CONTRIBUTIONS TO THE EXPERIMENTAL STUDY OF EPIDEMIOLOGY. A STUDY OF CAGE AGE AND RESISTANCE TO ENVIRONMENT.

By A. BRADFORD HILL.

Member of the Statistical Staff of the Medical Research Council.

(With 3 Figures in the Text.)

In previous experiments of this series attempts have been made to measure the effects of variation in environment (as measured by the prevailing level of mortality) upon the subsequent life history of mice of varying cage ages. The results reached have been inconclusive. The figures for B_6 experiment (*Bact. aertrycke* infection), reproduced in Table I[1], suggested that at the older cage ages, 35 and 40 days, mice were less sensitive to wide differences in the prevailing death-rate than were mice of younger cage ages. For instance, mice *entering* the cage at a time when the previous death-rate had been relatively high survived less than half as long as mice entering after a period of low death-rate—29·2 days as compared with 66·5 days. On the other hand, mice which had survived 40 days in the cage seemed to be equally indifferent to subsequent exposure to the high or low level of death-rates. Their survival time was just over 61 days in either case. At cage age 35 days the difference in survival time is also considerably less than that observed amongst the mice of younger cage age. It must, however, be noted that the numbers upon which the means are based are relatively small at the highest cage ages.

Table I.

Mean length of after-life in days from age x.

Cage age x (days)	Low death-rate (under 0·012) just before day x	High death-rate (over 0·026) just before day x	Difference in length of after-life
0	66·5 (*295*)*	29·2 (*538*)	37·3
5	57·05 (*266*)	29·96 (*534*)	27·09
10	55·00 (*233*)	25·53 (*524*)	29·47
15	52·42 (*194*)	18·51 (*454*)	33·91
20	50·26 (*148*)	18·48 (*360*)	31·78
25	51·00 (*125*)	19·16 (*243*)	31·84
30	60·62 (*72*)	32·93 (*140*)	27·69
35	51·55 (*39*)	39·96 (*82*)	11·59
40	61·30 (*31*)	61·29 (*70*)	0·01

* Figures in brackets are the number of mice upon which the means are based.

A further experiment, in which the fate of normal mice exposed to *Bact. aertrycke* infection was compared with that of mice vaccinated against this organism, gave a different result. The figures are reproduced in Table II[2]. Amongst the vaccinated, the mice exposed to the lower level of death-rates

[1] *J. Hygiene* (1930), xxx, 240.

[2] *J. Hygiene* (1931), xxxi, 257.

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show an advantage in length of survival over those exposed to the higher death-rates, but this advantage shows no decrease with cage age. Possibly vaccination confers all the advantage that can be acquired, so that prolonged survival in the cage is unlikely to add to it. Amongst the controls no significant difference in survival time is found under the two levels of mortality until cage age 35 days is reached, and at that point of time the survivors appear to be *more*, and not less, susceptible to the change in environment as measured by the prevailing death-rate. Again it must be observed that the numbers involved at these later cage ages are very small.

Table II.

Mean length of after-life in days from day x.

Cage age x (days)	Low death-rate (under 0·025) just before day x	High death-rate (over 0·035) just before day x	Difference in length of after-life
	Vaccinated mice.		
0	43·37 (*166*)*	32·60 (*267*)	10·77
5	34·37 (*380*)	26·33 (*100*)	8·04
10	30·11 (*136*)	26·31 (*220*)	3·80
15	31·92 (*118*)	21·59 (*247*)	10·33
20	22·82 (*204*)	15·95 (*149*)	6·87
25	22·32 (*145*)	8·85 (*60*)	13·47
30	27·32 (*33*)	12·05 (*116*)	15·27
35	48·27 (*35*)	16·94 (*62*)	31·33
40	42·97 (*66*)	32·33 (*27*)	10·64
	Control mice.		
0	25·35 (*166*)	27·20 (*258*)	– 1·85
5	22·48 (*366*)	20·35 (*98*)	2·13
10	16·20 (*132*)	19·21 (*198*)	– 3·01
15	13·37 (*120*)	15·26 (*217*)	– 1·89
20	11·33 (*166*)	9·82 (*125*)	1·51
25	11·88 (*120*)	10·23 (*42*)	1·65
30	9·25 (*12*)	15·08 (*76*)	– 5·83
35	29·43 (*15*)	9·05 (*30*)	20·38
40	32·81 (*36*)	14·73 (*11*)	18·08

* Figures in brackets are the number of mice upon which the means are based.

