FURTHER OBSERVATIONS ON THE RÔLE OF THE TWORT-D'HERELLE PHENOMENON IN THE EPIDEMIC SPREAD OF MOUSE-TYPHOID[1].

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(With 1 Chart.)

In a recent report (Topley, Wilson and Lewis, 1925) we described some observations on the rôle of the Twort-d'Herelle phenomenon in the epidemic spread of mouse-typhoid. In the experiments there recorded the lytic filtrate was administered by the mouth. The results obtained did not suggest that such administration exerted any appreciable influence on the spread of disease. It was shown, in a separate series of experiments, that intraperitoneal inoculation of such a filtrate afforded a marked degree of protection against subsequent inoculation of living cultures of *B. aertrycke*, provided that sufficient time had elapsed to allow of an immunising response, that no *immediate* protection was afforded by the inoculation of the lytic filtrate, and that neither immediate protection, nor subsequent immunisation, was afforded by the administration of the lytic filtrate by the mouth.

Before describing the present investigation, we would recall the results of two earlier series of experiments. It was found (Topley and Wilson, 1923) that active immunisation of mice, by intraperitoneal inoculation with killed cultures of *B. aertrycke*, afforded some protection against subsequent mouse-to-mouse infection, since it appeared to be difficult to initiate an epidemic of a mouse-typhoid amongst a population, each individual of which had been actively immunised in this way. There was no evidence, however, that the relative immunity of such mice would save them from infection and death, if they formed part of a herd containing susceptible animals, among which an epidemic was actively spreading.

In another series of experiments (Topley, 1922), the dispersal of a population into small groups, during the pre-epidemic stage of the spread of infection, resulted in a great decrease in mortality during the period of dispersal. The subsequent reaggregation of these small groups was followed by a further series of deaths from the specific infection, but the final mortality was markedly less than among similar groups which had been maintained undispersed throughout the whole epidemic period.

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The experiments recorded in the present report were designed to answer the following questions:

(*a*) Will the inoculation of a mouse-population with a lytic filtrate of *B. aertrycke*, during the rise of an epidemic wave of mouse-typhoid, check the epidemic immediately, as the result of a direct action of the lytic principle on the infecting bacteria?

(*b*) Will such inoculation produce an immunising response, sufficiently rapid, and sufficient in degree, to slow the epidemic in its later stages, and to reduce the final mortality?

(*c*) If neither of these effects be produced in a large herd maintained as one experimental unit, will an opportunity for successful immunising response be afforded by dispersing the population into small groups during the early stages of the epidemic, and reaggregating it during the later stages?

The experiment was carried out as follows. An epidemic of mouse-typhoid was started by feeding 80 mice on a culture of *B. aertrycke*, known to be sensitive to the lysin employed. Three weeks later, when several deaths from mouse-typhoid had occurred, 420 normal mice were added to the 60 survivors. During the following week there were 45 deaths among these 420 normal mice, due to *B. aertrycke* infection, showing that an epidemic was well under way.

At the end of this period 360 survivors from the 420 mice were treated as follows:

(*a*) Ninety mice were placed in a single experimental cage, and each mouse was inoculated intraperitoneally with 0·25 c.c. of a lytic filtrate of *B. aertrycke*. This herd was entered in the records as Series P 1.

(*b*) Ninety mice were placed in a similar cage, but were not inoculated. This herd was entered in the records as Series C 1.

(*c*) Ninety mice were inoculated in the same way as Series P 1, but were then dispersed into 18 groups of 5 mice each, housed in separate cages. This herd was entered in the records as Series P 2.

