RÔLE OF INBORN RESISTANCE FACTORS IN MOUSE POPULATIONS INFECTED WITH BACILLUS ENTERITIDIS

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The experiments described in this paper deal with the rôle of inborn resistance factors of the host in determining the severity of epidemics and with the question of whether inborn resistance or acquired immunity is the more important in determining survivorship.

Technique

Mice used in these experiments were of four sorts.

W-Swiss strain mice were used as carriers in Experiments 1 and 2. These mice have been selectively bred by us for susceptibility to central nervous system virus infections but not to mouse typhoid. Following a *per os* instillation of 5,000,000 *B. enteritidis* mouse typhoid bacilli, 50 to 60 per cent succumb regularly.

White-face strain mice were used as carriers in Experiment 3. These mice are regarded as a genetically pure line. Following a *per os* instillation of 5,000,000 mouse typhoid bacilli, 95 to 100 per cent succumb regularly (1).

Selectively bred susceptible and resistant Rockefeller Institute mice were the actual test animals employed in all experiments. These lines originated from the Rockefeller Institute strain, pen inbred and maintained on a special Steenbock diet, of which 42 per cent succumb to 5,000,000 *B. enteritidis* mouse typhoid organisms given by stomach tube. Following selective inbreeding of this R. I. strain (2), a resistant line was obtained, of which not more than approximately 10 per cent succumb to the standard test dose of *B. enteritidis*. A susceptible line was likewise selected, of which approximately 90 per cent succumb to the test dose. The resistant line also withstands 1,000 times the dose fatal to the susceptible line. We had for testing, therefore, individuals of high inbred resistance to mouse typhoid under standard conditions, nine of ten of which would survive or succumb to infection according to prediction.

These mice were combined in various proportions to make up populations into which mouse typhoid was introduced. A single cage of standard size was used for simplicity, although a crowding factor exerted a definite influence on mortality. Mouse typhoid was introduced by feeding *B. enteritidis* by stomach tube to certain individuals and subsequently adding them to the population and permitting the resulting infection to spread among the constituents "naturally." Cages were cleaned as routine. The modified Steenbock diet was employed (1). Dead mice were autopsied and cultures taken of spleen for identification.

The strain of *B. enteritidis* organisms used in these experiments was obtained origi-

nally from a wild mouse and since that time has been maintained in the laboratory under conditions in which virulence has remained at a constant level (3).

EXPERIMENTS

The first experiment was designed to study the epidemiology of mouse typhoid in a population in which at least 50 per cent of the mice were known to be inherently resistant.

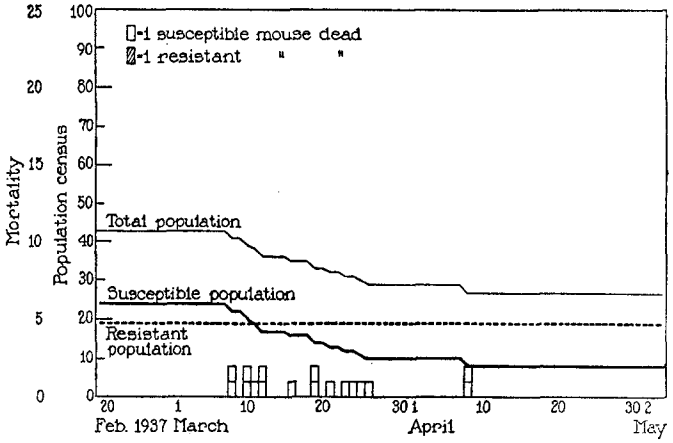
Experiment 1.—Twenty-four Swiss mice with identifying marks were placed in a pen with nineteen mice of the selected resistant strain likewise marked. Ten mice of the selected susceptible line were marked and each given by stomach tube 0.5 cc. of broth containing 5,000,000 *B. enteritidis* mouse typhoid organisms. 24 hours later they were added to the above population. The usual feeding and maintenance routines were instituted and mice prostrate or dead were autopsied as far as possible and cultured for the presence of mouse typhoid organisms.

The experimentally infected mice commenced dying on the 6th and were all dead of mouse typhoid by the 9th day. The Swiss contacts commenced dying on the 18th day and continued thereafter for 32 days (Text-fig. 1). During this period sixteen Swiss mice (66 per cent) died, of which thirteen were autopsied and proved positive for mouse typhoid bacilli. This 66 per cent mortality was in accord with the prediction based on *per os* titrations. We had, of course, no prior knowledge as to which Swiss individuals would succumb and therefore did not know whether the 34 per cent which survived were at the outset inherently resistant or had acquired an immunity through non-fatal infection and had therefore survived. 26 days following the last fatality the eight Swiss survivors were sacrificed and autopsied. Five (62 per cent) showed positive spleen cultures and one serum agglutinins titering 1 to 10.

