ON THE MECHANISM OF PROTECTION AGAINST INFECTIVE DISEASE.

By M. GREENWOOD, E. M. NEWBOLD, W. W. C. TOPLEY and J. WILSON.

In the course of a paper by the present writers (this Journal, xxv, 336–53) an attempt was made to assess the relative importance of selective mortality on the one hand and sub-lethal infection on the other in increasing herd resistance to subsequent exposure to infection. The subject was further considered by one of us (E.M.N.) in a later report (this Journal, xxvi, 19–27).

Our plan of investigation was, briefly, this. We measured, by the method of correlation, the influence of the conditions experienced by a group of mice exposed to *Pasteurella* infection upon the fates of the survivors of this group when again exposed to infection. We asked ourselves, for instance, whether mice which had been exposed for a long time to a relatively mild infection (so far as mildness *can* be gauged by the rate of mortality) were more resistant to subsequent exposure than mice which had survived for a shorter time a more virulent infection. Put more technically and also more precisely, we determined whether the correlation between length of life in the second period and length of exposure in the first period for a constant rate of mortality in the first period were higher than the correlation between rate of mortality in the first period and length of life in the second period for a constant length of exposure in the first period. In one set of experiments (those relating to Cages *A* and *B*) the first and second exposures were in different cages; in the other set, and those now to be described, both periods of exposure were in the same cage.

Our analyses led to the conclusion that length of exposure rather than the severity of the conditions of exposure was the more important element of prognosis; hence, while fully alive to the ambiguities of interpretation inherent in data of this kind, we suggested that direct immunisation consequent upon passing through a non-lethal attack was a more important element of herd resistance than weeding out of susceptibles by a selective mortality, although we did not—and do not—slight the general importance of selection in the establishment of herd immunity.

The experiment which furnished the data for E. M. Newbold's analysis has been continued and has provided us with material for repeating the comparison under quite different pathological conditions. In this community, the Exp. 2 of our first paper, we distinguish three periods: 2 *a*, during which the rate of addition was 3 mice daily and the reigning epidemic pasteurellosis; 2 *b*, during which the rate of addition was 1 mouse daily and aertrycke infection eventually completely superseded pasteurellosis; 2 *c*, during which the

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rate of addition was 6 mice daily and no pasteurellosis occurred at all, aertrycke infection being the reigning epidemic disease. Hence the period 2 *a* was suitable for a study of, substantially, pure pasteurellosis conditions, 2 *c* could be used for a corresponding study of aertrycke conditions, while 2 *b* could not be used at all for the present purpose. As we shall show in a separate paper, the epidemiology of aertrycke infection is essentially different from that of pasteurellosis.

Without trenching upon that subject here, we may note that the two infections would be assigned to different categories on the basis of the character and distribution of the lesions in fatal cases, since these would seem to indicate an essential difference in the mode of infection, and its spread within the body. *Bact. aertrycke* gives rise to a disease which bears many resemblances to enteric infection in man, although the visceral lesions, and especially those in the liver, are more extensive: *Pasteurella muris* produces its most characteristic lesions in the lungs, pleura and pericardium, although an associated suppurative peritonitis is of frequent occurrence. On the basis of the pathological pictures in mice, together with our knowledge of the lesions which organisms of the paratyphoid and *Pasteurella* groups produce in other laboratory animals, we are probably justified in regarding *Bact. aertrycke* infection in the mouse as analogous to an acute intestinal infection in man, and pasteurellosis as an example of an acute respiratory disease. The available data also suggests that infection with *Bact. aertrycke* is less acute, and perhaps less fatal, than infection with *Past. muris*. If the inferences drawn from our earlier experiments on pasteurellosis were correct, we should, on general grounds, expect to find the seeming advantage of length, as compared with severity of exposure, to be emphasised in the epidemic period here recorded. We have had the whole of the calculations described in the earlier papers upon the aertrycke data applied to the present (2 *c*) and are, as before, greatly indebted to our colleagues Mr W. J. Martin and Miss C. Thomas for the care and skill with which they have carried out a most laborious set of computations.

Only what we have termed *specific deaths* were in question, viz. the deaths of mice who were proved at autopsy to have died of aertrycke infection or whose bodies had been devoured by their companions. Mice surviving from a previous phase and 120 mice killed for a special purpose were omitted. After-life time limited to a period of 60 days was brought under analysis. At the end of the phase of the experiment during which the daily immigrants numbered six, 199 inhabitants were alive and of these 147 subsequently died of aertrycke infection (together with some which could not be examined); these 199 mice were included in respect of their survivorship within the 6-mouse period of the experiment. Table I sets out the scope of the available observations.

Tables II and III contain the statistical constants.