It is also important to note that the contrasted levels of mortality are not the same in Tables I and II. The lower limit of the "high" death-rate in Table I is approximately the same as the upper limit of the "low" death-rate in Table II. It is possible that the "low" death-rate in Table II is in actuality so high that it produces a maximal, or nearly maximal, effect upon survival, and extension to a still higher death-rate is therefore not likely to reduce the power of survival still more. On the other hand vaccination or survival in the cage for a relatively prolonged time may raise the level at which an increased risk of infection becomes critical. In other words, the "low" death-rates of Table II (under 0·025) are already so high that the reaction of mice will not differ under exposure to them and exposure to the "high" death-rates (over 0·035), unless their level of resistance has been raised by vaccination or by long survival in the cage. If this were true it would afford an explanation of the lack of difference between the two groups of controls in Table II until cage age 35 is reached, and of the discrepancy between Tables I and II.

Without some such hypothesis these previous results are inconclusive. A further study has now been made of the data provided by past and present experiments with the infections of *Bact. aertrycke*, *Pasteurella*, and *Ectromelia*. As before a comparison has been made between the average survival times of mice, of different cage ages, after exposure to various levels of mortality. For instance, the first line of Table III shows that there were 202 mice which entered the

Table III. *Bact. aertrycke.*

Average survival time in days (limited to 60 days) after day x*.

Cage age at day x	Average death-rate for 5 days before day x. 0·00–	0·01–	0·02–	0·03–	0·04–0·05
		Cage 2. 6 mice added daily. I.			
0	39 (*202* : *5255*)	28 (*601* : *27863*)	26 (*876* : *40377*)	24 (*340* : *12060*)	
5	37 (*184* : *5255*)	24 (*576* : *27863*)	23 (*862* : *40377*)	21 (*331* : *12060*)	
10	35 (*154* : *4984*)	20 (*553* : *27863*)	21 (*807* : *40377*)	18 (*297* : *12060*)	
20	38 (*92* : *4021*)	19 (*430* : *27863*)	17 (*583* : *40377*)	12 (*189* : *12060*)	
30	38 (*34* : *2532*)	26 (*232* : *27863*)	26 (*275* : *40377*)	22 (*56* : *12060*)	
40		38 (*124* : *27425*)	37 (*173* : *40377*)	34 (*30* : *12060*)	
50		44 (*99* : *25767*)	41 (*120* : *40377*)	40 (*33* : *12060*)	
60		48 (*88* : *24750*)	41 (*95* : *38872*)	38 (*34* : *12060*)	
80		49 (*68* : *24491*)	45 (*79* : *35008*)		
100		47 (*54* : *19433*)	45 (*63* : *34756*)		
		Cage 2. 3 mice added daily. II.			
0		28 (*212* : *7863*)	25 (*335* : *12137*)	26 (*381* : *13355*)	27 (*154* : *5127*)
5		23 (*215* : *7863*)	22 (*322* : *12137*)	22 (*382* : *13355*)	21 (*144* : *5127*)
10		19 (*204* : *7863*)	18 (*319* : *11941*)	18 (*350* : *12781*)	18 (*144* : *4944*)
20		16 (*167* : *7863*)	12 (*232* : *11941*)	12 (*247* : *12533*)	11 (*84* : *4213*)
30		16 (*71* : *7742*)	18 (*85* : *10844*)	17 (*78* : *12533*)	
40		29 (*32* : *6876*)	21 (*35* : *10481*)	29 (*39* : *12533*)	
50		32 (*14* : *5849*)	33 (*25* : *10372*)	44 (*21* : *12533*)	
		I and II combined.			
0	39 (*202* : *5255*)	28 (*813* : *35726*)	26 (*1211* : *52514*)	25 (*721* : *25415*)	27 (*154* : *5127*)
5	37 (*184* : *5255*)	24 (*791* : *35726*)	23 (*1184* : *52514*)	22 (*713* : *25415*)	21 (*144* : *5127*)
10	35 (*154* : *4984*)	20 (*757* : *35726*)	20 (*1126* : *52318*)	18 (*647* : *24841*)	18 (*144* : *4944*)
20	38 (*92* : *4021*)	18 (*597* : *35726*)	16 (*815* : *52318*)	12 (*436* : *24593*)	11 (*84* : *4213*)
30	38 (*34* : *2532*)	23 (*303* : *35605*)	24 (*360* : *51221*)	19 (*134* : *24593*)	
40		36 (*156* : *34301*)	35 (*208* : *50858*)	32 (*69* : *24593*)	
50		43 (*113* : *31616*)	40 (*145* : *50749*)		41 (*54* : *24593*)
60		48 (*88* : *24750*)	41 (*95* : *38872*)		38 (*34* : *12060*)
80		49 (*68* : *24491*)	45 (*79* : *35008*)		
100		47 (*54* : *19433*)	45 (*63* : *34756*)		

* The first figure in the bracket is in each case the number of mice upon which the average survival time is based; the second figure is the total number of mice producing the given death-rate, *i.e.* it is the *sum* of the average cage populations over each 5 days when a given death-rate prevailed. In these experiments a small proportion of mice were withdrawn from the cage and killed. These have been excluded in calculating the survival times and death-rates.