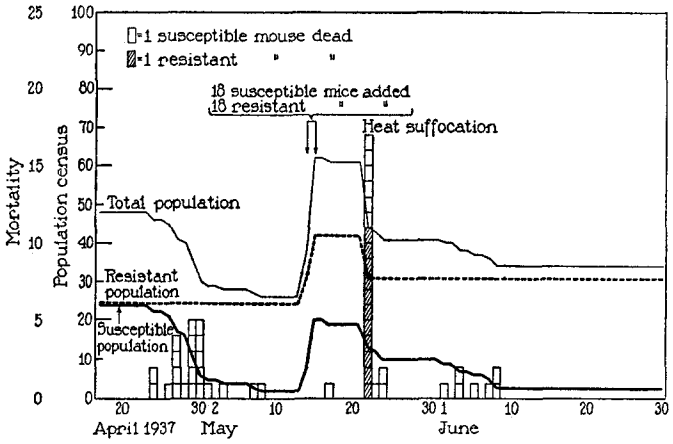
The striking result of this test is that, according to prediction, none of the inherently resistant mice succumbed. At autopsy, however, following completion of the experiment, eight (58 per cent) had positive spleens. The relative proportion of susceptibles and resistants infected was similar, although mortalities were widely different. This relationship has been pointed out before as indicating plainly that so called infectivity *versus* virulence phenomena cannot be regarded as distinctive properties of the parasite (Greenwood, Hill, Topley, and Wilson, 4), but can be shown by epidemiological experiment to be phenomena dependent upon host differences.

The second experiment was planned to study the epidemiology of mouse typhoid in a population in which the inherent resistance of each individual was predictable to within a 10 per cent error.

Experiment 2.—Twenty-four selected susceptible and twenty-four selected resistant mice were given identification marks and placed in a standard pen. 3 days later, sixteen Swiss mice were labeled and each given by stomach tube 0.5 cc. of broth containing 5,000,000 *B. enteritidis* mouse typhoid organisms. 24 hours later they were added to



TEXT-FIG. 1



TEXT-FIG. 2

TEXT-FIGS. 1 and 2. Fate of susceptible and resistant mice exposed to *B. enteritidis* mouse typhoid (Experiments 1 and 2).

the above population. Feeding, maintenance, autopsy, and culture routines were practiced as in Experiment 1.

The experimentally infected Swiss mice commenced dying of mouse typhoid on the 6th day and were all dead save three by the 10th day.

Another succumbed 7 days later, a second after 2 more weeks, and the remaining mouse survived. The susceptible contacts commenced dying on the 8th day (Text-fig. 2). During the next 15 days mortalities were of epidemic proportions, taking all but two. From the spleen of each fatal case, mouse typhoid bacilli were recovered.

The resistant contacts remained well according to prediction during this period in which their susceptible cage mates, in intimate contact, were experiencing an epidemic. When the outbreak subsided they were the sole survivors with the exception of two susceptible contacts plus two injected Swiss mice. It was clear, therefore, in this experiment that the twenty-six survivors of a mouse typhoid epidemic were the individuals (92 per cent) with high inborn resistance at the outset.

The failure of the susceptibles to survive through development of immunity was thought to be due possibly to the large dosage of organisms excreted by the infected Swiss mice. If susceptibles were exposed during the post-epidemic period, when no deaths were occurring and organisms were spread chiefly by the resistant survivors, the ensuing events might be different. Consequently, on the 28th day, six susceptible plus six resistant mice were added and on the 29th day, twelve susceptibles and twelve resistants.

On the 2nd day following, one of the original susceptibles died, leaving only one remaining. 5 days later an accident occurred resulting in heat suffocation of twenty mice in 3 days. Nine of these were original resistants. Only four could be autopsied but no typhoid was found. Two were resistant recruits, likewise negative for mouse typhoid. One was the last remaining original susceptible and one an original Swiss, while eight were susceptible recruits. Only six could be autopsied, but of these four were positive. This experience indicates that the resistants, although resistant to typhoid, were proportionately no more resistant to heat than the susceptibles.

8 to 15 days later a small outbreak occurred among the ten remaining susceptible recruits, fatal to seven. These were all positive for *B. enteritidis* at autopsy. After 21 days without fatalities, the experiment was discontinued.

Of all the susceptibles, only three remained, whereas all of the resistants remained except the eleven destroyed by suffocation. 90 per cent of the surviving population, therefore, was comprised of individuals known at the outset to have high inborn resistance.

Experiments 1 and 2 together show that (*a*) mortality from mouse typhoid was confined almost exclusively to the mice of the inherently sus-

ceptible line; (*b*) very few susceptibles survived, thus minimizing the possibility that survivors are immunized susceptibles; (*c*) all, or nearly all, the mice of the inherently resistant line remained well and hence constituted practically the entire population of survivors; (*d*) a considerable proportion of the resistant mice which survived had infected spleens, showing that a single strain of mouse typhoid bacilli can be infective but not lethal (virulent) in one strain of mice, and in another, under similar conditions, both infective and lethal; (*e*) infection was spread by the resistant survivors to the susceptible immigrants.

The next experiment was planned to test further the selective mortality among the susceptibles.

