THE RESISTANCE OF FOUR MOUSE LINES TO BACTERIAL INFECTION

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(With 10 Figures in the Text)

Up to the present the bulk of the published work on the genetic basis of resistance to infection has consisted of attempts to select animals of varying grades of natural immunity from heterogeneous stocks of animals. Experiments that have been carried out to compare different strains of the same species have not as a rule been planned with sufficient attention to genetical considerations.

A problem that has greatly vexed workers in this particular field has been to distinguish between genetic and non-genetic variation in resistance. The theory of inbreeding first developed by Jennings in 1915 enables this problem to be attacked. It has been shown that any system of inbreeding tends to decrease the proportion of heterozygotes in a population, the rate of decrease varying with the system of breeding employed. In animal experiments the closest system available is that of brother-sister mating; in such a system a close approximation to a genetically homogeneous stock is obtained after twenty generations. The effect of inbreeding will be counterbalanced to some extent by the occurrence of mutations, but, unless present estimates of mutation rates are far too low, continued brother-sister matings overwhelm these and the stock rapidly becomes homozygous again. Irwin (1933) appears to have found some evidence of genetical variation in the response to infection of a highly inbred strain of rats which was presumably the result of mutation.

Provided pedigree records are kept, it is possible to obtain evidence which can decide whether the variance observed in an inbred stock is genetic or not. If the variance is genetic in origin the anomaly should be confined to certain lines of descent, and it should be possible to segregate the different types by means of close inbreeding, or by means of selection as was done by Irwin (1933) with a highly inbred strain of rats.

In this paper a comparison is made between two selected stocks of mice obtained through the kindness of Dr L. T. Webster that had not been strictly inbred and two strains that were not selected but had been brother-sister inbred for over thirty generations. Below is an account of the strains used:

The A stock was selected by Webster (1933) as a strain relatively resistant to infection with *Salmonella enteritidis*. This he accomplished by breeding from the progeny of mice which survived infection with *S. enteritidis*. It is an albino

strain, probably homogeneous for the "Agouti" gene, but shown to be heterogeneous for the allelomorphs black and brown. All individuals tend to get very fat over the age of three months without becoming sterile.

The B stock was selected by Webster (1933) as a strain relatively susceptible to infection with *S. enteritidis*. It was obtained by breeding from the progeny of mice dying early after infections with this organism. It is likewise an albino strain whose colour genes have not been investigated. There is no tendency to obesity. The males are extremely pugnacious. Litters are with difficulty reared.

The D stock was established originally by Dr L. C. Strong at Bar Harbour, Maine, and was obtained from Dr Little of the Roscoe Jackson Memorial Laboratory there. It has been brother-sister inbred for over forty generations. The females are extremely prone to carcinoma mammae, and, like the B stock, very often eat their young. This cannibalism is accounted for by the fact that in this line a certain number of young are born with hare lip (Bittner, 1935) and probably other abnormalities interfering with viability. The strain is homozygous for brown and non-agouti.

The E stock obtained from Dr Dunn's laboratory has been brother-sister inbred for over thirty generations. It is coloured, black and non-agouti. The mice have a slight tendency to obesity.

The first two strains were used in order to obtain the greatest possible contrast in response to infection and to see how far the results obtained by Webster could be repeated, while the two pure lines were employed for the purpose of obtaining a stricter measure of genetic and non-genetic variance. It is intended to investigate the mechanisms underlying the responses given by the different stocks; experiments along these lines are reported in this paper.

Mouse breeding

The mice were all reared in a uniform environment on a uniform dry diet which consisted of dog biscuit and mixed seeds, water being supplied plentifully in bottles. An idea of the relative breeding powers of the four lines is given by the following details relative to a series of over two hundred matings in each case. In A stock the average litter number was 5·0, of which 65 per cent. were weaned, in B stock the corresponding figures were 4·2 and 41 per cent., in D stock they were 3·0 and 45 per cent., while for the E mice the figures were 4·5 and 72 per cent.

At one time with the hope of improving results, particularly in lines B and D, a much more elaborate moist diet containing fish, lights, milk, yeast, wheat germ, cabbage, bread and seeds was substituted, but failed to bring improvement.

