THE HEALTH OF LABORATORY MICE

A COMPARISON OF GENERAL HEALTH IN TWO BREEDING UNITS WHERE DIFFERENT SYSTEMS ARE EMPLOYED

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(With 5 Figures in the Text)

INTRODUCTION

The study of diseases in laboratory animals stems largely from the need of the laboratory worker for healthy experimental animals. Outbreaks of infectious disease among mice, in use for a particular investigation, have frequently vitiated completely the results. It therefore became necessary to study intensively the natural history of the common infectious diseases of laboratory animals in order to gain knowledge about their prevention. The investigations of Webster (1924*a–e*, 1946), Greenwood, Hill, Topley & Wilson (1936) and Fenner (1949) are almost the only examples of the experimental epidemiological approach to the problem of herd immunity and the behaviour of infection within a mouse colony. But whereas Topley's studies were concerned with a defined highly infectious disease, normally fatal to mice, and the effect of the disease on the colony as a whole, the present communication deals with the problem of general health of colonies of mice; it is a study of normal mouse populations in which two systems of breeding are compared from the standpoint of fertility, general health and freedom from specific infections. Throughout the study comprehensive records were maintained from breeding pairs and their litters and it is these records that form the basis of the discussions presented.

MATERIALS AND METHODS

Description of the colony

The mouse colony which is the subject of this study consists of two main units, referred to as Unit B and Unit A, which are housed in separate buildings and which do not accommodate any other animals. The house for Unit B consists of four small rooms opening off a common corridor. The house for Unit A is of similar construction but different layout and consists of two large interconnecting rooms. Both houses are heated by hot-water radiators in winter, but there is no air-conditioning system or conducted ventilation.

Food, water, bedding and cageing did not differ in the two units.

Food and water

Rowett cubes (Thomson, 1936) were provided in hoppers *ad lib.*, without supplements. Water was always available; the bottles were emptied two or three times a week and refilled with fresh water.

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Bedding

Wood chippings were used throughout and no other form of bedding or nesting was provided. The chippings were changed once a week in Unit A and twice a week in Unit B.

Cageing

The mice were housed in batteries of galvanized iron cages designed to fit as drawers in a specially constructed aluminium rack. Each cage measures 5 in. wide × 18 in. deep × 5 in. high and is fitted with a food-hopper and water-bottle in the front. The aluminium racks measure 4 ft. 9 in. wide × 18 in. deep × 5 ft. 3 in. high and each one can accommodate eighty cages (see Tuffery, 1958).

The mice in Unit B were housed as one pair per cage and in Unit A one male and four females (one harem) to each cage or one nursing female (v.i.).

Colony management and breeding methods

Unit B was run in two sections which were, however, not geographically separated. The most important section constituted the breeding stock, the offspring of which provided fresh breeding stock for its own section or for the production section—the other division of Unit B. All mice from the production section were destined for issue to other laboratories for experimental purposes so that although breeding records were maintained and normal colony management observed the data relating to them were not used in this study. All the information relating to Unit B recorded here was provided by the breeding stock.

The breeding methods for both sections of Unit B was the same; the monogamous pair system was used. Selected mice were mated at 10–12 weeks of age, after which they were not separated until they were finally discarded. As a consequence copulation occurred at the post-partum oestrus and the does were carrying one litter while nursing another. Weaning was carried out at about 21 days; the operation was done on 2 or 3 days of the week so that the actual age at weaning varied between the 20th and 23rd days. At weaning the parents and the litter were separated, each being transferred to freshly cleaned cages. If required for breeding the litter were sexed but still held in their recorded litter groups until ultimate disposal was decided; this depended on the fertility records maintained on the card-index system employed. The breeding pairs were held, as a general rule, until they were 46–48 weeks old, by which time they should have been able to produce seven to eight litters.

Unit A was also run with a breeding stock and a production stock section and the general organization of this unit was virtually the same as for Unit B. The choice of breeding stock was based on the same criteria but the details of mating differed.

In this unit one male was mated with four females and as soon as it was obvious that any one of these females would litter shortly it was transferred to an individual cage. When the young were weaned the doe was returned to the original buck and her companion does and the cycle was allowed to be repeated. This procedure

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doubled the interval between the litters, as compared with the mice in Unit B, since mating could not occur at the post-partum oestrus.

Breeding records

The breeding performance of each female in both units was carefully recorded. For the breeding stock in each unit complete records were held, while an abbreviated form was adopted in Unit A for the production stock. One card was allotted to each breeding pair in Unit B. In Unit A each female had a card and the performance of each harem was summarized on a male card. This male record card summarized the harem's production, and showed the date of birth of all litters sired by the buck, and the number of each litter weaned. In effect, it was only the females whose records were kept. On these cards were noted: parent's reference numbers, the breeding pair's (or harem's) own number and the date they were mated. Breeding performance data included the date of birth of each litter, the number born, number lost prior to weaning, and the number weaned, and the cumulative totals for each of these items. These figures were filled in as they became available. More occasional data, which were also noted as necessary, included the date any replacements were made (i.e. the replacements of dead or culled breeder adults) and the final post-mortem diagnosis if the animal was removed for any reason other than that it had finished its useful breeding life.