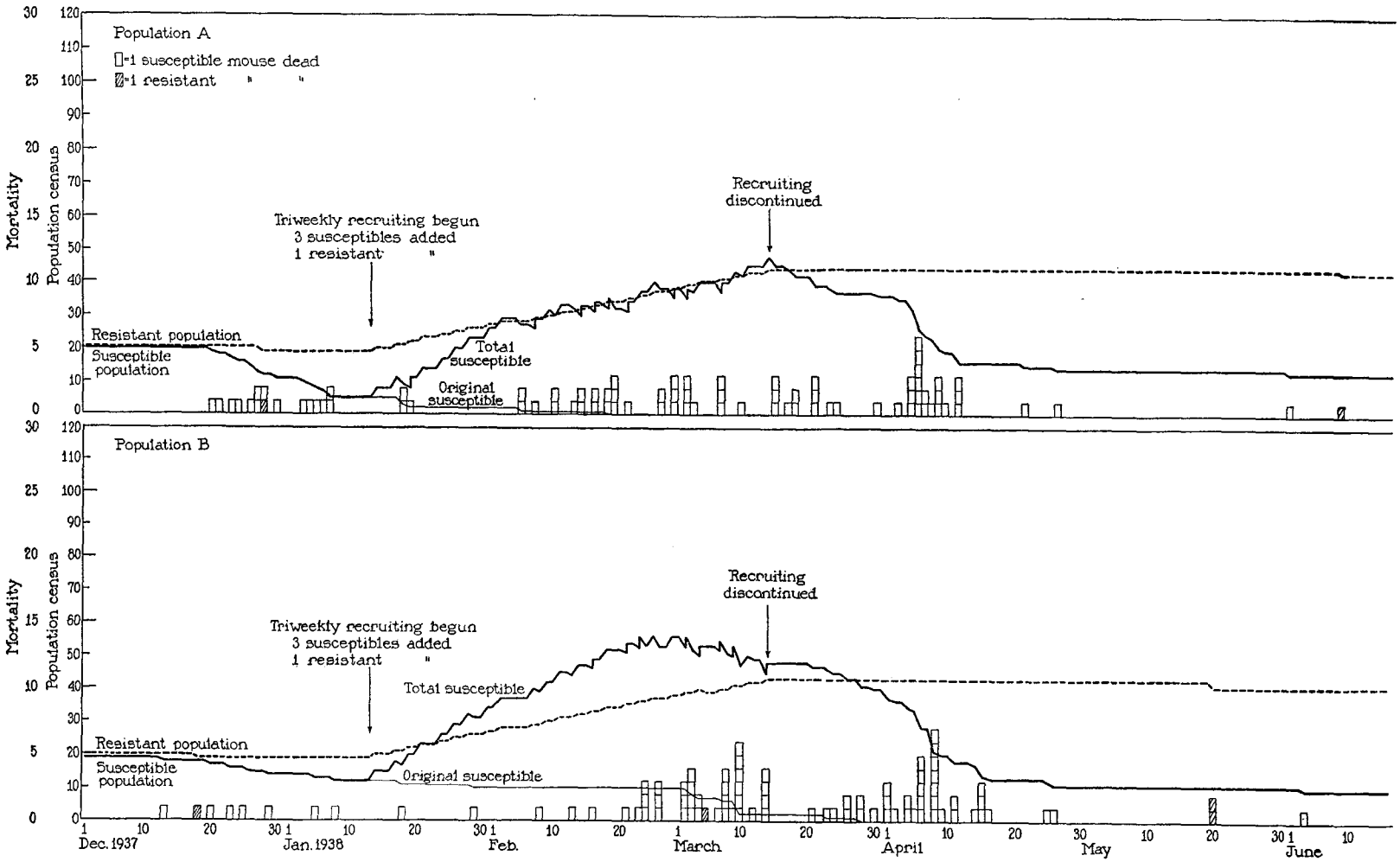
Experiment 3.—Each of four populations, A, B, C, and D, was made up by combining in a single pen twenty susceptibles with twenty resistants, all identified. Population E was set up with thirty resistants plus ten susceptibles and population F with ten resistants plus thirty susceptibles, all properly marked. On Dec. 1, 1937, there were added to each population ten white-face mice, each of which had received the standard dose of mouse typhoid bacilli the previous day. The same routine was then carried out as described in Experiments 1 and 2 and observations continued for 44 days.

The results are shown in Text-fig. 3 and Table I. 80 to 100 per cent of the white-face carriers introduced into the six pens died of mouse typhoid (Table I). Within a few days thereafter, the susceptible contacts commenced dying of typhoid. By the 44th day the epidemics had subsided and mortality had practically ceased. In populations A, B, C, and D mortalities among the susceptible contacts totalled 75, 37, 35, and 85 per cent respectively. In population E the susceptibles, although comprising only 33 per cent of the population, showed a 70 per cent mortality, and in F the susceptibles, 66 per cent of the population, showed a 57 per cent mortality. Of the total 119 susceptible contacts in the six pens, 70 (59 per cent) succumbed.