cage when for the 5 days previous to their entry the average death-rate (from all causes) had been between 0·00 and 0·01. The average length of life (limited to 60 days) of these mice after entry was 39 days. Contrasted with these are the 601 mice which entered the cage when the death-rate for the previous 5 days had averaged between 0·01 and 0·02. Their mean length of after-life was 28 days only, while the length of life of mice entering after prevailing death-rates of 0·02–0·03 and 0·03–0·04 was 26 and 24 days respectively. The later lines of

the table read as follows. Taking cage age 30 as an example, it will be seen that there were 34 mice which survived 30 days in the cage and for the last 5 days of that period were exposed to a cage death-rate of 0·00–0·01. Their average survival time from cage age 30 was 38 days. Contrasted with these were 56 mice which survived 30 days in the cage and for the last 5 days of that period were exposed to a cage death-rate of 0·03–0·04. Their survival time from cage age 30 was 22 days.

It must be observed that the total number of mice in any entry may be, and usually is, composed of mice entering the cage at widely differing points of time (in epidemics lasting months or even years). For instance of the 202 mice in the first column of Table III, some may have entered the cage at the beginning of the calendar year and some at the end of it; but they have in

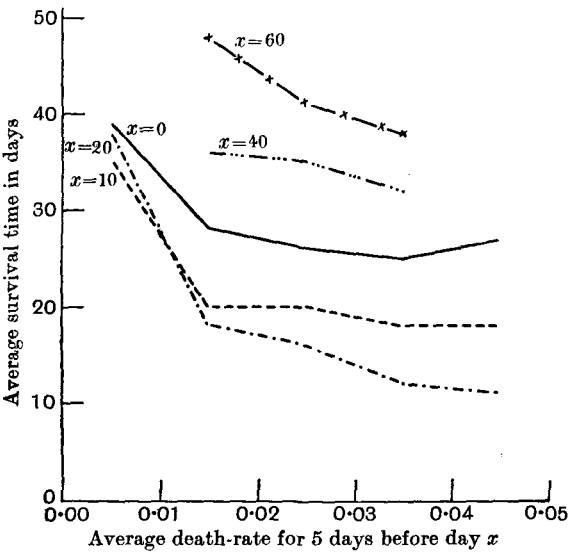

Fig. 1. *B. aertrycke* (Table III, Exps. I and II combined). Average survival time in days (limited to 60 days) after day x.

common the fact that they all entered after a prevailing mortality of 0·00–0·01. This applies to all the figures in Tables III, IV and VI.

Turning to the results, Exp. I in Table III, relating to *Bact. aertrycke*, shows at cage age 0, *i.e.* at entry into the cage, a progressively shortening duration of life with rising mortality in the cage just previous to day of entry. The only large difference is for mice entering after a period of very low mortality, their duration of life being 30–40 per cent. higher than that of mice entering after periods of higher mortality. This difference persists and even 30 days of cage life does not render the mice oblivious to the differences between mortality rates of 0·00–0·01 and 0·01–0·02. The effect of longer life in the cage cannot be measured, as the number of mice of higher age exposed to the lowest death-rates becomes too small. At the higher death-rates there is still a suggestion

Table IV. *Pasteurella.*

Average survival time in days (limited to 60 days) after day x.

Average death-rate for 5 days before x.

