HISTOCOMPATIBILITY DIFFERENCES IN WILD MICE; FURTHER EVIDENCE FOR THE EXISTENCE OF DEME STRUCTURE IN NATURAL POPULATIONS OF THE HOUSE MOUSE[1]

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IT has been known to ecologists for some time that the commensal house mouse, *Mus musculus*, has rather limited range of movement and that the mouse populations in different buildings are isolated from each other [see BLAIR (1953) for review]. It was also known that the different local groups differed in the frequencies of some genetically controlled traits (WEBER 1950; DEOL 1958; DUNN 1957). The subdivision of natural mouse populations into more or less isolated groups was furthermore required on some theoretical grounds. Most of the natural populations of this species are polymorphic for alleles at the *T-t* (Brachyury) locus (DUNN 1957). Calculations of the expected *t*-allele frequencies based on random mating and infinite population size led to a sharp discrepancy with frequencies actually observed (BRUCK 1957; DUNN and LEVENE 1961). To bring the expected and observed frequencies into agreement it must be assumed that the geographical population of the house mouse consists of small endogamous breeding units, or demes (LEWONTIN and DUNN 1960). On the basis of their cage population studies, REIMER and PETRAS (1967) postulated that a deme consists of a dominant male, several females, and several subordinate males. Empirical evidence for the existence of demes in the natural population was provided by studies of *t* alleles (ANDERSON 1964), protein variants (PETRAS 1967), and *H-2* polymorphism (KLEIN 1970). In this paper we present additional evidence from a study of histocompatibility differences in wild mice.

It was calculated that two different inbred strains of laboratory mice differed in at least 15 (BARNES and KROHN 1957) to 29 (BAILEY and MOBRAATEN 1969) histocompatibility (*H*) loci. All these loci can be studied simultaneously by tissue transplantation. In the present study skin grafting was used for comparison between mice of the same and geographically distant localities and for the calculation of the number of histocompatibility loci showing effective segregation in the wild population.

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MATERIALS AND METHODS

Mice: Wild mice were collected at 6 different farms in the vicinity of the city of Ann Arbor, Michigan. All the farms were at least 5 km beyond the city limits and usually at least 2 km apart. Small folding live traps (H. B. SHERMAN, De Land, Florida) were set up in granaries, corn cribs, and barns, and were checked once a day. Trapped mice were brought to the laboratory and wild males were bred with females of strain C3H/HeJ. (Wild females usually do not reproduce in captivity.) Hybrids between the wild males and C3H females were then used for skin grafting.

Skin grafting: The method of grafting was a modification of a technique described by BILLINGHAM and MEDAWAR (1951). The grafts were prepared from ears of the donors: The pinna was cut off at its base, split into two halves with fine iris scissors, and the cartilage was scraped off with a scalpel. Each donor thus provided 4 grafts. The recipient mice were 3 or more months old and of the same sex as the donor. The recipients were anesthesized with Pentobarbitone sodium (Nembutal) and immobilized on a cork board. The operation field of the recipient was shaved clean with an electric clipper and painted with collodion. The graft bed was prepared in the dorsal area by dissecting away the skin with curved iris scissors. Care was taken not to damage the underlying paniculus carnosus with its vasculature. Each recipient received 2 to 4 grafts. Separate beds were prepared for each graft in the shape and size of the pinna. Fitted grafts were fixed in place by a thin layer of collodion spread around the edges of the grafts. The area was then covered with a piece of gauze coated with white petrolatum. The mice were bandaged with Latex Bandage (The Sealtex Co., Chicago). Seven days after transplantation the bandage was removed under ether anesthesia, remnants of dry collodion were carefully peeled off, and the mouse was rebandaged with a Curad Plastic Bandage (The Kendall Co., Chicago). The second bandage was removed 2 days later. The grafts were inspected daily for the first 30 days and then once a week. In cases of chronic rejection, we found it easier to determine the beginning of the rejection than its completion. Therefore, we took the former rather than the latter as the day of rejection. The following criteria were used for rejection: thinning of the hair, appearance of a scar or ulcer, and thickening or edematous swelling of the graft.