Spontaneous disease in the colonies of mice was of very infrequent occurrence. Usually in such cases heart blood cultures produced *Bact. morgani* No. 1, *Bact. proteus* or coliform organisms, sometimes of doubtful aetiological significance while often no growth at all resulted. Two small epizootics with such

findings occurred at different times, one limited to line E and the other to line F. (This line F, used in one experiment only, was a pure line of agouti mice established by Strong.) In this latter case only bucks were affected, even does mated to such animals escaping infection. A third small epizootic occurred among the does of line D, the mice in this case dying before or during parturition; cultures made from the foetuses yielded streptococci alone or accompanied by a Gram-negative, non-motile rod; this bacterium grew yellow on agar, produced indole, gave alkalinity in milk and fermented glucose and saccharose with gas formation. In no case was a *Salmonella* or *Pasteurella* isolated from mice dying spontaneously. Certain mice of line A were affected at one time with a dermatitis, possibly of streptococcal aetiology. Healthy carriers of this infection were responsible for cases occurring many months after all visibly infected animals had been killed; with their recognition and destruction the outbreak came to an end. The epizootics were all very circumscribed and in no case spread from one line to another.

RESISTANCE TO EXPERIMENTAL INFECTION

The bacterial species chosen for the resistance tests upon the four mouse lines were largely those that Webster had employed in his experiments. Of the cultures used for infection, both the salmonellae were recently isolated virulent strains obtained from Dr Fritz Kauffmann (Copenhagen); the murine *Pasteurella* culture was of attenuated virulence and was supplied by Prof. Topley; the experiments with the *Pneumococcus* were very kindly carried out by Dr Morgan with a virulent strain in use at the Lister Institute, Elstree; the louping-ill virus obtained from Dr Weston Hurst was Pool's strain preserved in mouse brain.

The four bacterial cultures tested were broth grown and broth diluted. Half a cubic centimetre of these was inoculated intraperitoneally, the number of living organisms contained therein being determined by agar plating. The louping-ill inoculation was intracranial, 0·02 c.c. of a saline dilution of a lightly centrifuged suspension of brain tissue which had been ground in a mortar with sand and saline. The size of dose to be administered was determined by a preliminary test carried out with one-half of an infected mouse brain, the other half being meanwhile preserved at $-10°$ C. This mode of infection was chosen when it was discovered that nasal insufflation did not lead to a fatal infection.

In each contrasted pair of mouse lines, age and sex factors were carefully balanced.

The resistances of the four lines of mice to a series of such experimental infections are shown in Figs. 1–8, which illustrate the percentage of survivors on consecutive days after the test dose. The figures placed in brackets under the letter denoting the mouse-line record the number and sex of the mice used. A.L.F. denotes the average length of life of those dying during the period of observation.

Resistance to infection with *Salmonella* strains

Examination of the following graphs shows clearly that facing infection with organisms of the *Salmonella* group, either *S. typhi-murium* or *S. enteritidis*, two lines of mice (A, the resistant stock of Webster and D, the pure line

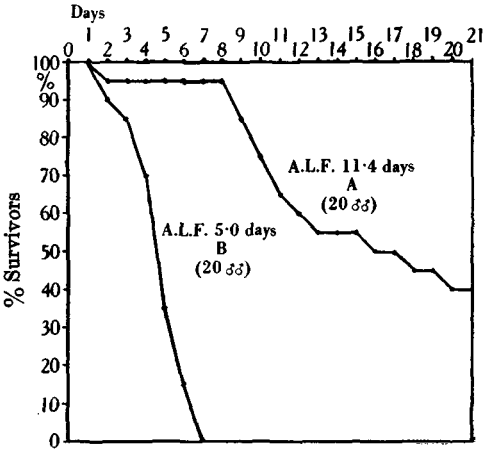

Fig. 1. Test-dose = 10,000 *S. typhi-murium* "6079".

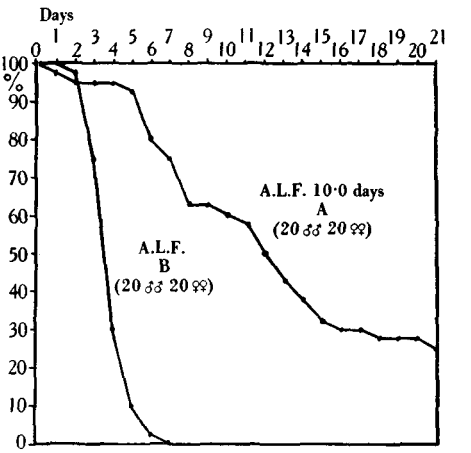

Fig. 2. Test-dose = 20,000 *S. typhi-murium* "6079".