Culling and autopsy procedure

The most important aspect in the management and care of laboratory animals of any sort is the daily inspection of the whole stock, by experienced animal technicians, for the early detection of illness or abnormal behaviour. The staff looking after Units A and B were specially experienced in the care of breeding-mice and it was virtually unchanged throughout the period of study reported here. A rigorous culling policy was enforced in both units and any sick or abnormal or suspect animal was immediately removed, killed and sent to the laboratory for post-mortem examination. Any animal found dead in a cage was treated in the same way. At week-ends carcases were refrigerated but otherwise the examinations were carried out the same day. The extent of the post-mortem examination depended on the preliminary findings and the clinical report from the technician responsible. Normally the examination was limited to the naked-eye appearance of all the organs; whenever any abnormal condition was noted or the clinical history suggested the need, full pathological or bacteriological investigations were carried out. The results of all post-mortem examinations were entered in the laboratory ledger and subsequently the relevant details were transferred to the record card kept for each animal in the colony.

Method of recording

Animals removed from the colony for any reason were classified under four headings:

Dead mice were those found dead in their cages. These were comparatively few and were always submitted to some form of laboratory examination.

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Culled mice were those removed from the colony and killed. Animals were culled mainly for health reasons or poor breeding or because they were contacts of sick animals. In the case of Unit B the partner of a culled mouse was automatically culled also. All culled mice had a post-mortem examination.

Cast mice were those removed from the colony solely because they had reached the end of their useful breeding life. Although healthy, these old mice were seldom suitable for experimental purposes and they were consequently discarded.

Issued mice were healthy mice removed from the colony, before they had finished their normal span of breeding life, for issue to local laboratories for experimental use. Although full records were maintained for these animals the data are not included in this study.

In the figures illustrating population curves, 'smoothed' values have been used throughout. That is to say, each point plotted represents the average of the five adjacent values round it. This method was used in order to smooth out minor irregular variations in the data, so that such real variations as occurred were easier to detect. The method is that used by Greenwood *et al.* (1936). All data were calculated on a weekly basis; thus the mortality and morbidity curves (referred to as q_x curves) were computed as follows:

$$q_xT = \text{probability of dying or being culled during week } x$$
$$= \frac{\text{smoothed no. of deaths and culls during week } x}{\text{smoothed no. alive at beginning of week } x}.$$

Similarly, the probability of being culled or dying at age

$$x = q_xA = \frac{\text{smoothed no. dying at age } x}{\text{smoothed no. alive at age } x}.$$

It was not possible to determine the exact date of birth of the mice from the records, but a fairly accurate estimate could be made. All matings were made between 10 and 12 weeks of age, and the exact date of death was always known. The date of mating also was known, so that the age calculated for a mouse was the interval between mating and dying, plus 11 weeks. This figure was used in all further calculations.

OBSERVATIONS

Table 1 summarizes the basic data relating to the two mouse units studied.

Losses with calendar time

In studying losses in a mouse colony, the most obvious method with which to begin is to assess the loss rate due to various diseases over the period of the colony's history.

In Figs. 1 and 2 are plotted graphs showing (*a*) population and (*b*) q_xT (both smoothed) for mice of Units B and A respectively. Certain points need to be emphasized with regard to these and all subsequent graphs. The term 'population' refers only to breeding adult mice and mice which will become breeders; unweaned mice, and mice destined for the issue stock are not included in any of these figures.

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The records included in this study are not completely synchronous. For example, week no. 1 in the Unit B graph corresponds to the week ending 10 April 1954 and in the Unit A mice graph to the week ending 6 April 1953; weeks nos. 1–91 (B) mice correspond to weeks nos. 45–135 (A) mice and covers the period April 1954 to December 1955.

Table 1. *Basic data referring to two units of a mouse breeding colony*

	Unit B	Unit A
Nos. of adults included ♂	512	215
♀	512	983
Total	1024	1198
Proportion of ♂:♀		
Expected*	1:1	1:4
Actual	1:1	1:4·57
Breeding system	Pairs	Harems
Period covered by analysis		
Dates	April 1954–April 1956	June 1953–January 1956
No. of months	24	31
Overall average length of life		
Actual	41·2 weeks	—
Expected*	46·48	Approx. 64
Average no. of litters reared per ♀		
Actual	6·38	5·32
Expected*	7–8	7–8
Age at mating	10–12 weeks	10–12 weeks
Total deaths		
♂	3	3
♀	50	56

* Values listed as 'expected' represent the standards aimed at by the technicians in managing the colony.