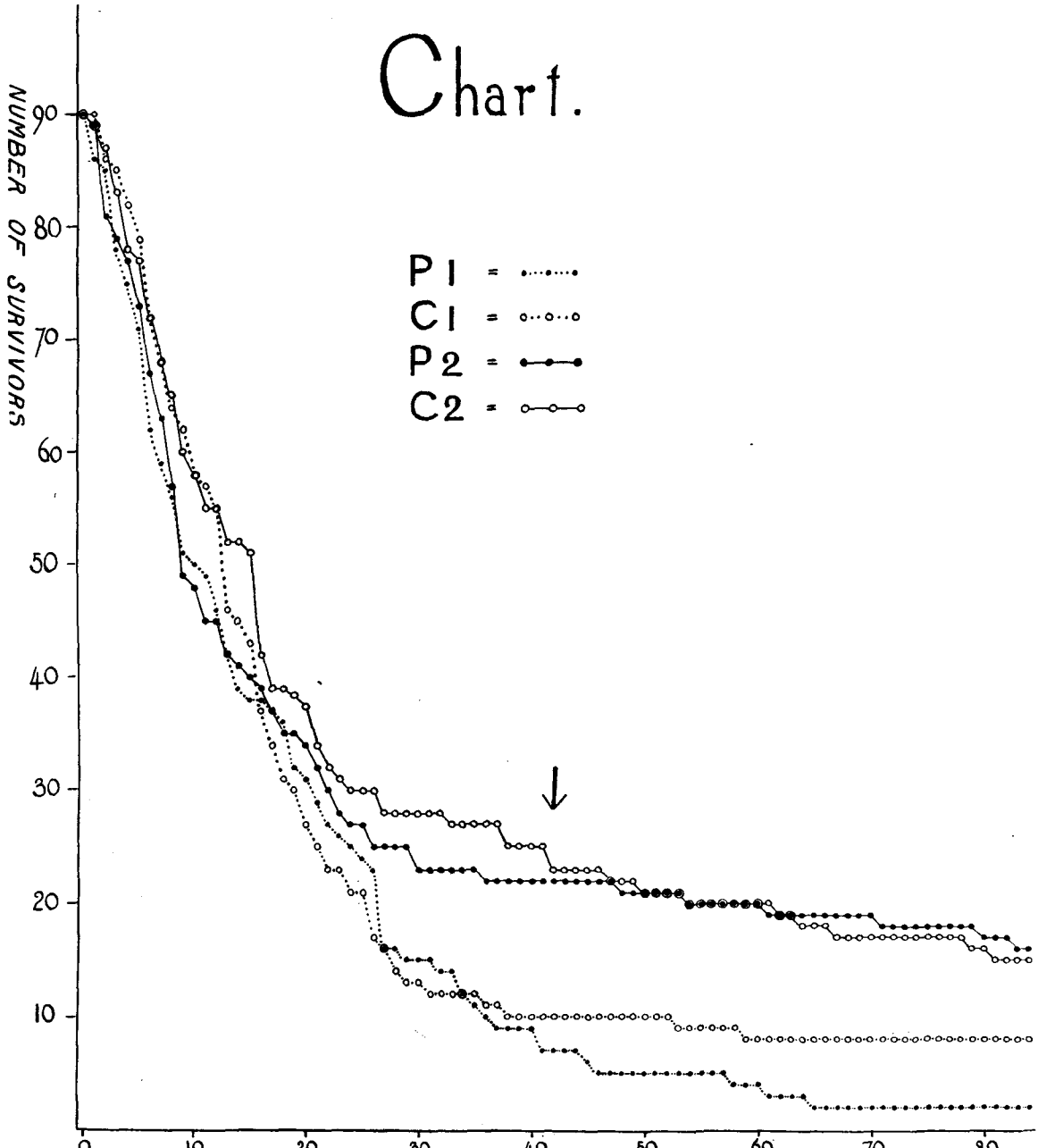
(*d*) Ninety mice were dispersed as in Series P 2, but were not inoculated. This herd was entered in the records as Series C 2.

The survivors from herds P 1 and P 2 were inoculated with the same dose of the same lytic filtrate one week later.

The survivors from Series P 2 and C 2 were reaggregated into single herds on the 42nd day of the experiment.

