25  | 3.3                    | 29  | -                      |     | 1.00                   | 44  |
| 9. PP                          | F   | 23  | 2.40   | 3   | -                      |     | 1.00                   | 15  | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | 1.00   | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 10. SS                         | F   | 20  | 0.80   | 3   | 0.85                   | 8   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | 0.95   | 4   | 0.50                   | 10  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | 1.05   | 5   | 0.65                   | 12  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 11. TS                         | F   | 21  | 2.82   | 5   | 5.39                   | 8   | -                      |     | 1.33                   | 26  | -                      |     | -                      |     | -                      |     |
|                                |     |     | 2.09   | 6   | 1.58                   | 11  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | 2.66   | 7   | 5.75                   | 13  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 12. SU                         | F   | 25  | 4.81   | 4   | -                      |     | 2.02                   | 18  | -                      |     | -                      |     | -                      |     | -                      |     |
| 13. YC                         | F   | 37  | -  |     | 2.28                   | 11  | 3.87                   | 16  | 2.66                   | 23  | 3.74                   | 33  | -                      |     | -                      |     |
| $\bar{x}_{II} \pm SD_{II}$     |     |     | 2.06 <sup>±</sup> 1.23                                       |     | 2.43 <sup>±</sup> 2.23 |     | 2.00 <sup>±</sup> 1.33 |     | 2.25 <sup>±</sup> 0.80 |     | 3.52 <sup>±</sup> 0.31 |     | -                      |     | 1.00 <sup>±</sup> 1.00 |     |
| $\bar{x}_{all} \pm SD_{all}$   |     |     | 2.03 <sup>±</sup> 1.12                                       |     | 2.83 <sup>±</sup> 1.80 |     | 2.23 <sup>±</sup> 0.95 |     | 2.17 <sup>±</sup> 0.67 |     | 3.52 <sup>±</sup> 0.31 |     | 2.24 <sup>±</sup> 1.50 |     | 1.00 <sup>±</sup> 1.00 |     |
| The overall mean concentration |     |     | = 2.40 <sup>±</sup> 1.35                                     |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |



**Table 2** Serum INH Concentrations After 3-hr Administration at Various Intervals in Patients with Tuberculous Meningitis.

| Patients                       | Sex | Age | serum INH concentrations (mcg/ml) after 3-hr administration at |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |
|--------------------------------|-----|-----|--|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|
|                                |     |     | days 1-7   |     | days 8-14              |     | days 15-21             |     | days 22-28             |     | days 29-35             |     | days 36-42             |     | days 43-49             |     |
|                                |     |     | conc   | day | conc                   | day | conc                   | day | conc                   | day | conc                   | day | conc                   | day | conc                   | day |
| Group I                        |     |     |  |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |
| 1. IT                          | M   | 25  | -  |     | 2.33                   | 11  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 2. SP                          | F   | 20  | 3.15   | 4   | 4.15                   | 8   | -                      |     | 4.60                   | 25  | -                      |     | -                      |     | -                      |     |
|                                |     |     | -  |     | 3.85                   | 10  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | -  |     | 4.60                   | 11  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 3. CT                          | M   | 24  | -  |     | -                      |     | 0.88                   | 15  | -                      |     | -                      |     | -                      |     | -                      |     |
| 4. SSR                         | M   | 22  | -  |     | 0.87                   | 14  | -                      |     | -                      |     | -                      |     | 2.11                   | 39  | -                      |     |
| 5. PV                          | F   | 19  | 2.19   | 6   | 2.81                   | 10  | 2.98                   | 19  | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | -  |     | 3.44                   | 13  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 6. PT                          | M   | 35  | 1.68   | 4   | 1.79                   | 9   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 7. SM                          | F   | 23  | -  |     | 5.50                   | 10  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| $\bar{x}_I \pm SD_I$           |     |     | 2.34 <sup>+</sup> 0.75   |     | 3.26 <sup>±</sup> 1.46 |     | 1.93 <sup>±</sup> 1.49 |     | 4.60 <sup>±</sup> 2.15 |     | -                      |     | 2.11 <sup>±</sup> 1.45 |     | -                      |     |
| Group II                       |     |     |  |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |
| 8. SG                          | M   | 70  | 6.10   | 2   | -                      |     | 3.55                   | 16  | -                      |     | -                      |     | -                      |     | 2.55                   | 44  |
| 9. PP                          | F   | 23  | 6.00   | 3   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | 2.65   | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 10. SS                         | F   | 20  | 2.00   | 3   | 2.65                   | 8   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | 2.90   | 4   | 1.25                   | 10  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | 3.20   | 5   | 2.05                   | 12  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 11. TS                         | F   | 21  | 2.09   | 5   | 2.33                   | 8   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | 3.14   | 6   | 3.38                   | 13  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                |     |     | 2.17   | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 12. YC                         | F   | 37  | -  |     | 2.70                   | 11  | 3.53                   | 16  | 3.96                   | 23  | 3.96                   | 33  | -                      |     | -                      |     |
| $\bar{x}_{II} \pm SD_{II}$     |     |     | 3.36 <sup>±</sup> 1.59   |     | 2.39 <sup>±</sup> 0.72 |     | 3.54 <sup>±</sup> 0.01 |     | 3.96 <sup>±</sup> 1.99 |     | 3.96 <sup>±</sup> 1.99 |     | -                      |     | 2.55 <sup>±</sup> 1.60 |     |
| $\bar{x}_{all} \pm SD_{all}$   |     |     | 3.11 <sup>±</sup> 1.47   |     | 2.91 <sup>±</sup> 1.26 |     | 2.74 <sup>±</sup> 1.27 |     | 4.28 <sup>±</sup> 0.45 |     | 3.96 <sup>±</sup> 1.99 |     | 2.11 <sup>±</sup> 1.45 |     | 2.55 <sup>±</sup> 1.60 |     |
| The overall mean concentration |     |     | = 3.03 <sup>±</sup> 1.27                                       |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |

Table 3 CSF Pyrazinamide Concentrations after 3-hr Administration at Various Intervals in Patients with Tuberculous Meningitis.

| Patients                       | Sex | Age |                            |     |                          |     |                          |     |                          |     |                         |     |                         |     |
|--------------------------------|-----|-----|----------------------------|-----|--------------------------|-----|--------------------------|-----|--------------------------|-----|-------------------------|-----|-------------------------|-----|
|                                |     |     | days 1-7                   |     | days 8-14                |     | days 15-21               |     | days 22-28               |     | days 29-35              |     | days 43-49              |     |
|                                |     |     | conc                       | day | conc                     | day | conc                     | day | conc                     | day | conc                    | day | conc                    | day |
| Group I                        |     |     |                            |     |                          |     |                          |     |                          |     |                         |     |                         |     |
| 1. IT                          | M   | 25  | -                          |     | 29.00                    | 11  | 26.40                    | 18  | -                        |     | -                       |     | -                       |     |
| 2. SP                          | F   | 20  | 48.30                      | 4   | 43.80                    | 8   | -                        |     | 43.20                    | 25  | -                       |     | -                       |     |
|                                |     |     | -                          |     | 41.40                    | 10  | -                        |     | -                        |     | -                       |     | -                       |     |
|                                |     |     | -                          |     | 34.90                    | 11  | -                        |     | -                        |     | -                       |     | -                       |     |
| 3. SSR                         | M   | 22  | -                          |     | 15.30                    | 12  | -                        |     | -                        |     | -                       |     | -                       |     |
|                                |     |     | -                          |     | 51.40                    | 14  | -                        |     | -                        |     | -                       |     | -                       |     |
| 4. PRT                         | M   | 22  | -                          |     | 22.80                    | 9   | -                        |     | -                        |     | -                       |     | -                       |     |
|                                |     |     | -                          |     | 59.95                    | 12  | -                        |     | -                        |     | -                       |     | -                       |     |
| 5. PV                          | F   | 19  | 27.09                      | 6   | 16.12                    | 10  | 23.78                    | 19  | -                        |     | -                       |     | -                       |     |
|                                |     |     | -                          |     | 18.67                    | 12  | -                        |     | -                        |     | -                       |     | -                       |     |
| 6. PT                          | M   | 35  | -                          |     | 14.07                    | 9   | 13.30                    | 15  | -                        |     | -                       |     | -                       |     |
| 7. SM                          | F   | 23  | -                          |     | 28.2                     | 10  | 42.96                    | 15  | -                        |     | -                       |     | -                       |     |
| $\bar{x}_I \pm SD_I$           |     |     | 37.70 <sup>±</sup> 15.00   |     | 31.30 <sup>±</sup> 15.50 |     | 26.54 <sup>±</sup> 12.16 |     | 43.20 <sup>±</sup> 6.57  |     | -                       |     | -                       |     |
| Group II                       |     |     |                            |     |                          |     |                          |     |                          |     |                         |     |                         |     |
| 8. SG                          | M   | 70  | 11.80                      | 2   | -                        |     | 38.00                    | 16  | 42.00                    | 25  | 48.50                   | 29  | 26.50                   | 44  |
| 9. PP                          | F   | 23  | 60.70                      | 3   | -                        |     | 25.00                    | 15  | 72.00                    | 24  | -                       |     | -                       |     |
|                                |     |     | 52.80                      | 7   | -                        |     | -                        |     | -                        |     | -                       |     | -                       |     |
| 10. SS                         | F   | 20  | 39.30                      | 3   | 39.30                    | 3   | 20.00                    | 8   | -                        |     | -                       |     | -                       |     |
|                                |     |     | 34.60                      | 4   | 23.90                    | 10  | -                        |     | -                        |     | -                       |     | -                       |     |
|                                |     |     | 14.30                      | 5   | 26.90                    | 12  | -                        |     | -                        |     | -                       |     | -                       |     |
| 11. SU                         | F   | 25  | 23.90                      | 4   | -                        |     | 40.00                    | 18  | -                        |     | -                       |     | -                       |     |
| 12. TS                         | F   | 21  | 45.50                      | 5   | 44.20                    | 8   | -                        |     | -                        |     | -                       |     | -                       |     |
|                                |     |     | 48.40                      | 6   | -                        |     | -                        |     | -                        |     | -                       |     | -                       |     |
|                                |     |     | 44.00                      | 7   | -                        |     | -                        |     | -                        |     | -                       |     | -                       |     |
| 13. YC                         | F   | 37  | -                          |     | -                        |     | 37.00                    | 16  | 40.70                    | 23  | -                       |     | -                       |     |
| $\bar{x}_{II} \pm SD_{II}$     |     |     | 37.53 <sup>±</sup> 16.31   |     | 28.75 <sup>±</sup> 10.68 |     | 35.00 <sup>±</sup> 6.78  |     | 51.57 <sup>±</sup> 17.71 |     | 48.50 <sup>±</sup> 6.96 |     | 26.50 <sup>±</sup> 5.15 |     |
| $\bar{x}_{all} \pm SD_{all}$   |     |     | 37.56 <sup>±</sup> 15.43   |     | 30.67 <sup>±</sup> 13.88 |     | 30.77 <sup>±</sup> 10.18 |     | 49.48 <sup>±</sup> 15.05 |     | 48.50 <sup>±</sup> 6.96 |     | 26.50 <sup>±</sup> 5.15 |     |
| The overall mean concentration |     |     | = 34.78 <sup>±</sup> 14.42 |     |                          |     |                          |     |                          |     |                         |     |                         |     |

Table 4 Serum Pyrazinamide Concentrations after 3-hr Administration at Various Interval in Patients with Tuberculous Meningitis.

| Patients                       | Sex | Age | Serum pyrazinamide concentration (mcg/ml) after 3-hr administration at |     |                          |     |                          |     |                          |     |                         |     |                         |     |   |  |
|--------------------------------|-----|-----|--|-----|--------------------------|-----|--------------------------|-----|--------------------------|-----|-------------------------|-----|-------------------------|-----|---|--|
|                                |     |     | days 1-7   |     | days 8-14                |     | days 15-21               |     | days 22-28               |     | days 29-35              |     | days 43-47              |     |   |  |
|                                |     |     | conc   | day | conc                     | day | conc                     | day | conc                     | day | conc                    | day | conc                    | day |   |  |
| Group I                        |     |     |  |     |                          |     |                          |     |                          |     |                         |     |                         |     |   |  |
| 1. IT                          | M   | 25  | -  |     | 41.00                    | 11  | 41.90                    | 18  | -                        |     | -                       |     | -                       |     | - |  |
| 2. SP                          | F   | 20  | 43.60  | 4   | 39.00                    | 8   | -                        |     | 43.10                    | 25  | -                       |     | -                       |     | - |  |
|                                |     |     | -  |     | 44.00                    | 10  | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
|                                |     |     | -  |     | 47.90                    | 11  | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
| 3. SSR                         | M   | 22  | -  |     | 18.50                    | 12  | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
|                                |     |     | -  |     | 45.80                    | 14  | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
| 4. PV                          | F   | 19  | 37.96  | 6   | 19.08                    | 10  | 23.27                    | 19  | -                        |     | -                       |     | -                       |     | - |  |
|                                |     |     | -  |     | 20.00                    | 12  | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
| 5. PT                          | M   | 35  | -  |     | 16.29                    | 9   | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
| 6. SM                          | F   | 23  | -  |     | 26.00                    | 10  | 56.30                    | 15  | -                        |     | -                       |     | -                       |     | - |  |
| $\bar{x}_I \pm SD_I$           |     |     | 40.78 <sup>±</sup> 3.99  |     | 31.76 <sup>±</sup> 12.88 |     | 40.49 <sup>±</sup> 16.56 |     | 43.10 <sup>±</sup> 6.57  |     | -                       |     | -                       |     | - |  |
| Group II                       |     |     |  |     |                          |     |                          |     |                          |     |                         |     |                         |     |   |  |
| 7. SG                          | M   | 70  | 15.40  | 2   | -                        |     | 37.30                    | 16  | -                        |     | 44.60                   | 29  | 36.90                   | 44  |   |  |
| 8. PP                          | F   | 20  | 77.00  | 3   | -                        |     | -                        |     | 73.70                    | 24  | -                       |     | -                       |     | - |  |
|                                |     |     | 61.50  | 7   | -                        |     | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
| 9. SS                          | F   | 20  | 40.00  | 3   | 31.40                    | 8   | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
|                                |     |     | 26.00  | 4   | 34.50                    | 10  | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
|                                |     |     | -  |     | 34.60                    | 12  | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
| 10. SU                         | F   | 25  | 25.50  | 4   | -                        |     | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
| 11. TS                         | F   | 21  | 40.90  | 5   | -                        |     | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
|                                |     |     | 47.40  | 6   | -                        |     | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
|                                |     |     | 50.50  | 7   | -                        |     | -                        |     | -                        |     | -                       |     | -                       |     | - |  |
| 12. YC                         | F   | 37  | -  |     | -                        |     | 40.70                    | 16  | 37.30                    | 23  | -                       |     | -                       |     | - |  |
| $\bar{x}_{II} \pm SD_{II}$     |     |     | 42.69 <sup>±</sup> 19.18   |     | 36.93 <sup>±</sup> 7.01  |     | 39.00 <sup>±</sup> 2.40  |     | 55.50 <sup>±</sup> 25.74 |     | 44.60 <sup>±</sup> 6.68 |     | 36.90 <sup>±</sup> 6.08 |     |   |  |
| $\bar{x}_{all} \pm SD_{all}$   |     |     | 42.34 <sup>±</sup> 5.19  |     | 33.23 <sup>±</sup> 11.49 |     | 39.89 <sup>±</sup> 5.28  |     | 51.37 <sup>±</sup> 19.56 |     | 44.60 <sup>±</sup> 6.68 |     | 36.90 <sup>±</sup> 6.08 |     |   |  |
| The overall mean concentration |     |     | = 39.03 <sup>±</sup> 14.44   |     |                          |     |                          |     |                          |     |                         |     |                         |     |   |  |