Cage age at day x	0·00–	0·01–	0·02–	0·03–	0·04–	0·05–	0·09+
			Cage G. 3 mice added daily. I.				
0	34 (*141 : 6271*)	30 (*303 : 13852*)	31 (*231 : 9622*)	26 (*69 : 2295*)	26 (*48 : 1706*)	28 (*108 : 3748*)	
5	32 (*137 : 6271*)	28 (*295 : 13852*)	28 (*217 : 9567*)	22 (*64 : 2295*)	22 (*47 : 1706*)	23 (*96 : 3748*)	
10	28 (*130 : 6271*)	28 (*268 : 13852*)	27 (*199 : 9450*)	21 (*56 : 2117*)	17 (*43 : 1706*)	16 (*83 : 3748*)	
20	34 (*98 : 5965*)	29 (*206 : 13645*)	23 (*134 : 9259*)	12 (*38 : 2117*)	16 (*27 : 1706*)	13 (*48 : 3748*)	
30	39 (*67 : 5797*)	32 (*138 : 13088*)	33 (*77 : 9072*)	20 (*26 : 3823*)*		24 (*26 : 3748*)	
40	42 (*51 : 5797*)	37 (*98 : 13088*)	34 (*53 : 8470*)		23 (*41* : 7169)		
50	47 (*31 : 5797*)	41 (*68 : 12579*)	40 (*57 : 8169*)		25 (*28* : 6974)		
60	41 (*25 : 5797*)	40 (*62 : 12472*)	41 (*46 : 7183*)		34 (*22* : 6974)		
80	47 (*27 : 5622*)	38 (*45 : 12066*)	37 (*31 : 6995*)				
			Cage 2. 3 mice added daily. II.				
0	36 (*123 : 5104*)	30 (*174 : 5604*)	20 (*198 : 5925*)	17 (*246 : 5657*)	16 (*243 : 4920*)	16 (*876 : 15019*)	17 (*303 : 4292*)
5	40 (*117 : 5104*)	30 (*159 : 5604*)	15 (*171 : 5925*)	16 (*223 : 5657*)	16 (*204 : 4920*)	15 (*656 : 15019*)	13 (*196 : 4292*)
10	43 (*109 : 5104*)	30 (*125 : 5604*)	17 (*136 : 5925*)	18 (*169 : 5657*)	16 (*141 : 4828*)	15 (*448 : 14950*)	14 (*113 : 4292*)
20	41 (*86 : 5104*)	35 (*86 : 5604*)	25 (*76 : 5885*)	21 (*75 : 5615*)	21 (*74 : 4672*)	19 (*179 : 14861*)	23 (*41 : 4204*)
30	45 (*68 : 5104*)	37 (*71 : 5604*)	24 (*51 : 5885*)	26 (*40 : 5615*)	23 (*39 : 4672*)	27 (*86 : 14782*)	
40	47 (*55 : 5104*)	34 (*51 : 5480*)	25 (*48 : 5814*)	26 (*26 : 5615*)	25 (*27 : 4639*)	24 (*62 : 14750*)	
50	48 (*42 : 5104*)	34 (*47 : 5480*)	22 (*36 : 5663*)	22 (*39 : 10200*)		21 (*47 : 14478*)	
60	51 (*33 : 5104*)	35 (*29 : 5373*)	24 (*35 : 5437*)	22 (*29 : 10045*)		22 (*40 : 14427*)	
			I and II combined.				
0	35 (*264 : 11375*)	30 (*477 : 19456*)	26 (*429 : 15547*)	19 (*315 : 7952*)	18 (*291 : 6626*)	17 (*984 : 18767*)	17 (*303 : 4292*)
5	36 (*254 : 11375*)	29 (*454 : 19456*)	22 (*388 : 15492*)	18 (*287 : 7952*)	18 (*251 : 6626*)	16 (*752 : 18767*)	13 (*196 : 4292*)
10	35 (*239 : 11375*)	29 (*393 : 19456*)	23 (*335 : 15375*)	19 (*225 : 7774*)	16 (*184 : 6604*)	15 (*531 : 18698*)	14 (*113 : 4292*)
20	37 (*184 : 11069*)	31 (*292 : 19249*)	24 (*210 : 15144*)	18 (*113 : 7732*)	20 (*101 : 6378*)	18 (*227 : 18609*)	23 (*41 : 4204*)
30	42 (*135 : 10901*)	33 (*209 : 18692*)	29 (*128 : 14957*)	26 (*56 : 7732*)	21 (*49 : 6378*)	27 (*112 : 18530*)	
40	45 (*106 : 10901*)	36 (*149 : 18568*)	30 (*101 : 14284*)	22 (*33 : 7430*)	25 (*34 : 6245*)	25 (*89 : 18498*)	
50	47 (*73 : 10901*)	38 (*115 : 18059*)	33 (*93 : 13832*)	23 (*26 : 7333*)	26 (*26 : 6093*)	21 (*62 : 18226*)	
60	47 (*58 : 10901*)	39 (*91 : 17845*)	34 (*81 : 12620*)	27 (*35 : 13271*)		24 (*56 : 18175*)	
80	47 (*27 : 5622*)	38 (*45 : 12066*)	37 (*31 : 6995*)				

* The separate values at these points are:

		0·03–	0·04–	0·05–0·09
Cage G	30	24 (*16 : 2117*)	14 (*10 : 1706*)	
	40	7 (*7 : 1815*)	26 (*7 : 1606*)	27 (*27 : 3748*)
	50	36 (*4 : 1718*)	30 (*9 : 1508*)	19 (*15 : 3748*)
	60	41 (*3 : 1718*)	60 (*3 : 1508*)	28 (*16 : 3748*)
Cage 2	50	20 (*22 : 5615*)	24 (*17 : 4585*)	
	60	20 (*15 : 5460*)	25 (*14 : 4585*)	

of a falling survival time with increased severity of exposure even amongst the mice of older ages. In Exp. II periods in which very low death-rates prevailed were absent, and in the range of higher death-rates available there is very little evidence of any shortened duration of life with increasing severity of exposure. Generally, the larger combined experience (graphically shown in Fig. 1) suggests that a slight decline in mean length of after-life results from exposure to higher death-rates, irrespective of cage age.