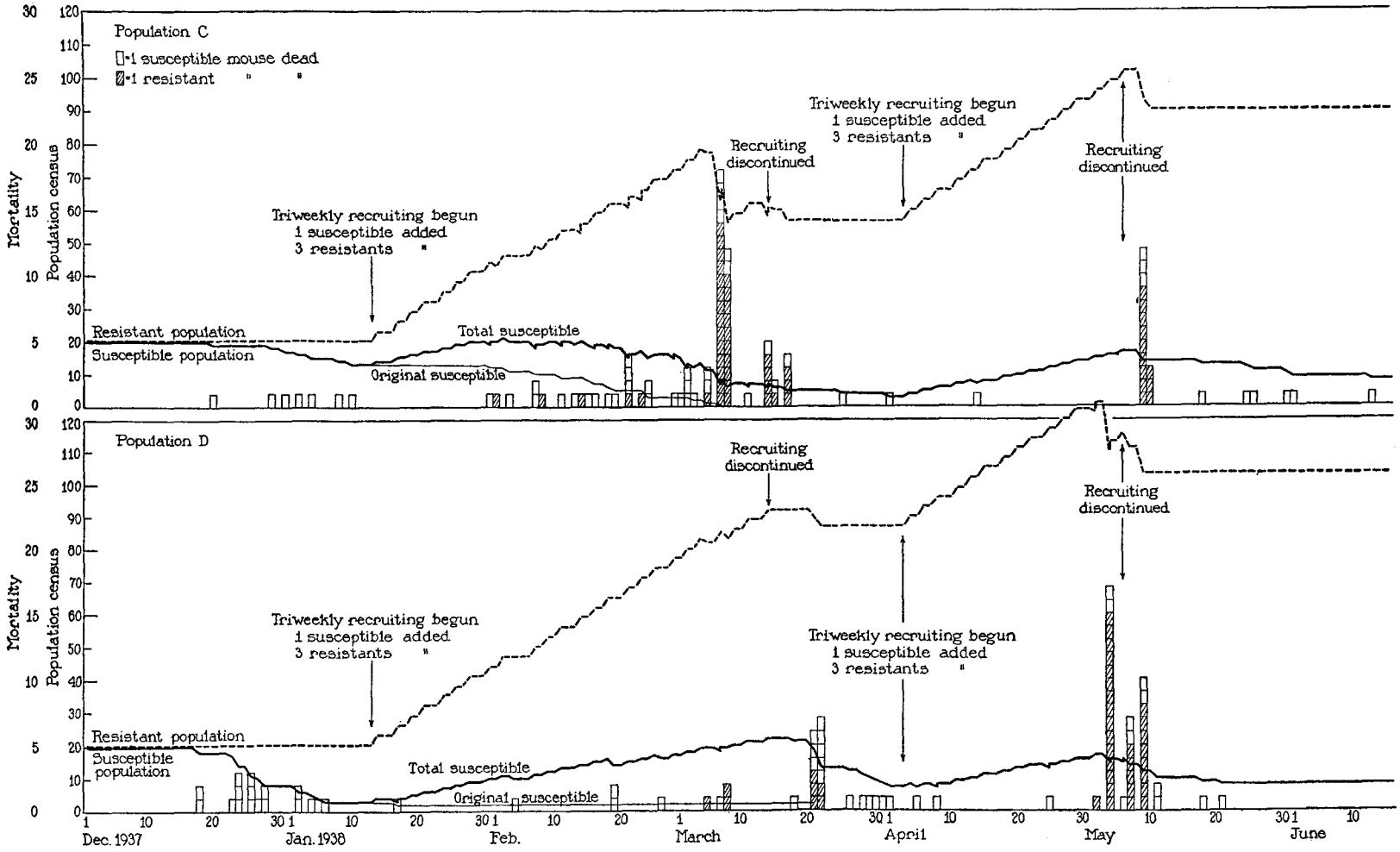
In contrast, only five of 120 resistant contacts succumbed and of these three only died of mouse typhoid (2.5 per cent). This difference shows clearly that in populations with various proportions of susceptibles and resistants, mortality is confined almost exclusively to those contacts known at the outset to be inherently susceptible.

The further fate of these populations is described in Experiments 4 and 5. Population E, however, was observed for an additional 30 days, during which time one more susceptible but no resistant contacts died of mouse typhoid. This population was then discarded.