RESULTS

Description of the grafts: Three different groups of grafts were performed: In group 1, grafts were exchanged between littermates; in group 2, the donor and recipient were sired by different wild parents but the two wild males came from the same locality; in group 3, the wild parents of the donor and the recipient were captured at different, widely separated localities. Usually, each hybrid recipient received 3 grafts, one of each group. Some recipients, however, received only one graft, others two or four grafts, depending on the number of mice available (Table 1). A total of 350 grafts were transplanted and of those, 118 were in group 1, 64 in group 2, and 168 in group 3. The three groups of transplants differed in the mean survival time (MST), number of permanently surviving grafts, and behavior of the individual grafts. The survival times of the individual grafts in groups 1–3 are shown in Figures 1, 2, and 3, the MST for each of the 3 groups is shown in Table 2. Group 1 displayed the longest MST (17 days) and had the highest number of grafts surviving permanently (5). In addition, the rejection times of individual grafts were spread over a relatively long range (from 9 to 43 days), and the grafts quite often underwent a chronic rejection, lasting in some cases several weeks.

Typically, the graft, after losing part of its hair crop developed bald, shiny

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TABLE 1

Number of progeny produced by different wild mice and used as recipients for skin grafts

Wild mice	Group 1	Type of exchange Group 2	Group 3
KE15	5	4	5
KE16	10	10	10
KE17	7	3	5
KE4	4	3	3
KE5	5	7	7
KP88	6	6	6
KP128	12	7	15
KP668	4	..	4
GA20	10	10	8
GA23	12	8	13
SA141	8	4	8
SA139	6	..	7
DE137	12	..	12
BA77	12	..	12

Group 1 = littermates.
Group 2 = wild parents from the same locality.
Group 3 = wild parents from different localities.

TABLE 2

*Mean survival times of grafts exchanged between wild × C3H hybrids**

Group	Sex of the recipient	Total number of grafts	MST ± std. dev.
1. Littermates	♀♀	51	14.7 ± 4.3
	♂♂	62	19.1 ± 7.6
	♀♀ + ♂♂	113	17.1 ± 6.7
2. Wild parents from the same locality	♀♀	30	13.4 ± 4.4
	♂♂	32	14.0 ± 3.6
	♀♀ + ♂♂	62	13.8 ± 4.0
3. Wild parents from different localities	♀♀	74	10.5 ± 2.1
	♂♂	93	10.6 ± 2.4
	♀♀ + ♂♂	167	10.6 ± 2.3

* Grafts that had survived longer than 100 days are not included in this table.

areas, while the rest of the graft surface stayed in relatively good condition. Only after several days or even weeks was the rest of the hair crop also lost and the skin of the graft slowly replaced by scar. These are signs of relatively weak histocompatibility differences (e.g., GRAFF, LAPPÉ and SNELL 1969). In group 2, the MST was shorter (14 days), there were fewer permanently surviving grafts (2), the rejection times of individual grafts were less scattered on the time scale (range from 9 to 32 days), and the occurrence of chronic rejection was less frequent than in group 1. Group 3 differed sharply from the two previous groups. Its MST was only 10.6 days, there were no permanently surviving grafts in this group,

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and only 4 grafts survived longer than 16 days. The majority of the grafts were rejected by an acute process. Of the 3 groups, only group 1 showed a significant sex difference in graft rejection (MST of 19.1 days in males *vs.* 14.7 days in females).

