THE CHEMOTHERAPY OF INTRA-
CRANIAL INFECTIONS

IV. THE TREATMENT OF PNEUMOCOCCAL MENINGITIS BY
INTRATHECAL ADMINISTRATION OF PENICILLIN*

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(Received for publication December 21, 1943)

In a previous study,¹ penicillin administered intrathecally, even in rela-
tively small doses, was found to be beneficial in experimental staphylococ-
cal meningitis in dogs. We wish here to report a similar study of meningi-
itis due to the pneumococcus, Type I.

A virulent strain of this organism was inoculated into the cerebrospinal
fluid of a number of successive dogs until the resulting meningitis was rela-
tively consistent in its course, nearly always terminating fatally in two to
seven days, with viscid, grossly purulent cerebrospinal fluid. A large amount
of an eighteen-hour culture of the organism (in saline suspension) was then
sealed in sterile glass ampoules and preserved in the frozen state, as with
the cultures of staphylococci previously reported.¹

Meningitis was produced in a number of groups of ten to fourteen dogs
by injection of approximately 3,000,000 pneumococci into the cisterna
magna. Half of each group of animals was treated, the remaining half was
used as controls. Daily (or more frequent) cultures of blood and cerebro-
spinal fluid were made, clinical observations were recorded and necropsy
was carried out at the termination of all experiments. Histologic studies were
made on most animals. Surviving animals were sacrificed only after cultures
had been sterile and symptoms absent for at least ten days.

RESULTS

Control experiments were strikingly similar in most groups. Only two of
forty-six control animals recovered (4.3 per cent). Death occurred within
three days (usually on the third day) in nearly half and from three to seven
days (usually on the fourth or fifth days) in nearly all the remainder.

In the first series of 48 experiments, divided into four groups, intracisternal
injection of 50 units† of penicillin (dissolved in 1 c.c. of saline solution) twice
daily was the therapy employed (Fig. 1). In each of the four groups, results

* The work described in this paper was done under a contract, recommended by the Committee on
Medical Research, between the Office of Scientific Research and Development and the Vanderbilt
University. The penicillin was furnished by E. R. Squibb and Sons and by Charles Pfizer, Inc., New York,
on recommendation of the Committee on Chemotherapeutic and Other Agents of the National Research
Council.

† This very small dosage was employed partly because very little penicillin was available to us at
the time and partly because it seemed advantageous nevertheless to determine the effects of the same
minimal dosage employed in previous experiments on staphylococcal meningitis.
were slightly but definitely more favorable in the treated than in the untreated animals. Of 22 untreated dogs, only one survived, whereas four of 26 treated dogs recovered. Furthermore, the incidence of early death was distinctly higher among the control animals.

In the next two groups of 12 dogs each, treatment consisted of intracisternal administration of 100 and 200 units of penicillin, respectively, twice daily (Fig. 2). One treated animal is not included in the chart because a positive culture was not obtained in the cerebrospinal fluid at any time in a period of 12 days and it was thought possible that the organisms had been injected epidurally.

Among the twelve control animals, only one survived, whereas five of the eleven treated dogs recovered.

It was observed in these groups that the cerebrospinal fluid of all treated animals was grossly clear with a very moderate pleocytosis, whereas in the control dogs, the fluid was invariably grossly purulent and frequently so viscid that only small specimens could be obtained by cisternal puncture.
(Fig. 3). This observation was confirmed at necropsy. Furthermore, the blood cultures of the treated animals invariably were positive for the pneumococcus and frequently remained so for some days (Fig. 2). At necropsy most of the treated animals that failed to survive were found to have lobar pneumonia from which the pneumococcus could be recovered.

Since the gradual absorption of the small and infrequent intrathecal doses of penicillin could not be expected to produce a therapeutically significant blood level of the drug, it seemed likely that pneumonia was responsible for many of the deaths among the treated animals. That this was not equally true in the control experiments was evidenced by the grossly purulent cerebrospinal fluid and post-mortem histological evidence of severe and extensive meningitis in these animals.

In order to obviate the factor of pneumonia as far as possible, two addi-
Fig. 3. Specimens of cerebrospinal fluid obtained from simultaneously infected groups of treated and untreated animals three days after infection. Treatment consisted of intracisternal injection of 200 units of penicillin twice daily.

Fig. 4
Fig. 5. Specimens of cerebrospinal fluid obtained from simultaneously infected groups of treated and untreated animals two days after infection. Treatment consisted of intracisternal injection of 200 units of penicillin twice daily and intravenous injection of 1000 units of penicillin three times daily.

Additional groups of dogs were treated by intrathecal injection of 200 units of penicillin twice daily and intravenous injection of 1000 units of penicillin three times daily. All injections were spaced approximately evenly in each 24 hours.

In these 24 experiments, the results in the treated animals were even more strikingly favorable (Fig. 4). No control animal recovered, as compared
with six recoveries among the treated dogs.* Five control dogs did not survive three days and six control dogs died in the three-to-seven day period. On the other hand, only one treated dog died within three days and only one other in the three-to-seven day period.

In these animals, as in the previous groups, the cerebrospinal fluid presented a striking contrast in the treated and untreated groups (Fig. 5).

COMMENT

Composite results of all the experiments herein reported are shown in Fig. 6.

Despite the relatively small number of experiments (ninety-six) and the difficulty of statistical analysis in experiments designed to simulate clinical conditions, the results of this study indicate clearly that the intrathecal injection of penicillin was of marked benefit under these experimental conditions. They also indicate that intravenous or intramuscular administrations of penicillin should not be neglected when intrathecal therapy is being employed.

Although pneumococcal meningitis sometimes responds favorably to some of the sulfonamides when administered systemically, penicillin offers the additional advantage of an effective chemotherapeutic agent which may be injected intrathecally. In this manner a very high concentration may safely be maintained at the site of infection.

The amounts of penicillin employed in these experiments should not be taken as a guide to dosage in human beings. Penicillin may produce a moderately severe irritative meningeal reaction when injected intrathecally,¹ but Rammelkamp and Keefer⁶ have injected as much as 10,000 units into the lumbar subarachnoid space in normal men without serious after-effects. Similarly, intravenous and intramuscular dosage should be much larger and more frequent than in these experiments.

SUMMARY

The effects of intrathecal administration of penicillin in Type I pneumococcal meningitis have been studied in 96 experiments on dogs.

This method of therapy, even with small dosage, was found to reduce the mortality rate and prolong the survival time.

The beneficial effects of intrathecal therapy were markedly increased by the addition of the intravenous administration of penicillin (since secondary infection of the blood stream was invariably present and lobar pneumonia frequently developed if intravenous therapy were not employed).

REFERENCES


* One additional treated dog, apparently recovering, after repeated negative cultures, was sacrificed and discarded because of suspected rabies.