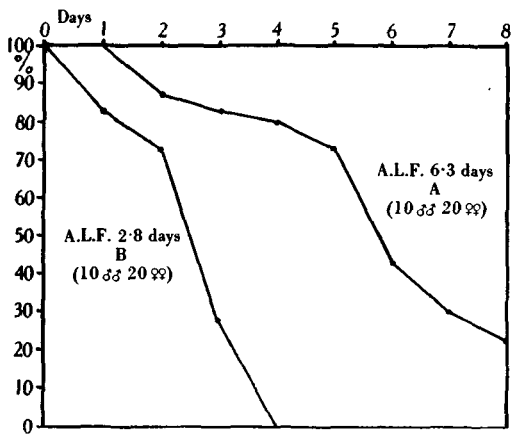

Fig. 3. Test-dose = 843,000 *S. enteriditis* var. *danysz* "4444".

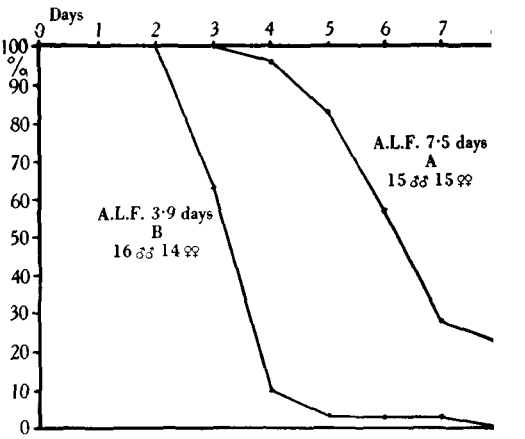

Fig. 4. Test-dose = 28,000 *S. enteritidis* var. *danysz* "4444".

mice of Strong), succumb to the diseases less readily than do the other two lines under examination (B, the non-resistant stock of Webster and E, the pure line mice of Dunn). Line A, which was specially selected for its resistance to infection with salmonellae, exhibits this quality to a greater extent than does the pure line D. These latter mice, however, behave very differently from the

other pure line E mice with which they are contrasted. For example, in Figs. 5, 6, 7 and 8 after 5, 5, 3 and 4 days respectively the percentages surviving in the two groups E and D are seen to be 10 and 95, 12 and 65, 25 and 95, 5 and 85, and indicate differences in resistance which, although not maintained, are very striking. The shortness of this period of resistance to infection which is

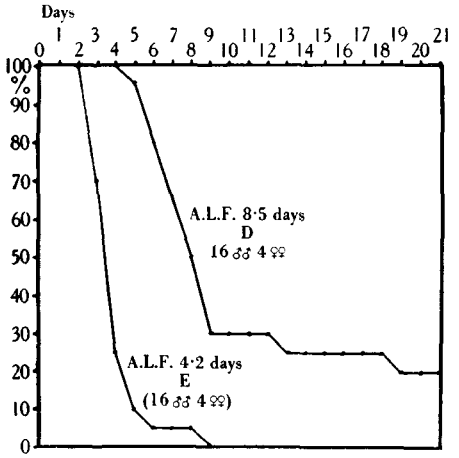

Fig. 5. Test-dose = 12,000 *S. typhi-murium* "6079'.

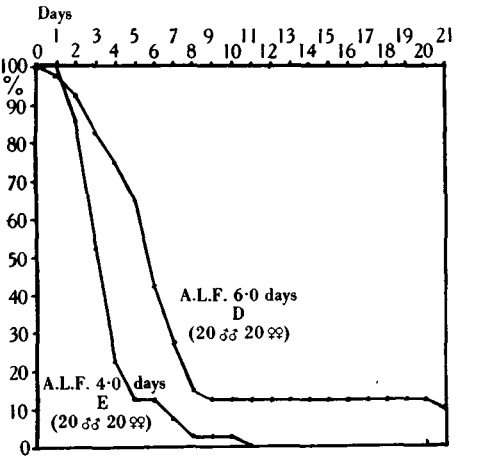

Fig. 6. Test-dose = 20,000 *S. typhi-murium* "6079".