Estimating the number of segregating histocompatibility loci: The usual objective of experiments in which graft survival data are obtained from segregating generations is to estimate the number of segregating *H* loci. Such an objective, however, is made difficult in data on wild mice, such as those obtained here, for

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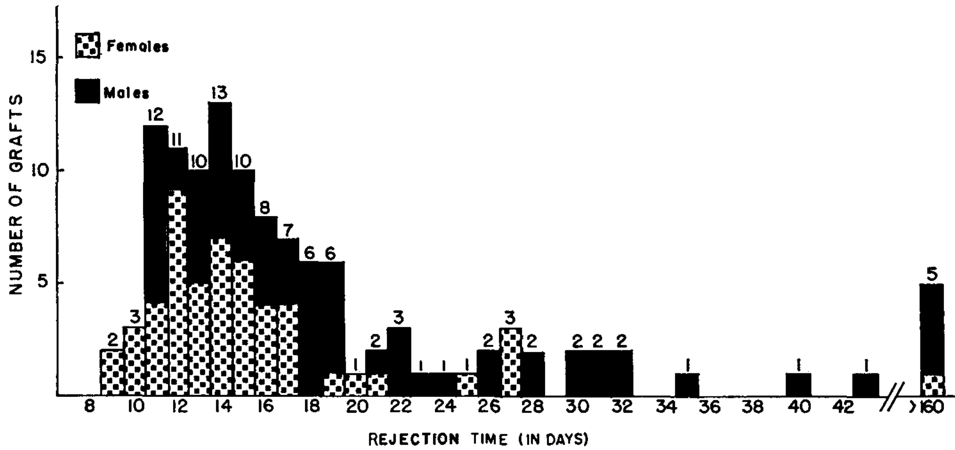

FIGURE 1.—Frequency distribution of skin graft rejection times. Group 1: Littermates.

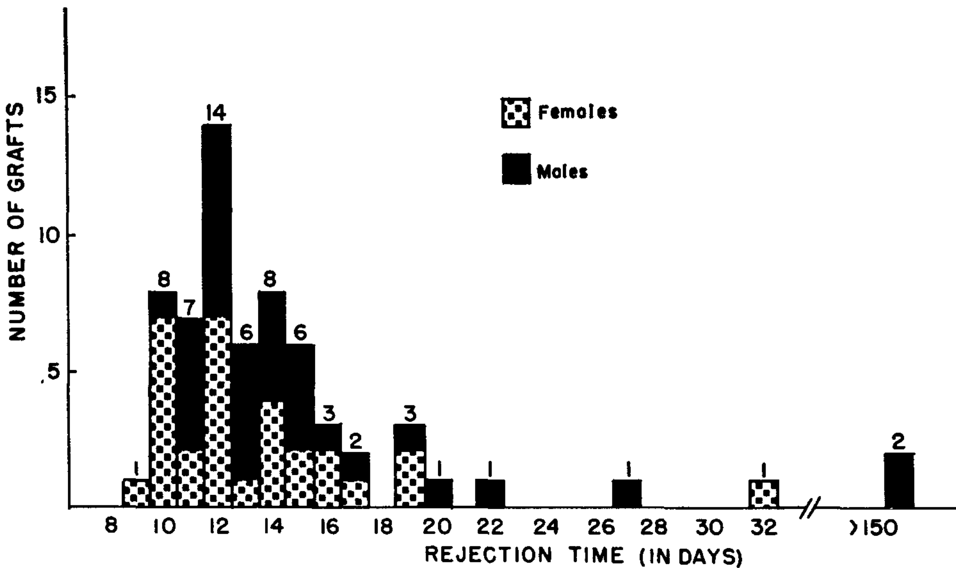

FIGURE 2.—Frequency distribution of skin graft rejection times. Group 2: Progeny sired by wild males from the same locality.