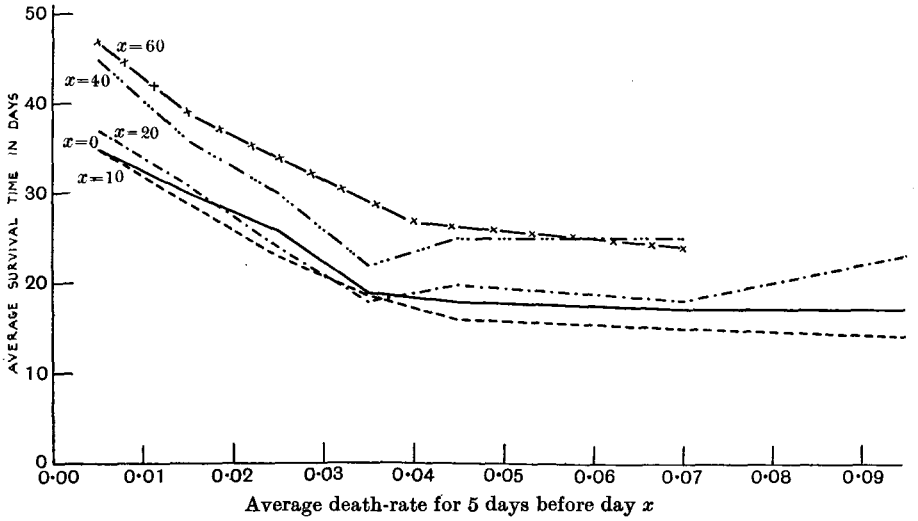

Fig. 2. *Pasteurella* (Table IV, Exps. I and II combined).
Average survival time in days (limited to 60 days) after x

The *Pasteurella* experiments in Table IV (Fig. 2) give, on the whole, a similar result. There is generally a drop in the mean length of after-life with increasing death-rates, though, judging by the combined experience, further increase of the death-rates beyond 0·03–0·04 has little effect upon length of survival. This is shown, perhaps more clearly, in Table V, in which the length of after-life at each death-rate level is shown as a percentage of the corre-

Table V. *Pasteurella. I and II combined.*

Average survival time after day x, the averages at higher death-rates being expressed as percentages of the averages at 0·00–0·01.

Cage age at day x	Average death-rate for 5 days before x						
	0·00–	0·01–	0·02–	0·03–	0·04–	0·05–	0·09+
0	100	86	74	54	51	49	49
5	100	81	61	50	50	44	36
10	100	83	66	54	46	43	40
20	100	84	65	49	54	49	62
30	100	79	69	62	50	64	—
40	100	80	67	49	56	56	—
50	100	81	70	49	55	45	—
60	100	83	72	57		51	—
80	100	81	79	—	—	—	—

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sponding length of after-life that followed exposure to the lowest death-rate level. The trend of the percentages at each cage age remains, on the whole, remarkably constant.

With *Ectromelia* (Table VI and Fig. 3) there is again a difference in survival time between mice entering after a period of very low mortality and those entering after a period of higher mortality. The difference is slight, only of the order of 3 or 4 days, but with the lowest range of death-rates, 0·00–0·01 and 0·01–0·02, it persists throughout cage life. On the other hand at higher rates of mortality there is no evidence of any further decrease in length of after-life; in fact after cage age 20 days the length of survival time *rises* with exposure to a severe environment (when the level 0·02–0·03 is reached), possibly the result of a more complete immunity being secured by survivors of a high

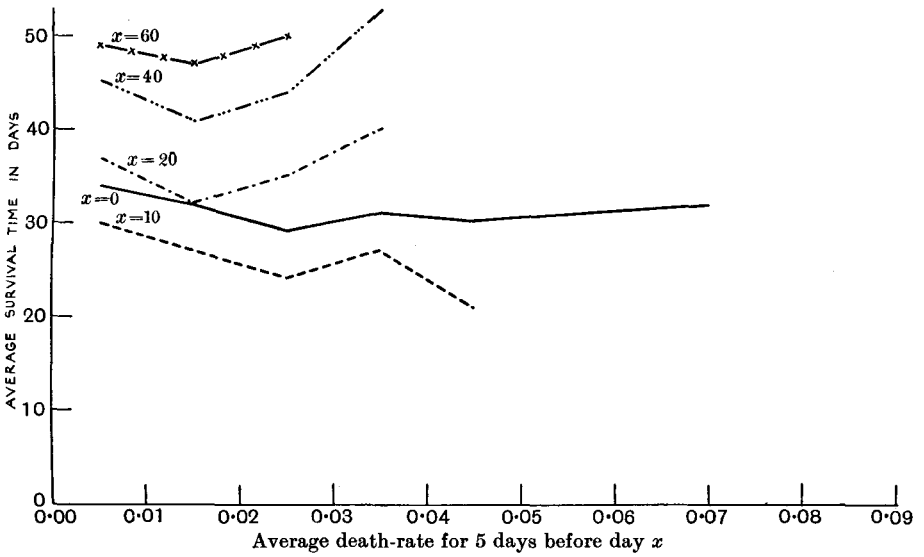

Fig. 3. *Ectromelia* (Table VI, Exps. I and II combined).
Average survival time in days (limited to 60 days) after day x.

mortality period (though this was not observed with *Bact. aertrycke* and *Pasteurella*).