The important coefficients from the present point of view are the second order correlations between length of after-life and previous exposure (death-rates constant) and length of after-life and death-rate during previous

Table I. *Numerical data of Exp.* 2 *c.*

(1) Length of previous exposure (days)	(2) No. of mice surviving this length of exposure	(3) No. of mice surviving this but not the next length of exposure	(4) No. of observations contributed by each mouse of column (3)	(5) Total no. of observations contributed
0	1887	175	1	175
10	1712	486	2	972
20	1226	677	3	2031
30	549	255	4	1020
40	294	81	5	405
50	213	33	6	198
60	180	23	7	161
70	157	157	8	1256
Totals	6218	1887	—	6218

exposure (length of previous exposure and death-rate during subsequent exposure constant), and it is seen that this study leads to coefficients confirmatory of the earlier findings; indeed, the importance of length of previous exposure in comparison with severity of exposure, *so far as it is capable of measurement by this technic*, is greater than before.

We must, however, warn the reader that this conclusion must not be pressed beyond the limits implicitly imposed upon it by the indirect nature of the reasoning. It is quite certain, for instance, that the advantage conferred by length of exposure does not increase indefinitely with length of exposure.

The apparently unfavourable effect of exposure to a high rate of mortality in the first period upon survival in the subsequent period must also, we think, not be regarded as unequivocal evidence against the value (from the herd standpoint) of selective mortality; it may be largely a reflection of the probable fact that the mean duration from time of infection to time of death of an aertrycke infection is longer than of a *Pasteurella* infection. The correlation-analysis of the relation between previous rate of mortality and subsequent survival must measure a heterogeneous effect. On the one hand, there is (on the hypothesis of selection) the *favourable* effect of a weeding out of susceptibles; on the other hand, there is the *unfavourable* effect due to the fact that when the death-rate is high, the infection-rate is probably high, so that in a period of high death-rate the proportion of animals who will die of infection *then acquired* increases and this will lead to an increase of the herd rate of mortality after an interval, equal to the average duration of attack, from the first point in time. Hence, all we can really infer is that, of these two factors, the latter is the more important.

As will be seen in Table IV, what may be called the mean severity of testing-exposure is not much less than that of 2 *a*, while the severity of ultimate exposure is the least of the three series.

We have already said that the pathological conditions of this study were quite different from those of the two previous studies; the same remark applies to the evolution of mortality rates with age. We do not propose to discuss that aspect at any length because it will form part of another paper, but a brief

Table II. *Correlation coefficients, total correlations.* (*Specific deaths only.*)