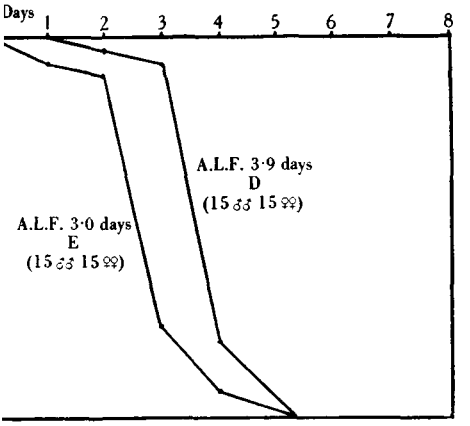

Fig. 7. Test-dose = 28,000 *S. enteritidis* var. *danysz* "4444".

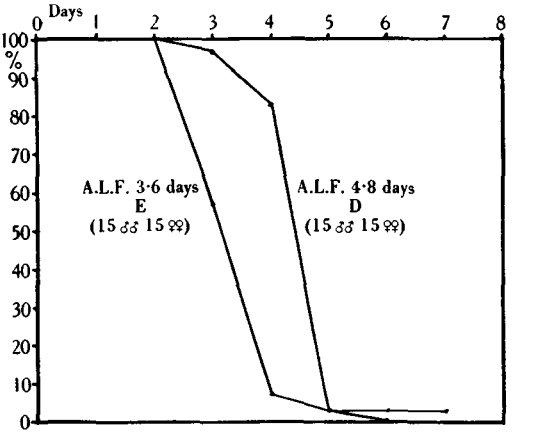

Fig. 8. Test-dose = 9400 *S. enteritidis* var. *danysz* "4444".

exhibited by line D is reflected in the smaller differences in the average length of the life figures for the two lines D and E. These are seen in the four experiments under consideration to be roughly in days 4 and 8, 4 and 6, 3 and 4, 4 and 5, as compared with the 5 and 11, 4 and 10, 3 and 6, 4 and 7 days of survival in the case of the lines B and A.

Resistance to infection with a *Pasteurella* strain and the virus of louping-ill

When, however, the infective agent with which the mice are tested does not belong to the *Salmonella* group of organisms, the relative resistance of the mice is completely changed.

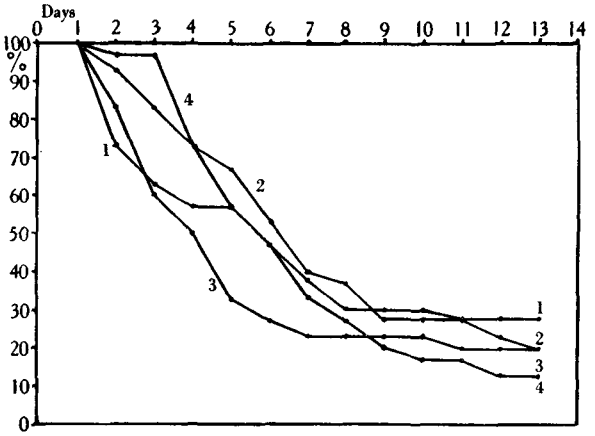

Fig. 9. Test-dose = 2278 *P. muriseptica* "P.M. 3".
1 = Mice A (15 ♂♂ 15 ♀♀), average length of life = 4·5 days.
2 = Mice B (15 ♂♂ 15 ♀♀), average length of life = 6·1 days.
3 = Mice D (7 ♂♂ 23 ♀♀), average length of life = 4·1 days.
4 = Mice E (7 ♂♂ 23 ♀♀), average length of life = 6·0 days.

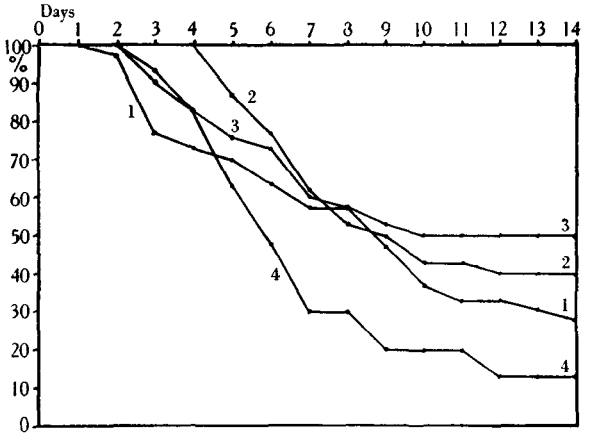

Fig. 10. Test-dose = 7800 *P. muriseptica* "P.M. 3".
1 = Mice A (20 ♂♂ 10 ♀♀), average length of life = 6·8 days.
2 = Mice B (20 ♂♂ 10 ♀♀), average length of life = 7·3 days.
3 = Mice D (20 ♂♂ 10 ♀♀), average length of life = 6·0 days.
4 = Mice E (20 ♂♂ 10 ♀♀), average length of life = 6·3 days.