The next experiment was planned to test the effect of immigration upon



TEXT-FIG. 3—*Continued on Next Page*



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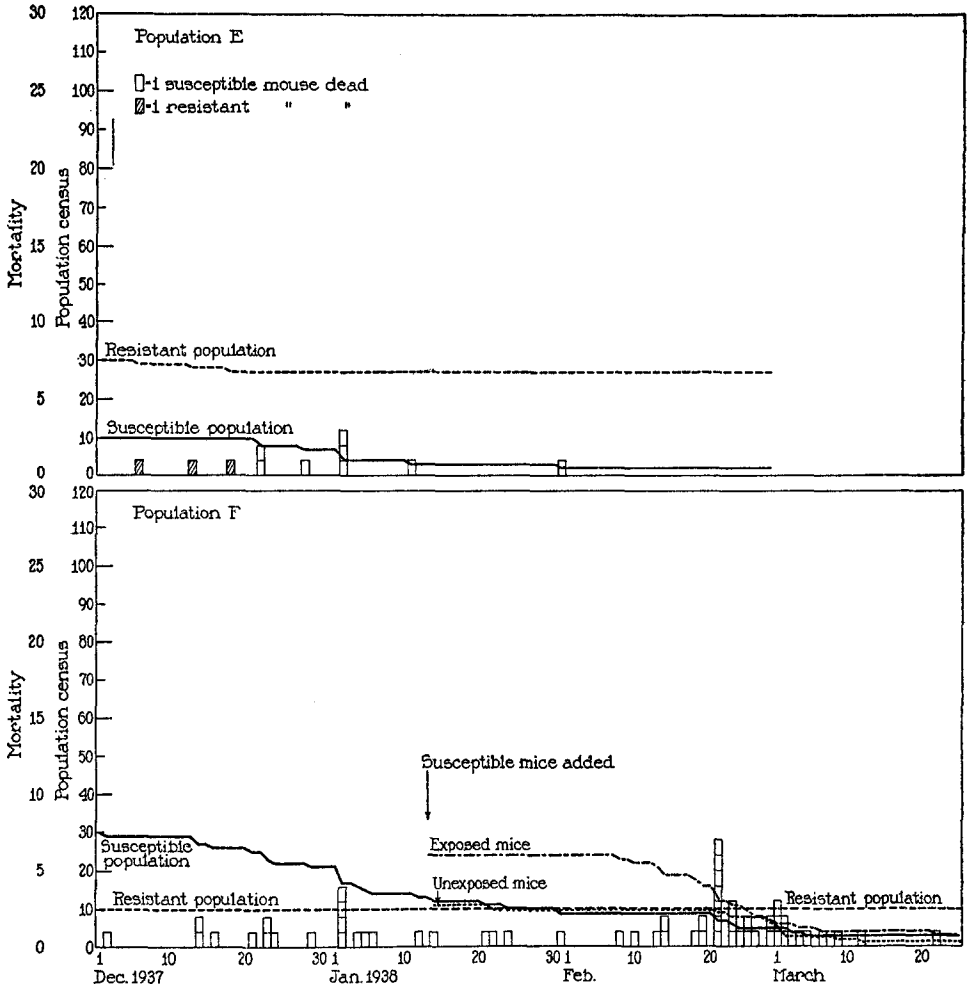
TEXT-FIG. 3. Fate of susceptible and resistant mice exposed to *B. enteritidis* mouse typhoid (Experiments 3 and 4).



TEXT-FIG. 3—*Concluded*

selective mortality among both the original constituents and the recent recruits.

Experiment 4.—To populations A, B, C, and D recruits were added, commencing on Jan. 13, 1938, 44 days after the populations were first infected. A and B received batches of three susceptibles plus one resistant three times per week, and C and D three resistants plus one susceptible at the same intervals. Recruiting was discontinued on Mar. 14, 2 months later. After another 21 days, on Apr. 4, recruiting was resumed in populations C and D and again discontinued after 31 days on May 6. Observations on all four populations were continued until June 16, a total period of 5 months after recruiting had been commenced. Autopsies and bacteriological identification procedures were carried out on more than 95 per cent of the mice found dead.

TABLE I

Fate of Susceptible and Resistant Mice Exposed to Bacillus enteritidis Mouse Typhoid

Population	Number susceptible	Number resistant	Fate of white-face carriers						Fate of susceptible contacts						Fate of resistant contacts					
			Original number	Final number	Number dead	Number autopsied	Per cent positive	Estimated per cent of total number dead of mouse typhoid	Original number	Final number	Number dead	Number autopsied	Per cent positive	Estimated per cent of total number dead of mouse typhoid	Original number	Final number	Number dead	Number autopsied	Per cent positive	Estimated per cent of total number dead of mouse typhoid
A	20	20	10	2	8	7	100	80	20	5	15	13	100	75	20	19	1	1	100	5
B	19	20	10	1	9	9	100	90	19	12	7	7	100	37	20	19	1	1	100	5
C	19	20	10	2	8	7	100	80	20	13	7	6	100	35	20	20	0	0	—	0
D	19	20	10	1	9	8	100	90	20	3	17	16	100	85	20	20	0	0	—	0
E	10	30	10	0	10	9	100	100	10	3	7	7	100	70	30	27	3	3	33.3	3.3
F	30	10	10	2	8	7	100	80	30	13	17	17	94	57	10	10	0	0	—	0

The results of this experiment are shown in Text-fig. 3 and in Table II. Events in populations A and B differed from those in C and D and hence will be described separately. In A and B, in which triweekly recruiting of three susceptibles plus one resistant was practiced, the census following commencement of recruiting increased relatively steadily until a maximum of 92 and 93 was reached. At this point an equilibrium seemed to be established between number of recruits and amount of mortality. Following the cessation of recruiting, however, mortality still continued at a high rate for about 1 month, reducing the census by more than 50 per cent. Following this few deaths occurred for 2 months.