Table 5 CSF Rifampin Concentrations after 3-hour Administration at Various Intervals  
in Patients with Tuberculous Meningitis

| Patients                         | Sex | Age | CSF rifampin concentrations (mcg/ml) after 3-hr administration at |     |                        |     |                        |     |                        |     |                        |     |                        |      |    |  |
|----------------------------------|-----|-----|---|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|------|----|--|
|                                  |     |     | days 1-7  |     | days 8-14              |     | days 15-21             |     | days 22-28             |     | days 29-35             |     | days 36-42             |      |    |  |
|                                  |     |     | conc  | day | conc                   | day | conc                   | day | conc                   | day | conc                   | day | conc                   | day  |    |  |
| Group I                          |     |     |   |     |                        |     |                        |     |                        |     |                        |     |                        |      |    |  |
| 1. SP                            | F   | 20  | 0.30  | 7   | 0.16                   | 8   | -                      |     | -                      |     | -                      |     | -                      |      | -  |  |
|                                  |     |     | -   |     | 0.08                   | 10  | -                      |     | -                      |     | -                      |     | -                      |      | -  |  |
|                                  |     |     | -   |     | 0.06                   | 11  | -                      |     | -                      |     | -                      |     | -                      |      | -  |  |
| 2. CT                            | M   | 24  | -   |     | -                      |     | 0.23                   | 15  | -                      |     | -                      |     | -                      |      | -  |  |
| 3. SSR                           | M   | 22  | -   |     | 0.54                   | 12  | -                      |     | -                      |     | -                      |     | -                      | 0.20 | 39 |  |
|                                  |     |     | -   |     | 0.39                   | 14  | -                      |     | -                      |     | -                      |     | -                      | -    |    |  |
| 4. CK                            | F   | 47  | 0.47  | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    |    |  |
| 5. PV                            | F   | 19  | 0.20  | 6   | 0.08                   | 10  | 0.12                   | 19  | -                      |     | -                      |     | -                      | -    |    |  |
|                                  |     |     | -   |     | 0.12                   | 13  | -                      |     | -                      |     | -                      |     | -                      | -    |    |  |
| 6. CP                            | M   | 68  | -   |     | -                      |     | 0.09                   | 20  | -                      |     | -                      |     | -                      | -    |    |  |
| 7. PT                            | M   | 35  | 0.10  | 4   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    |    |  |
| $\bar{x}_I \pm SD_I$             |     |     | 0.27 <sup>+</sup> 0.16  |     | 0.20 <sup>+</sup> 0.19 |     | 0.15 <sup>+</sup> 0.07 |     | -                      |     | -                      |     | 0.20 <sup>+</sup> 0.45 |      |    |  |
| Group II                         |     |     |   |     |                        |     |                        |     |                        |     |                        |     |                        |      |    |  |
| 8. SG                            | M   | 70  | 0.95  | 5   | -                      |     | -                      |     | 0.32                   | 23  | 0.29                   | 29  | -                      | -    |    |  |
|                                  |     |     | -   |     | -                      |     | -                      |     | 0.21                   | 25  | -                      |     | -                      | -    |    |  |
| 9. PP                            | F   | 23  | 0.48  | 3   | 0.66                   | 10  | -                      |     | 0.47                   | 24  | -                      |     | -                      | -    |    |  |
|                                  |     |     | 1.16  | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    |    |  |
| 10. SS                           | F   | 20  | 0.14  | 3   | 0.08                   | 8   | -                      |     | -                      |     | -                      |     | -                      | -    |    |  |
|                                  |     |     | 0.10  | 4   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    |    |  |
|                                  |     |     | 0.11  | 5   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    |    |  |
| 11. SU                           | F   | 25  | -   |     | -                      |     | 0.26                   | 18  | -                      |     | -                      |     | -                      | -    |    |  |
| 12. TS                           | F   | 21  | 0.31  | 5   | 0.31                   | 8   | -                      |     | 0.16                   | 26  | -                      |     | -                      | -    |    |  |
|                                  |     |     | 0.18  | 6   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    |    |  |
|                                  |     |     | 0.26  | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    |    |  |
| 13. YC                           | F   | 37  | -   |     | -                      |     | -                      |     | -                      |     | 0.21                   | 33  | -                      | -    |    |  |
| $\bar{x}_{II} \pm SD_{II}$       |     |     | 0.41 <sup>+</sup> 0.39  |     | 0.35 <sup>+</sup> 0.29 |     | 0.26 <sup>+</sup> 0.51 |     | 0.29 <sup>+</sup> 0.14 |     | 0.25 <sup>+</sup> 0.05 |     | -                      |      |    |  |
| $\bar{x}_{all} \pm SD_{all}$     |     |     | 0.37 <sup>+</sup> 0.33  |     | 0.25 <sup>+</sup> 0.22 |     | 0.18 <sup>+</sup> 0.08 |     | 0.29 <sup>+</sup> 0.14 |     | 0.25 <sup>+</sup> 0.05 |     | 0.20 <sup>+</sup> 0.45 |      |    |  |
| The overall mean concentration = |     |     | 0.29 <sup>+</sup> 0.25  |     |                        |     |                        |     |                        |     |                        |     |                        |      |    |  |



Table 6 Serum Rifampin Concentrations after 3-hour Administration at Various Intervals in Patients with Tuberculous Meningitis

| Patients                         | Sex | Age | serum rifampin concentrations (mcg/ml) after 3 hr administration at |     |                        |     |                        |     |                        |     |                        |     |                        |      |    |   |
|----------------------------------|-----|-----|---|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|------|----|---|
|                                  |     |     | days 1-7  |     | days 8-14              |     | days 15-21             |     | days 22-28             |     | days 29-35             |     | days 36-42             |      |    |   |
|                                  |     |     | conc  | day | conc                   | day | conc                   | day | conc                   | day | conc                   | day | conc                   | day  |    |   |
| Group I                          |     |     |   |     |                        |     |                        |     |                        |     |                        |     |                        |      |    |   |
| 1. SP                            | F   | 20  | 4.41  | 7   | 4.98                   | 8   | -                      | -   | -                      | -   | -                      | -   | -                      | -    | -  | - |
|                                  |     |     | -   |     | 9.45                   | 10  | -                      | -   | -                      | -   | -                      | -   | -                      | -    | -  | - |
| 2. CT                            | M   | 24  | -   |     | -                      |     | 7.27                   | 15  | -                      | -   | -                      | -   | -                      | -    | -  | - |
| 3. SSR                           | M   | 22  | -   |     | 3.47                   | 12  | -                      | -   | -                      | -   | -                      | -   | -                      | 9.11 | 39 | - |
| 4. CK                            | F   | 47  | 5.76  | 7   | -                      |     | -                      | -   | -                      | -   | -                      | -   | -                      | -    | -  | - |
| 5. PV                            | F   | 19  | 11.64   | 6   | 7.23                   | 13  | 9.22                   | 19  | -                      | -   | -                      | -   | -                      | -    | -  | - |
| 6. PT                            | M   | 35  | 4.53  | 4   | -                      |     | -                      | -   | -                      | -   | -                      | -   | -                      | -    | -  | - |
| 7. CP                            | M   | 68  | -   |     | -                      |     | 11.64                  | 20  | -                      | -   | -                      | -   | -                      | -    | -  | - |
| $\bar{X}_I \pm SD_I$             |     |     | 6.59 <sup>+</sup> 3.43  |     | 6.28 <sup>+</sup> 2.62 |     | 9.38 <sup>+</sup> 2.19 |     | -                      |     | -                      |     | 9.11 <sup>+</sup> 3.02 |      | -  |   |
| Group II                         |     |     |   |     |                        |     |                        |     |                        |     |                        |     |                        |      |    |   |
| 8. SG                            | M   | 70  | -   |     | -                      |     | -                      |     | 4.31                   | 23  | 4.95                   | 29  | -                      | -    | -  | - |
|                                  |     |     | -   |     | -                      |     | -                      |     | -                      |     | 5.57                   | 32  | -                      | -    | -  | - |
| 9. PP                            | F   | 23  | 6.71  | 3   | 6.66                   | 10  | -                      |     | 7.10                   | 24  | -                      |     | -                      | -    | -  | - |
|                                  |     |     | 4.62  | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    | -  | - |
| 10. SS                           | F   | 20  | 14.36   | 3   | 12.54                  | 8   | -                      |     | -                      |     | -                      |     | -                      | -    | -  | - |
|                                  |     |     | 6.83  | 4   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    | -  | - |
|                                  |     |     | 12.71   | 5   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    | -  | - |
| 11. SU                           | F   | 25  | -   |     | -                      |     | 4.34                   | 18  | -                      |     | -                      |     | -                      | -    | -  | - |
| 12. TS                           | F   | 21  | 4.81  | 5   | 7.26                   | 8   | -                      |     | -                      |     | -                      |     | -                      | -    | -  | - |
|                                  |     |     | 2.88  | 6   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    | -  | - |
|                                  |     |     | 6.74  | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      | -    | -  | - |
| 13. YC                           | F   | 37  | -   |     | -                      |     | -                      |     | -                      |     | 9.10                   | 33  | -                      | -    | -  | - |
| $\bar{X}_{II} \pm SD_{II}$       |     |     | 7.46 <sup>+</sup> 4.01  |     | 8.82 <sup>+</sup> 3.24 |     | 4.34 <sup>+</sup> 2.08 |     | 5.70 <sup>+</sup> 1.98 |     | 6.54 <sup>+</sup> 2.24 |     | -                      |      | -  |   |
| $\bar{X}_{all} \pm SD_{all}$     |     |     | 7.17 <sup>+</sup> 3.69  |     | 7.37 <sup>+</sup> 2.96 |     | 8.12 <sup>+</sup> 3.09 |     | 5.70 <sup>+</sup> 1.98 |     | 6.54 <sup>+</sup> 2.24 |     | 9.11 <sup>+</sup> 3.02 |      | -  |   |
| The overall mean concentration = |     |     | 7.25 <sup>+</sup> 3.04  |     |                        |     |                        |     |                        |     |                        |     |                        |      |    |   |

Table 7 CSF Streptomycin Concentrations after 3-hour Administration at Various Intervals in Patients with Tuberculous Meningitis.