The general inference from the data provided by these experiments is that variations of severity of exposure (*i.e.* within the range of these high epidemic death-rates) *do* affect subsequent mortality, although previous residence in the cage may have been of considerable length. Reading the columns of Tables III, IV, and VI vertically, it will be seen that there is an increased length of life at the higher cage ages, at each level of mortality, compared with the length of life of the newly entered; but the *relative* effect of variations in environment does not disappear with cage age in *Bact. aertrycke* and *Pasteurella*, though with *Ectromelia* the effect is only apparent at the lowest level of mortality.

Table VI. *Ectromelia.*

Average survival time (limited to 60 days) after day x.

Cage age at day x	Average death-rate for 5 days before day x. 0·00–	0·01–	0·02–	0·03–	0·04–	0·05–0·09
	Cage 1. 3 mice added daily. I.					
0	31 (*189 : 9790*)	31 (*747 : 41204*)	29 (*345 : 15882*)	32 (*75 : 2143*)	23 (*24 : 448*)	19 (*12 : 221*)
5	30 (*187 : 9790*)	27 (*737 : 41204*)	27 (*343 : 15882*)	19 (*75 : 2143*)	28 (*24 : 448*)	25 (*12 : 221*)
10	28 (*163 : 9715*)	26 (*695 : 41204*)	23 (*301 : 15882*)	30 (*56 : 2143*)	19 (*15 : 448*)	
20	33 (*105 : 9565*)	30 (*413 : 41163*)	33 (*171 : 15755*)	44 (*30 : 2096*)		
30	39 (*78 : 9565*)	35 (*271 : 41163*)	40 (*125 : 15755*)	48 (*23 : 1886*)		
40	44 (*64 : 9565*)	38 (*228 : 41163*)	43 (*89 : 15755*)	55 (*16 : 1598*)		
50	41 (*41 : 9565*)	43 (*193 : 40669*)	46 (*80 : 15558*)			
60	48 (*47 : 9565*)	47 (*159 : 40669*)	49 (*59 : 15235*)			
80	54 (*32 : 9565*)	50 (*121 : 39904*)	54 (*54 : 14342*)			
100	56 (*19 : 9565*)	54 (*115 : 39371*)	60 (*25 : 13048*)			
	Cage 2. 3 mice added daily. II.					
0	36 (*417 : 27813*)	32 (*471 : 28619*)	29 (*204 : 8567*)	31 (*57 : 2015*)	39 (*18 : 514*)	43 (*15 : 387*)
5	34 (*414 : 27813*)	28 (*460 : 28619*)	27 (*202 : 8567*)	29 (*57 : 2015*)	21 (*18 : 514*)	34 (*15 : 387*)
10	31 (*384 : 27738*)	30 (*434 : 28619*)	25 (*171 : 8567*)	24 (*49 : 2015*)	23 (*14 : 514*)	
20	38 (*259 : 27415*)	35 (*283 : 28569*)	39 (*102 : 8567*)	33 (*15 : 2015*)		
30	44 (*196 : 27415*)	43 (*200 : 28405*)	42 (*59 : 8318*)	42 (*16 : 1826*)		
40	46 (*164 : 27415*)	44 (*169 : 28405*)	45 (*56 : 8184*)	51 (*14 : 1629*)		
50	50 (*148 : 27415*)	43 (*129 : 28094*)	52 (*52 : 7828*)			
60	49 (*99 : 27415*)	48 (*142 : 27928*)	52 (*33 : 7121*)			
80	57 (*87 : 27415*)	49 (*102 : 27643*)	51 (*28 : 6558*)			
100	58 (*84 : 27415*)	54 (*72 : 26970*)	51 (*18 : 5586*)			
	I and II combined.					
0	34 (*606 : 37603*)	32 (*1218 : 69823*)	29 (*549 : 24449*)	31 (*132 : 4158*)	30 (*42 : 962*)	32 (*27 : 608*)
5	33 (*601 : 37603*)	28 (*1197 : 69823*)	27 (*545 : 24449*)	23 (*132 : 4158*)	25 (*42 : 962*)	30 (*27 : 608*)
10	30 (*547 : 37453*)	27 (*1129 : 69823*)	24 (*472 : 24449*)	27 (*105 : 4158*)	21 (*29 : 962*)	
20	37 (*364 : 36980*)	32 (*696 : 69732*)	35 (*273 : 24322*)	40 (*45 : 4111*)		
30	43 (*274 : 36980*)	39 (*471 : 69568*)	40 (*184 : 24073*)	46 (*39 : 3712*)		
40	45 (*228 : 36980*)	41 (*397 : 69568*)	44 (*145 : 23939*)	53 (*30 : 3227*)		
50	48 (*189 : 36980*)	43 (*322 : 68763*)	48 (*132 : 23386*)			
60	49 (*146 : 36980*)	47 (*301 : 68597*)	50 (*92 : 22356*)			
80	56 (*119 : 36980*)	50 (*223 : 67547*)	53 (*82 : 20900*)			
100	57 (*103 : 36980*)	54 (*187 : 66341*)	56 (*43 : 18634*)			

