CONTROL OF MATING PREFERENCES IN MICE BY GENES IN THE MAJOR HISTOCOMPATIBILITY COMPLEX*

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While observing AKR and AKR backcross mice being bred to produce an AKR-*H-2*^{b} congenic mouse strain, one of us (J. B.) noticed that homozygous *H-2*^{b} ♂♂ were more attracted to heterozygous *H-2*^{b}:*H-2*^{k} ♀♀ than to *H-2*^{b} homozygous ♀♀. Meanwhile another of us (L. T.), unaware of these observations, arrived at the theoretical conclusion that histocompatibility antigens might act as olfactory self-markers distinguishing different members of a population from one another (1).

This article is an account of our study of *H-2*-associated "mating preference." By "*H-2*" we imply the chromosomal region including *H-2* which differentiates congenic stocks from their partner strains. We used a straightforward experimental design: A ♂ mouse (e.g., **"bb"**) was caged with two *H-2* congenic ♀♀ (e.g., **"bb"** and **"kk"**), in estrus, and the trio was observed continuously until the ♂ successfully mated with one of the ♀♀.

Materials and Methods

The convention "cross 1," "cross 2," "cross 3," refers to the systems in which mating preference was studied (Table I; reference 2). The mice were bred and maintained in plastic cages, and were weaned and numbered at an age of 18–21 days. At weaning, the progeny were sexed and transferred to stock cages holding 8–10 ♂♂ or ♀♀. Neither the breeding cages nor stock cages were segregated from cages of various other strains being bred in the same quarters.

All ♂♂ were vasectomized at an age of about 10 wk, and then each was separately caged. Vasectomy was performed to obviate pregnancy and allow the ♀♀ to be used more frequently in the tests.

The ♀♀ of each strain were caged together. Pro-estrus, and estrus (on the following day), were determined visually (3). After use in tests, ♀♀ with vaginal plugs were caged together. The pseudopregnancy induced by sterile mating conveniently provided ♀♀ in roughly synchronous estrus 8–10 days later (4) for use in further tests. Throughout most of this study, ♀♀ of congenic pairs, e.g. BALB and BALB.B, or B6 and B6-*H-2*^{k}, were caged together after use, to save space. Later we caged ♀♀ of each stock separately. A light-dark cycle of 16:8 h was maintained (light period 10–2 a.m.) to condition the ♀♀ to ovulate at about 10 a.m., roughly 4 h after the mid-point of the dark period (4).

Design of Experiments

"Mating" refers to successful copulation verified by observation of a vaginal plug. At 10–10:30 a.m. the cage of each isolated vasectomized ♂ was placed on a bench for continuous observation.

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TABLE I
General Information

	Mouse strain*	*H-2* type	No. of ♂♂ tested	No. of valid trials	No. of hybrid ♂♂ tested	No. of valid trials
Cross 1	BALB	**d**	26	128	27	165
	BALB.B‡	**b** (from B10)	26	133		
Cross 2	B6	**b**	19	66	25	86
	B6-*H-2*^{k}	**k** (from AKR)	23	79		
Cross 3	B10	**b**	18	99	–	–
	B10.A	**a** (from A)	18	92		

Abbreviations: BALB, BALB/c; B6, C57BL/6; and B10, C57BL/10.

* For description and alternative notation of congenic stocks, see Klein (2).

‡ Breeding stock kindly provided by Dr. Frank Lilly, Albert Einstein College of Medicine, Bronx, N. Y.

Two estrous ♀♀ of selected *H-2* types were then put in. The preference of the ♂ was usually soon obvious from his more frequent attempts, after inspection of his prospective mates, to mount one rather than the other. After one of the ♀♀ had mated, both were removed. The mated ♀ (with vaginal plug) was returned to stock. The second (unmated) ♀ was tested with a fresh ♂. If mating occurred, the trial was scored "valid." If not, the test was scored "invalid" on the grounds that the second ♀ may not have been in estrus.

