

Cure of Experimental Staphylococcal Meningitis.*

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Purulent meningitis was induced in rabbits, employing a technical procedure essentially the same as that of Felton¹ and Wegeforth, by intracisternal injection of *Staphylococcus aureus*, using cultures of a strain (Sca) derived from human meningitis and also cultures of the same strain after rabbit passage (237). Some of these animals were then subjected to treatment with bacteriophage, sulfathiazole or with both these agents.

Table I presents briefly the results in a preliminary group of 6 rabbits. The untreated controls died on the second day. The other 4 animals were treated with bacteriophage, beginning a few hours after inoculation. Only one survived, Rabbit 261, apparently the pioneer observation of recovery from experimental staphylococcal meningitis. The culture strain Sca, maintained on agar slants, gradually lost virulence so that not every control animal inoculated with a minute dose would die of meningitis.

The results in a group of 10 rabbits inoculated with strain 237 on March 31 are shown in Table II. The 4 untreated control animals all died of meningitis by the 5th day. The other 6 animals were treated

TABLE I.

Experiment 8. All rabbits were inoculated with 0.2 cc bacterial suspension, representing 11,000 living cocci of *Staphylococcus aureus*, Sca, into the cisterna magna, while under deep ether anesthesia on February 3, 1942. All these animals had positive cultures of fluid withdrawn by cisternal tap on February 5. Two controls (C) were untreated; the others were treated with bacteriophage. (I) inoculation; (T) treatment; (D) death; (L) lived.

	Feb. 3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
225 C	I		D				hemorrhage; meningitis; culture	positive										
260 C	I		D															
228 T	I	T	TD				hemorrhage;											
227 T	I	T	T	TD														
226 T	I	T	T	TD														
261 T	I	T	T	T	T	T	T	T	T	T	T							

accidental death

L
cisternal tap Feb. 18; culture negative

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¹ Weed, Lewis H., Wegeforth, Paul, Ayer, James B., and Felton, Lloyd D., *Monographs of the Rockefeller Institute for Medical Research*, No. 12, 1920, 5.

TABLE II.

Experiment 16. All rabbits were inoculated with 0.2 cc bacterial suspension representing 21,000 living cocci of *Staphylococcus aureus*, 237, into the cisterna magna, while under deep ether anesthesia on March 31, 1942. All these animals had positive cultures of fluid withdrawn by cisternal tap on April 1. Four controls (C) were untreated; the others were treated with sulfathiazole. (I) inoculation; (T) treatment; (D) death; (L) lived.

	Mar. 31	Apr. 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
935 C		I	D						meningitis;							positive
941 C		I	D						"				"			"
944 C		I			D				"			"	"			"
993 C		I			D				"			"	"			"
930 T		I	T	TD					"			"	"			"
936 T		I	T	T	D				"			"	"			"
928 T		I	T	T	T	TD			"			"	"			"
969 T		I	T	T	T	T	D		"			"	"			"
965 T		I	T	T	T	T	T	D	"			"	"			"
959 T		I	T	T	T	T	T		negative cisternal fluid 4/14							L

with sulfathiazole beginning on the day of inoculation, and of these 5 died of meningitis and one survived.

Other experiments, in which this same culture strain was used and both bacteriophage and sulfathiazole were administered revealed a sharper contrast between treated and untreated animals.

Table III indicates briefly the result in one such experiment. All 4 of the untreated controls developed purulent meningitis and were dead on the 4th day. The 3 treated late with bacteriophage and sulfathiazole were likewise all dead on the 4th day. Of the 4 treated

TABLE III.

Experiment 13. All rabbits were inoculated with 0.2 cc bacterial suspension, representing 21,000 living cocci of *Staphylococcus aureus*, 237, into the cisterna magna, while under deep anesthesia, on March 10, 1942. All these animals had positive cultures of fluid withdrawn by cisternal tap on March 12. Four controls (C) were untreated; 4 were treated early with sulfathiazole and bacteriophage; 3 were treated late with the same agents. (I) inoculation; (T) treatment; (D) death; (L) lived. Cisternal fluids of rabbits 285, 286 and 287, taken March 23, were negative on culture.

	Mar. 10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
293 C		I		D										meningitis;				positive
292 C		I		D										"				"
294 C		I		D										"				"
295 C		I		D										during tap;	"			"
289 T		I	T	D										meningitis;	"			"
288 T		I	T	T	D									"				"
290 T		I	T	T	D									"				"
284 T		I	T	T	TD									during tap; hemorrhage;				
														meningitis; culture positive				
285 T		I	T	T	T	T	T	T	T	T	T	T	T	—	} cis- ternal fluids			L
286 T		I	T	T	T	T	T	T	T	T	T	T	T	—				L
287 T		I	T	T	T	T	T	T	T	T	T	T	T	—				L

within a few hours after inoculation, 1 died of hemorrhage from injury by cisternal tap, but the other 3 survived and on the 14th day of the experiment all 3 had negative cisternal fluids, sterile on culture. The protocol of one of these animals may serve to illustrate the rather strenuous therapeutic program.

