13679 P

Therapeutic Effect in Guinea Pigs of Hyperimmune Epidemic Typhus Antiserum.

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Although some studies[1] have been made of the properties of the sera of animals hyperimmunized with murine-typhus rickettsiæ, it has only recently been possible to get enough epidemic-typhus rickettsiæ for the preparation of a promising epidemic-typhus antiserum. A year ago we[2] pointed out that an antiserum of high neutralizing power could be produced by injecting rabbits with yolk-membrane suspensions from chick embryos infected with Breinl strain of typhus rickettsiæ inoculated according to the method of Cox.[3] A similar serum[4] made by injecting horses and donkeys with epidemic-typhus-diseased mouse-lungs has also been described. The present note records some preliminary studies of the therapeutic value in guinea pigs of our rabbit antiserum.

Topping[5] has shown that a good Rocky Mountain spotted-fever antiserum has a clearly demonstrable therapeutic value when injected into infected guinea pigs and monkeys. His original serum was made with an antigen prepared from infected ticks, but we have found[2] that a serum of powerful neutralizing titer can be made from spotted fever-infected egg-membranes. It is easy to show that rabbit antiserum prepared with this egg-propagated antigen has the same therapeutic value in guinea pigs that Topping[5] has described for the tick-antigen serum. Administration of these hyperimmune sera to guinea pigs infected with a virulent strain of Rocky Mountain spotted fever does not immediately suppress the febrile reaction and other clinical symptoms of the disease; instead, it shortens the febrile reaction and leads to prompt recovery of animals which otherwise would usually die. A similar modifying, rather than immediately curative, action is to be expected from the administration of typhus

1 Nicolle and Blaizot, *Ann. Inst. Pasteur*, 1916, **30**, 446; Zinsser, H., and Castaneda, *J. Exp. Med.*, 1933, **57**, 391.

2 Kurotchkin, T. J., van der Scheer, J., and Wyckoff, R. W. G., PROC. SOC. EXP. BIOL. AND MED., 1940, **45**, 323.

3 Cox, H. R., *U. S. Public Health Rep.*, 1938, **53**, 2241.

4 Durand, P., and Balozet, L., *Arch. Inst. Pasteur* (Tunis), 1940, **29**, 363; 1941, **30**, June.

5 Topping, N. H., *U. S. Public Health Rep.*, 1940, **55**, 41.

antiserum to epidemic typhus-diseased guinea pigs. Our experiments clearly demonstrate that such a positive therapeutic effect can be obtained.

In these experiments, guinea pigs have been infected by the intra-abdominal injection of typhus-diseased guinea-pig brain (Breinl strain*). Some of these infected animals were left untreated to serve as controls. Others received a single subcutaneous injection of ½ cc of a refined hyperimmune rabbit-serum concentrate (total protein = 7%). This serum was administered after an interval of

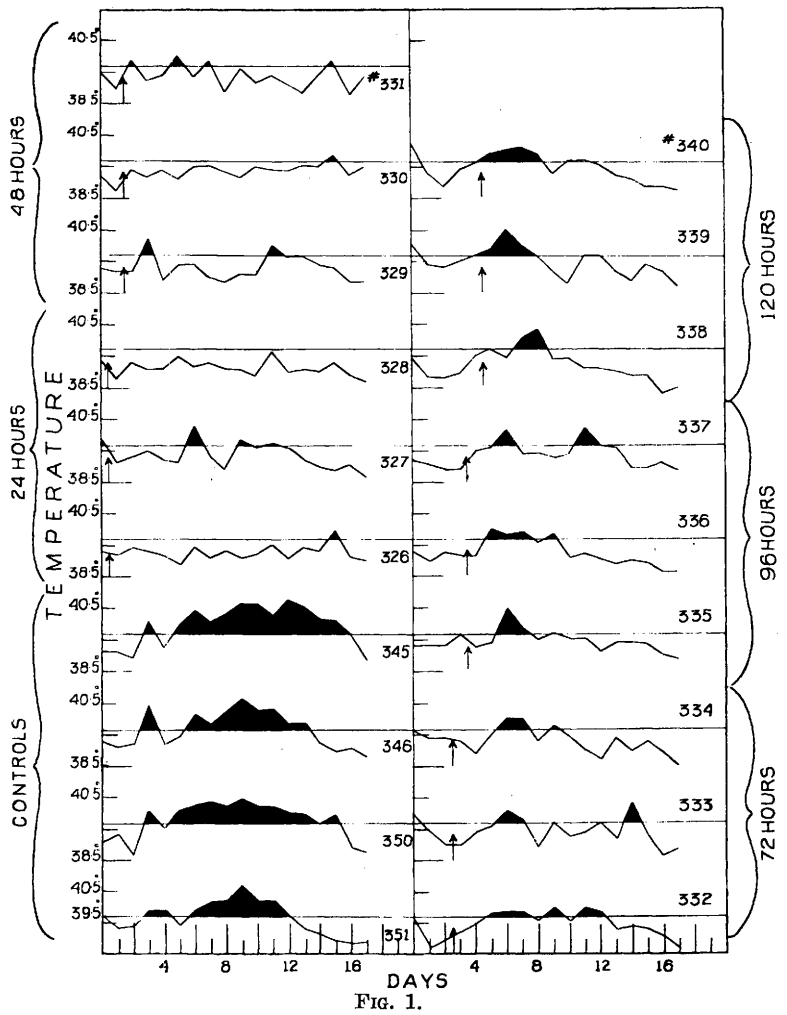

FIG. 1.