In Figs. 9 and 10 are plotted the survival curves for all four lines after infection with a *Pasteurella* of low virulence. In neither of the experiments is there any indication that the lines resistant to salmonellae are also resistant

to this *Pasteurella*. In Fig. 10 one group, that of line E, shows less resistance than the others, but this result is not confirmed in the first experiment recorded in Fig. 9, where all four curves approximate to one another. Nor do the figures for average length of life indicate that increased resistance to *Salmonella* infection implies a similar resistance to infection by a *Pasteurella*; on the contrary, in every case the opposite is suggested. A similar inversion of relative resistance was noted by Webster (1933) on passing from inoculation with salmonellae to infection with louping-ill virus. Reference to Table I shows, however, that this observation with louping-ill could not be repeated when the mode of infection was by intracranial infection in place of the nasal insufflation method as carried out by Webster.

Table I

Resistance to infection with louping-ill

Exp.	Mice	Percentage survivors	Average length of life in days
1	A (20 ♂♂, 10 ♀♀)	10	10·2
	B (20 ♂♂, 10 ♀♀)	10	10·2
	D (14 ♂♂, 6 ♀♀)	10	8·2
	E (12 ♂♂, 6 ♀♀)	33	7·8
2	A (15 ♂♂, 15 ♀♀)	86	13·7
	B (15 ♂♂, 15 ♀♀)	72	12·3
	D (15 ♂♂, 15 ♀♀)	41	9·7
	E (15 ♂♂, 15 ♀♀)	59	8·2

Resistance to infection with Pneumococcus, *Type I*

Exp.	Mice	Percentage survivors	Average length of life in hours
1	A (15 ♂♂, 15 ♀♀)	33	65
	B (15 ♂♂, 15 ♀♀)	55	92
2	A (15 ♂♂, 15 ♀♀)	10	55
	B (15 ♂♂, 15 ♀♀)	17	55
	D (30 ♂♂, 30 ♀♀)	15	52
	E (30 ♂♂, 30 ♀♀)	16	61

In Table I the contrasted mouse lines A and B, D and E show very similar survival rates and average lengths of life, though it is a curious fact that in each experiment the Webster stock, both A and B, contrast favourably with the pure line mice D and E in respect of resistance to louping-ill.

RESISTANCE TO INFECTION WITH A *PNEUMOCOCCUS* STRAIN

In the second half of Table I are recorded the results obtained after intraperitoneal inoculation with the *Pneumococcus*, and here in Exp. 1 the inversion of resistance already suggested in the *Pasteurella* experiment is again indicated; the *Salmonella* resistant line A shows a lowered resistance to the *Pneumococcus* both in survival rate and average length of life as compared with the B stock. This interesting result was, however, not confirmed in Exp. 2, possibly because the dose on this second occasion being more than three times that given in Exp. 1 all resistances were equally swamped. Further experiments on a

larger number of animals with dosage graded down to the lowest possible level are needed. Perhaps a *Pneumococcus* of attenuated virulence might be used, just as was done in the case of the *Pasteurella*. Webster, working with highly virulent *Pneumococcus* and *Pasteurella* cultures, was unable to give the test dose other than intranasally. Tested in this manner, the mouse lines that were resistant to salmonellae were resistant to the *Pneumococcus* and *Pasteurella*, while those susceptible to the *Salmonella* were also susceptible to the other two. The results of Webster's experiments and those recorded here being taken together, perhaps one can say that in these four mouse lines protection against invasion by salmonellae administered intraperitoneally is associated with protection against the *Pneumococcus* and *Pasteurella* when these are administered intranasally, but not when these last are given, like the salmonellae, intraperitoneally. Possibly the fact that normal entrance of both *Pneumococcus* and *Pasteurella* is by the nasal passages explains why the true resistance of the animal is declared only when infection with these organisms is carried out by this route.

Sex differences

In the course of these experiments on resistance to experimental infection it was noted that this characteristic was to some extent associated with sex. In the following Tables II, III and IV this fact is demonstrated by giving the survival rates and average length of life figures for bucks and does separately in those experiments where their respective numbers make comparison possible.