The whole series of epidemics were observed over a period of 84 days. All mice which died, and which were not devoured by their companions, were submitted to the usual post-mortem examination. The cultures from the heart and spleen were examined for the presence of an active lysin, as well as for the presence of *B. aertrycke*.

On the 84th day the faeces of the surviving mice were examined for the presence of a lytic principle, active against *B. aertrycke*, with negative results. The survivors were then killed, cultures were taken from the spleen, and were examined for the presence of *B. aertrycke*, and for an active lysin. The



↓ P_2 AND C_2 REAGGREGATED ON 42ND DAY.

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technique employed was identical with that described in previous reports, and need not be repeated here.

The results are recorded in Chart 1 and Tables I and II, and need little additional comment.

Table I.

	Herd							
	P 1		C 1		P 2		C 2	
Day	Number living	Deaths	Number living	Deaths	Number living	Deaths	Number living	Deaths
0	90	—	90	—	90	—	90	—
1	86	4	90	0	89	1	89	1
2	85	1	86	4	81	8	87	2
3	78	7	85	1	79	2	83	4
4	75	3	82	3	77	2	78	5
5	71	4	79	3	73	4	77	1
6	62	9	72	7	67	6	72	5
7	59	3	68	4	63	4	68	4
8	56	3	64	4	57	6	65	3
9	51	5	62	2	49	8	60	5
10	50	1	58	4	48	1	58	2
11	49	1	57	1	45	3	55	3
12	46	3	55	2	45	0	55	0
13	42	4	46	9	42	3	52	3
14	39	3	45	1	41	1	52	0
15	38	1	43	2	40	1	51	1
16	38	0	37	6	39	1	42	9
17	37	1	34	3	37	2	39	3
18	36	1	31	3	35	2	39	0
19	32	4	30	1	35	0	38	1
20	31	1	27	3	34	1	37	1
21	29	2	25	2	32	2	34	3
22	27	2	23	2	30	2	32	2
23	26	1	23	0	28	2	31	1
24	25	1	21	2	27	1	30	1
25	24	1	21	0	27	0	30	0
26	23	1	17	4	25	2	30	0
27	16	7	16	1	25	0	28	2
28	16	0	14	2	25	0	28	0
29	15	1	13	1	25	0	28	0
30	15	0	13	0	23	2	28	0
31	15	0	12	1	23	0	28	0
32	14	1	12	0	23	0	28	0
33	14	0	12	0	23	0	27	1
34	12	2	12	0	23	0	27	0
35	11	1	12	0	23	0	27	0
36	10	1	11	1	22	1	27	0
37	9	1	11	0	22	0	27	0
38	9	0	10	1	22	0	25	2
39	9	0	10	0	22	0	25	0
40	9	0	10	0	22	0	25	0
41	7	2	10	0	22	0	25	0
42	7	0	10	0	22	0	23	2
43	7	0	10	0	22	0	23	0
44	7	0	10	0	22	0	23	0
45	6	1	10	0	22	0	23	0
46	5	1	10	0	22	0	23	0
47	5	0	10	0	22	0	22	1
48	5	0	10	0	21	1	22	0
49	5	0	10	0	21	0	22	0
50	5	0	10	0	21	0	21	1
51	5	0	10	0	21	0	21	0
52	5	0	10	0	21	0	21	0
53	5	0	9	1	21	0	21	0
54	5	0	9	0	20	1	20	1
55	5	0	9	0	20	0	20	0

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Table I (*contd.*).