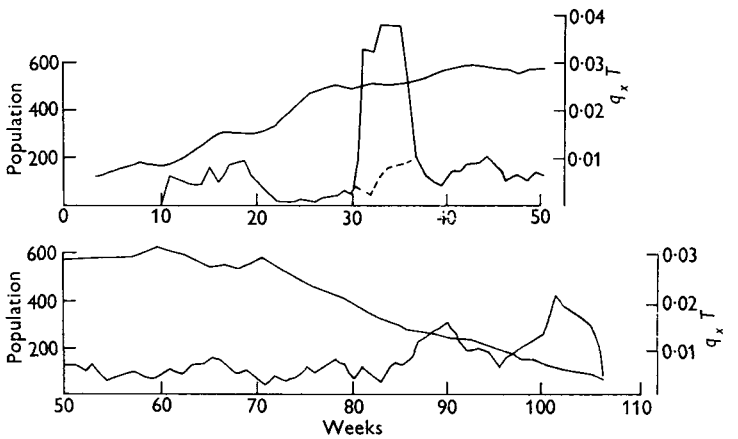

Fig. 1. Unit B—population and $q_x T$ curves.

Ignoring the declining portions of these population curves, it can be seen that the population of Unit A is about a third greater than the population of Unit B at any point in its history. The total numbers of mice in each unit are, however,

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very much the same—see Table 1. The reason for this is that the breeding system practised in Unit A (harems) gives a longer period between successive litters, so that in order to maintain a given output per week, more mice must be kept in Unit A at any time than in Unit B. Further, the mice in Unit A, to be economic producers, must be held for a longer period. There are thus two epidemiological factors which differentiate the two units. There is always a larger population at risk at any given time in Unit A and in this larger population mice remain at risk for a longer period than the mice in Unit B.

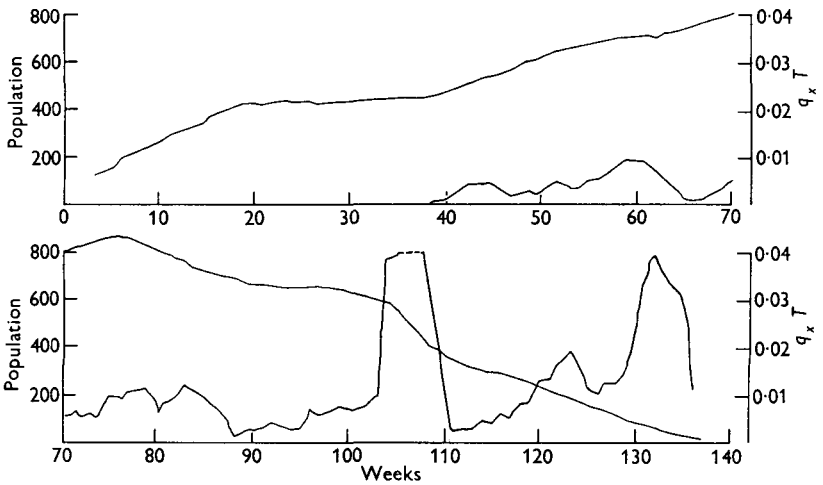

Fig. 2. Unit A—population and $q_x T$ curves.

In Unit B it was the practice to mate new breeders intended to replace old pairs in batches at monthly intervals. These batches will be referred to as 'mating groups'. In Unit A replacements were mated at weekly intervals, so for the purpose of comparison with Unit B, mating groups in Unit A were collected from mice whose date of birth fell within the same calendar month. In this way, fourteen mating groups were found in Unit A, and thirteen in Unit B. The latest of these mating groups in each unit was set up a year or more after the first, and it is possible that these later groups were exposed to risks different from that of earlier groups.

Taking into consideration the longer average life-span of the mice in Unit A, it will be seen that each individual mouse in this unit is, on the average, in contact with (i.e. alive at the same time as) a greater number of mice in a greater number of mating groups than a Unit B mouse in its population. Members of a greater number of different mating groups will be alive at the same time in Unit A than in Unit B. There was, for example, at least one mouse of mating group I still alive when members of group XIV were some 6–8 weeks old in Unit A (a span of fourteen groups), whereas the maximum number of groups spanned by at least one mouse in Unit B was ten. There is thus a third differentiating factor—more mating groups of differing herd experience were alive at the same time in the population of Unit A than in the population of Unit B.

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In both Unit A and Unit B mice were constantly being added to, and subtracted from, the population. The 'turnover' rate, however, would be different in each unit—1024 in 24 months in Unit B, and 1198 in 31 months in Unit A.

With reference to the q_xT curves in Fig. 1 (Unit B) it will be noted that after an initial rise and fall, the q_xT fluctuates about 0·005 throughout most of the period covered in this study (i.e. 2 years) with a slight rise towards the end of the period, from the 86th week onwards, and one relatively marked rise during weeks nos. 31–35, when the q_xT rose to nearly 0·04 (which is still only about 3 % loss at that time). This very large rise can be accounted for by seventy-six mice which were all culled on one day, and recorded as being infested with lice. The trouble never recurred, and though at the time it represented a high mortality among the breeders, it cannot be considered a serious source of loss in this colony. If the q_xT is adjusted by ignoring these mice, it drops to the average level (dotted portion, Fig. 1). The slight rise at the end of the period covered—as from about week no. 86—is probably due to the decreasing numbers of mice included in its computation, rather than to any other factors. The shape of the curve does not suggest that a disease factor ever entered the colony, or suddenly became overt and gave rise to any abnormal losses. Tyzzer's disease, which was present during all this time, contributed only a very small part to the q_xT values calculated.

