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Chemotherapy of Pneumococcal (Type II) Meningitis in the Rat.

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While it has been shown that sulfanilamide produced a high percentage of cures in mice,[1-5] rats,[3, 5-9] and rabbits[10, 11] infected by different routes with pneumococci (Types I, II, III, VII, and XIV), studies of experimental pneumococcal meningitis have not been reported, although successful sulfonamide therapy in human pneumococcal meningitis has been observed.[12, 13, 14]

In this report the results obtained in a preliminary series of 56 rats with Type II pneumococcal meningitis, produced by intracranial inoculation, are presented.

A 25-gauge needle, 3.0 mm long and attached to a tuberculin syringe, was pushed to the hilt through the carbolized skin and the skull of etherized rats at a point about 4 mm to the left of the sagittal suture and half way between eye and ear. The inoculum, consisting of 0.1 cc of an 18-hour broth culture (Binda strain) diluted 10^{-5}, was slowly injected. Two rats, similarly inoculated but with 0.1 cc of the same culture diluted 10^{-6}, died in less than 93 hours.

The progress of the infection was then determined by killing 2 rats 3 and 5 hours after inoculation. Direct smears from the spinal cords (lower lumbar portion) of the 3-hour rats were negative for pneumococci, but contained many polymorphonuclear leukocytes,

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3 Rosenthal, S. M., Bauer, H., and Branham, S. E., *Pub. Health Rep.*, 1937, **52**, 662.

4 Schmidt, L. H., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 205.

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6 Gross, P., and Cooper, F. B., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 225.

7 Gross, P., and Cooper, F. B., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 535.

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10 Locke, A., Locke, R. B., Bragdon, R. J., and Mellon, R. R., *Science*, 1937, **86**, 228.

11 Kreidler, W. A., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 146.

12 Neal, J. B., and Appelbaum, *Am. J. M. Sc.*, 1937, **195**, 175.

13 Tixier, L., Eck, M., and Grossiard, *Presse méd.*, 1938, **46**, 599.

14 Martin, R., *Presse méd.*, 1938, **46**, 599.

whereas the smears from the cords of the 5-hour rats contained in addition many pneumococci. Cultures from all 4 cords and the corresponding heart blood were positive with the exception of the blood of one 3-hour rat. These findings demonstrated that spinal meningitis was well established at the third hour.

Treatments were begun 6 hours following infection. A group of 15 rats were given 100 mg of sulfanilamide* and a second group of 15 were given 100 mg of 4,4'-di-(acetylamino)-diphenylsulfone,† both orally, and the third group of 20 rats were reserved as untreated controls. The 100 mg oral doses were given twice daily for 2 days and then once daily for 8 subsequent days.

The survivors were killed after 3 weeks and cultures and smears made of the heart blood and the distal portion of the lumbar cord from all animals.

All of the 20 control rats died within 68 hours following the inoculation and with an average survival time of 36.5 hours. Of the 15 sulfone-treated rats, 9 (60%) died with an average survival time of 68 hours. In the sulfanilamide-treated group only 4 (26.7%) died and the average survival time of these rats was 8.5 days.

All cultures of both blood and spinal cord of the control animals were positive. There was only one negative cord culture in the fatalities of the sulfone group, while all blood cultures were positive for pneumococci. Among the 4 fatalities of the sulfanilamide group, only one positive cord culture was obtained, although only one animal showed a negative blood culture. All blood and spinal cord cultures of the survivors were negative for pneumococci.

Histologically, the lesions of the rats that died consisted of a thick, fibrino-purulent, pial exudate involving the brain and the entire cord. The ventricles and the central canal of the cord contained pus and extensions of the purulent process into the brain and cord substance through ulcerated foci in the ependymal lining were demonstrable. In some rats there was also superficial cortical and more extensive cerebellar leukocytic infiltration.

Conclusions. A cerebro-spinal meningitis due to a Type II pneumococcus has been produced in the rat. Oral treatment with sulfanilamide, instituted after this disease was well established, resulted in 73.3% cures; with 4,4'-di-(acetylamino)-diphenylsulfone, 40% cures, and with no treatment, 100% fatality. It is quite evident that the sulfone compound was not as effective against this pneumococcal strain as sulfanilamide.

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† Synthesized and donated to us by the Monsanto Chemical Company, St. Louis, Missouri.