The most striking example of resistance to infection being related to sex is shown in Table II, where the infecting organism is *S. typhi-murium*. The survival rate (except for the non-resistant lines B and E which contain no

Table II. *Resistance of bucks and does infected with* S. typhi-murium

Experiment with	Survival rate		Average length of life in days	
	Bucks	Does	Bucks	Does
Mice A	1/20	9/20	8·2	13·5
Mice B	0/20	0/20	3·7	4·6
Mice D	1/20	3/20	4·5	7·6
Mice E	0/20	0/20	3·6	4·5

Table III. *Resistance of bucks and does to infection with* S. enteritidis *var.* danysz

Experiment with	Survival rate		Average length of life in days	
	Bucks	Does	Bucks	Does
Mice A	0/10	4/20	6·2	6·0
Mice A	0/15	1/15	7·5	6·8
Mice B	0/10	0/20	3·0	2·7
Mice B	0/16	0/14	4·1	3·7
Mice D	0/15	0/15	3·9	4·3
Mice D	0/15	0/15	4·8	4·8
Mice E	0/20	0/10	2·3	3·2
Mice E	0/15	0/14	2·8	3·5
Mice E	0/15	0/14	3·5	3·6

Table IV. *Resistance of bucks and does to infection with Pasteurella* muriseptica

Experiment with	Survival rate		Average length of life in days	
	Bucks	Does	Bucks	Does
Mice A	6/15	2/15	5·4	3·8
Mice A	8/20	0/10	9·3	3·8
Mice B	1/15	5/15	6·9	5·1
Mice B	9/20	3/10	7·8	6·4
Mice D	1/7	5/23	3·5	4·3
Mice D	11/20	4/10	5·6	6·5
Mice E	1/7	3/23	5·2	6·3
Mice E	2/20	2/10	6·6	5·5

survivors) and the figures for average length of life all give evidence for the greater resistance enjoyed by the does in each mouse line. In the case of infection with *S. enteritidis* (Table III), however, this characteristic is much less noticeable. In only two experiments, both of them with line E mice, is the difference between the figures for average length of life over 20 per cent.; but in both these the greater resistance is possessed by the does. In all the remaining experiments the differences are minimal and without significance, and owing to the virulence of the microbe there are only five survivors in all, but it must be noted that all these were does.

Infection with the *Pasteurella* (Table IV) gives a less consistent picture. The survival rate figures suggest a lowered resistance for does, roughly alike throughout the lines, the total surviving for all experiments being 39/124 or 30 per cent. for the bucks and 24/116 or 20 per cent. for the does. Yet, the average length of life figures indicate a distinct difference in reaction between the mouse lines. In lines A and B the does appear less resistant, while in lines D and E the does seem possessed of increased powers of resistance, all differences between the sexes being above or close upon 20 per cent.

Though these observations are based on small numbers, it is clear that in experiments dealing with resistance to infection it is necessary, as has been done throughout these investigations, to balance the numbers of the sexes in each contrasted group.

Infection with the *Pneumococcus* or the virus of louping-ill revealed no correlation between sex and resistance to these agents.

SEROLOGY

Normal antibodies

The presence of normal antibodies in the serum of mice as a factor in and an indication of this resistance to disease is a possibility to be considered. In pursuit of this idea the sera of the four lines of mice considered here were examined for the presence of agglutinins related to the salmonellae employed in the infection experiments. In no case, however, could they be detected even in such low serum dilutions as one in five.

In a further series of experiments devised to detect a difference in normal bactericidins between the different mouse lines, evidence of a serological difference was obtained.

The method employed was varied slightly in the earlier experiments but finally was carried out as follows.