In studying the q_xT curve for the mice in Unit A it must be appreciated this unit was formed about a year before Unit B and at that time the policy of rigorous culling had not been introduced. It was only after several months in the history of Unit A that the value of such a system was realized and the decision to develop it fully was made, so that the q_xT curve for the mice evolved as Unit A was developed. By the time Unit B was formed, however, the rigorous culling policy was standardized, as far as was possible, and applied strictly to both units.

In Fig. 2 (lower half), with a population of about 600 mice in Unit A at the 108th week, it will be seen that the q_xT rose sharply to a peak figure of 0·04 which strongly suggested some outbreak of disease was responsible for these losses. Reference to the records showed that Tyzzer's disease accounted for these, but this point will be discussed in detail later.

The small peak during December 1955 is partly due to the decreasing numbers of mice included in these records, and possibly also due to some kind of seasonal rise towards the end of the year. The q_xT curve for November, December 1953 and January 1954 also tended to be a little above the average level.

Throughout this discussion it is assumed that the q_xT curve is an estimate of the overall health of the colony. This seems to be a reasonable assumption, provided that the criteria used for deciding to cull certain animals remain reasonably constant during the period covered by this study. The same personnel were in charge of mice and mouse autopsies and there had not been any significant changes in procedure during the period. We may, then, summarize our observations so far by saying that the colony with the largest number of mice alive at any one time maintained the highest average q_xT.

The q_xT curves plotted in Figs 1 and 2 are an estimate of the health of the mice in these two units throughout the unit's existence, i.e. they are a measure of losses

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against calendar time. But they do not give any information about the age distribution of losses, and to do this, a life-table system is required. The risk of dying, or being culled, at each week of age (q_xA) was calculated for all the mice in each unit. These q_xA values are shown in Figs. 3 and 4, together with curves showing the number of mice alive at each week of age, and the percentage which survive to final casting for each week of age. It can be seen that the risk of dying or being culled changes throughout the life of each mouse, and that the changes are not the same in each unit. Thus for the mice in Unit B there is clearly a greater risk at

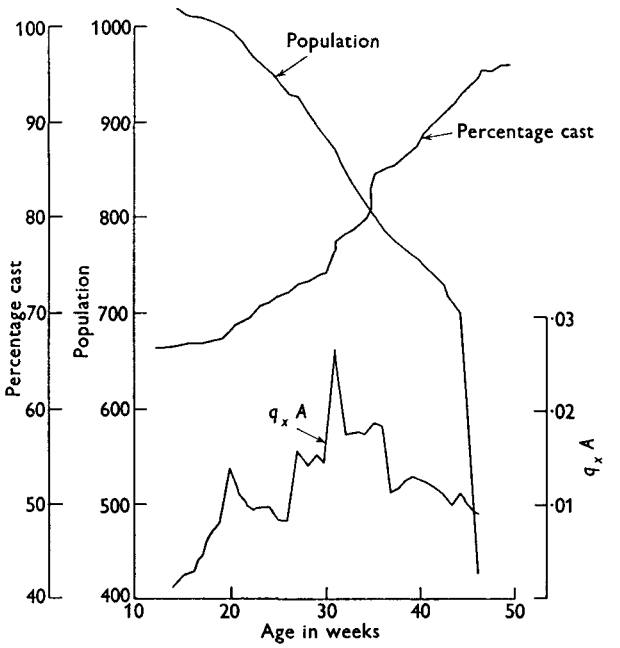

Fig. 3. Unit B—curves showing number of mice alive at any week of age, percentage alive at any age which survive to casting, and q_xA.

about middle age (26–35 weeks) than at either earlier or later ages, but in Unit A the risk rises continuously from mating to about early old age (67 weeks) and from then on very rapidly. Part at least of this rapid rise is due to the decreasing number of mice still alive over 70 weeks of age. Nevertheless, up to the 40th week the risk is still lower for mice in Unit A than for those in Unit B at any age, but from the 40th week onward the curve for Unit A rises steadily so that the average q_xA from 40 to the end of their life is higher than the average for the whole life-span of the mice in Unit B.

Now the average losses per calendar week throughout the lifetime of 1198 Unit A mice was higher than that for 1024 Unit B mice, as was also the total percentage lost as deaths and culls, and the calculation of the curves in Fig. 4 demonstrated that it was the older mice that accounted for this difference. Further, the fact that it was old mice that contributed significantly to the weekly losses helps to explain the longer delay after setting up Unit A before the q_xT became comparable with that at the beginning of the B unit's history. While in

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neither unit was there ever a serious disease problem (epidemic, etc.) the general level of health (as judged by the weekly loss rate) was better among the monogamous pairs than the harem groups. Keeping the mice to an older age under the harem system meant that, once the unit was established, a higher average weekly loss rate had to be accepted and that older animals had to be culled more and more heavily.