| Patients  | Sex | Age | CSF streptomycin concentrations (mcg/ml) after 3-hr administration at |     |                        |     |                         |     |                        |     |                         |     |                  |     |
|---|-----|-----|---|-----|------------------------|-----|-------------------------|-----|------------------------|-----|-------------------------|-----|------------------|-----|
|   |     |     | days 1-7  |     | days 8-14              |     | days 15-21              |     | days 22-28             |     | days 29-35              |     | days 36-42       |     |
|   |     |     | conc  | day | conc                   | day | conc                    | day | conc                   | day | conc                    | day | conc             | day |
| Group I   |     |     |   |     |                        |     |                         |     |                        |     |                         |     |                  |     |
| 1. SP   | F   | 20  | 0   | 7   | 0                      | 8   | -                       |     | 0                      | 25  | -                       |     | -                |     |
|   |     |     | -   |     | 2.66                   | 10  | -                       |     | -                      |     | -                       |     | -                |     |
|   |     |     | -   |     | 0                      | 11  | -                       |     | -                      |     | -                       |     | -                |     |
| 2. CT   | M   | 24  | -   |     | -                      |     | 0                       | 15  | 0                      | 27  | -                       |     | -                |     |
| 3. SSR  | M   | 22  | -   |     | 0                      | 12  | -                       |     | -                      |     | -                       |     | 0                | 39  |
|   |     |     | -   |     | 0                      | 14  | -                       |     | -                      |     | -                       |     | -                |     |
| 4. PV   | F   | 19  | 4.16  | 4   | 4.34                   | 10  | 0                       | 19  | -                      |     | -                       |     | -                |     |
|   |     |     | 0   | 6   | 3.76                   | 13  | -                       |     | -                      |     | -                       |     | -                |     |
| 5. PRT  | M   | 22  | 0   | 7   | 4.78                   | 9   | -                       |     | -                      |     | -                       |     | -                |     |
|   |     |     | -   |     | 7.82                   | 12  | -                       |     | -                      |     | -                       |     | -                |     |
| 6. CP   | M   | 68  | -   |     | -                      |     | 0                       | 20  | -                      |     | -                       |     | -                |     |
| 7. PT   | M   | 35  | 0   | 4   | 0                      | 9   | -                       |     | -                      |     | -                       |     | -                |     |
| 8. CK   | F   | 47  | 11.25   | 7   | -                      |     | -                       |     | -                      |     | -                       |     | -                |     |
| $\bar{X}_I \pm SD_I$                                    |     |     | 2.57 <sup>+</sup> 4.57  |     | 2.34 <sup>+</sup> 2.78 |     | 0 <sup>±</sup> 0        |     | 0 <sup>±</sup> 0       |     | -                       |     | 0 <sup>±</sup> 0 |     |
| Group II  |     |     |   |     |                        |     |                         |     |                        |     |                         |     |                  |     |
| 9. SG   | M   | 70  | 10.02   | 5   | -                      |     | -                       |     | 9.6                    | 23  | 0                       | 29  | -                |     |
|   |     |     | -   |     | -                      |     | -                       |     | 6.75                   | 25  | -                       |     | -                |     |
| 10. PP  | F   | 23  | 10.25   | 3   | 9.7                    | 10  | 16.5                    | 15  | 12.25                  | 24  | -                       |     | -                |     |
| 11. SS  | F   | 20  | 0   | 3   | 0                      | 8   | -                       |     | -                      |     | -                       |     | -                |     |
|   |     |     | 0   | 4   | 0                      | 10  | -                       |     | -                      |     | -                       |     | -                |     |
|   |     |     | 0   | 5   | 0                      | 12  | -                       |     | -                      |     | -                       |     | -                |     |
| 12. TS  | F   | 21  | 1.52  | 5   | 3.85                   | 8   | -                       |     | -                      |     | -                       |     | -                |     |
|   |     |     | 4.40  | 6   | 4.36                   | 11  | -                       |     | -                      |     | -                       |     | -                |     |
|   |     |     | 4.68  | 7   | 4.48                   | 13  | -                       |     | -                      |     | -                       |     | -                |     |
| 13. YC  | F   | 37  | -   |     | 4.96                   | 11  | 5.28                    | 16  | 11.33                  | 23  | 15.33                   | 33  | -                |     |
| $\bar{X}_{II} \pm SD_{II}$                              |     |     | 3.86 <sup>+</sup> 4.31  |     | 3.42 <sup>+</sup> 3.36 |     | 10.89 <sup>+</sup> 7.93 |     | 9.98 <sup>+</sup> 2.42 |     | 7.67 <sup>+</sup> 10.84 |     | -                |     |
| $\bar{X}_{all} \pm SD_{all}$                            |     |     | 3.31 <sup>+</sup> 4.30  |     | 2.82 <sup>+</sup> 3.01 |     | 4.36 <sup>+</sup> 7.16  |     | 6.66 <sup>+</sup> 5.49 |     | 7.67 <sup>+</sup> 10.89 |     | 0 <sup>±</sup> 0 |     |
| The overall mean concentration = 3.78 <sup>+</sup> 4.67 |     |     |   |     |                        |     |                         |     |                        |     |                         |     |                  |     |

Table 8 Serum Streptomycin Concentrations after 3-hour Administration at Various Intervals in Patients with Tuberculous Meningitis

| Patients                         | Sex | Age | serum streptomycin concentrations (mcg/ml) after 3-hr administration at |     |                           |     |                           |     |                          |     |                           |     |                           |     |
|----------------------------------|-----|-----|---|-----|---------------------------|-----|---------------------------|-----|--------------------------|-----|---------------------------|-----|---------------------------|-----|
|                                  |     |     | days 1-7  |     | days 8-14                 |     | days 15-21                |     | days 22-28               |     | days 29-35                |     | days 36-42                |     |
|                                  |     |     | conc  | day | conc                      | day | conc                      | day | conc                     | day | conc                      | day | conc                      | day |
| Group I                          |     |     |   |     |                           |     |                           |     |                          |     |                           |     |                           |     |
| 1. SP                            | F   | 20  | 1.98  | 7   | 5.94                      | 8   | -                         |     | 12.56                    | 25  | -                         |     | -                         |     |
|                                  |     |     | -   |     | 30.50                     | 10  | -                         |     | -                        |     | -                         |     | -                         |     |
| 2. CT                            | M   | 24  | -   |     | -                         |     | 8.33                      | 15  | 20.83                    | 27  | -                         |     | -                         |     |
| 3. SSR                           | M   | 22  | -   |     | 2.85                      | 14  | -                         |     | -                        |     | -                         |     | 12.08                     | 39  |
| 4. PV                            | F   | 19  | 34.43   | 4   | 34.03                     | 10  | 35.55                     | 19  | -                        |     | -                         |     | -                         |     |
|                                  |     |     | 12.83   | 6   | 32.79                     | 13  | -                         |     | -                        |     | -                         |     | -                         |     |
| 5. CP                            | M   | 68  | -   |     | -                         |     | 3.52                      | 20  | -                        |     | -                         |     | -                         |     |
| 6. CK                            | F   | 47  | 6.91  | 7   | -                         |     | -                         |     | -                        |     | -                         |     | -                         |     |
| 7. PT                            | M   | 35  | 10.61   | 4   | 24.31                     | 9   | -                         |     | -                        |     | -                         |     | -                         |     |
| $\bar{X}_I \pm SD_I$             |     |     | 13.35 <sup>+</sup> -12.48   |     | 21.74 <sup>+</sup> -13.88 |     | 15.80 <sup>+</sup> -17.27 |     | 16.70 <sup>+</sup> -5.85 |     | -                         |     | 12.08 <sup>+</sup> -3.48  |     |
| Group II                         |     |     |   |     |                           |     |                           |     |                          |     |                           |     |                           |     |
| 8. SG                            | M   | 70  | -   |     | -                         |     | -                         |     | -                        |     | 0                         | 29  | -                         |     |
| 9. PP                            | F   | 23  | 20.7  | 3   | 13.5                      | 10  | 22.5                      | 15  | 16.5                     | 24  | -                         |     | -                         |     |
| 10. SS                           | F   | 20  | 1.42  | 3   | 1.95                      | 8   | -                         |     | -                        |     | -                         |     | -                         |     |
|                                  |     |     | 2.17  | 4   | 10.34                     | 10  | -                         |     | -                        |     | -                         |     | -                         |     |
|                                  |     |     | 1.55  | 5   | 40.00                     | 12  | -                         |     | -                        |     | -                         |     | -                         |     |
| 11. TS                           | F   | 21  | 4.49  | 5   | 17.11                     | 8   | -                         |     | -                        |     | -                         |     | -                         |     |
|                                  |     |     | 17.36   | 6   | 24.77                     | 11  | -                         |     | -                        |     | -                         |     | -                         |     |
|                                  |     |     | 16.43   | 7   | 22.40                     | 13  | -                         |     | -                        |     | -                         |     | -                         |     |
| 12. YC                           | F   | 37  | -   |     | 19.23                     | 11  | 22.89                     | 16  | 22.77                    | 23  | 22.89                     | 33  | -                         |     |
| $\bar{X}_{II} \pm SD_{II}$       |     |     | 9.16 <sup>+</sup> -8.58   |     | 18.66 <sup>+</sup> -11.24 |     | 22.70 <sup>+</sup> -0.28  |     | 19.64 <sup>+</sup> -4.43 |     | 11.45 <sup>+</sup> -16.19 |     | -                         |     |
| $\bar{X}_{all} \pm SD_{all}$     |     |     | 10.91 <sup>+</sup> -10.07   |     | 19.98 <sup>+</sup> -12.03 |     | 18.56 <sup>+</sup> -12.79 |     | 18.17 <sup>+</sup> -4.56 |     | 11.45 <sup>+</sup> -16.19 |     | 12.08 <sup>+</sup> -3.48  |     |
| The overall mean concentration = |     |     |   |     |                           |     |                           |     |                          |     |                           |     | 16.08 <sup>+</sup> -11.17 |     |

Table 9 CSF/Serum Ratios of INH after 3-hour Administration at Various Intervals in Patients with Tuberculous Meningitis.

| Patients                           | Sex | Age | CSF/serum ratio of INH after 3-hr administration at |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |
|------------------------------------|-----|-----|---|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|
|                                    |     |     | days 1-7  |     | days 8-14              |     | days 15-21             |     | days 22-28             |     | days 29-35             |     | days 36-42             |     | days 43-49             |     |
|                                    |     |     | ratio   | day | ratio                  | day | ratio                  | day | ratio                  | day | ratio                  | day | ratio                  | day | ratio                  | day |
| Group I                            |     |     |   |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |
| 1. IT                              | M   | 25  | -   |     | 2.46                   | 11  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 2. SP                              | F   | 20  | 0.32  | 4   | 0.36                   | 8   | -                      |     | 0.42                   | 25  | -                      |     | -                      |     | -                      |     |
|                                    |     |     | -   |     | 0.87                   | 10  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | -   |     | 0.75                   | 11  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 3. CT                              | M   | 24  | -   |     | -                      |     | 2.26                   | 15  | -                      |     | -                      |     | -                      |     | -                      |     |
| 4. SSR                             | M   | 22  | -   |     | 1.77                   | 14  | -                      |     | -                      |     | -                      |     | 1.06                   | 39  | -                      |     |
| 5. PV                              | F   | 19  | 1.33  | 6   | 1.67                   | 10  | 0.73                   | 19  | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | -   |     | 1.06                   | 13  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 6. PT                              | M   | 35  | 0.76  | 4   | 1.07                   | 9   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 7. SM                              | F   | 23  |   |     | 0.46                   | 10  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| $\bar{X}_I \pm SD_I$               |     |     | 0.80 <sup>+</sup> 0.51                              |     | 1.16 <sup>+</sup> 0.68 |     | 1.50 <sup>+</sup> 1.08 |     | 0.42 <sup>±</sup> 0.65 |     | -                      |     | 1.06 <sup>±</sup> 1.03 |     | -                      |     |
| Group II                           |     |     |   |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |
| 8. SG                              | M   | 70  | 0.34  | 2   | -                      |     | 0.31                   | 16  | -                      |     | -                      |     | -                      |     | 0.39                   | 44  |
| 9. PP                              | F   | 23  | 0.40  | 3   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | 0.38  | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 10. SS                             | F   | 20  | 0.40  | 3   | 0.32                   | 8   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | 0.33  | 4   | 0.40                   | 10  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | 0.33  | 5   | 0.32                   | 12  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 11. TS                             | F   | 21  | 1.35  | 5   | 2.31                   | 8   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | 0.67  | 6   | 1.70                   | 13  | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | 1.22  | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 12. YC                             | F   | 37  | -   |     | 0.84                   | 11  | 1.10                   | 16  | 0.67                   | 23  | 0.94                   | 33  | -                      |     | -                      |     |
| $\bar{X}_{II} \pm SD_{II}$         |     |     | 0.60 <sup>±</sup> 0.40                              |     | 0.98 <sup>±</sup> 0.84 |     | 0.71 <sup>±</sup> 0.56 |     | 0.67 <sup>±</sup> 0.82 |     | 0.94 <sup>±</sup> 0.97 |     | -                      |     | 0.39 <sup>±</sup> 0.63 |     |
| $\bar{X}_{all} \pm SD_{all}$       |     |     | 0.65 <sup>±</sup> 0.42                              |     | 1.09 <sup>±</sup> 0.73 |     | 1.1 <sup>±</sup> 0.84  |     | 0.55 <sup>±</sup> 0.18 |     | 0.94 <sup>±</sup> 0.97 |     | 1.06 <sup>±</sup> 1.03 |     | 0.39 <sup>±</sup> 0.63 |     |
| The overall mean CSF/serum ratio = |     |     | 0.89 <sup>±</sup> 0.62                              |     |                        |     |                        |     |                        |     |                        |     |                        |     |                        |     |