Throughout the 5 months period, mortality was limited almost exclusively to the innately susceptible mice and these all died of mouse typhoid (Table II). The remaining original susceptibles succumbed within $2\frac{1}{2}$ months, thus failing to show any evidence that they had been im-

munized through exposure. 83 per cent of recruits in A and 87 per cent in B succumbed within 5 months, probably all of mouse typhoid (Table II). In contrast, practically all resistants, both original constituents and later recruits, remained well. One died in A and three in B but not of mouse typhoid.

To populations C and D recruits had been added in the proportion of three resistants to one susceptible. Following this procedure, census levels rose higher than in A and B, to 101 and 114 respectively. At this point the mice were crowded to the utmost and appeared hot, moist, and extremely irritable. Recruiting was discontinued as in A and B on Mar. 14, but within 2 days thirty mice died in C and thirteen in D, apparently from smothering. 2 weeks later, when the survivors seemed adapted to the

TABLE II

Mortality in Mouse Populations Infected with Mouse Typhoid and Recruited with Inherently Susceptible and Resistant Mice

Population	Original susceptibles		Susceptible recruits						Total resistants—Originals plus recruits					
	Number at commencement of recruiting	Number 2½ mos. after commencement of recruiting	Total added	Number remaining	Number dead	Number autopsied	Per cent positive for mouse typhoid	Estimated per cent of total recruits dead of mouse typhoid	Total added	Number remaining	Number dead	Number autopsied	Per cent positive for mouse typhoid	Estimated per cent of total recruits dead of mouse typhoid
A	5	0	75	13	62	50	100	83	44	43	1	0	—	0–2.2
B	12	0	75	10	65	60	100	87	44	41	3	3	0	0
C	13	0	40	8	32	24	100	80	140	90	50	26	54	19.2
D	3	0	40	8	32	26	89	71	140	103	37	25	36	3.7

crowded conditions, recruiting was commenced again,—three resistants to one susceptible, as previously. On May 4, with the C population at a maximum of 119 and D at 142, recruiting was again discontinued but not soon enough to prevent the death of fifteen in 2 days in C and thirty-five in 6 days in D. With the populations again reduced to numbers which could survive in the crowded environment and with no further additions to the populations, mortalities practically ceased.

During this 5 month period, mortality in C and D was limited chiefly but not entirely to the susceptible line. Nearly all of these latter died of mouse typhoid (Table II). The remaining original susceptibles were dead within 2½ months after commencement of recruiting, demonstrating again, as in A and B, no tendency to become immunized through exposure to small

doses. Of forty susceptible recruits in population C and forty in D, 80 and 71 per cent respectively succumbed to mouse typhoid. These percentages approximate the 83 and 87 per cent mortalities among each of 75 susceptible recruits in A and B. In C and D, at the close of the 5 month period of recruiting, eight susceptibles remained in C and eight in D.

The resistant line of mice, both originals and recruits, remained well for the most part except during the periods of extreme overcrowding. When the census exceeded 100, however, resistants occasionally succumbed and during the smothering episodes, two in C and one in D, approximately six resistants died to one susceptible. This proportion of 6 to 1 approximates roughly the proportion of resistants to susceptibles actually in these populations, thus indicating that the crowding and smothering hazard was entirely non-specific in its effect, fatal to resistants and susceptibles alike according to their proportionate numbers. At autopsy, on these occasions, 46 per cent of the resistants dying in C and 64 per cent in D showed no evidence of mouse typhoid. Of the remaining positive cases, all but a few showed organisms in the spleen without gross lesions in any organ. Doubtless most of these latter were merely healthy carriers, as observed in Experiment 1. In all, 19.2 per cent of the total 140 resistants in C and 3.7 per cent in D were estimated to have succumbed to mouse typhoid, leaving a surviving population of 90 resistants in C and 103 in D. The virulence of *B. enteritidis* obtained from the spleens of resistants was tested on several occasions according to methods described elsewhere (3). These cultures showed similar mortalities and similar capabilities of spreading and initiating epidemics to cultures obtained from spleens of susceptibles.

Experiment 5.—A final test was made of the ability of susceptible survivors to withstand a subsequent epidemic due to further recruiting of susceptibles. Commencing June 15, and at intervals of 3 to 5 days thereafter, batches of susceptibles were added to A, B, C, and D, until a total of fifty recruits per population was reached.

Epidemics broke out among the susceptible recruits within a few weeks, proving fatal to about 80 per cent. Within 1 month the previous susceptible survivors in C and D were reduced from eight and eight (Table II) to two and one. Similarly, the thirteen and ten in A and B were reduced in 3 months to four and eight. Meanwhile, only three resistants in A, four in B, none in C, and two in D succumbed and these showed no mouse typhoid. The experiment was terminated Oct. 1, 1938.