The overall health record of the two units showed that the Unit A mice suffered slightly greater weekly losses, and markedly greater total losses, than those in Unit B; they also lost proportionately more mice near the end of their lives. Another method of comparing these two units is to plot the percentage of mice alive

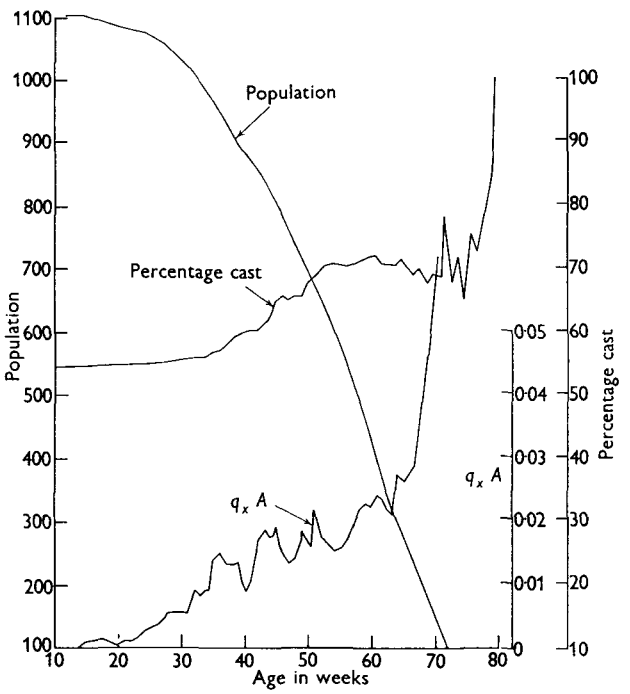

Fig. 4. Unit A—curves showing number of mice alive at any week of age, percentage alive at any age which survive to casting, and $q_x A$.

at each given age who are finally cast, i.e. killed only because they have reached the end of their useful breeding life. The two curves illustrating this are shown in Figs. 3 and 4. The monogamous pairs system will be seen to be more efficient and to maintain a better level of health. In Unit B mice, some 65 % of those mated could expect to be cast and the percentage cast rose steadily as the mice grew older. Among the Unit A mice, 55 % of those alive at mating age were cast but the percentage showed a steady rise only around middle age, when it reached 70 %.

The number of mice surviving to the end of a useful breeding life is clearly a measure of the general health and efficiency of the breeding colony, and provided the rigorous standards controlling the system of culling are maintained the mice that escape culling must be presumed to be healthy. If any had been exposed to any special risk as contacts of sick animals they would have been automatically

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culled. In Unit B the rate of culling was roughly constant except for an increase at middle age, and this maintained a steadily improving performance on the part of the unit in terms of numbers of mice reaching the end of their useful breeding life. In the Unit A mice the rate of culling steadily increased, but this procedure was effective only in improving the unit's performance at middle age; at other ages it had little effect. The high level of culling among older mice (about 55–70th weeks) made no improvements in the percentage cast beyond that achieved by the age of 53 weeks. In other words, the practice of culling among the monogamous pairs resulted in an improved breeding performance at all ages, but among the harem mice it was a profitable practice only during middle age. Culling maintained a fairly high level (low q_xA) in terms of general health at all ages including old age among Unit B mice, but did not prevent a fall among the older mice in Unit A (a rise in the q_xA).

Losses in mating groups

The comparison of losses in the two units on the basis of risk of being culled and percentage survival to casting at different ages may be also applied to individual mating groups. That is, one may calculate the percentage of mice in each mating group at given ages that survive to final casting, and similarly q_xA values can also be calculated. A study of these figures for each mating group will demonstrate any difference there may be between the health of mice mated at different stages of the colony's history, or at different times of the calendar year.

In Unit B the percentage cast ranged between 35 % (mating group II) and 91 % (mating group XI), with an overall average of 68·2 %. Unit A showed a worse record—ranging from 28 % (mating group X) to only 65 % (mating group I) with an overall average of 49·2 %. The percentages cast within each mating group of both Units are shown graphically in Fig. 5. The figures for Unit B show a definite improvement from the beginning of the colony's history, though it is doubtful whether it is a continuous improvement; with group V (i.e. about the 40th week of the unit's existence) the maximum level appears to have been reached, and further groups show performances fluctuating around this level. With Unit A, however, there are no signs of any improvement, or even change in performance, throughout the whole of fourteen mating groups, in 18 months. (The figures for groups I, X and XI are the only ones to differ significantly from the mean value of 49·2 %, values of P being respectively 0·3, 0·5 and 1·8 %.) In this respect, then, the mice mated 18 months after the colony's foundation were no more efficient than the foundation stock.