Table 10 CSF/Serum Ratios of Pyrazinamide after 3-hour Administration at Various Intervals in Patients with Tuberculous Meningitis

| Patients                           | Sex | Age | CSF/serum ratios of pyrazinamide after 3-hr administration at |     |                        |     |                        |     |                        |     |                        |     |                        |     |
|------------------------------------|-----|-----|---|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|------------------------|-----|
|                                    |     |     | days 1-7  |     | days 8-14              |     | days 15-21             |     | dayd 22-28             |     | days 29-35             |     | days 43-49             |     |
|                                    |     |     | ratio   | day | ratio                  | day | ratio                  | day | ratio                  | day | ratio                  | day | ratio                  | day |
| Group I                            |     |     |   |     |                        |     |                        |     |                        |     |                        |     |                        |     |
| 1. IT                              | M   | 25  | -   |     | 0.71                   | 11  | 0.63                   | 18  | -                      |     | -                      |     | -                      |     |
| 2. SP                              | F   | 20  | 1.11  | 4   | 1.12                   | 8   | -                      |     | 1.00                   | 25  | -                      |     | -                      |     |
|                                    |     |     | -   |     | 0.94                   | 10  | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | -   |     | 0.73                   | 11  | -                      |     | -                      |     | -                      |     | -                      |     |
| 3. SSR                             | M   | 22  | -   |     | 0.83                   | 12  | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | -   |     | 1.12                   | 14  | -                      |     | -                      |     | -                      |     | -                      |     |
| 4. PV                              | F   | 19  | 0.71  | 6   | 0.85                   | 10  | 1.02                   | 19  | -                      |     | -                      |     | -                      |     |
|                                    |     |     | -   |     | 0.93                   | 12  | -                      |     | -                      |     | -                      |     | -                      |     |
| 5. PT                              | M   | 35  | -   |     | 0.86                   | 9   | -                      |     | -                      |     | -                      |     | -                      |     |
| 6. SM                              | F   | 23  | -   |     | 1.09                   | 10  | 0.76                   | 15  | -                      |     | -                      |     | -                      |     |
| $\bar{x} \pm SD$                   |     |     | 0.91 <sup>+</sup> 0.28  |     | 0.92 <sup>+</sup> 0.15 |     | 0.80 <sup>+</sup> 0.20 |     | 1.00 <sup>±</sup> 1.00 |     | -                      |     | -                      |     |
| Group II                           |     |     |   |     |                        |     |                        |     |                        |     |                        |     |                        |     |
| 7. SG                              | M   | 70  | 0.77  | 2   | -                      |     | 1.02                   | 16  | -                      |     | 1.09                   | 29  | 0.72                   | 44  |
| 8. PP                              | F   | 23  | 0.79  | 3   | -                      |     | -                      |     | 0.98                   | 24  | -                      |     | -                      |     |
|                                    |     |     | 0.86  | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 9. SS                              | F   | 20  | 0.98  | 3   | 0.64                   | 8   | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | 1.33  | 4   | 0.69                   | 10  | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | -   |     | 0.78                   | 12  | -                      |     | -                      |     | -                      |     | -                      |     |
| 10. SU                             | F   | 25  | 0.94  | 4   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 11. TS                             | F   | 21  | 1.11  | 5   | 0.94                   | 8   | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | 1.02  | 6   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
|                                    |     |     | 0.87  | 7   | -                      |     | -                      |     | -                      |     | -                      |     | -                      |     |
| 12. YC                             | F   | 37  | -   |     | -                      |     | 0.91                   | 16  | 1.09                   | 23  | -                      |     | -                      |     |
| $\bar{x}_{II} \pm SD_{II}$         |     |     | 0.96 <sup>+</sup> 0.18  |     | 0.76 <sup>+</sup> 0.13 |     | 0.97 <sup>+</sup> 0.08 |     | 1.04 <sup>+</sup> 0.08 |     | 1.09 <sup>±</sup> 1.04 |     | 0.72 <sup>±</sup> 0.85 |     |
| $\bar{x}_{all} \pm SD_{all}$       |     |     | 0.96 <sup>+</sup> 0.18  |     | 0.87 <sup>+</sup> 0.16 |     | 0.87 <sup>+</sup> 0.17 |     | 1.02 <sup>+</sup> 0.06 |     | 1.09 <sup>±</sup> 1.04 |     | 0.72 <sup>±</sup> 1.85 |     |
| The overall mean CSF/serum ratio = |     |     | 0.91 <sup>+</sup> 0.17  |     |                        |     |                        |     |                        |     |                        |     |                        |     |

Table 11 CSF/Serum Ratios of Rifampin after 3-hour Administration at Various Intervals in Patients with tuberculous Meningitis

| Patients  | Sex | Age | CSF/serum ratios of rifampin after 3-hr administration at |     |                               |     |                               |     |                               |     |                               |        |                               |     |
|---|-----|-----|---|-----|-------------------------------|-----|-------------------------------|-----|-------------------------------|-----|-------------------------------|--------|-------------------------------|-----|
|   |     |     | days 1-7  |     | days 8-14                     |     | days 15-21                    |     | days 22-28                    |     | days 29-35                    |        | days 36-42                    |     |
|   |     |     | ratio   | day | ratio                         | day | ratio                         | day | ratio                         | day | ratio                         | day    | ratio                         | day |
| Group I   |     |     |   |     |                               |     |                               |     |                               |     |                               |        |                               |     |
| 1. SP   | F   | 20  | 0.0680  | 7   | 0.0315                        | 8   | -                             | -   | -                             | -   | -                             | -      | -                             |     |
|   |     |     | -   |     | 0.0085                        | 10  | -                             | -   | -                             | -   | -                             | -      | -                             |     |
| 2. CT   | M   | 24  | -   |     | -                             |     | 0.0316                        | 15  | -                             | -   | -                             | -      | -                             |     |
| 3. SSR  | M   | 22  | -   |     | 0.1556                        | 12  | -                             | -   | -                             | -   | -                             | 0.0220 | 39                            |     |
| 4. CK   | F   | 47  | 0.0816  | 7   | -                             |     | -                             |     | -                             |     | -                             | -      |                               |     |
| 5. PV   | F   | 19  | 0.0172  | 6   | 0.0166                        | 13  | 0.0130                        | 19  | -                             | -   | -                             | -      | -                             |     |
| 6. CP   | M   | 68  | -   |     | -                             |     | 0.0077                        | 20  | -                             | -   | -                             | -      | -                             |     |
| 7. PT   | M   | 35  | 0.0221  | 4   | -                             |     | -                             |     | -                             | -   | -                             | -      | -                             |     |
| $\bar{x}_I \pm SD_I$  |     |     | 0.0472 <sup>±</sup><br>0.0324                             |     | 0.0531 <sup>±</sup><br>0.0690 |     | 0.0174 <sup>±</sup><br>0.0126 |     | -                             |     | -                             |        | 0.0220 <sup>±</sup><br>0.1483 |     |
| Group II  |     |     |   |     |                               |     |                               |     |                               |     |                               |        |                               |     |
| 8. SG   | M   | 70  | -   |     | -                             |     | -                             |     | 0.0741                        | 23  | 0.0576                        | 29     | -                             |     |
| 9. PP   | F   | 23  | 0.0715  | 3   | 0.0991                        | 10  | -                             |     | 0.0662                        | 24  | -                             |        | -                             |     |
|   |     |     | 0.2511  | 7   | -                             |     | -                             |     | -                             |     | -                             |        | -                             |     |
| 10. SS  | F   | 20  | 0.0097  | 3   | 0.0064                        | 8   | -                             |     | -                             |     | -                             |        | -                             |     |
|   |     |     | 0.0146  | 4   | -                             |     | -                             |     | -                             |     | -                             |        | -                             |     |
|   |     |     | 0.0087  | 5   | -                             |     | -                             |     | -                             |     | -                             |        | -                             |     |
| 11. SU  | F   | 25  | -   |     | -                             |     | 0.0599                        | 18  | -                             |     | -                             |        | -                             |     |
| 12. TS  | F   | 21  | 0.0644  | 5   | 0.0427                        | 8   | -                             |     | -                             |     | -                             |        | -                             |     |
|   |     |     | 0.0625  | 6   | -                             |     | -                             |     | -                             |     | -                             |        | -                             |     |
|   |     |     | 0.0386  | 7   | -                             |     | -                             |     | -                             |     | -                             |        | -                             |     |
| 13. YC  | F   | 37  | -   |     | -                             |     | -                             |     | -                             |     | 0.0231                        | 33     | -                             |     |
| $\bar{x}_{II} \pm SD_{II}$                                    |     |     | 0.0651 <sup>±</sup><br>0.0794                             |     | 0.0494 <sup>±</sup><br>0.0467 |     | 0.0599 <sup>±</sup><br>0.2447 |     | 0.0702 <sup>±</sup><br>0.0056 |     | 0.0404 <sup>±</sup><br>0.0244 |        | -                             |     |
| $\bar{x}_{all} \pm SD_{all}$                                  |     |     | 0.0592 <sup>±</sup><br>0.0662                             |     | 0.0515 <sup>±</sup><br>0.0558 |     | 0.0281 <sup>±</sup><br>0.0236 |     | 0.0702 <sup>±</sup><br>0.0056 |     | 0.0404 <sup>±</sup><br>0.0244 |        | 0.0220 <sup>±</sup><br>0.1483 |     |
| The overall mean CSF/serum ratio = 0.0509 <sup>±</sup> 0.0523 |     |     |   |     |                               |     |                               |     |                               |     |                               |        |                               |     |

Table 12 CSF/Serum Ratios of Streptomycin after 3-hour Administration at Various Intervals in Patients with Tuberculous Meningitis

| Patients                           | Sex | Age | CSF/serum ratios of streptomycin after 3-hr administration at |     |                               |     |                               |     |                               |     |                               |     |                       |     |
|------------------------------------|-----|-----|---|-----|-------------------------------|-----|-------------------------------|-----|-------------------------------|-----|-------------------------------|-----|-----------------------|-----|
|                                    |     |     | days 1-7  |     | days 8-14                     |     | days 15-21                    |     | days 22-28                    |     | days 29-35                    |     | days 36-42            |     |
|                                    |     |     | ratio   | day | ratio                         | day | ratio                         | day | ratio                         | day | ratio                         | day | ratio                 | day |
| Group I                            |     |     |   |     |                               |     |                               |     |                               |     |                               |     |                       |     |
| 1.SP                               | F   | 20  | 0   | 7   | 0                             | 8   | -                             |     | 0                             | 25  | -                             |     | -                     |     |
|                                    |     |     | -   |     | 0.0872                        | 10  | -                             |     | -                             |     | -                             |     | -                     |     |
| 2.CT                               | M   | 24  | -   |     | -                             |     | 0                             | 15  | 0                             | 27  | -                             |     | -                     |     |
| 3.SSR                              | M   | 22  | -   |     | 0                             | 14  | -                             |     | -                             |     | -                             |     | 0                     | 39  |
| 4.PV                               | F   | 19  | 0.1208  | 4   | 0.1275                        | 10  | 0                             | 19  | -                             |     | -                             |     | -                     |     |
|                                    |     |     | 0   | 6   | 0.1147                        | 13  | -                             |     | -                             |     | -                             |     | -                     |     |
| 5.CP                               | M   | 68  | -   |     | -                             |     | 0                             | 20  | -                             |     | -                             |     | -                     |     |
| 6.CK                               | F   | 47  | 1.6281  | 7   | -                             |     | -                             |     | -                             |     | -                             |     | -                     |     |
| 7.PT                               | M   | 35  | 0   | 4   | 0                             | 9   | -                             |     | -                             |     | -                             |     | -                     |     |
| $\bar{X}_I \pm SD_I$               |     |     | 0.3498 <sup>±</sup><br>0.7165                                 |     | 0.0549 <sup>±</sup><br>0.0615 |     | 0 <sup>±</sup><br>0-0         |     | 0 <sup>±</sup><br>0-0         |     | -                             |     | 0 <sup>±</sup><br>0-0 |     |
| Group II                           |     |     |   |     |                               |     |                               |     |                               |     |                               |     |                       |     |
| 8.SG                               | M   | 70  | -   |     | -                             |     | -                             |     | 0                             | 29  | -                             |     | -                     |     |
| 9.PP                               | F   | 23  | 0.4952  | 3   | 0.7185                        | 10  | 0.7333                        | 15  | 0.7424                        | 24  | -                             |     | -                     |     |
| 10.SS                              | F   | 20  | 0   | 3   | 0                             | 8   | -                             |     | -                             |     | -                             |     | -                     |     |
|                                    |     |     | 0   | 4   | 0                             | 10  | -                             |     | -                             |     | -                             |     | -                     |     |
|                                    |     |     | 0   | 5   | 0                             | 12  | -                             |     | -                             |     | -                             |     | -                     |     |
| 11.TS                              | F   | 21  | 0.3385  | 5   | 0.2250                        | 8   | -                             |     | -                             |     | -                             |     | -                     |     |
|                                    |     |     | 0.2535  | 6   | 0.1760                        | 11  | -                             |     | -                             |     | -                             |     | -                     |     |
|                                    |     |     | 0.2848  | 7   | 0.2000                        | 13  | -                             |     | -                             |     | -                             |     | -                     |     |
| 12.YC                              | F   | 37  | -   |     | 0.2579                        | 11  | 0.2307                        | 16  | 0.4976                        | 23  | 0.6697                        | 33  | -                     |     |
| $\bar{X}_{II} \pm SD_{II}$         |     |     | 0.1960 <sup>±</sup><br>0.1984                                 |     | 0.1972 <sup>±</sup><br>0.2371 |     | 0.4820 <sup>±</sup><br>0.3554 |     | 0.6200 <sup>±</sup><br>0.1731 |     | 0.3349 <sup>±</sup><br>0.4736 |     | -                     |     |
| $\bar{X}_{all} \pm SD_{all}$       |     |     | 0.2601 <sup>±</sup><br>0.4631                                 |     | 0.1362 <sup>±</sup><br>0.1925 |     | 0.1928 <sup>±</sup><br>0.3182 |     | 0.3100 <sup>±</sup><br>0.3717 |     | 0.3349 <sup>±</sup><br>0.4736 |     | 0 <sup>±</sup><br>0-0 |     |
| The overall mean CSF/serum ratio = |     |     | 0.2079 <sup>±</sup> - 0.3332                                  |     |                               |     |                               |     |                               |     |                               |     |                       |     |

Table 13. The Average Concentrations in Serum and CSF and the Average Percent Penetration into CSF of Antituberculous Drugs.

| Drugs        | The overall mean concentration (mcg/ml) |       | The average percent penetration into CSF |
|--------------|---|-------|--|
|              | Serum                                   | CSF   |  |
| Isoniazid    | 3.03                                    | 2.40  | 89.08                                    |
| Pyrazinamide | 39.03                                   | 34.78 | 91.23                                    |
| Rifampin     | 7.25                                    | 0.29  | 5.09                                     |
| Streptomycin | 16.08                                   | 3.78  | 20.79                                    |