We use the terms "strain preference" and "consistency of choice" for two aspects of the data. Strain preference refers to any tendency of the ♂ population of a given strain to mate with ♀♀ of one *H-2*-type rather than another. Consistency of choice concerns the mating preferences of individual ♂♂ of such a population. It refers to any tendency of particular ♂♂, on repeated testing, to mate with ♀♀ of the *H-2* type they mated with before. From a mathematical standpoint, strain preference and consistency of choice need not be related to one another. To take an extreme case, if 50% of genetically identical ♂♂ always chose ♀♀ of one *H-2* type, and the other 50% always chose ♀♀ of the other, there would be no strain preference, but complete consistency of choice. Similarly, strain preference could occur without a greater consistency of choice than is implicit in strain preference.

We have tested heterozygous ♂♂, as well as homozygous ♂♂. As illustrated in Fig. 1, their situation is different. Our test system confronts the homozygous ♂ with one of the three pairs of alternative choices which the three following types of ♀ allow: (*a*) A homozygous ♀ genetically the same as himself. (*b*) A dissimilar homozygous ♀. (*c*) A hybrid ♀ with whom he shares one *H-2* haplotype. But the hybrid ♂ can be offered only ♀♀ who share at least one *H-2* haplotype with him and do not bear an *H-2* haplotype foreign to him. The use of symbols such as **bb** and (**b**) to indicate the choices made is explained and illustrated in Fig. 1.

Results and Discussion

Evidence that H-2 Influences Mating Preference (Table II; reference 5)

STRAIN PREFERENCE OF MICE OF DIFFERENT *H-2* GENOTYPES. In cross 1, **dd** ♂♂ mated with (**b**) ♀♀ in 52% of trials, i.e., there was no strain preference. The **bb** ♂♂ mated with (**b**) ♀♀ in 70% of trials. Thus **bb** ♂♂ show strain preference in favor of ♀♀ of the same *H-2* type as the ♂. The results for hybrid ♂♂ are intermediate, with a rate of 58% for (**b**) ♀♀, and this ordering in the degree of strain preference is statistically significant; the latter two proportions, 58 and 70%, are significantly different from 50%.

In cross 2, homozygous ♂♂ of both types showed strain preference for ♀♀ of

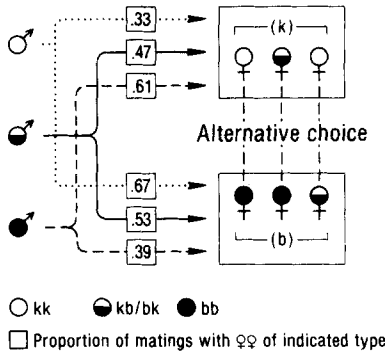

FIG. 1. Schematic representation of the strain preference of cross 2 (Table II); use of symbols to indicate choices made. In the text and tables, double symbols are used to indicate the results of trials involving only homozygous ♀♀. Thus, e.g. for cross 2, **kk** indicates choices of a **kk** ♀ in preference to a **bb** ♀. A single symbol in parenthesis, e.g. (**b**) in lower right box, is used to refer collectively to such trials and also trials involving hybrid ♀♀. The figure shows that (**b**) includes trials in which (1) a **bb** ♀ was preferred to a **kk** ♀, (2), a **bb** ♀ was preferred to a **kb** or **bk** ♀, and (3) a **kb** or **bk** ♀ was preferred to a **kk** ♀. This indicates the meaning of the term "Prob(**b**)," the estimated probability of mating with a (**b**) ♀, which appears frequently in the tables. Hybrids are denoted **kb/bk** (below) to indicate that reciprocal hybrids (**kk** ♀ × **bb** ♂; **bb** ♀ × **kk** ♂) have given similar results; the data for reciprocal hybrid ♂♂ and ♀♀ have therefore been combined.

the dissimilar *H-2* type. Thus **kk** ♂♂ mated with (**b**) ♀♀ at the rate of 67%, and **bb** ♂♂ mated with (**b**) ♀♀ at the rate of 39%. Again the rate for hybrid ♂♂ was intermediate.

In cross 3, where only homozygous ♂♂ and ♀♀ were tested, the rate of mating with **bb** ♀♀ was 60% for **aa** ♂♂ and 39% for **bb** ♂♂. Again the choices of both male types were for ♀♀ of dissimilar type. Strain preference is schematically represented for cross 2 in Fig. 1.