Taken together, Experiments 3, 4, and 5 show plainly that when populations comprised of known susceptible and resistant mice are infected with mouse typhoid through the introduction of carriers, mortality is confined

almost exclusively to the susceptible constituents, regardless of whether they be present in relatively small or large proportions. Moreover, nearly all of them succumb promptly with no tendency to become immunized and survive. The known resistant constituents, on the contrary, remain well and comprise almost exclusively the surviving population. Again, when populations of survivors, most of them resistants among which no deaths are occurring, are recruited by batches of susceptibles plus resistants in different proportions, mouse typhoid spreads to both classes of immigrants but mortality from the disease is again limited to the susceptibles, whether present in few or relatively large numbers. These latter nearly all succumb within a relatively short time, leaving as survivors only those known to have been resistant at the outset.

In view of the complete failure of susceptible constituents of an infected population to become immunized through prolonged exposure, the effect of repeated short exposures was tested.

Experiment 6.—Population F, at the close of Experiment 3, consisted of thirteen susceptible plus ten resistant survivors. To these mice, some of which were presumably infected and discharging mouse typhoid bacilli in their feces, twenty-five additional susceptible mice were exposed in the following manner. Each was taken from its individual cage and in batches of four was placed in the box with population F for 2 minutes. This procedure was continued mostly daily twenty-nine times. Stool cultures after the sixth exposure contained no typhoid bacilli. One mouse died following the twentieth exposure and was proved to harbor mouse typhoid. This indicated that the immigrants actually had been exposed to the infectious agent.

On Jan. 14 the twenty-four exposed mice plus eleven similar unexposed susceptibles were added permanently to population F to determine whether the exposed mice would prove relatively immune. The contrary proved to be the case. Within 4 weeks an epidemic started among the immigrants which proved fatal in 3 weeks to twenty-one of twenty-four exposed susceptibles (87 per cent) and ten of eleven unexposed susceptibles (91 per cent). Meanwhile, eleven of the thirteen original susceptible survivors had succumbed (85 per cent). In contrast, all of the original ten resistants remained well until the population was discarded 6 weeks later, on Apr. 25.

This experiment shows that repeated short exposure of susceptibles to an infected population, sufficient to bring about a fatal typhoid infection in one individual, nevertheless failed to immunize the remaining to the slightest degree when exposed to an infected yet surviving population in which no deaths were occurring.

A final test was made of the immunizing effect of repeated sublethal doses of mouse typhoid bacilli given *per os* to susceptible mice.

Experiment 7.—Twenty susceptible mice were each given by stomach tube 250 mouse typhoid bacilli in 0.5 cc. of broth daily for 3 days. Subsequently 2,500 organisms were

given daily for 3 days. Stool cultures made each day for 10 days were positive in nine of the twenty mice. 3 weeks later, all were given 500,000 mouse typhoid bacilli by stomach tube. Twenty unexposed controls received the same test dose.

Within 3 weeks, both groups had succumbed to the test dose which was not greater than 10 M.L.D.

The experiment was repeated with thirty mice in each group. Those exposed received double the above number of organisms and four of the thirty succumbed. Twenty-one of the twenty-six survivors showed positive stools. 3 weeks later, following the test dose, none of the exposed nor controls survived.

These experiments failed to show that sublethal doses of mouse typhoid bacilli administered to mice *via* the normal portal of entry immunized them to a subsequent test infection by mouth.

The same results were obtained in mice given repeated nasal instillations of a sublethal dose of St. Louis encephalitis virus followed 4 weeks later by a test nasal instillation of 10 M.L.D.

DISCUSSION

By using mice whose individual susceptibilities, both innate and environmental, are known and controlled, direct experimental data have been obtained for the first time on the following epidemiological problems.

Fluctuations in infectivity and virulence in infected mouse populations as investigated thus far prove to be manifestations of differences in host resistance rather than in parasite potentialities. Thus, in the foregoing experiments, plus others reported earlier (1, 3), a single strain of mouse typhoid bacilli spread equally to resistant and to susceptible mice but showed at the same time a high killing potency in susceptibles and a low killing potency in resistants. Altering resistance through diet (3) alters killing potency but not infectivity. On the other hand, when host resistance factors are kept constant and uniform through the use of mice of known susceptibility, infectivity and virulence likewise remain constant.

Mortality from mouse typhoid in exposed or infected populations is conditioned by the number of highly susceptible constituents. If the number is few, deaths are sporadic; if great, epidemic; if susceptibles are depleted, mortality subsides. Previously it was known that fresh mice added to an infected population initiate or maintain mortality at epidemic levels, but their exact rôle has remained uncertain. Topley and Greenwood who considered the fresh mice to be alike in their individual susceptibilities furnished no experimental data as to their function. We found that the fresh mice differed in their initial susceptibilities (1) but were in doubt as to whether these individual differences or the average level of susceptibility was the more important. It now appears that the presence of the in-

dividual with high susceptibility initiates the outbreak, no matter what the general level of susceptibility may be. If these individuals are few in number, mortality remains sporadic; if numerous, it becomes and remains epidemic. Finally, if and when the susceptibles are depleted, mortality subsides. Thus the danger to an already infected population resides not alone in a general fall of the resistance level but in an immigration of highly susceptible individuals.