	Herd							
	P 1		C 1		P 2		C 2	
Day	Number living	Deaths	Number living	Deaths	Number living	Deaths	Number living	Deaths
56	5	0	9	0	20	0	20	0
57	5	0	9	0	20	0	20	0
58	4	1	9	0	20	0	20	0
59	4	0	8	1	20	0	20	0
60	4	0	8	0	20	0	20	0
61	3	1	8	0	19	1	20	0
62	3	0	8	0	19	0	19	1
63	3	0	8	0	19	0	19	0
64	3	0	8	0	19	0	18	1
65	2	1	8	0	19	0	18	0
66	2	0	8	0	19	0	18	0
67	2	0	8	0	19	0	17	1
68	2	0	8	0	19	0	17	0
69	2	0	8	0	19	0	17	0
70	2	0	8	0	19	0	17	0
71	2	0	8	0	18	1	17	0
72	2	0	8	0	18	0	17	0
73	2	0	8	0	18	0	17	0
74	2	0	8	0	18	0	17	0
75	2	0	8	0	18	0	17	0
76	2	0	8	0	18	0	17	0
77	2	0	8	0	18	0	17	0
78	2	0	8	0	18	0	17	0
79	2	0	8	0	18	0	16	1
80	2	0	8	0	17	1	16	0
81	2	0	8	0	17	0	15	1
82	2	0	8	0	17	0	15	0
83	2	0	8	0	16	1	15	0
84	2	0	8	0	16	0	15	0

Table II.

Showing the bacteriological results of the post-mortem examination of mice dying during these experiments.

	P 1	C 1	P 2	C 2
Number of mice exposed to risk	90	90	90	90
Number of mice which died during epidemic	88	82	74	75
Number examined P.-M.	83	74	73	71
Number from which *B. aertrycke* was recovered ...	77	74	70	69
Number from which an active lysin was recovered ...	0	0	2	0
Number of survivors	2	8	16	15
Number from whose spleens *B. aertrycke* was recovered	1	4	7	1
Number from whose spleens a lysin was recovered ...	0	0	0	0

DISCUSSION.

It is clear that the inoculation of this lytic filtrate, active against *B. aertrycke* when tested in the usual manner on cultures of that organism, had no effect in checking the course of these epidemics, either by the immediate action of the lytic principle itself, or as the result of an immunising response on the part of the tissues of the host. That this filtrate was capable of producing such a response was known from the results of previous experiments. It is, however, not a matter for surprise that such response was inoperative under the conditions of these experiments. Our earlier investigations had not led us to expect that active immunisation, during the rise of a severe epidemic wave, would lead to any marked reduction in mortality.

The effect of dispersal may be compared with the results of our earlier experiments (Topley, 1922). In those experiments dispersal was carried out during the pre-epidemic phase, and its effect was immediate. The mortality during the period of dispersal was greatly reduced. Reaggregation was, however, followed by a secondary series of deaths from mouse-typhoid. The final total mortality was 98 per cent. in the undispersed group, and 76 per cent. in the dispersed group. The specific mortality was more markedly in favour of the dispersed group. In the present experiment, in which dispersal was carried out after the pre-epidemic phase, and when the epidemic wave was rising towards its crest, the immediate effect of this procedure was slight. It became manifest later, and reaggregation was in this case followed by no appreciable secondary wave of mortality. The final death-rates were 97·7 per cent. and 91·1 per cent. among the undispersed groups and 82·2 per cent. and 83·3 per cent. among the dispersed groups. In this case the specific mortality did not differ significantly from the total mortality. It would seem that dispersal had an appreciable effect, even at this late stage, in increasing the final proportion of survivors; but it is much less efficacious in its immediate results than when carried out during the pre-epidemic phase.

The almost complete absence of the lytic principle from the tissues of the infected mice is a matter of some interest. Comparing these results with those obtained in a previous investigation (Topley, Wilson and Lewis, 1925) it would appear that administration of a lytic filtrate by the mouth is a far more effective method of ensuring its presence in the infected tissues, together with the homologous bacterium, than is its administration by intraperitoneal inoculation.

Conclusion.

With the lytic filtrate and the sensitive strain of *B. aertrycke* employed in these experiments there was no evidence that the intraperitoneal inoculation of the filtrate, during the period covered by the rise of the epidemic wave, had any appreciable effect on the subsequent course of the epidemic.

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