The mice were bled by heart puncture, the blood of several individuals of the same group being combined to supply the required amount of serum and give an average picture of the serum of that group. Mouse serum being deficient in end-piece (Ritz, 1911), guinea-pig complement was needed for the test. After being taken the blood was kept in the cold room overnight; the serum was separated and used the following day. A broth culture of *S. enteritidis* was grown at 37° C. for 18 hours and diluted with saline to an estimated concentration of 1000 organisms per c.c., the actual bacterial content being established by plating. A mixture of broth, bacterial suspension and complement was prepared by adding 2·0 c.c. broth, 1·6 c.c. bacterial suspension and 0·8 c.c. guinea-pig serum to 11·6 c.c. saline, thus giving concentrations of 1/8 broth, 1/10 bacterial suspension, 1/20 guinea-pig serum; of this mixture 0·9 c.c. was added to 0·1 c.c. undiluted mouse serum in a hard glass tube, all processes being carried out in a sterile manner. After 4 hours' incubation at 37° C. the tubes were placed in the cold room for half an hour so that active multiplication might be brought to a standstill and the experimental error due to the difference in time between the examination of the first and the last tubes minimised. The examination consisted in the plating of five capillary drops of the shaken content of each tube, the process being carried out in duplicate. The colonial growth in the plates gave a numerical indication of the influence of the mouse serum upon the multiplication of the micro-organism. No matter how small the seeding, and in general this lay between fifteen and twenty organisms, there was never any sterilisation of the inoculum. The effect of an active serum was rather to interfere with the normal rate of increase. For this reason it is probably erroneous to talk of any bactericidal action. Possibly the lower counts might be due to interference with nutrition or some other metabolic process. Whatever the explanation an inhibiting or bacteriostatic effect, as the following tables will show, certainly appears to be exerted and to a greater extent by the sera of those mouse lines which are more resistant to disease. A preliminary experiment to demonstrate the lack of influence of mouse serum or guinea-pig serum alone is given in Table V; the effect of guinea-pig end-

Table V. *Number of colonies of* S. enteritidis *var.* danysz *on plating with five capillary drops taken after* 4 *hours' incubation*

From tube containing					
				Mouse A serum *plus* guinea-pig	
No serum	Mouse A serum	Guinea-pig serum	Guinea-pig end-piece	Serum	End-piece
1320	1764	1792	1400	108	197

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piece prepared according to Ledingham and Dean (1912) is also tested. In all subsequent experiments normal guinea-pig serum only was used to complement the mouse sera.

Table V shows that the serum of mouse line A complemented with either guinea-pig serum or end-piece is able to inhibit the multiplication of the *Salmonella* seeding to such an extent that instead of reaching a number in the neighbourhood of 1500 the resultant colonial count is round about 150, while the presence of mouse serum, guinea-pig serum or end-piece alone does not occasion inhibition at all. The reliability of the method having been established, a series of experiments was carried out in which the influence of A serum was contrasted with that of B, and the effect of D serum compared with that of E. On occasion the mouse sera were tested in saline dilutions of $\frac{1}{2}$ and $\frac{1}{4}$ as well as undiluted and with a varying complement appeared to give optimal results at a varying dilution. Such an experiment is reproduced in Table VI.

Table VI. *Tubes seeded with* 22 *organisms of* S. enteritidis *var.* danysz *and after* 4 *hours at* 37° C. *tested for increase in numbers by plating five capillary drops in duplicate*

Tubes containing mouse serum	Give colonies on plates	Indicating No. of organisms per c.c.
A undiluted	36; 47	415
B undiluted	88; 100	940
A diluted 1/2	37; 48	425
B diluted 1/2	212; 230	2210
A diluted 1/4	162; 189	1750
B diluted 1/4	332; 361	3465
A diluted 1/16	574; 631	6025
B diluted 1/16	582; 598	5900

Table VI shows that the *Salmonella* implant multiplies less rapidly in the presence of A serum than it does in that of B serum, that with undiluted serum the percentage difference in favour of bacteriostasis by serum is 125, with $\frac{1}{2}$ serum 400, with $\frac{1}{4}$ serum 100, but that when the sera are diluted as much as 1/16 there is no appreciable difference, the organism probably not being inhibited at all by either A or B. As will appear in Tables VII and VIII, results fluctuated considerably from experiment to experiment. It even happened that on occasion the difference was in favour of A serum and as much as 50 per cent. Although it is possible that the small number of mice, usually four or five, supplying blood for an experiment may not give a perfectly average serum, yet it is more probable that these fluctuations are due to some experimental error or errors, the source of which has not been elicited.

In Tables VII and VIII the results of a number of experiments are given; the figures demonstrate the percentage difference in growth obtained, one mouse line serum being compared with the other. Although the fluctuations already mentioned are very noticeable, it is obvious that on the whole mouse A serum inhibits growth more than does mouse B serum, mouse D serum being likewise more inhibiting than mouse E serum.

Similar experiments were carried out with *S. typhi-murium*. They were fewer in number but gave comparable results.