Table 14 Comparison of the Overall Mean Concentrations of Antituberculous Drugs in CSF with MIC against Mycobacterium tuberculosis

| Drugs        | The overall mean concentrations in CSF (mcg/ml) | MIC against <u>M. tuberculosis</u> (mcg/ml)                                |      |
|--------------|---|--|------|
|              |   | from the textbook  | mean |
| Isoniazid    | 2.40  | 0.05-0.2 <sup>(75)</sup><br>0.2 <sup>(11)</sup><br>0.2-0.5 <sup>(14)</sup> | 0.23 |
| Pyrazinamide | 34.78   | 20 <sup>(75)</sup>   | 20   |
| Rifampin     | 0.29  | 0.005-0.2 <sup>(14)</sup><br>0.1 <sup>(11)</sup><br>0.5 <sup>(75)</sup>    | 0.23 |
| Streptomycin | 3.78  | 2.0-5.0 <sup>(11)</sup>  | 3.5  |

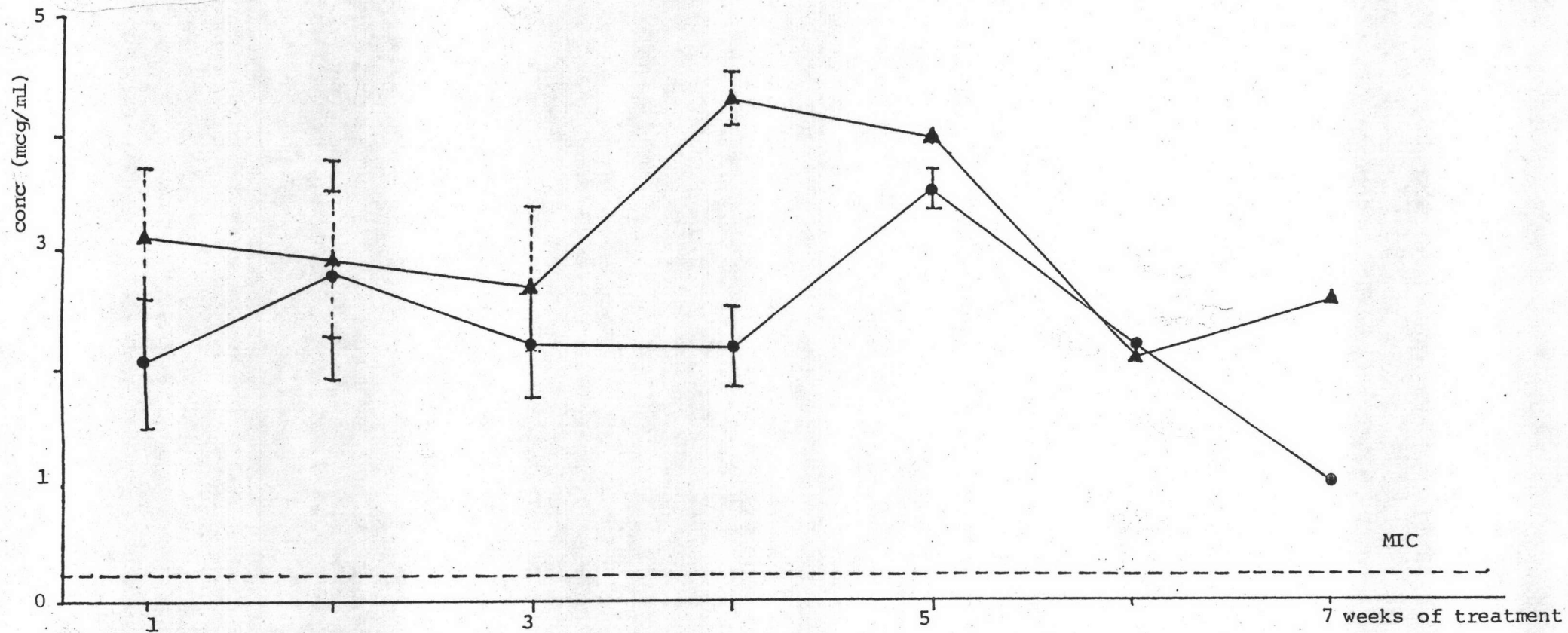


Figure 1 : The mean concentrations of isoniazid in CSF (●) and serum (▲) at various intervals in patients with tuberculous meningitis

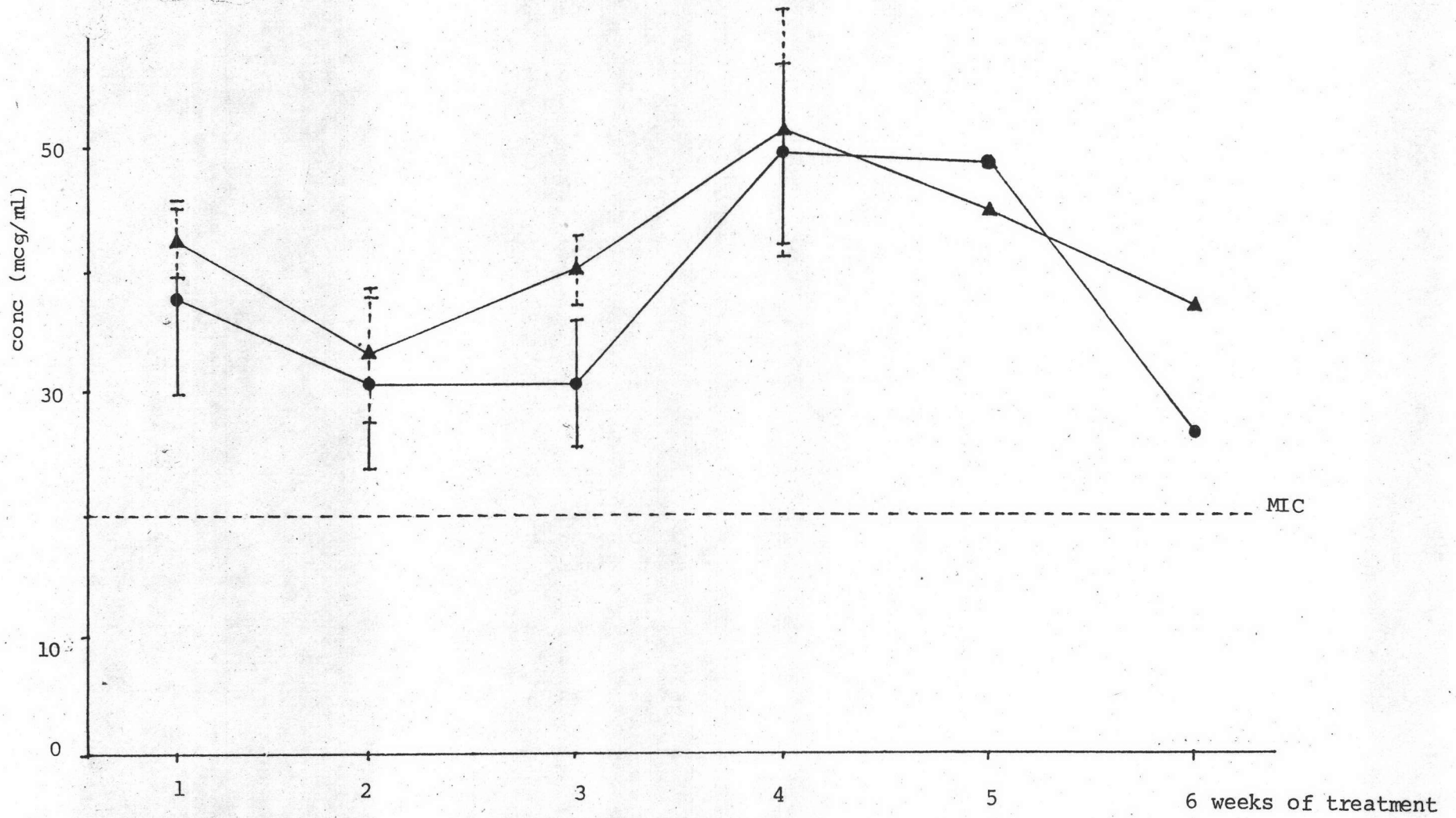


Figure 2 : The mean concentrations of pyrazinamide in CSF (●) and serum (▲) at various intervals in patients with tuberculous meningitis

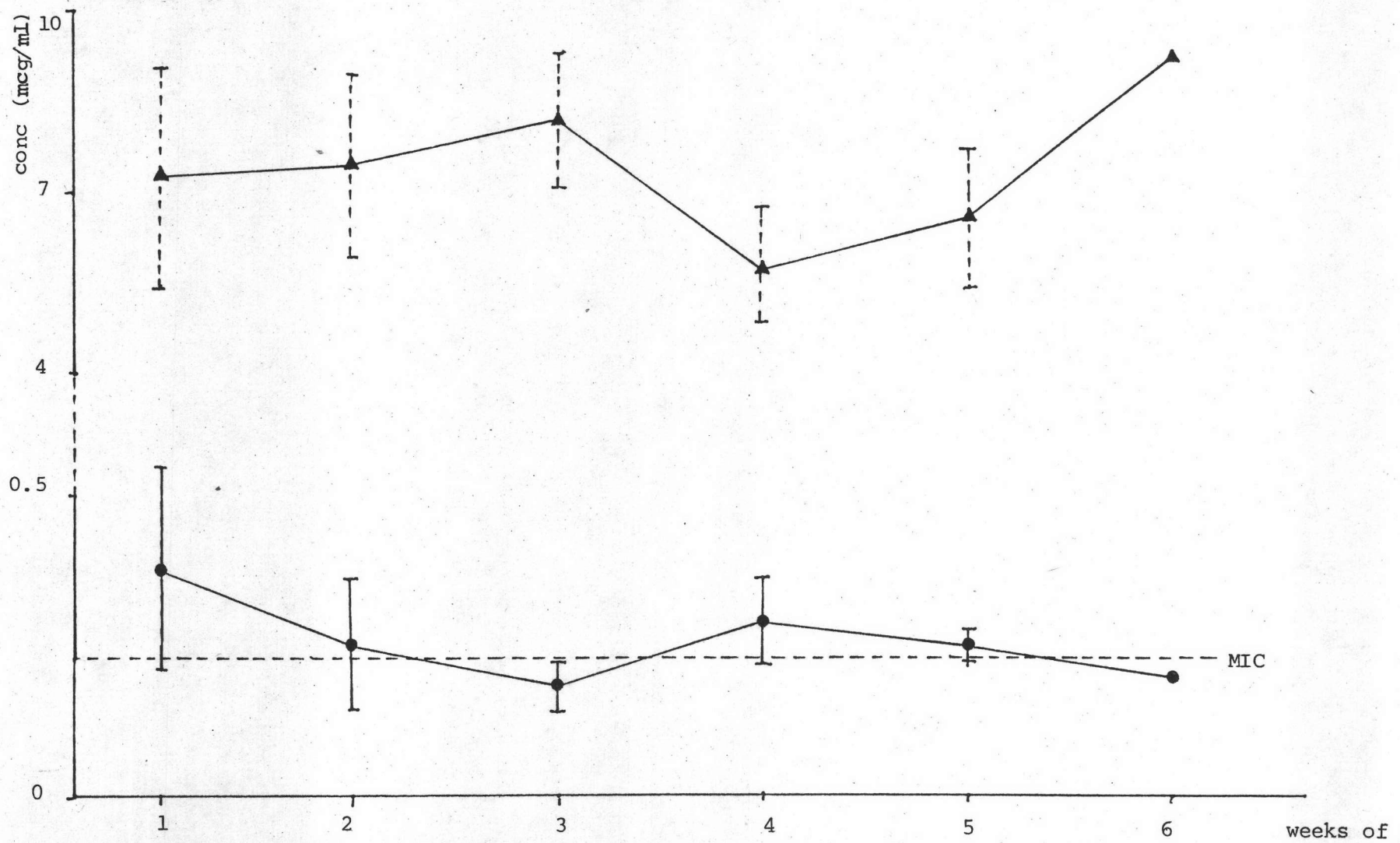


Figure 3 : The mean concentrations of rifampin in CSF (●) and serum (▲) at various intervals in patients with tuberculous meningitis