Further breaking down of the figures for mating groups has revealed little else of interest, except that the trends observed for each unit as a whole (shape of q_xA curves, etc.) continues throughout the whole of the period covered in this analysis. Thus, in Unit A both the earliest and the latest mating groups show the increased risk of culling among the oldest animals; they also show that, in general, culling of poor animals tends to reach its maximum around middle age (40–50 weeks), and that at this age it leads to the greatest improvements in the percentage of mice which survive until they are finally cast. The amount of culling

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done at earlier or later ages than this was in every group insufficient to lead to a better performance among those retained. In Unit B, culling rates were about equal at all ages in all the mating groups, although perhaps slightly less at ages of 10–20 weeks. The net result of this was a more or less steady improvement as mouse age increased.

Among both Units A and B the actual mortality rate was so small as to allow of no conclusions being drawn, save that no epidemic was ever present.

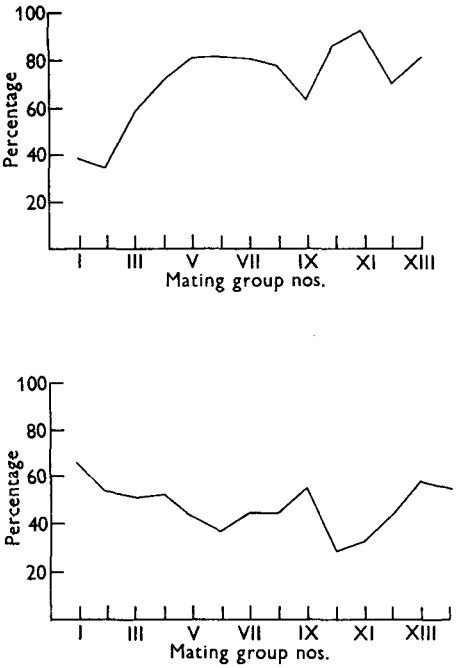

Fig. 5. Percentage cast in each mating group. Above, Unit B. Below, Unit A

Cause of losses

A total of 329 mice in Unit B and 503 in Unit A were culled or found dead. All these animals were autopsied, and the findings are listed in Table 2.

Tyzzer's disease was responsible for the only real marked increase in losses which occurred in either group during the period covered by this survey. Fig. 2 shows that there was a fairly well defined increase in the q_xT value in Unit A during weeks 103–110 (i.e. about June 1955) and analysis of the record cards shows most of this to be ascribable to Tyzzer's disease. During this period (May, June and July), 152 mice were culled or found dead, of which fifteen were typical cases, and 102 were contacts but without evidence of the disease. Fourteen of these cases occurred between weeks 106 and 110 and were found in mating groups nos. VII, X, XI and XIII. The average age in weeks of affected animals in these groups were: VII—62, X—49, XI—41, XII—43 and XIII—37. The numbers of cases within these groups was VII—2, X—2, XI—6, XII—1 and XIII—3. Cases thus occurred among the youngest and the oldest mice alive at this time.

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Table 2

Diagnosis	A mice			B mice		
	No. culled	No. dead	% of population	No. culled	No. dead	% of population
Tyzzer's disease	37	5	3·82	3	5	0·78
Negative contacts of Tyzzer's disease	141	0	12·82	6	0	0·58
Dystocia and pregnancy complications	1	3	0·36	2	7	0·88
Ear mange	20	0	1·82	0	0	0
Nasal alopecia	0	0	0	12	0	1·17
Lice	0	0	0	76	0	7·49
Impaction	35	5	3·63	4	13	1·66
Enteritis	5	22	2·45	1	5	0·58
Infertile	66	0	6·00	22	0	2·15
Poor performance	22	0	2·00	14	0	1·37
Exp. investigation	20	0	1·82	16	0	1·56
Pneumonia	11	6	1·54	1	2	0·29
Abscesses	11	0	1·00	1	0	0·09
Cysts	4	2	0·54	0	0	0
Tumours	12	1	1·18	3	3	0·58
Oedema	11	0	1·00	0	2	0·19
*N.A.D.	22	1	2·09	110	1	10·84
Putrid	2	8	0·91	0	3	0·29
Miscellaneous	25	5	2·09	6	11	1·66
	420	53	45·07	171	41	32·16

* N.A.D. = nothing abnormal detected at autopsy.

DISCUSSION

There are four recognized diseases of mice that are of special importance to mouse-breeding establishments—salmonellosis, ectromelia (mousepox), Tyzzer's disease, and epidemic diarrhoea of infant mice—because of the general frequency of their occurrence and the possible severity of outbreaks. A recent survey of a number of the major mouse-breeding establishments in this country (Tuffery, 1956) fully confirmed this.

Salmonella infections and mousepox have long been known as the most serious hazards to mouse breeders and the pathology and epidemiology of these conditions have been very fully investigated. Nevertheless, so frequent is the presence of these infective agents in mouse colonies that comparatively few establishments have been able to claim freedom from them over long periods.

Tyzzer's disease, as fully manifest, presents an easily recognized pathological picture at post-mortem examination, but our knowledge of its infectiousness and epidemiology generally is very inexact.