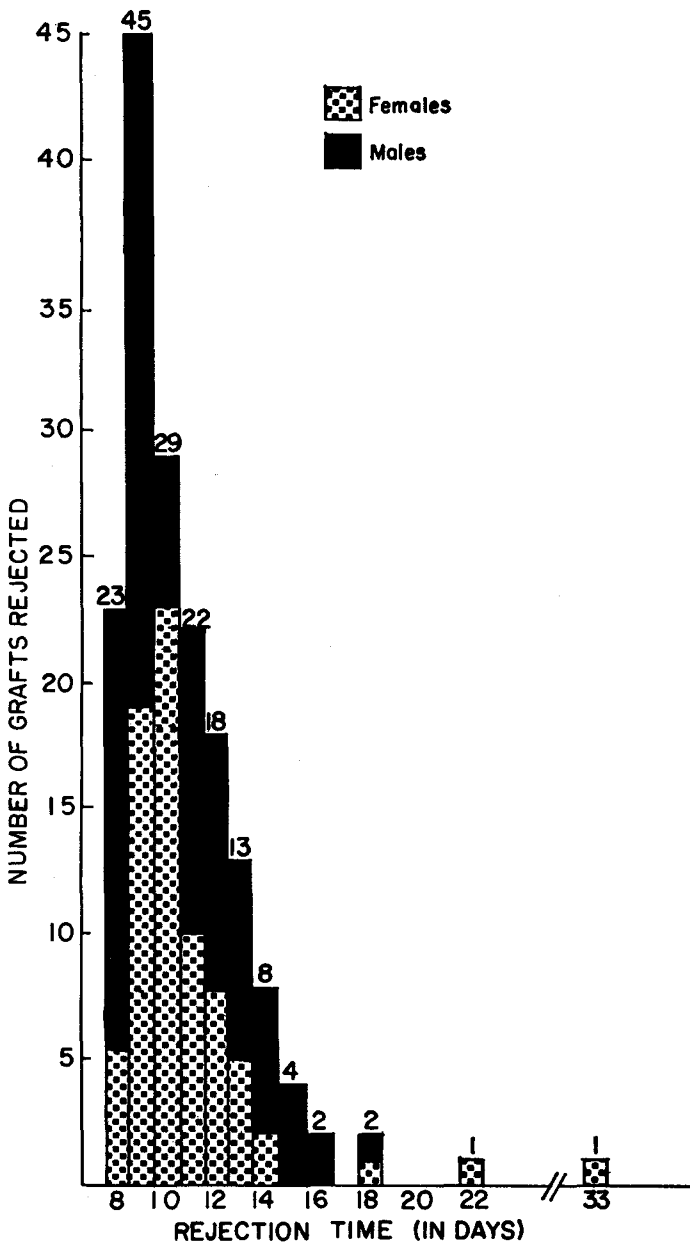

FIGURE 3.—Frequency distribution of skin graft rejection times. Group 3: Progeny sired by wild males from different localities.

the number and frequencies of alleles at each locus are unknown. The approach taken to attain that same objective here employs two steps, namely, estimating the *effective number of alleles* per locus from the proportion of grafts that survive, and then estimating the number of segregating loci from that estimated

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number of effective alleles. In so doing, we must assume (1) a fixed number of H loci for the species, (2) the populations from which the wild males came underwent random mating, and (3) no histocompatibility allele in the wild male is identical to that of the inbred strain to which he is crossed. [The effective number (a) of alleles maintained at a locus is a concept developed by CROW and KIMURA (1970) and is the reciprocal of the sum of squares of the allelic frequencies.]

Derivation of the Equations

Group 1 data: The probability of the wild male being homozygous at one locus would be $\sum_i p_i^2$, and the probability of being heterozygous would be $1 - \sum_i p_i^2$, where p_i is the frequency of the ith allele. When the wild male is homozygous, the probability of graft survival is 1, and when heterozygous, ½. Thus in consideration of but one locus when the genotype of the sire is unknown, the probability for a graft to survive would be:

$$S = (1)\ (\sum_i p_i^2) + (\tfrac{1}{2})(1 - \sum_i p_i^2) = (1 + \sum_i p_i^2)/2$$

and in consideration of all (L) histocompatibility loci in the species:

$$S = \prod_h^L (1 + \sum_i p_i^2)h/2$$

where p_i is the frequency of the ith allele at the hth locus.