	Cages *A* and *B*			Cage 2 *a* (3-mouse period)			Cage 2 *c* (6-mouse period)		
	r	η^*	η^2-r^2	r	η	η^2-r^2	r	η	η^2-r^2
Length of after-life and length of previous exposure ...	0·214 ± 0·016	0·244 ± 0·016	0·014 ± 0·004	*0·015* 0·227 ± 0·009	*0·015* 0·252 ± 0·009	*0·003* 0·012 ± 0·002	*0·015* 0·180 ± 0·008	*0·014* 0·351 ± 0·008	*0·009* 0·091 ± 0·005
Length of after-life and average death-rate during previous exposure	0·119 ± 0·017	0·254 ± 0·016	0·052 ± 0·008	*0·016* −0·054 ± 0·010	*0·014* 0·328 ± 0·009	*0·010* 0·105 ± 0·006	*0·015* −0·203 ± 0·008	*0·014* 0·278 ± 0·008	*0·006* 0·036 ± 0·003
Length of after-life and average death-rate during after-life ...	−0·152 ± 0·017	0·237 ± 0·016	0·033 ± 0·006	*0·012* −0·469 ± 0·008	*0·012* 0·508 ± 0·007	*0·006* 0·039 ± 0·004	*0·014* −0·272 ± 0·008	*0·013* 0·430 ± 0·007	*0·010* 0·111 ± 0·006
Length of after-life and "total"† previous exposure	0·237 ± 0·016	0·241 ± 0·016	0·002 ± 0·001	*0·016* 0·083 ± 0·010	*0·015* 0·259 ± 0·009	*0·008* 0·060 ± 0·005	*0·015* 0·087 ± 0·008	*0·014* 0·327 ± 0·008	*0·010* 0·099 ± 0·005
Length of after-life and average death-rate during previous exposure for the last 10 days before "transfer"	0·110 ± 0·017	0·186 ± 0·016	0·022 ± 0·005	*0·016* −0·078 ± 0·010	*0·013* 0·383 ± 0·009	*0·012* 0·141 ± 0·007	*0·015* −0·183 ± 0·008	*0·015* 0·238 ± 0·008	*0·005* 0·023 ± 0·003
Length of previous exposure and average death-rate during previous exposure	0·410 ± 0·014	0·802 ± 0·006	0·475 ± 0·024	*0·014* 0·326 ± 0·009	*0·007* 0·721 ± 0·005	*0·020* 0·414 ± 0·013	*0·012* 0·499 ± 0·006	*0·009* 0·651 ± 0·005	*0·013* 0·175 ± 0·007
Length of previous exposure and average death-rate during after-life	0·047 ± 0·017	0·158 ± 0·017	0·023 ± 0·005	*0·015* −0·198 ± 0·010	*0·015* 0·256 ± 0·009	*0·005* 0·026 ± 0·003	*0·016* 0·005 ± 0·009	*0·015* 0·141 ± 0·008	*0·004* 0·020 ± 0·002
Length of previous exposure and average death-rate during previous exposure for the last 10 days before "transfer" ...	0·453 ± 0·014	0·758 ± 0·007	0·370 ± 0·021	*0·014* 0·343 ± 0·009	*0·008* 0·701 ± 0·005	*0·019* 0·373 ± 0·012	*0·011* 0·543 ± 0·006	*0·009* 0·633 ± 0·005	*0·010* 0·106 ± 0·006
Average death-rate during after-life and average death-rate during previous exposure for the period of exposure ...	0·026 ± 0·017	0·422 ± 0·014	0·178 ± 0·014	*0·015* 0·193 ± 0·010	*0·012* 0·468 ± 0·008	*0·013* 0·182 ± 0·009	*0·014* 0·271 ± 0·008	*0·011* 0·513 ± 0·006	*0·014* 0·190 ± 0·007
Average death-rate during after-life and "total"† previous exposure	−0·083 ± 0·017	0·285 ± 0·016	0·075 ± 0·009	*0·016* 0·075 ± 0·010	*0·014* 0·336 ± 0·009	*0·010* 0·107 ± 0·007	*0·015* 0·145 ± 0·008	*0·014* 0·307 ± 0·008	*0·008* 0·073 ± 0·005
Average death-rate during after-life and average death-rate during previous exposure for the last 10 days before "transfer"	−0·051 ± 0·017	0·339 ± 0·015	0·113 ± 0·015	*0·015* 0·193 ± 0·010	*0·012* 0·483 ± 0·008	*0·014* 0·196 ± 0·009	*0·014* 0·260 ± 0·008	*0·012* 0·493 ± 0·006	*0·013* 0·176 ± 0·007

* The variable that was found in terms of the other is given first.

η's were corrected by the formula $\eta^2 = \dfrac{(\text{crude } \eta^2) - \frac{K-3}{N}}{1 - \frac{K-3}{N}}$, where K = no. of groups.

† This is a rather arbitrary measure given by the product of the length of previous exposure and the average death-rate during it.

The figures for the probable errors were calculated using N = total no. of observations.

The italicised figures for the probable errors were calculated using N = the actual no. of mice. The true probable error lies between these two.

Specific deaths for Cages *A* and *B* and Cage 2 *a* (3-mouse period) = *Pasteurella* + N.E. and for Cage 2 *c* (6-mouse period) = *B. aertrycke* + N.E.

Table III. *Partial correlations.* (*Specific deaths only.*)