Before accepting these inferences, certain critical objections must be met. Since the average survival time of groups of mice is being related to particular death-rates within the cage, it is essential to show that these groups did not form any very appreciable proportion of the population upon which each death-rate was based. For if they did form any such appreciable proportion, there is clearly likely to be a correlation between prevailing death-rate and length of survival. For this reason Tables III, IV and VI show the number of mice upon which each mean survival time is based and the corresponding number of mice in the cage, at the same points of calendar time, upon which the death-rate is based. At cage age 0 the survival time is that of mice who cannot have contributed to the prevailing death-rate, since the death-rate relates to the 5 days before day x, *i.e.* in this case before entry. At later cage ages the mice whose survival time is measured must form part of the population producing the death-rate to which the survival time is related, but even at cage age 5, when the proportion is at its highest, they never form as much as 5 per cent. of the cage population, and rarely reach as much as 3 per cent. At later cage ages the proportion becomes negligible, and it may be concluded that the mice whose length of life is measured form only a very small proportion of the total cage population at each point of time.

A second point of importance is as follows. The figure for the general cage death-rate for the 5 days before entry, or before any given cage age, has been taken as a measure of the risk of infection at that time; but since the cage death-rate at any one period is highly correlated with the death-rate in the periods immediately preceding and following it, the effect of high and low death-rates will, in general, spread beyond the period specified. The effect of this upon the survival time measured has to be considered. At cage ages 0 and 5 days, only a slight modification in the conclusions reached is required. For these mice there is no "past" exposure to complicate the measure of survival time; they are exposed *at entry* to a certain death-rate level, which extends over a period not necessarily confined to the 5 days mentioned; assuming that *subsequent* fluctuations, during the 60 days to which after-life has been arbitrarily limited, are averaged out, the survival time measures the reaction of the group to these periods of high or low mortality rates. That the period of high or low rates is actually longer than the selected 5 days is unimportant. At later cage ages, however, there is the difficulty that, owing to the correlation between secular death-rates, the "past" exposure of the mice exposed to the different 5-day mortality levels has not been the same. The survival time may therefore be affected not only by the level of the death-rate at cage age x, but by the correlated level previous to day x, *i.e.* the mice may have been infected at earlier ages and therefore survive a shorter time after cage age x. On the other hand, if the survivors to high cage ages, 50 or 60 days, be taken as examples of mice who, having lived some 30 days in the cage, are later exposed to a series of high or low death-rates there is, especially in the *Pasteurella* experiments, no evidence that survival for 30 days in the cage has

made them impervious to the subsequent level of the death-rate. A more conclusive answer has been sought by partial correlation methods. Using the material of Cage G (*Pasteurella*, I of Table IV), the correlation between survival time (unlimited) from entry (day 0) and the death-rate prevailing in the first 5 days of cage life is found to be $-0{\cdot}1610 \pm 0{\cdot}033$[1]. The correlation between survival time from cage age 30 and death-rate for 5 days after cage age 30 is nearly identical, $-0{\cdot}1693 \pm 0{\cdot}056$. When the average death-rate for the first 30 days of cage life is kept constant this coefficient falls to $-0{\cdot}1055 \pm 0{\cdot}057$. On the other hand the coefficient rises to $-0{\cdot}2089 \pm 0{\cdot}080$ at cage age 60 (*i.e.* correlation between survival time after age 60 with death-rate for 5 days after age 60, keeping constant the average death-rate from age 30 to age 60). The period of six daily additions in Cage 2 (*Bact. aertrycke*, I of Table III) gives a similar result. The correlation between survival time and death-rate at entry is $-0{\cdot}1884 \pm 0{\cdot}021$. Between survival time beyond age 30 and death-rate for 5 days from cage age 30, with the average death-rate for the first 30 days kept constant, it falls to $-0{\cdot}1269 \pm 0{\cdot}040$, but at age 60, with the previous 30 days' death-rate kept constant, rises again to $-0{\cdot}2240 \pm 0{\cdot}064$.

One objection to these coefficients is that the average death-rate over 30 days may be derived from widely differing distributions of death-rates over that period. For instance the death-rates may be very high at the beginning of the 30 days, *i.e.* at the point most removed from the 5-day period the effect of which it is desired to measure. Or they may be high immediately before the 5-day period. The two averages may be identical. It is possible that the death-rates close to the 5-day period are more important than those that are relatively remote. As a rough test the mean 30 days' death-rate has been calculated for the *Bact. aertrycke* experiment (for survivors at cage age 60), allotting a weight of 1 to the first 10 days' death-rates, 2 to the second 10 days, and 3 to the last 10 days. The correlation between survival time from cage age 60 and the 5 days' death-rate at age 60, keeping constant the previous 30 days' death-rate, is not appreciably altered. It becomes $-0{\cdot}2062 \pm 0{\cdot}065$ compared with the value previously found of $-0{\cdot}2240 \pm 0{\cdot}064$. These various coefficients are set out in Table VII. They do not suggest (though, it must be observed, their size is very small) that mice of advanced cage age are indifferent to severity of environment.