This equation would appropriately apply only if each graft-exchange pair were independent of all other pairs, that is, if each pair were sired by a different wild male. In the present experiment, graft exchanges were made among many offspring from each wild male. Therefore, another equation is derived, based upon the proportion of histocompatibility loci that are heterozygous in a single male.

The probability of heterozygosity at any one locus, as stated above, is $1 - \Sigma p_i^2$. Therefore, the number of heterozygous loci borne by any one wild male would be:

$$\sum_h^L (1 - \Sigma p_i^2) = (L - \sum_h \sum_i p_i^2) = L(1 - \overline{\Sigma p_i^2})$$

where $\overline{\Sigma p_i^2}$ is the mean of the sum of squares of allelic frequencies of all histocompatibility loci of the species.

If a wild male is heterozygous at but one locus, the probability that a graft exchanged between his offspring will survive would be $S = ½$, and if heterozygous at the number of loci expected from the above consideration, the probability that a graft will survive would be:

$$S = (\tfrac{1}{2})^{L(1-\overline{\Sigma p_i^2})}$$

Furthermore, since

$$\log S = L(1 - \overline{\Sigma p_i^2}) \times \log \tfrac{1}{2},$$

or

$$\overline{\Sigma p_i^2} = 1 - \frac{\log S}{L \log \tfrac{1}{2}},$$

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an estimate of the average effective number of alleles at all H loci (defined by CROW and KIMURA (1970) as $1/\Sigma p_i^2$) can then be made:

$$\hat{a} = 1/\overline{\Sigma p_i^2} = \frac{L \log 1/2}{L \log 1/2 - \log S} \quad (1)$$

Group 2: In this case we must consider the genotypes of wild males taken two at a time, that is, the two that sired the test mice with exchanged grafts. The frequency distribution of all possible zygotes (representing genotypes of wild males) at a single locus can be described by expanding $(\sum_i p_i)^2$ to:

$$\sum_i p_i^2 + 2 \sum_{i<j} p_i p_j$$

where p_i and p_j refer to the frequencies of the ith and jth allele. When males of these zygotic types are combined in pairs, the distribution of zygotic combinations can be described by the expansion of the square of the above expression:

$$\sum_i (p_i^2)(p_i^2) + 4 \sum_{i<j} (p_i^2)(p_i p_j) + 4 \sum_{i<j} (p_i p_j)(p_i p_j) +$$
$$8 \sum_{i<j<k} (p_i p_j)(p_i p_k) + 8 \sum_{i<j<k<l} (p_i p_j)(p_k p_l) + 4 \sum_{i<j<k} (p_i^2)(p_j p_k) +$$
$$2 \sum_{i<j} (p_i^2)(p_j^2)$$

where p_i, p_j, p_k, and p_l are frequencies of the ith, jth, kth, and lth alleles.

The probability of grafts surviving when exchanged between test mice sired by males defined by each of the zygotic combinations (terms in the above expansion) would be: 1, ½, ½, ¼, 0, 0, 0, respectively. Each of the zygotic combinations can then be weighted with its respective probability of graft survival to express the overall probability of graft survival when the genotypes of the sires are unknown:

$$S = \sum_i (p_i^2)(p_i^2) + 2 \sum_{i<j} (p_i p_j)(p_i p_j) + 2 \sum_{i<j} (p_i^2)(p_i p_j) +$$
$$2 \sum_{i<j<k} (p_i p_j)(p_i p_k).$$

These terms are equivalent, respectively, to those in the expression:

$$S = \sum_i (p_i^2)(p_i^2) + 2 \sum_{i<j} (p_i^2)(p_j^2) + 2 \sum_{i<j} (p_i^2)(p_i p_j) + 2 \sum_{i<j<k} (p_i^2)(p_j p_k)$$

which is an expansion of $(\Sigma p_i^2)(\Sigma p_i)^2$. And since $(\Sigma p_i)^2 = 1$, the expression simplifies to $S = \sum_i p_i^2$.