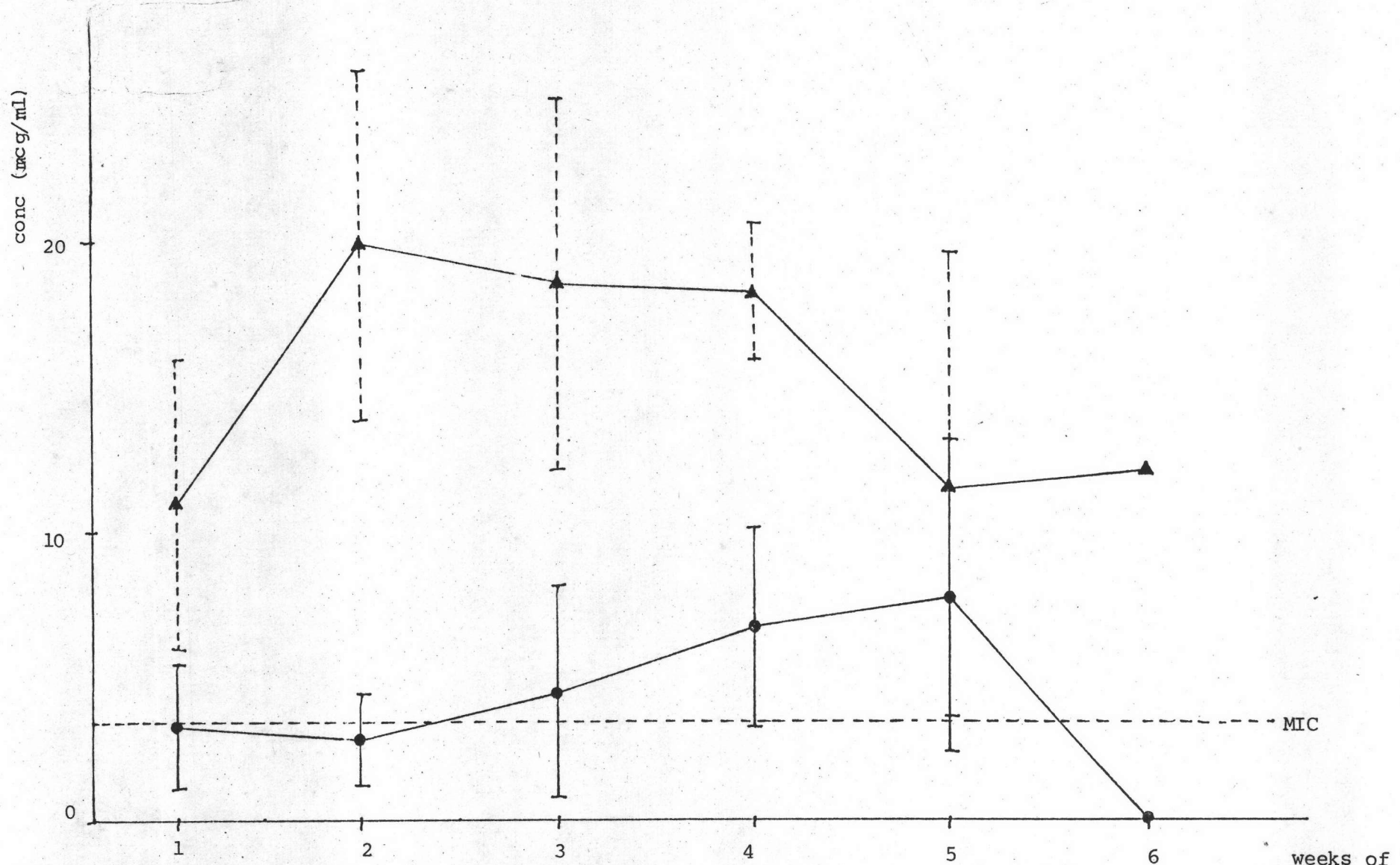


Figure 4 : The mean concentrations of streptomycin in CSF (●) and serum (▲) at various intervals in patients with tuberculous meningitis