In discussing the paradoxical results of Tables I and II, it was suggested that an increase in the death-rate beyond some critical limit may have a maximal effect on the expectation of life, and that this critical level may vary according to the previous experience of the mice at risk. In the *Bact. aertrycke* experiments (Table III) the most striking difference in length of after-life is produced by an increase in death-rate beyond 0·00–0·01. In the *Pasteurella* experiments (Tables IV and V) the most noticeable feature is that an increase in death-rate from 0·00–0·01 to 0·03–0·04 is associated with a progressive

[1] Standard errors are given throughout. In this cage there were a few old survivors when the experiment came to an end. Their survival time is therefore understated.

decrease in the length of after-life to about half its value at the lowest death-rates; a further increase in death-rate is associated with a relatively trivial further decrease in length of survival. On the other hand in neither the *Bact. aertrycke* nor *Pasteurella* experiments is there any suggestion, so far as these figures go, that the critical level is shifting with increasing cage age to a higher point on the death-rate scale.

It seems possible that the difference in the effect of increasing death-rate noted between *Ectromelia* on the one hand and *Bact. aertrycke* and *Pasteurella* on the other, may be due to the fact that effective natural immunisation is common in the first infection and rare in the other two. Exposure to risk will

Table VII. *Correlations between survival time and death-rates.*

Cage age x	Number of mice	Correlation coefficient between: Survival time from cage age x and death-rate from cage age x to $x+4$	Survival time from cage age x and death-rate for 30 days previous to day x	Death-rate from cage age x to $x+4$ and death-rate for 30 days previous to day x	Survival time from cage age x and death-rate from cage age x to $x+4$, keeping constant death-rate for 30 days previous to day x	Survival time from cage age x and death-rate for 30 days previous to day x, keeping constant death-rate from cage age x to $x+4$
Cage G. 3 mice added daily. *Pasteurella.*						
0	882	$-0{\cdot}1610 \pm 0{\cdot}033$*				
30	306	$-0{\cdot}1693 \pm 0{\cdot}056$	$-0{\cdot}1998 \pm 0{\cdot}055$	$+0{\cdot}3658 \pm 0{\cdot}050$	$-0{\cdot}1055 \pm 0{\cdot}057$	$-0{\cdot}1503 \pm 0{\cdot}056$
60	144	$-0{\cdot}2286 \pm 0{\cdot}079$	$-0{\cdot}1010 \pm 0{\cdot}082$	$+0{\cdot}3024 \pm 0{\cdot}076$	$-0{\cdot}2089 \pm 0{\cdot}080$	$-0{\cdot}0343 \pm 0{\cdot}084$
Cage 2. 6 mice added daily. *Bact. aertrycke.*						
0	2032	$-0{\cdot}1884 \pm 0{\cdot}021$				
30	594	$-0{\cdot}1895 \pm 0{\cdot}040$	$-0{\cdot}1557 \pm 0{\cdot}040$	$+0{\cdot}5383 \pm 0{\cdot}029$	$-0{\cdot}1269 \pm 0{\cdot}040$	$-0{\cdot}0649 \pm 0{\cdot}041$
60	218	$-0{\cdot}2604 \pm 0{\cdot}063$	$-0{\cdot}1555 \pm 0{\cdot}066$	$+0{\cdot}3336 \pm 0{\cdot}060$	$-0{\cdot}2240 \pm 0{\cdot}064$	$-0{\cdot}0754 \pm 0{\cdot}067$
60†	218	$-0{\cdot}2604 \pm 0{\cdot}063$	$-0{\cdot}1708 \pm 0{\cdot}066$	$+0{\cdot}4837 \pm 0{\cdot}052$	$-0{\cdot}2062 \pm 0{\cdot}065$	

* Standard error.

† Death-rate for previous 30 days weighted as described in text.

give a measure of the chance of fatal infection *and* of natural immunisation in both cases; the risk of fatal infection may dominate in mouse typhoid and pasteurellosis, the chance of natural immunisation in ectromelia infection.

CONCLUSION.

On the whole, this further examination of the data relating to *Bact. aertrycke* and *Pasteurella* suggests that variations in severity of exposure, as measured by prevailing death-rate in the cage, continue to influence the power of survival, even of mice who have lived a relatively long time in the cage. With *Ectromelia* variations in the death-rate have a much less effect at all cage ages upon the length of survival time, and at older cage ages the mice become, on the average, relatively indifferent to exposure to higher death-rates.

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