Epidemic diarrhoea of infant mice is known to be a very highly infectious disease of suckling mice that appears to be innocuous to older mice. The virus causing the condition has not been properly identified but epidemiological studies indicate that it is air-borne and control of infection is only possible by the employment of elaborate precautions which require 'filter-cages' for each pregnant female near term (Kraft, 1958).

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In so far as this colony is concerned there has been no evidence of infections with salmonella organisms or the virus of mousepox since it was first formed in 1953. The nine breeding pairs that constituted the original Unit A were very carefully selected from clean stock and from that date onward the colony has been developed in isolated accommodation without additions from outside stock. The colony management has been in the hands of specially trained animal technicians, not employed on other duties, who have been constantly on the watch for any sign of these infections. Salmonella surveys have been negative throughout and although specific tests for the mousepox virus were not undertaken there was never any suggestion from routine examinations, clinical observations or epidemiological records of this infection either within the colony or in issued stock to local laboratories.

There was only one outbreak of illness that could be regarded as serious—fifteen cases of Tyzzer's disease occurring over a period of about 7 weeks during the summer of 1955—and because of this there was very heavy culling of contacts and others. Whether this drastic action was responsible for limiting the outbreak is uncertain; even the intravenous injection of presumably infective material is only irregularly successful in reproducing the disease. The organism, *Bacillus piliformis*, originally described by Tyzzer (1917) as responsible for the disease, has never been cultivated on laboratory media and from the evidence available from the experience of Gard (1944) and others it would appear that, whatever the aetiological position ascribed to *Bacillus piliformis* may be, the initiation or development of the disease, *per se*, would appear to depend on factors not yet defined. Gard's experience suggested that a moist stock diet in the summer months may be related to the initiation of the disease. The diet of the colony concerned in this study has been standardized from its inception as a proprietary brand of a dry cube diet with water separately available from individual bottles and it would be expected that this standardization would eliminate the hazard. Experience has shown, however, that proprietary diets may vary in actual constituents although maintaining the correct balance of protein, carbohydrate, etc., and it may well be that the outbreak was related to a combination of slightly changed conditions affecting mice which, for some reason, were more sensitive to the change than the rest of the colony.

Epidemic diarrhoea of suckling mice is usually a serious and highly infectious disease that appears to attack only the unweaned mouse. Both units of the colony have on occasions been severely affected, but between such outbreaks they have been entirely free from the disease. Unfortunately, it is only recently that disease records have been kept for suckling mice so that reliable information about the effect of the disease on the two units of the colony is not available.

One other factor has not, so far, been discussed—the sex ratio of losses. Table 1 shows that the totals of mice found dead in their cages or dying were small for both units, but that the females accounted for most in each case, by a very big margin. It was presumed that this might be associated with the strain of litter-bearing, but it is interesting to note that those mice which would be expected to have been so affected (i.e. the monogamous pairs) are just the ones who show the

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better records. Although it is frequently assumed that litter-bearing influences the female's susceptibility to disease, it would seem that other factors (colony management, etc.) have a greater influence on sickness records, where different breeding systems are being compared.

The ratio of deaths to culls in both units of mice can be regarded as reasonably satisfactory from the breeder's point of view. There is little doubt that culling animals in the early stages of many diseases can reduce the chances of cross-infection. In this colony, it is likely that sick or poor animals were removed just as early as was possible, because the technical staff have been trained to examine all mice daily and to cull any doubtful animals. Subsequent proceedings ensured that whenever urgent action was indicated it was taken without delay. Further culling was always done whenever the preliminary examinations suggested an infective condition.

Throughout this survey it has been obvious that the Unit A mice have a worse health record than those in Unit B. This is contrary to the reported experience of others, who consider that harem breeding, because the females are not so frequently mated, results in better stock. So far as the health of this colony is concerned, there is no evidence to support this opinion, though on productivity questions the mice of Unit A may show certain advantages (Bruce (1954) has compared certain aspects of breeding economy for harem- and pair-bred mice), but this subject is outside the scope of this paper.

Unit A, throughout most of its history, suffered a higher total weekly loss rate than Unit B, and the morbidity curve shows at least one minor epidemic peak; Unit B shows no sign of any peak. A study of the age relations in Unit A revealed that it was the older animals which were responsible for the higher loss rate. A study of the loss rate/age curve and the estimation of the percentage of mice of each age which were finally cast (i.e. did not leave the colony prematurely through sickness) showed that the culling practice resulted in different effects in the two units. Thus, among Unit B, a more or less steady rate of culling was kept up throughout the unit's history, and (with reference to mouse age) a maximum culling rate was reached during middle age; this resulted in a steadily increasing proportion of mice reaching the end of their potential life-span as age increased. This high proportion of mice serving their entire useful life-span (approx. 48 weeks) was reached about 1 year after the founding of the unit, and was maintained thereafter. In Unit A a steady culling rate was finally reached about 1 year after the unit's foundation, but there was little improvement in the proportion of mice that served their full breeding life throughout the whole 31 months covered by this survey. Further, the culling rate increased more or less steadily as mouse age increased, but it effected an improvement in the proportion of mice serving their full life-span only for the middle period. (Middle age in the A mice, of course, being older than in the B mice—about 30–35 weeks and 40 weeks, respectively.)