weeks of treatment

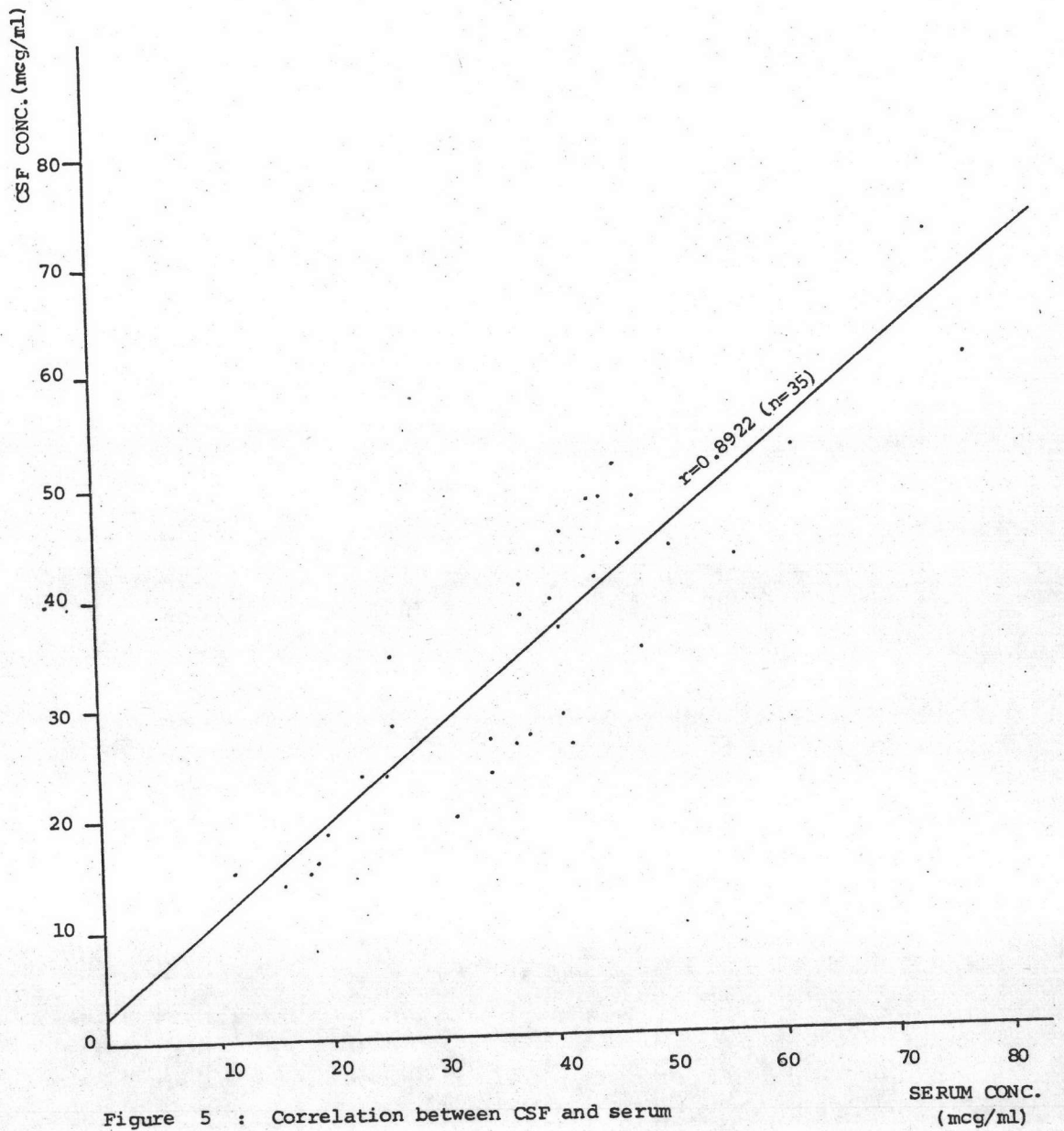


Figure 5 : Correlation between CSF and serum concentrations of pyrazinamide

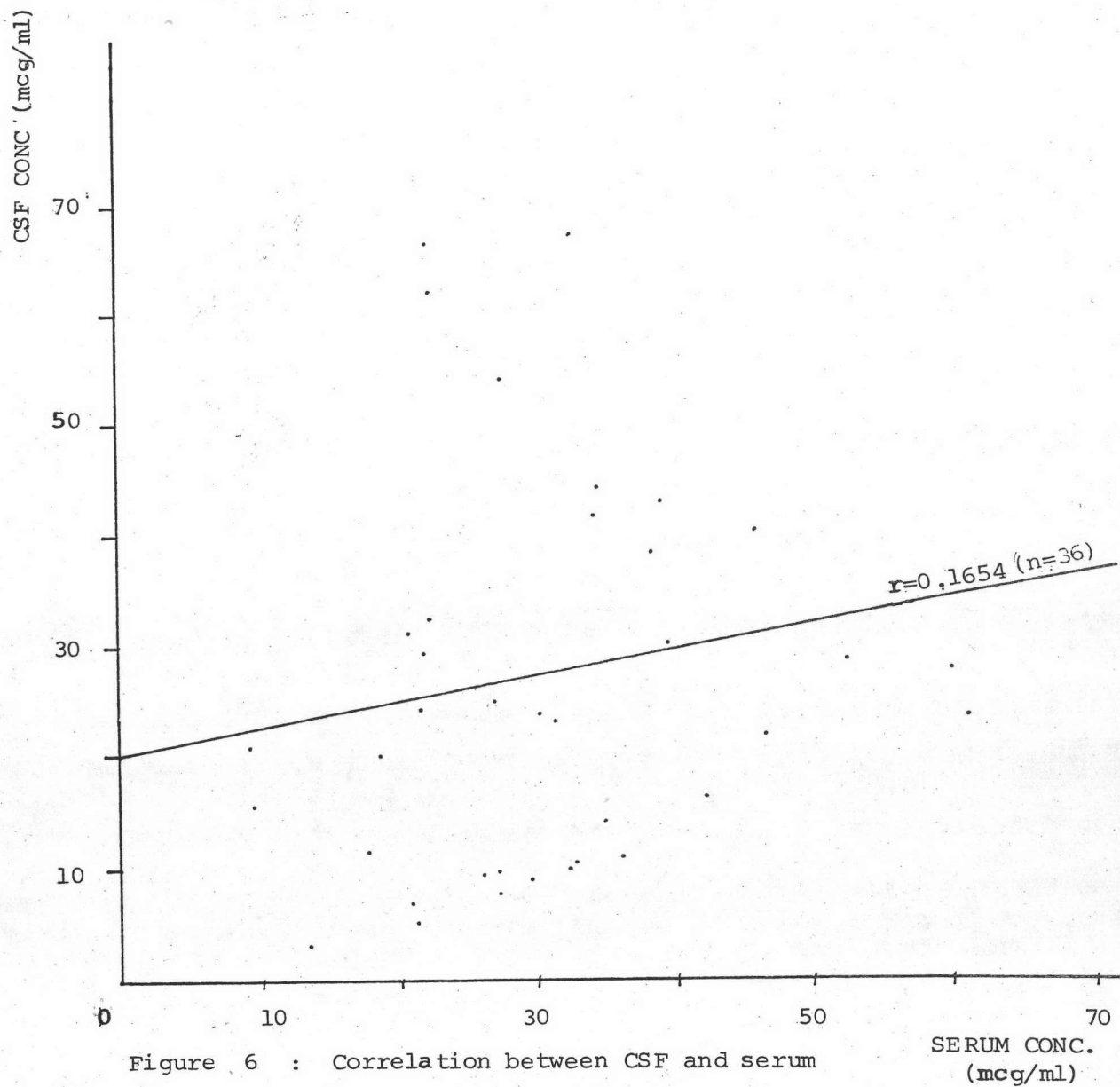


Figure 6 : Correlation between CSF and serum concentrations of isoniazid

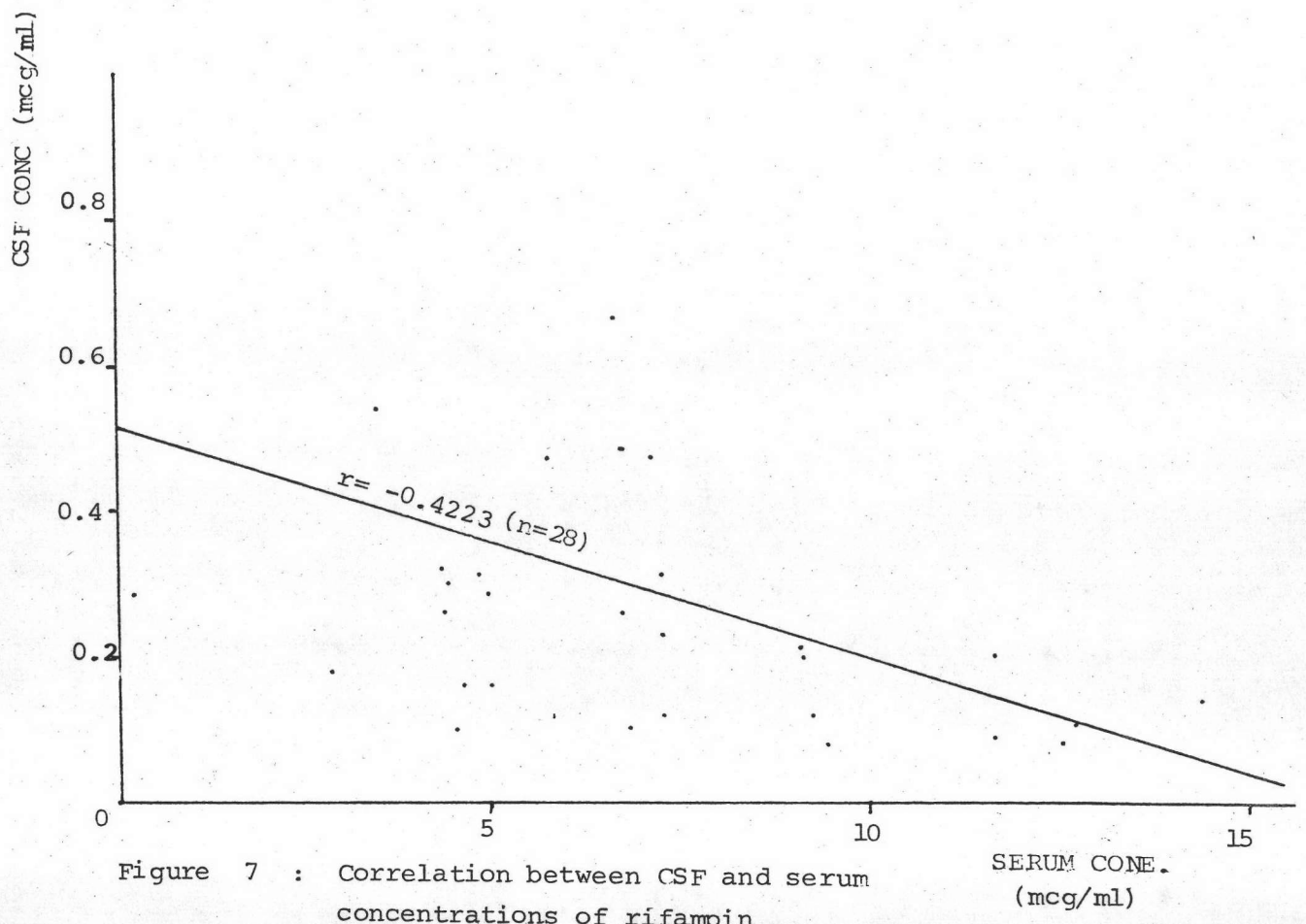


Figure 7 : Correlation between CSF and serum concentrations of rifampin



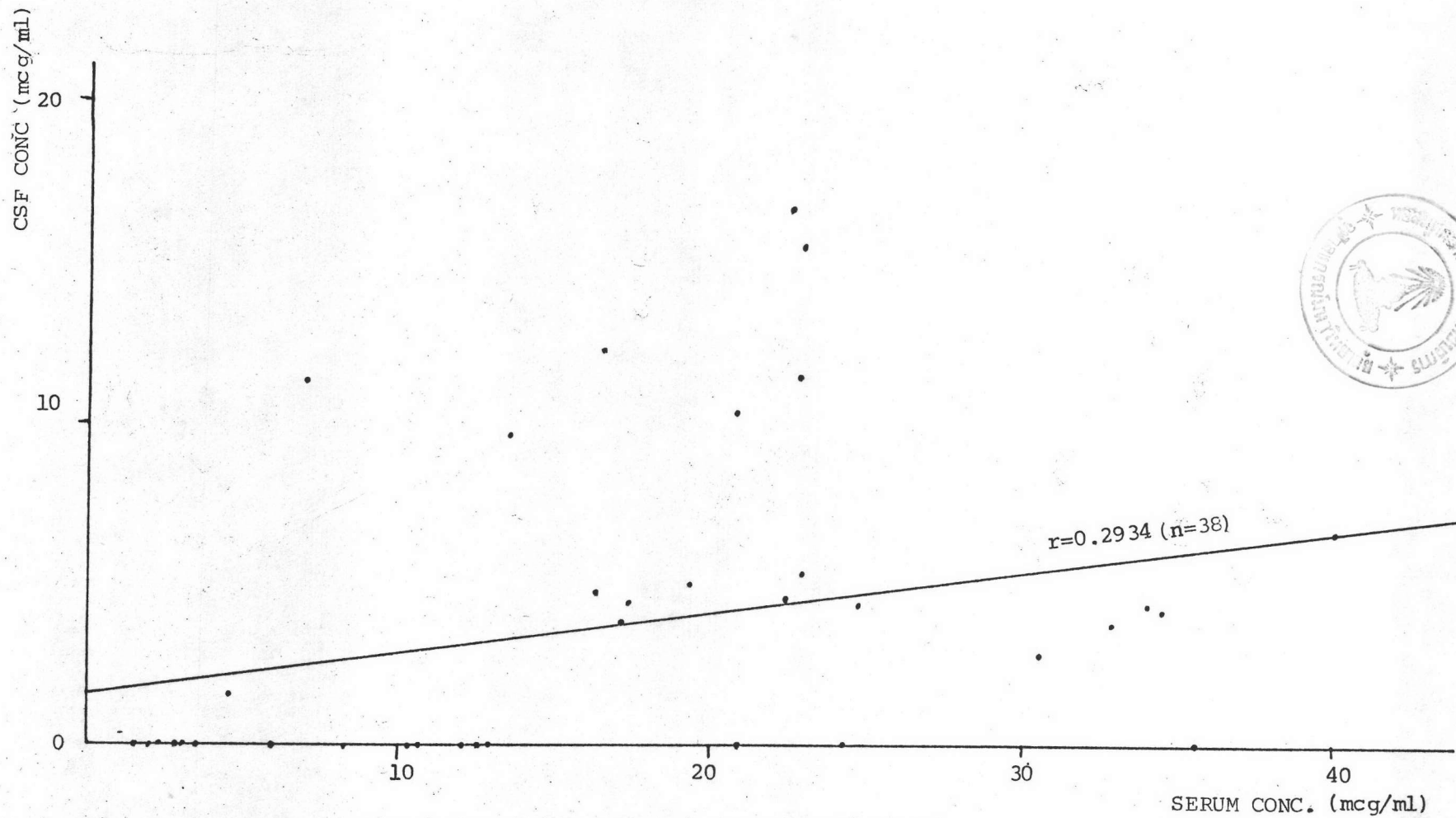


Figure 8 : Correlation between CSF and serum concentrations of streptomycin



II. Comparative Concentrations in CSF and Serum of Antituberculous Drugs between Patients with and without Concomitant Corticosteroids

The mean concentrations of isoniazid in CSF and serum at various intervals in two groups of patients, in which group I were patients receiving only antituberculous drugs and group II were patients receiving both antituberculous drugs and corticosteroid, were shown in Table 15. The mean concentration of INH at days 1 - 7 in group I was compared with the mean concentration at days 1 - 7 in gr II by using non - parametric statistic, Mann - Whitney U - test. The mean concentrations at days 8 - 14, days 15 - 21 and days 22 - 28 between two groups of patients were also compared. There was no statistically significant difference between the mean concentrations of isoniazid in CSF and serum in two groups at various intervals with the p - value  $> 0.05$ . The total mean concentrations in CSF and serum of group I and group II showed no significant difference by using unpaired t - test too.

The mean concentrations of pyrazinamide, rifampin and streptomycin in CSF and serum in two groups of patients at various intervals as shown in Table 16, 17 and 18 were also compared by using the same method as isoniazid but the total means of the drugs between two groups were compared by unpaired t - test. The differences between the mean concentrations of pyrazinamide, rifampin and streptomycin in CSF and serum in two groups of patients at various intervals and the total means were not statistically significant ( $p > 0.05$ ) except that the total CSF mean concentration of streptomycin in gr II was higher than in gr I ( $p < 0.01$ ).

The mean CSF/serum ratios of isoniazid, pyrazinamide, rifampin and streptomycin in two groups of patients at various intervals and the total mean CSF/serum ratios, as illustrated in Table 15,16,17, and 18, were compared by the same method as mentioned above. Statistical analysis revealed no significant difference between the mean CSF/serum ratios and the total means of the drugs in two groups of patients at various intervals ( $p > 0.05$ ).

**Table 15** Comparison of the Mean Concentrations in CSF and Serum and CSF/Serum Ratio of Isoniazid at Various Intervals.

| Specimen        | Group   | The mean concentrations ( $\mu\text{g/ml}$ ) after 3 hr administration of isoniazid at |                           |                           |                           |                           |                           |                           |                            |
|-----------------|---------|--|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|----------------------------|
|                 |         | days 1-7   | days 8-14                 | days 15-21                | days 22-28                | days 29-35                | days 36-42                | days 43-49                | Total                      |
| CSF             | I       | $1.95^{\pm}0.95$<br>(n=4)  | $3.15^{\pm}1.44$<br>(n=9) | $2.42^{\pm}0.61$<br>(n=5) | $1.95^{\pm}1.40$<br>(n=1) | -                         | $2.24^{\pm}1.50$<br>(n=1) | -                         | $2.62^{\pm}1.17$<br>(n=20) |
|                 | II      | $2.06^{\pm}1.23$<br>(n=10)   | $2.43^{\pm}2.23$<br>(n=7) | $2.00^{\pm}1.33$<br>(n=4) | $2.25^{\pm}0.80$<br>(n=3) | $3.52^{\pm}0.31$<br>(n=2) | -                         | $1.00^{\pm}1.00$<br>(n=1) | $2.24^{\pm}1.47$<br>(n=27) |
|                 | p-value | NS   | NS                        | NS                        | NS                        | -                         | -                         | -                         | NS*                        |
| Serum           | I       | $2.34^{\pm}0.75$<br>(n=3)  | $3.26^{\pm}1.46$<br>(n=9) | $1.93^{\pm}1.49$<br>(n=2) | $4.60^{\pm}2.15$<br>(n=1) | -                         | $2.11^{\pm}1.45$<br>(n=1) | -                         | $2.93^{\pm}1.36$<br>(n=16) |
|                 | II      | $3.36^{\pm}1.59$<br>(n=9)  | $2.39^{\pm}0.72$<br>(n=6) | $3.54^{\pm}0.01$<br>(n=2) | $3.96^{\pm}1.99$<br>(n=1) | $3.96^{\pm}1.99$<br>(n=1) | -                         | $2.55^{\pm}1.60$<br>(n=1) | $3.11^{\pm}1.22$<br>(n=20) |
|                 | p-value | NS   | NS                        | NS                        | -                         | -                         | -                         | -                         | NS*                        |
| CSF/serum ratio | I       | $0.80^{\pm}0.51$<br>(n=3)  | $1.16^{\pm}0.68$<br>(n=9) | $1.50^{\pm}1.08$<br>(n=2) | $0.42^{\pm}0.65$<br>(n=1) | -                         | $1.06^{\pm}1.03$<br>(n=1) | -                         | $1.08^{\pm}0.66$<br>(n=16) |
|                 | II      | $0.60^{\pm}0.40$<br>(n=9)  | $0.98^{\pm}0.84$<br>(n=6) | $0.71^{\pm}0.56$<br>(n=2) | $0.67^{\pm}0.82$<br>(n=1) | $0.94^{\pm}0.97$<br>(n=1) | -                         | $0.39^{\pm}0.63$<br>(n=1) | $0.74^{\pm}0.55$<br>(n=20) |
|                 | p-value | NS   | NS                        | NS                        | -                         | -                         | -                         | -                         | NS*                        |

n = number of sample

NS = not significant at level = 0.05

p-value by Mann-Whitney U-test (2-tailed), p-value\* by unpaired-t-test

**Table 16** Comparison of the Mean Concentrations in CSF and Serum and CSF/Serum Ratios of Pyrazinamide at Various Intervals

| Specimen        | Group   | The mean concentrations (ug/ml) after 3-hr administration of pyrazinamide at |                                    |                                   |                                   |                                  |                                  |                                    |
|-----------------|---------|--|------------------------------------|-----------------------------------|-----------------------------------|----------------------------------|----------------------------------|------------------------------------|
|                 |         | days 1-7   | days 8-14                          | days 15-21                        | days 22-28                        | days 29-35                       | days 43-49                       | Total                              |
| CSF             | I       | 37.70 <sup>±</sup> 15.00<br>(n=2)  | 31.30 <sup>±</sup> 15.15<br>(n=12) | 26.54 <sup>±</sup> 12.16<br>(n=4) | 43.20 <sup>±</sup> 6.57<br>(n=1)  | -                                | -                                | 31.60 <sup>±</sup> 13.96<br>(n=19) |
|                 | II      | 37.53 <sup>±</sup> 16.31<br>(n=10)   | 28.75 <sup>±</sup> 10.68<br>(n=4)  | 35.00 <sup>±</sup> 6.78<br>(n=4)  | 51.57 <sup>±</sup> 17.71<br>(n=3) | 48.50 <sup>±</sup> 6.96<br>(n=1) | 26.50 <sup>±</sup> 5.15<br>(n=1) | 37.39 <sup>±</sup> 14.56<br>(n=23) |
|                 | p-value | NS   | NS                                 | NS                                | NS                                | -                                | -                                | NS*                                |
| Serum           | I       | 40.78 <sup>±</sup> 3.99<br>(n=2)   | 31.76 <sup>±</sup> 12.88<br>(n=10) | 40.49 <sup>±</sup> 16.56<br>(n=3) | 43.10 <sup>±</sup> 6.57<br>(n=1)  | -                                | -                                | 35.23 <sup>±</sup> 12.61<br>(n=16) |
|                 | II      | 42.69 <sup>±</sup> 19.18<br>(n=9)  | 36.93 <sup>±</sup> 7.01<br>(n=4)   | 39.00 <sup>±</sup> 2.40<br>(n=2)  | 55.50 <sup>±</sup> 25.74<br>(n=2) | 44.60 <sup>±</sup> 6.68<br>(n=1) | 36.90 <sup>±</sup> 6.08<br>(n=1) | 42.23 <sup>±</sup> 15.42<br>(n=19) |
|                 | p-value | NS   | NS                                 | NS                                | -                                 | -                                | -                                | NS*                                |
| CSF/serum ratio | I       | 0.91 <sup>±</sup> 0.28<br>(n=2)  | 0.92 <sup>±</sup> 0.15<br>(n=10)   | 0.80 <sup>±</sup> 0.20<br>(n=3)   | 1.00 <sup>±</sup> 1.00<br>(n=1)   | -                                | -                                | 0.90 <sup>±</sup> 0.17<br>(n=16)   |
|                 | II      | 0.96 <sup>±</sup> 0.18<br>(n=9)  | 0.76 <sup>±</sup> 0.13<br>(n=4)    | 0.97 <sup>±</sup> 0.08<br>(n=2)   | 1.04 <sup>±</sup> 0.08<br>(n=2)   | 1.09 <sup>±</sup> 1.04<br>(n=1)  | 0.72 <sup>±</sup> 0.85<br>(n=1)  | 0.92 <sup>±</sup> 0.17<br>(n=19)   |
|                 | p-value | NS   | NS                                 | NS                                | -                                 | -                                | -                                | NS*                                |

n = number of sample

NS = not-significant at level = 0.05

p-value by Mann-Whitney U-test (2-tailed), p-value\* by unpaired t-test (2-tailed)