A proportion of survivors are infected and remain the reservoir from which the infectious agent spreads to incoming susceptibles.

Clearly from these experiments, survivors are the initially resistant constituents and there is little or no tendency for susceptibles to become immunized through exposure to chance small doses.

At this point it may be objected that these populations of extremely resistant plus susceptible individuals have no counterpart in nature and hence that their behavior is not analogous to that of populations comprised mainly of individuals of intermediate grades of susceptibility. In reply we argue that the extreme individuals are in reality closely related both to one another and to the moderately susceptible individuals (2). In some cases the relation is that of siblings—in all events, the differences are those which may occur normally among individuals of the same family. The behavior of infected populations comprised solely of individuals with extreme differences in susceptibility has not differed qualitatively in so far as we have observed from populations comprised of individuals with all grades of susceptibility (3). We conclude, therefore, that the amount of resistance of each individual at the outset determines whether it will survive an epidemic of mouse typhoid. If it survives, there is a possibility, not yet demonstrated experimentally, that it may develop, through infection, what might be termed a luxury immunity.

Reinoculation of survivors, as ordinarily practiced, is not a test of active immunity. Armstrong, for example, reports that since mice surviving nasal instillation of St. Louis virus are relatively resistant to a second instillation, they have been immunized (5). Such a conclusion is unwarranted without knowledge of whether some animals were resistant at the outset or whether all were susceptible. We have been unable to immunize known susceptible mice by instilling nasally sublethal doses of St. Louis encephalitis virus. In our opinion a test for active immunity must be made on batches of animals known to be at least 90 per cent susceptible to the test agent given by a normal portal of entry.

Continued resistance of survivors does not depend necessarily upon the

presence of bacilli in the tissues. If initial resistance is high, bacilli persist indefinitely in the spleen without harm and without altering the already adequate level of resistance.

In the foregoing experiments we are mindful that the resistance actually displayed by the individual was a summation of inherent components which were altered experimentally, plus environmental ones associated with age, regimen, and diet which were kept constant. Moreover, we know by experiments under similar herd conditions that diet exerts equally important effects in epidemics under conditions in which inherited components are kept constant (3). The main point, after all, is that inherited and general environmental components of resistance are of fundamental importance, whereas immunological components associated with infection are of negligible importance in mouse typhoid infection.

This finding that inherited resistance factors exercise a fundamental control, whereas specific immunity factors play a minor rôle in mouse typhoid, is at present of limited application. It would hold, we believe, among both individuals and populations under the following circumstances: (*a*) infections gaining access and spreading for the first time, (*b*) infections associated with high mortality rates, and (*c*) infections with low morbidity rates. In infections with high morbidity and low mortality rates, however, we would look for specific immunity factors to be important in preventing recurrence. Pending experiments on this latter type of infection, one can state merely that the theory of immunity through subclinical infection has been overextended and that misleading conclusions have been drawn from the classical experiment of reinoculating survivors.

CONCLUSIONS

1. Under conditions in which mouse typhoid is allowed to spread naturally among herds of mice comprised of different proportions of individuals of innately high or low susceptibility: (*a*) 85 to 95 per cent of the innately susceptible succumb to mouse typhoid in contrast to less than 5 per cent of the innately resistant, regardless of whether either constitutes 25, 50, or 75 per cent of the population respectively. (*b*) The surviving population is therefore comprised largely of individuals known at the outset to be innately resistant. These resistants are, nevertheless, apt to have become infected and to harbor mouse typhoid bacilli in their spleens and feces.

2. Under conditions in which recruits are added to surviving populations comprised chiefly of innately resistants among which mortalities have practically ceased: (*a*) Mouse typhoid infection spreads to both innately

resistant and susceptible recruits. (*b*) Mortality from mouse typhoid is limited almost exclusively to the innately susceptible recruits and is "sporadic" or "epidemic" in character according to the numbers and proportion of susceptibles added. (*c*) Innately resistant recruits remain well unless subjected to some non-specific hazard, such as heat or overcrowding, in which case both they and the susceptibles succumb in proportions similar to their relative numbers in the population.

3. It was plain that survivors are almost exclusively the individuals known at the outset to have been innately resistant.

4. There was no tendency for known susceptibles to become immunized through herd exposure at epidemic times, at postepidemic times in which the dosage of mouse typhoid bacilli was relatively small, nor at repeated short intervals. Finally, susceptibles given repeated, known, sublethal doses of mouse typhoid bacilli or St. Louis encephalitis virus by a natural route failed to develop immunity against a subsequent test dose.

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