The actual losses in the two units are listed in Table 2 in accordance with the diagnosis made at the post mortem of mice found dead or killed after culling. Although there would seem to be no doubt from these figures that the mice in

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Unit A had a worse health record than those in Unit B, this table has a wider interest than illustrating the variety of abnormal conditions found in a mouse colony with reasonably good health records over a period of nearly 6 years. The interest centres round Tyzzer's disease and the very significant difference between the incidence of the disease in Units A and B. In the light of our very incomplete knowledge of this condition it is not reasonable to classify it as a straightforward infectious disease and to put it in the same category as salmonellosis. From the results of previous studies (Tyzzer (1917), Gard (1944)) it is possible that Tyzzer's bacillus (*Bacillus piliformis*) may be widespread in some mouse colonies. It would appear that the organism is normally non-pathogenic or of a very low pathogenicity, and does not invade the tissues and give rise to disease unless changed conditions, which at present cannot be defined, upset the existing equilibrium. These could be climatic, dietary, or possibly trivial conditions of temporary unfitness. It is suggested that the increased incidence of Tyzzer's disease in Unit A, together with the possibility that some of the cases of acute enteritis were early manifestations of the same disease, are all expressions of the inferior general health of Unit A as compared with Unit B.

In comparing the two units there were many factors common to both. Apart from the more suitable accommodation for Unit B with its four small separate rooms against the two large connecting rooms for Unit A, the methods of cageing, racking, bedding and feeding were identical. Different staff cared for each unit, but the techniques employed were as far as possible the same—these included the daily examination of all cages and the policy governing culling and the maintenance of records. Post-mortem procedure was the same for the two units. The fundamental differences between the two was the method of breeding and it may be of interest to consider various details that might expose mice in Unit A to greater risks which could be related to the harem system of breeding, taking into consideration the fact that this unit was founded in March 1953 whereas Unit B, which stemmed from the other, was not properly organized until December 1954. Thus the records for Unit A covered a longer period and a somewhat larger total population. There were more mice in this unit at any one time and they remained in it for a longer period. Although the females bore litters half as often as those in Unit B the mice were moved to other sites within their own unit with some frequence, and because the females were isolated to litter-down they were handled very much more often. In addition, replacements from the production stock of the unit were made in suitable cases; replacements were never made in Unit B in any circumstances. Finally, the fact that mice in Unit A were retained for a longer period than those in Unit B meant that there were more old mice and the records showed that these contributed significantly to the total losses in the unit.

In considering the present study as an epidemiological investigation it cannot be properly compared with the experimental epidemiological studies of herd immunity of Topley and his colleagues (Topley, 1942). These workers were studying a defined highly infectious disease of mice and its effect on the colony, whereas this report is concerned with the comparison of the general health and

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virility of two groups of mice raised by two different breeding methods, where the maintenance of group-health was very largely influenced by a rigorous culling procedure applied equally to the two groups being studied. Although for the purpose of a strictly controlled experiment it can be argued that the two units were not exactly comparable, it seems reasonable to conclude, under the conditions obtaining, that the monogamous-pair breeding system was superior to the harem breeding system.

SUMMARY

Two units, within a mouse-breeding colony, with different breeding systems, have been compared from the point of view of general healthiness of the breeding stock. In one unit the monogamous-pair system, involving post-partum oestrus mating, was employed and in the other the harem system, with isolation of the pregnant females for each litter-down until after the post-partum oestrus. The two units were housed separately and had different staffs. The monogamous-pair unit was accommodated in four small rooms not directly connected; the harem unit in two larger connecting rooms. The methods of cageing, bedding, feeding, watering, care, culling and subsequent procedures were identical for both units and the same system of recording individual detailed information relating to health and breeding was followed for the two units. The size of the two populations studied was 1198 and 1024, respectively, the larger number belonging to the harem unit in which the mice were retained for a significantly longer period. These mice were moved more frequently and handled much more often.

Apart from a small outbreak of Tyzzer's disease (in the harem-bred unit) and sporadic cases in both units spread over the whole period of the survey—some 3–4 years—the general health of the two units was good. There were no cases of salmonella infection, mousepox, pasteurellosis or other serious infections. Throughout the period both units maintained a high standard of productivity and there was no evidence that the mating of the monogamous pairs at the post-partum oestrus led to any weakness or ill health. As would be expected, however, the losses from death and culling were greater among the females in both units.

The health record of the monogamous-pair bred unit was consistently higher than that of the harem-bred unit. There were more cases of Tyzzer's disease in the harem-bred mice and more evidence generally of ill health in this unit. Infertility was three times greater with the harem-bred mice as compared with those in the monogamous-pair unit.

Details of the two systems are discussed and although the records maintained for the two may not be strictly comparable it is concluded that, under the conditions obtaining, the monogamous-pair breeding system yielded a healthier colony of mice than the harem breeding system.

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