**Table 17** Comparison of the Mean Concentrations in CSF and Serum and CSF/Serum Ratios of Rifampin at Various Intervals

| Specimen        | Group   | The mean concentrations (µg/ml) after 3-hr administration of rifampin at |                                     |                                     |                                     |                                     |                                     |                                      |
|-----------------|---------|--|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|
|                 |         | days 1-7   | days 8-14                           | days 15-21                          | days 22-28                          | days 29-35                          | days 36-42                          | Total                                |
| CSF             | I       | 0.27 <sup>±</sup> 0.16<br>(n=4)  | 0.20 <sup>±</sup> 0.19<br>(n=7)     | 0.15 <sup>±</sup> 0.07<br>(n=3)     | -                                   | -                                   | 0.20 <sup>±</sup> 0.45<br>(n=1)     | 0.21 <sup>±</sup> 0.15<br>(n=15)     |
|                 | II      | 0.41 <sup>±</sup> 0.39<br>(n=9)  | 0.35 <sup>±</sup> 0.29<br>(n=3)     | 0.26 <sup>±</sup> 0.51<br>(n=1)     | 0.29 <sup>±</sup> 0.14<br>(n=4)     | 0.25 <sup>±</sup> 0.05<br>(n=2)     | -                                   | 0.35 <sup>±</sup> 0.29<br>(n=19)     |
|                 | p-value | NS   | NS                                  | NS                                  | -                                   | -                                   | -                                   | NS*                                  |
| Serum           | I       | 6.59 <sup>±</sup> 3.43<br>(n=4)  | 6.28 <sup>±</sup> 2.62<br>(n=4)     | 9.38 <sup>±</sup> 2.19<br>(n=3)     | -                                   | -                                   | 9.11 <sup>±</sup> 3.02<br>(n=1)     | 7.39 <sup>±</sup> 2.82<br>(n=12)     |
|                 | II      | 7.46 <sup>±</sup> 4.01<br>(n=8)  | 8.82 <sup>±</sup> 3.24<br>(n=3)     | 4.34 <sup>±</sup> 2.08<br>(n=1)     | 5.70 <sup>±</sup> 1.98<br>(n=2)     | 6.54 <sup>±</sup> 2.24<br>(n=3)     | -                                   | 7.15 <sup>±</sup> 3.26<br>(n=17)     |
|                 | p-value | NS   | NS                                  | NS                                  | -                                   | -                                   | -                                   | NS*                                  |
| CSF/serum ratio | I       | 0.0472 <sup>±</sup> 0.0324<br>(n=4)                                      | 0.0531 <sup>±</sup> 0.0690<br>(n=4) | 0.0174 <sup>±</sup> 0.0126<br>(n=3) | -                                   | -                                   | 0.0220 <sup>±</sup> 0.1483<br>(n=1) | 0.0396 <sup>±</sup> 0.0432<br>(n=12) |
|                 | II      | 0.0651 <sup>±</sup> 0.0794<br>(n=8)                                      | 0.0494 <sup>±</sup> 0.0467<br>(n=3) | 0.0599 <sup>±</sup> 0.2447<br>(n=1) | 0.0702 <sup>±</sup> 0.0056<br>(n=2) | 0.0404 <sup>±</sup> 0.0244<br>(n=2) | -                                   | 0.0594 <sup>±</sup> 0.0581<br>(n=16) |
|                 | p-value | NS   | NS                                  | NS                                  | -                                   | -                                   | -                                   | NS*                                  |

n = number of sample

NS = not significant at level = 0.05

p-value by Mann-Whitney U-test (2-tailed), p-value\* by unpaired t-test (2-tailed)

**Table 18** Comparison of the Mean Concentrations in CSF and Serum and CSF/Serum Ratios of Streptomycin at Various Intervals

| Specimen        | Group   | The mean concentrations (ug/ml) after 3-hr administration of streptomycin at |                                   |                                   |                                  |                                   |                                  |                                    |
|-----------------|---------|--|-----------------------------------|-----------------------------------|----------------------------------|-----------------------------------|----------------------------------|------------------------------------|
|                 |         | days 1-7   | days 8-14                         | days 15-21                        | days 22-28                       | days 29-35                        | days 36-42                       | Total                              |
| CSF             | I       | 2.57 <sup>±</sup> 4.57<br>(n=6)  | 2.34 <sup>±</sup> 2.78<br>(n=10)  | 0 <sup>±</sup> 0<br>(n=3)         | 0 <sup>±</sup> 0<br>(n=2)        | -                                 | 0 <sup>±</sup> 0<br>(n=1)        | 1.76 <sup>±</sup> 3.08<br>(n=22)   |
|                 | II      | 3.86 <sup>±</sup> 4.31<br>(n=8)  | 3.42 <sup>±</sup> 3.36<br>(n=8)   | 10.89 <sup>±</sup> 7.93<br>(n=2)  | 9.98 <sup>±</sup> 2.42<br>(n=4)  | 7.67 <sup>±</sup> 10.84<br>(n=2)  | -                                | 5.64 <sup>±</sup> 5.15<br>(n=24)   |
|                 | p-value | NS   | NS                                | NS                                | NS                               | -                                 | -                                | p* < 0.01                          |
| Serum           | I       | 13.35 <sup>±</sup> 12.48<br>(n=5)  | 21.74 <sup>±</sup> 13.88<br>(n=6) | 15.80 <sup>±</sup> 17.27<br>(n=3) | 16.70 <sup>±</sup> 5.85<br>(n=2) | -                                 | 12.08 <sup>±</sup> 3.48<br>(n=1) | 17.06 <sup>±</sup> 12.37<br>(n=17) |
|                 | II      | 9.16 <sup>±</sup> 8.58<br>(n=7)  | 18.66 <sup>±</sup> 11.24<br>(n=8) | 22.70 <sup>±</sup> 0.28<br>(n=2)  | 19.64 <sup>±</sup> 4.43<br>(n=2) | 11.45 <sup>±</sup> 16.19<br>(n=2) | -                                | 15.28 <sup>±</sup> 10.34<br>(n=21) |
|                 | p-value | NS   | NS                                | NS                                | NS                               | -                                 | -                                | NS*                                |
| CSF/serum ratio | I       | 0.35 <sup>±</sup> 0.72<br>(n=5)  | 0.06 <sup>±</sup> 0.06<br>(n=6)   | 0 <sup>±</sup> 0<br>(n=3)         | 0 <sup>±</sup> 0<br>(n=2)        | -                                 | 0 <sup>±</sup> 0<br>(n=1)        | 0.12 <sup>±</sup> 0.39<br>(n=17)   |
|                 | II      | 0.20 <sup>±</sup> 0.20<br>(n=7)  | 0.20 <sup>±</sup> 0.24<br>(n=8)   | 0.48 <sup>±</sup> 0.36<br>(n=2)   | 0.62 <sup>±</sup> 0.17<br>(n=2)  | 0.34 <sup>±</sup> 0.47<br>(n=2)   | -                                | 0.28 <sup>±</sup> 0.27<br>(n=21)   |
|                 | p-value | NS   | NS                                | NS                                | NS                               | -                                 | -                                | NS*                                |

n = number of sample

NS = not significant at level = 0.05

p-value by Mann-Whitney U-test (2-tailed), p-value\* by unpaired t-test (2-tailed)

### III. Clinical Evaluation of Antituberculous Drugs in Tuberculous Meningitis Patients during Hospitalization.

There were sixteen patients in this study, 7 males and 9 females. Most patients were admitted at the Department of Medicine, Ramathibodi Hospital, only one (PV) was at Chulalongkorn Hospital. Age of the patients ranged from 19 to 70 years with the average of  $31.31 \pm 16.52$  years. The patients were divided into two groups. Group I consisted of 6 males and 4 females and the ages ranged from 19 - 68 years with the average of  $30.50 \pm 15.69$  years. Five females and 1 male were in group II with the average of  $32.67 \pm 19.29$  years and the ages were in the range of 20 - 70 years. The distribution of the patients' age was shown in Table 19 which suggested that most of patients who developed tuberculous meningitis were in the early adult life. In addition, the statistical analysis (chi - square test) showed that the distribution of age of the patients in two groups was not statistically different ( $p > 0.05$ ).

Three patients in group II and one in group I had the history of tuberculous contact. There was evidence of tuberculous infection elsewhere in six patients. The chest x - ray revealed miliary pattern in 3 patients in group I. In group II, pulmonary tuberculosis was discovered in 3 patients and tuberculous chorioretinitis was also involved in one patient whereas tuberculosis in lymph node and in kidney was shown in the another one.

The admission clinical signs and symptoms were listed in Table 20. Headache and fever were common in the patients. Neck stiffness was also present in almost every case of meningitis. Kernig's sign



was positive in 7 and 2 patients in group I and II respectively, and negative in 1 and 3 patients in group I and II respectively. In 2 and 1 patients in group I and II, kernig 's sign was not recorded. Other signs and symptoms were nausea, vomiting, drowsiness, confusion, visual difficulties and anorexia. Convulsion was found in only one patient in group I.

Table 21 showed results of examination of the first CSF sample. In all cases, the CSF was under increased pressure. In the majority of cases, the cell count was less than 500 cells per cu. mm with mononuclear cell preponderance. In 10 cases the protein levels were between 49 and 200 mg %, and 5 cases with levels more than 200 mg %. In one case the protein level was not examined. The CSF glucose level in 14 cases was less than 40 mg % i.e. less than half of the serum glucose level. Though the CSF glucose level in 2 cases was greater than 50 mg %, it was less than half of the serum level.

The confirmation of diagnosis depends on identification of M. tuberculosis in the CSF, but the bacilli were often not demonstrated. In the study, not only acid - fast bacilli were not seen on microscopic examination but also CSF cultures were negative in all cases.

The dose of isoniazid in the patients during the determination of the CSF levels was 300 mg orally in the morning. Only one patient (SG) the dose given was 400 mg orally in the morning for 20 days and the CSF and serum levels were not different from the above patients. Pyrazinamide was given orally 1.5 gm daily in all cases but 2 cases (PV and PT) in group I were given in three divided doses. Rifampin in the dose of 600 mg once daily in the morning was given orally except in 2

patients (SP and CK), the dose of 450 mg once daily was given. The doses of streptomycin given during the determination of CSF and serum levels were 0.75 gm in 12 patients (8 in group I and 4 in group II) and 1 gm in 4 patients (2 in each group), given intramuscularly once daily in the morning.

Corticosteroids used in patients group II were dexamethasone in oral and parenteral form and prednisolone in oral form. All patients were started with dexamethasone intravenous injection for 1 - 7 days except that one (YC) who was started with prednisolone in the oral form. Then all patients were changed to oral prednisolone except one case (SU), oral dexamethasone was given instead.

The duration of hospital stay, averaged from 11 patients (7 from group I and 4 from group II), was 33 days (27.14 days for group I and 43.25 days for group II). The data of 3 patients in group I and 2 in group II was not all collected, so it was incomplete. Two patients (CT and YC) required operation for ventriculoperitoneal (VP) shunt insertion.

After hospitalization, the patients were evaluated as summarized in Table 22. Clinical signs and symptoms of 4 patients in group I and 1 in group II were improved and no neurological sequelae was found. Though clinical signs and symptoms of 2 patients in group I and 2 patients in group II were improved, neurological deficits were found. In group I, one (SSR) developed generalized seizure while another one (CP) had cerebral atrophy. In group II, right lateral rectus palsy was found in one whereas ptosis of right eye was found in another one. In addition,

three patients in group I and two patients in group II had clinical signs and symptoms improved but they were not concluded because of disappearance of the hospital charts. One patient (PP) in group II was discharged with improved clinical signs and symptoms but was readmitted later on due to the non-compliance of the patient and finally was dead.

Table 19 The Distribution of Age of Patients

| Patients | Age (years) |       |       |      | Total |
|----------|-------------|-------|-------|------|-------|
|          | 16-30       | 31-45 | 46-60 | > 60 |       |
| Group I  | 7           | 1     | 1     | 1    | 10    |
| Group II | 4           | 1     | -     | 1    | 6     |
| Total    | 11          | 2     | 1     | 2    | 16    |

Table 20 The Admission Signs and Symptoms

| Signs and Symptoms  | Number of Cases |          |       |
|---------------------|-----------------|----------|-------|
|                     | group I         | group II | Total |
| Headache            | 9               | 6        | 15    |
| Fever               | 9               | 6        | 15    |
| Neck Stiffneck      | 9               | 5        | 14    |
| Kernig's sign       | 7               | 2        | 9     |
| Nausea and Vomiting | 6               | 3        | 9     |
| Drowsiness          | 4               | 1        | 5     |
| Confusion           | 2               | 3        | 5     |
| Visual difficulties | 2               | 2        | 4     |
| Anorexia            | 2               | 1        | 3     |
| Convulsion          | 1               | -        | 1     |

Table 21 Admission Values in CSF

| CSF                           | Number of Cases |          |       |
|-------------------------------|-----------------|----------|-------|
|                               | group I         | group II | Total |
| Pressure, mm H <sub>2</sub> O |                 |          |       |
| 90 - 200                      | 2               | 1        | 3     |
| 201 - 400                     | 6               | 3        | 9     |
| 401 - 600                     | 2               | 1        | 3     |
| > 600                         | 0               | 1        | 1     |
| Cell count, cells/cu mm       |                 |          |       |
| 26 - 499                      | 5               | 5        | 10    |
| ≥ 500                         | 5               | 1        | 6     |
| % mononuclear cell            |                 |          |       |
| 51 - 60                       | 3               | 0        | 3     |
| 61 - 70                       | 2               | 0        | 2     |
| 71 - 80                       | 0               | 1        | 1     |
| 81 - 90                       | 2               | 2        | 4     |
| Protein level, mg %           |                 |          |       |
| 49 - 200                      | 7               | 3        | 10    |
| 201 - 400                     | 1               | 2        | 3     |
| 401 - 600                     | 0               | 0        | 0     |
| > 600                         | 1               | 1        | 2     |
| Glucose level, mg %           |                 |          |       |
| 10 - 20                       | 2               | 2        | 4     |
| 21 - 30                       | 5               | 2        | 7     |
| 31 - 40                       | 1               | 2        | 3     |
| 41 - 50                       | 0               | 0        | 0     |
| > 50                          | 2               | 0        | 2     |

Table 22 Results of Treatment

|                         | Number of Cases |          |       |
|-------------------------|-----------------|----------|-------|
|                         | Group I         | Group II | Total |
| Survived                | 10              | 5        | 15    |
| No neurological deficit | 5               | 1        | 6     |
| Neurological deficits   | 2               | 2        | 4     |
| generalized seizure     | 1               | -        | 1     |
| cerebral atrophy        | 1               | -        | 1     |
| rectus palsy            | -               | 1        | 1     |
| ptosis of eye           | -               | 1        | 1     |
| Undetermined            | 3               | 2        | 5     |
| Death                   | 1               | 0        | 1     |