	Cages *A* and *B*	Cage 2 *a* (3-mouse period)	Cage 2 *c* (6-mouse period)
	r	*r*	*r*
1st order.			
Length of after-life and length of previous exposure (keeping constant death-rate during previous exposure)	0·185 ± 0·016	*0·015* 0·259 ± 0·009	*0·014* 0·331 ± 0·008
Length of after-life and death-rate during previous exposure (keeping constant length of previous exposure)	0·027 ± 0·017	*0·015* − 0·139 ± 0·010	*0·014* − 0·343 ± 0·008
Length of after-life and length of previous exposure (keeping constant death-rate during after-life)	0·224 ± 0·016	*0·015* 0·155 ± 0·010	*0·015* 0·188 ± 0·008
Length of after-life and death-rate during previous exposure (keeping constant death-rate during after-life)	0·117 ± 0·017	*0·016* 0·042 ± 0·010	*0·015* − 0·139 ± 0·008
Length of after-life and "total" previous exposure (keeping constant death-rate during after-life)	0·228 ± 0·016	*0·015* 0·134 ± 0·010	*0·015* 0·132 ± 0·008
Length of after-life and death-rate during previous exposure for 10 days before "transfer" (keeping constant death-rate during after-life)	0·119 ± 0·017	*0·016* 0·014 ± 0·010	*0·015* − 0·121 ± 0·008
Length of after-life and death-rate during previous exposure for 10 days before "transfer" (keeping constant length of previous exposure)	0·015 ± 0·017	*0·015* − 0·171 ± 0·010	*0·014* − 0·340 ± 0·008
Length of previous exposure and death-rate during previous exposure for 10 days before "transfer" (keeping constant death-rate during after-life)	0·452 ± 0·014	*0·013* 0·396 ± 0·008	*0·011* 0·561 ± 0·006
Length of previous exposure and average death-rate for previous exposure (keeping constant death-rate during after-life)	0·410 ± 0·014	*0·013* 0·379 ± 0·009	*0·011* 0·517 ± 0·006
2nd order.			
Length of after-life and length of previous exposure (keeping constant death-rate during previous exposure and death-rate during after-life)	0·194 ± 0·016	*0·015* 0·150 ± 0·010	*0·014* 0·307 ± 0·008
Length of after-life and death-rate during previous exposure for the last 10 days before "transfer" (keeping constant length of previous exposure and death-rate during after-life) ...	0·021 ± 0·017	*0·016* − 0·052 ± 0·010	*0·014* − 0·278 ± 0·008
Length of after-life and death-rate during previous exposure (keeping constant length of previous exposure and death-rate during after-life)	0·029 ± 0·017	*0·016* − 0·018 ± 0·010	*0·014* − 0·282 ± 0·008
Multiple correlations. Length of after-life with length of previous exposure and average death-rate during previous exposure	0·215*	0·228	0·382
Multiple partial correlations†. Length of after-life with length of previous exposure and average death-rate during previous exposure (keeping constant multiple average death-rate during after-life)	0·225	0·396	0·510

* Root mean square value for independence by Yule's formula $\sqrt{\frac{n-1}{N}}$, where n = no. of variables and N = no. of observations, is for Cages *A* and *B* 0·036, for Cage 2 *a* (3-mouse period) 0·021 and for Cage 2 *c* (6-mouse period) 0·018.

† Found from the formula $r_{2(13)\cdot 4} = \frac{r_{2(13)} - r_{42} r_{4(13)}}{\sqrt{(1 - r^2_{24})(1 - r^2_{4(13)})}}$.

Table IV. *Average Specific Death-rate per mouse per day in each experiment.*

	Whole period	Average of all periods of previous exposure	Average of all periods of subsequent exposure
Cage 2 *c* (6-mouse period)	0·0204	0·014	0·022
Cage 2 *a* (3-mouse period)	0·0366	0·019	0·042
Cage *A*	0·0212	0·009	—
Cage *B*	0·0297	—	0·031

discussion is relevant to the present topic. In Table V we give the probabilities of dying within 5 days from day 0, 5, 10, etc., extracted from complete life tables (all deaths) of which that relating to 2 *a* has already been published.

Table V. *Probability of dying in the next five days. Deduced from the Life Tables constructed from the three populations*, viz. 3-*mouse Period* (2 *a*); 1-*mouse Period* (2 *b*); 6-*mouse Period* (2 *c*).

Day	2 *a*	2 *b*	2 *c*	2 *a*	2 *b*	2 *c*
0	0·1969	0·1177	0·0230	62	62	7
5	0·2774	*0·1888*	0·0575	87	100	18
10	0·2567	0·1618	0·1079	80	86	34
15	*0·3200*	0·1578	0·1564	100	84	49
20	0·2607	0·1560	0·2496	81	83	78
25	0·1785	0·1159	*0·3185*	56	61	100
30	0·1295	0·0698	0·2638	40	37	83
35	0·1070	0·1583	0·1473	33	83	46
40	0·0947	0·1051	0·1031	30	56	32
45	0·1085	0·1532	0·0952	34	81	30
50	0·1354	0·1222	0·0527	42	65	17
55	0·1238	0·0370	0·0540	39	20	17
60	0·1314	0·0577	0·0518	41	31	16

For convenience we have added three columns expressing the actual figures as percentages of their respective maxima. In the present phase, the maximum of mortality occurs later in cage life than in the two former (in one of which pasteurellosis was the reigning epidemic disease and in the other a substantial factor). It would be rash, in our present state of knowledge, to put any confident interpretation of the results forward, but the following speculations are tempting. We might suppose that in infection with *Bact. aertrycke* a large majority of the members of an infected community are infected and that the issue, death or survival, is gradually led up to, more gradually than when the more virulent infection of *Pasteurella* is in question. This would explain the later culmination of the mortality in terms of cage-age and might also explain the advantage in respect of immunisation enjoyed by the population. This, however, is hardly the place to pursue these speculations; it seems at least clear that these results confirm our earlier conclusions that, on the whole, actual immunisation rather than weeding out by death of susceptibles is, in our mice communities, the more important determinant of average survivorship.

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