If we consider all histocompatibility loci in the species, the expression becomes:

$$S = \prod_h^L (\sum_i p_i^2) h$$

and

$$\log S = \sum_h^L (\log \Sigma p_i^2) h$$
$$= L \overline{\log \Sigma p_i^2}$$

where $\overline{\log \Sigma p_i^2}$ is the mean of the log of the sum of squares of allelic frequencies.

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Furthermore, since $\log^{-1}[(\log S)/L] = \log^{-1}\overline{[\log \Sigma p_i^2]} = \overline{\overline{\Sigma p_i^2}}$ an estimate of a can be obtained:

$$\hat{a} = 1/\overline{\overline{\Sigma p_i^2}} = 1/\left[\log^{-1}\left(\frac{\log S}{L}\right)\right] \quad , \tag{2}$$

where $\overline{\overline{\Sigma p_i^2}}$ is the *geometric* mean of the sum of squares of allelic frequencies. The geometric mean will provide a larger estimate of â than will the arithmetic mean in equation (1). This equation applies only to populations with genotype frequencies that obey the Hardy-Weinberg law.

In order to convert the estimated number of effective alleles per locus into effective numbers of segregating loci, we must assume that (1) the segregating alleles have neutral selective value, (2) they have essentially an infinite number of mutable forms, and (3) these alleles are distributed among the H loci according to the Poisson. Then, from the estimate of â, we can estimate the effective number of loci showing segregation (those loci with more than one effective allele) by the equation:

$$\hat{L}' = (1 - e^{1-\hat{a}})\ (L) \tag{3}$$

Application of the Equations

Equations (1) and (2) can be used to estimate â from graft survival data once we have assumed a value for the number of H loci in the species. There are published minimal estimates available, from which we shall take 30 as a reasonable (rounded) estimate (BAILEY and MOBRAATEN 1969). Since that estimate for several reasons is considered to be minimal, then the resulting estimates of numbers of effective alleles would be considered maximal and of segregating loci minimal.

Estimates of â and L' as calculated from the data of Groups 1 and 2 as well as from IVÁNYI and DÉMANT (1970) for purposes of discussion are presented in Table 3.

Greater reliance can be placed on the estimates from Group 1 data since effects of inbreeding are compatible with equation (1). Moreover, the estimates are

TABLE 3

Estimates of the parameters â *and* L′ *from graft-survival data*

Source of data	Proportion of grafts surviving (S)		Number of effective alleles ($\hat{a}$)	Number of effective loci ($\hat{L}'$)
Group 1	Mean	.042	1.179	5.0
	Lower limit	.014	1.258	3.6
	Upper limit	.097	1.127	6.8
Group 2	Mean	.031	1.122	3.4
	Lower limit	.004	1.204	2.0
	Upper limit	.097	1.069	5.6
IVÁNYI and DÉMANT (1970)	Mean	.174	1.092	2.6
	Lower limit	.150	1.100	2.4
	Upper limit	.208	1.082	2.8

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directly comparable with estimates obtained from applying equation (1) to the data of IVÁNYI and DÉMANT (1970).

Considering the 95% confidence limits of estimates derived from Group 1 data, our analysis indicates there are from 4 to 7 segregating H loci in the Michigan mouse populations, and the data of IVÁNYI and DÉMANT indicate there are from 2 to 3 segregating H loci in the Czechoslovakian populations.

The estimate from our Group 2 data employing equation (2) is more in agreement with that from the data of IVÁNYI and DÉMANT, but it is bound to be an underestimate due to the equation being applicable solely to random mating populations, and mouse populations have been shown repeatedly to be subdivided into a deme structure (ANDERSON 1964; PETRAS 1967; KLEIN 1970). Moreover, since equation (2) incorporates the geometric instead of the arithmetic mean of Σp_i^2, the derived estimate of L' is expected to be smaller.