Rabbit 286 was subjected to cisternal tap on March 10, with removal of 1 cc clear fluid and intracisternal injection of 0.2 cc bacterial suspension (21,000 living cocci). He was in good condition after the tap. After an interval of $4\frac{1}{2}$ hours, treatment was begun and on this first day sodium sulfathiazole, 500 mg, was given by intravenous injection, sulfathiazole, 250 mg, intraperitoneally and bacteriophage, 100 cc, intravenously in 5 doses. On March 11, sodium sulfathiazole, 250 mg, was given intravenously, sulfathiazole, 250 mg, intraperitoneally and bacteriophage, 40 cc, in 2 intravenous doses. On March 12 there was generalized tremor. Cisternal tap yielded 0.2 cc bloody fluid containing many pus cells with rich growth of *Staphylococcus aureus* in 24 hours. The animal was distinctly weaker after the tap. Again sodium sulfathiazole, 750 mg, intravenously in 2 doses, and sulfathiazole, 250 mg, intraperitoneally, were given during the day as well as 100 cc bacteriophage in 5 intravenous doses. At the end of the day the rabbit was weaker, tense and jittery. On March 13 he appeared very weak but was again able to eat. Two intravenous injections of sodium sulfathiazole, each 250 mg, were given and also 2 intravenous doses of bacteriophage, each 20 cc. On March 14, sodium sulfathiazole, 250 mg, was given intravenously and 40 cc bacteriophage in 2 intravenous injections. The animal was much improved. For the next 3 days he received only one daily intravenous injection of 20 cc bacteriophage and on March 18, 19 and 20, only one daily injection of 10 cc, followed by an injection of 20 cc on March 21. After a free interval of 2 days a cisternal tap on March 23 yielded 0.2 cc clear fluid, the culture of which remained sterile. The animal has remained well, without sequelae.

Table IV summarizes the preliminary group of experiments with staphylococcal strain Sca. The later experiments in which the more satisfactory strain 237 was employed are summarized in Table V. The efficiency of the combined treatment with bacteriophage and sulfathiazole was very striking, especially when the animal survived the 3rd day.

Further studies will undoubtedly permit simplification of the therapeutic program and will probably permit a larger proportion of recoveries. Intrathecal injection of the therapeutic agents has shown

TABLE IV.

Summary of Experimental Staphylococcal Meningitis in 49 Rabbits Inoculated by Cisternal Puncture with Bacterial Strain Sea.

	Day of death											Meningitis	
	1	2	3	4	5	6	7	8	9	10	Later	Died	Lived
Untreated	—	1	4	4	1	—	—	1	—	—	2	13	4
Early Sulfathiazole	—	1	2	4	2	3	1	—	—	—	1	14	1
Early Bacteriophage	—	1	5	2	—	—	—	—	—	—	—	8	3
Late Sulfathiazole	—	2	2	—	—	—	—	—	—	—	—	4	0
Late Bacteriophage	—	—	1	1	—	—	—	—	—	—	—	2	0

TABLE V.

Summary of Experimental Staphylococcal Meningitis in 56 Rabbits Inoculated by Cisternal Puncture with Bacterial Strain 237.

	Day of death											Meningitis	
	1	2	3	4	5	6	7	8	9	10	Later	Died	Lived
Untreated	—	7	6	5	2	—	3	—	—	—	—	23	0
Early Sulfathiazole	—	1	1	1	1	—	—	1	—	—	—	5	1
Early Sulfathiazole and Bacteriophage	1	7	5	—	—	—	—	—	—	—	—	13	9
Late Sulfathiazole and Bacteriophage	—	1	1	2	1	—	—	—	—	—	—	5	0

promising results, in spite of the risk of death by trauma in the presence of increased vascularity incident to the disease in animals with such small cisternal spaces. The timing of the doses and the sympathetic care of the animals has seemed important.

These observations are in accord with our knowledge of human staphylococcal meningitis,² which, until recently, has been almost invariably fatal.

² MacNeal, Ward J., *N. Y. State J. Med.*, 1941, **41**, 1531; Weary, Willard B., and Lyons, John J. A., *N. Y. State J. Med.*, 1941, **41**, 2124; MacNeal, Perry S., and Foster, D. Bernard, *Am. J. Med. Sci.*, 1941, **202**, 874.