* Obtained from the U. S. National Institute of Health and carried serially through guinea pigs.

TABLE I.

Guinea pig No.	cc of serum	Serum × hrs after infection, hrs	Area under fever curve	Guinea pig No.	cc of serum	Serum × hrs after infection, hrs	Area under fever curve
U 45	0	—	173	344	0	—	144
46	0	—	152	345	0	—	254
47	0	—	165	346	0	—	133
48	0	—	88	347	0	—	101
49	0	—	173	349	0	—	178
50	0	—	110	350	0	—	150
51	0	—	165	351	0	—	121
52	0	—	252	326	.5	24	0
53	.5	24	30	327	.5	24	4
54	.5	24	20	328	.5	24	0
55	.5	24	5	329	.5	48	22
56	.5	24	12	330	.5	48	0
57	.5	48	2	331	.5	48	16
58	.5	48	10	332	.5	72	32
59	.5	48	0	333	.5	72	30
60	.5	48	26	334	.5	72	18
61	.5	72	31	335	.5	96	26
62	.5	72	40	336	.5	96	18
63	.5	72	12	337	.5	96	21
64	.5	72	30	338	.5	120	28
65	.5	96	19	339	.5	120	39
66	.5	96	20	340	.5	120	36
67	.5	96	0				
68	.5	96	0	Avg	0	—	155
				”	.5	24	1
Avg	0	—	160	”	.5	48	13
”	.5	24	17	”	.5	72	27
”	.5	48	10	”	.5	96	22
”	.5	72	28	”	.5	120	34
”	.5	96	10				

from one to 5 days following injection of virus. Temperatures were taken on all animals for a period of 18 days and the height and duration of the febrile reaction were taken as a measure of the severity of infection. In all experiments a uniform infecting dose of virus was used. This consisted of 1 cc of a freshly prepared 10% suspension in saline of a guinea-pig brain harvested on the third day of fever. In the present series of experiments serum was administered from 1 to 5 days after infection. Other experiments are now under way in which serum is being given at still longer intervals following virus administration.

Three experiments have thus far been carried out, with similar results in each case. Febrile curves from one series are reproduced in Fig. 1. It is obvious from them that serum administered after infection has a well-defined effect upon the course of an epidemic-typhus infection in the guinea pig. In order to find out how great an interval may be allowed to elapse between infection and injection of serum before this effect is no longer demonstrable, it is clearly

necessary to have some sort of quantitative measure of the febrile reaction. This is most simply obtained by determining with a planimeter areas under the febrile portion of the temperature-curve. Such areas from the experimental series illustrated in Fig. 1 and from a second similar series are listed in Table I. Throughout this work a guinea pig is considered to be febrile whenever its temperature exceeds 39.7°C. The data from the third series of experiments are less complete because of seriously interfering intercurrent infection in the available guinea pigs; none of the results of this third series, however, conflicts in any respect with those outlined above. It is obvious from the foregoing that serum administered as much as 5 days following infection has a positive therapeutic effect in guinea pigs diseased with epidemic typhus.

13680 P

Lesions Produced with Sulfadiazine.*

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This study was undertaken to note the effects of sulfadiazine on the tissues of the dog.

Changes apparently due to the sulfonamides have been reported in man and in experimental animals by several investigators.[1-7] Some of the changes observed by us have not been hitherto described.

Eight dogs, weighing from 8.2 to 16.4 kg, were used. In a 20% aqueous solution, one-tenth g of sodium sulfadiazine per kg of animal weight was injected subcutaneously twice daily. Tissues were examined from 6 to 21 days after the initial dose of this drug.

* The sodium sulfadiazine used in this experiment was supplied by Lederle Laboratories, Inc.

1 French, A. J., and Weller, C. V., *Am. J. Path.*, 1942, **1**, 109.

2 Antopol, W., and Robinson, H., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 428; *Ibid., Arch. Path.*, 1940, **29**, 67.

3 Antopol, W., Lehr, D., Churg, J., and Sprinz, H., *Arch. Path.*, 1941, **31**, 592.

4 Stryker, W. A., *J. A. M. A.*, 1940, **114**, 953.

5 Davis, H. A., and Higgins, G. M., *Am. J. M. Sc.*, 1939, **198**, 804.

6 Toomey, J. A., Reichle, H. S., and Takacs, W. S., *J. Pediat.*, 1940, **16**, 179.

7 Machella, T. E., and Higgins, G. M., *Am. J. M. Sc.*, 1939, **198**, 804.