Table VII. *Bacteriostatic effect of A and B sera. Percentage difference in growth obtained*

Nineteen experiments in favour of A serum: 400, 350, 150, 150, 150, 125, 100, 100, 90, 80, 60, 50, 50, 50, 20, 15, 10, 10, 10
Three experiments in favour of B serum: 50, 30, 10

Table VIII. *Bacteriostatic effect of D and E sera. Percentage difference in growth obtained*

Ten experiments in favour of D serum: 200, 180, 180, 70, 70, 50, 50, 50, 10, 10
Seven experiments in favour of E serum: 80, 20, 15, 15, 5, 5, 5

Capacity from antibody production

The agglutinin response of the Webster resistant and non-resistant mice elicited by inoculation with killed vaccine has been studied by Hudack and McMaster (1934). These workers found that after five intradermal injections of *S. enteritidis* the serum of the resistant A mice possessed on the average only half the agglutinin titre (whether H or O was not specified) which the serum of the non-resistant B mice showed. This perhaps unexpected power of non-resistant mice to produce more antibody than do resistant mice was investigated in an experiment on similar lines by the present authors. In this case twenty mice of each of the lines A, B and E received three subcutaneous injections of 60°-killed *S. typhi-murium* vaccine, the doses of 25, 50 and 100 millions being given at intervals of a week. Ten days after the third inoculation the mice were bled by snipping off the end of the tail under anaesthesia and the sera titrated. The results are shown in Table IX.

Table IX. H *agglutin titres of mice inoculated with* S. typhi-murium

Mouse line	No. tested	No. of mice having titres							
		<1/50	1/50	1/100	1/200	1/400	1/800	1/1600	1/3200
A	20	4	7	5	2	0	0	1	1
B	18	3	4	9	0	2	0	0	0
E	19	0	9	8	0	1	1	0	0

From Table IX it would seem that the resistant Webster mice of line A produce a higher mean H titre than do the corresponding non-resistant Webster mice of line B or the non-resistant pure-line mice E. None of these last two lines shows a titre over 1/800, while in the A group there occurs a titre of 1/3200 as well as another of 1/1600. Bearing in mind the small number of mice tested and their individual variability one may regard the average titres of the three lines as being roughly A = 1/320, B = 1/130, E = 1/130. Further verification of these results is needed, as also of the observation which may be noted but not stressed, that members of the pure line E seem to react with greater regularity than do those of the genetically heterogeneous lines

A and B. All but two mice in the E group give titres between 1/50 and 1/100, while in the A and B lines the titres lie scattered over a greater range.

The test for immunity carried out 3 weeks after the last immunising dose by the intraperitoneal inoculation of ½ c.c. of a 1/20 dilution of a 24-hour broth culture of *S. typhi-murium* proved that either the immunising doses were too small or the test dose too severe for a satisfactory immunity experiment, for only two mice survived the period of observation, 21 days. These two mice were, however, of line A, and the average length of life of those dying in the three groups was as follows: 8·1 days for A mice, 3·2 days for B mice, 3·0 days for E mice; it may be noted that the mice in this last pure line stock all died on the same (third) day after the test dose, perhaps an indication of their homogeneity, whereas the range of days in the case of the genetically heterogeneous B mice was from the second to the fifth, A mice dying at dates varying from the first to the twenty-first day.

SUMMARY

A comparison of Webster's selected, genetically heterogeneous resistant and non-resistant mice (here called mice A and B) has been made with two pure lines of mice (here called D and E) which were discovered to be similarly resistant and non-resistant to certain bacterial infections. In both cases, resistance and non-resistance were very marked characteristics when the infection in question was intraperitoneal inoculation with an organism of the *Salmonella* group; when the infective test dose consisted of intraperitoneal inoculations with a *Pasteurella* or *Pneumococcus* or of intracranial inoculation with the virus of louping-ill, these characteristics were no longer maintained, there being no certain difference in the mortality rates of the four mice lines.

In an attempt to discover some factor which might help to explain the very notable differences in resistance to *Salmonella* infection which exist between these mouse lines, the normal antibody content of their sera was investigated.

In experiments modelled on the bactericidal test, but possibly assessing rather the power of the sera to inhibit growth, it has been shown that both resistant races A and D possess this power to a much greater extent than do the two non-resistant races B and E.

A further examination was the estimation of the antibody response after inoculation with killed *Salmonella* vaccine. So far as mouse numbers permit of judgment it was seen that the resistant race A produced a higher mean titre of H agglutinin than the non-resistant races B and E.

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