DISCUSSION

If wild mice indeed live in demes and if it is true that interdemic migration is very rare, as postulated by LEVIN, PETRAS and RASMUSSEN (1969), then the inbreeding coefficient of a deme should be relatively high and the frequency of heterozygotes sharply reduced. In terms of histocompatibility, this would mean that mice within a deme should be more compatible than mice of different demes. This indeed seems to be the case. Data presented in this communication indicate that there is a correlation between skin graft survival and geographical relationship of individual mice. Graft exchanges between progeny of mice captured at the same locality behave differently from grafts exchanged with progeny of mice captured miles away. In the former case, the MST is higher, there are some permanently surviving grafts, and the mode of rejection is usually different than in the latter case. The difference is slightly more pronounced if the males are the recipients of the grafts instead of females. Dependence of graft survival on the sex of the recipient is well documented in the literature (GRAFF, LAPPÉ and SNELL 1969).

In the present study, each recipient usually received more than one graft. The question could therefore be raised whether this arrangement did not obscure the results by cooperation on one hand and interference on the other hand between antigens of different H systems in different grafts. LENGEROVÁ and MATOUŠEK (1968) have demonstrated that grafts bearing distinctive antigens when placed on the same host are rejected independently. We therefore assume that the results of the experiments described in this communication were not greatly influenced by the fact that multiple grafts were placed on individual recipients.

Exchange of skin grafts between (wild × C57BL/10) hybrids has been reported recently by IVÁNYI and DÉMANT (1970). These authors exchanged grafts between littermates only (like our group 1) and found 31 to survive out of 178 grafts observed at 100 days. (We have truncated their observations at 100 days to make them comparable with ours.) Theirs is a statistically significantly higher frequency of long-surviving grafts than we observed in this study.

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The larger proportion of surviving grafts with the resulting lower estimated number of segregating *H* loci in the Czechoslovakian mice, on the one hand, can be explained as an effect of more intensive inbreeding. Although the allelic-frequency difference could be a result of natural selection, it more reasonably reflects fixation and loss of alleles due to a smaller deme size.

On the other hand, the larger proportion of surviving grafts can be explained by the wild mice bearing alleles that are identical to those of the laboratory strain to which the wild males were crossed. Such a condition could possibly have arisen in the mice trapped by IVÁNYI and DÉMANT at the Zoological Garden of Prague by the introduction of genes from escaped laboratory mice. The likelihood of this happening, however, seems remote.

The advantage of the skin grafting method in demonstrating polymorphism and heterozygosity in mice is that 30 different loci are tested by one graft. In contrast, isozyme gel electrophoresis methods (SELANDER and YANG 1969) require multiple tests. The disadvantage of the skin grafting method is that the loci and their alleles are not identifiable.

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SUMMARY

Wild mice collected in farm buildings in the vicinity of Ann Arbor, Michigan, were mated with laboratory mice of strain C3H/HeJ. Skin grafts were exchanged between the resulting hybrids in three groups: between littermates, between mice sired by males from the same locality (presumably belonging to the same deme), and between mice sired by males from different localities (different demes). A total of 350 grafts were exchanged. Grafts in the first two groups (intrademic) showed a relatively high mean survival time, long rejection range, and frequent occurrence of chronic rejections. Seven out of 182 grafts survived permanently. There were no permanently surviving grafts in the third group (interdemic transplants), the mean survival time was low, the rejection range short, and the rejection very fast. These findings are interpreted as further evidence for the deme structure of natural mouse populations.—Equations for calculating the effective number of alleles per locus and effective number of segregating *H* loci in a wild population were derived. When applied to the empirical results, these equations led to estimates of 1.13 to 1.26 effective alleles per *H* locus and of 4 to 7 *H* loci showing segregation.

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