STRAIN PREFERENCE FOR SIMILAR AND DISSIMILAR *H-2* TYPE. In cross 1, **bb** ♂♂ preferred **bb** ♀♀, the similar *H-2* type; but in crosses 2 and 3 **bb** ♂♂ preferred the dissimilar *H-2* type, **kk** ♀♀ and **aa** ♀♀, respectively (Table II). Evidently ♂♂ of a particular *H-2* type (**bb** in this case) may prefer ♀♀ of similar or dissimilar *H-2* type, depending on which particular *H-2* type is offered as the alternative. This suggests a scale of preferences in which the similar *H-2* type of the ♀ may rank lower or higher than other *H-2* types. It would not be safe to assume that **bb** ♂♂ would always prefer ♀♀ in the order **kk** or **aa, bb, dd,** because the **bb/dd** choice (cross 1) was tested on a BALB background, whereas the **bb/kk** choice (cross 2) was tested on a B6 background, and the **bb/aa** choice (cross 3) on a B10 background.

INTERMEDIATE STRAIN PREFERENCE RATES FOR HYBRID ♀♀. Crosses 1 and 2 were analyzed further by comparing the data for all trials involving only homozygote-homozygote ♀ partners with the data for all trials involving only homozygote-hybrid ♀ partners. As Table III shows, there was no difference in the case of **dd** ♂♂ (.51 vs. .53), as expected from the fact that BALB **dd** ♂♂ showed no strain preference. For the three qther cases (**bb** ♂♂ in cross 1; **kk** and **bb** ♂♂ in cross 2) the degree of strain preference was less for trials in which one of the ♀ partners was a hybrid.

TABLE II
Strain Preference According to ♂ Genotype

♂♂	No. of matings		Total trials	Prob(b)	95% Confidence interval
	♀♀				
Cross 1	(d)*	(b)			
dd	61	67	128	.52	.44–.61
db/bd	69	96	165	.58	.51–.66
bb	40	93	133	.70	.62–.78
χ^2 for trend in proportions‡ (1 df) = 8.07; $P < 0.005$					
Cross 2	(k)	(b)			
kk	26	53	79	.67	.57–.77
kb/bk	40	46	86	.53	.43–.64
bb	40	26	66	.39	.28–.51
χ^2 for trend in proportions (1 df) = 10.53; $P < 0.002$					
Cross 3	**aa***	**bb**			
aa	37	55	92	.60	.50–.70
bb	60	39	99	.39	.30–.49
χ^2 (1 df) = 7.14; $P < 0.008$					

* The use of symbols to indicate choices is explained and illustrated in Fig. 1. Briefly, **(d)** *e.g.* includes tests involving a hybrid ♀ as well as tests involving only homozygous ♀♀, and **aa** *e.g.* refers exclusively to tests involving only homozygous ♀♀.

‡ See Armitage (5) for discussion of the statistical techniques used.

TABLE III
Strain Preference for Hybrid ♀♀: Degrees of Strain Preference in Trials with Homozygote-Hybrid ♀ Partners Compared with Trials in which the ♀ Partners were Dissimilar Homozygotes

		No. of matings		Prob(b)
Cross 1		**dd/(d)**	**bb/(b)**	
dd ♂♂	Dissimilar ♀ homozygotes	34	36	.51
	Homozygote and hybrid ♀♀	27	31	.53
bb ♂♂	Dissimilar ♀ homozygotes	18	54	.75
	Homozygote and hybrid ♀♀	22	39	.64
Cross 2		**kk/(k)**	**bb/(b)**	
kk ♂♂	Dissimilar ♀ homozygotes	19	42	.69
	Homozygote and hybrid ♀♀	7	11	.61
bb ♂♂	Dissimilar ♀ homozygotes	34	17	.33
	Homozygote and hybrid ♀♀	6	9	.60

STRAIN PREFERENCE OF ♂♂ IN SUCCESSIVE TRIALS. Is strain preference enhanced or lessened as the ♂♂ age or acquire more mating experience? All data for crosses 1 to 3 are included in Table IV, where the mating scores are analyzed according to their place in the sequence of trials. There is no significant trend in these proportions except in cross 2 **bb** ♂♂, but the latter may be explained by

TABLE IV
Strain Preference on Successive Trials; Hybrid ♀♀ Included

♂♂	♀♀	Trial no.						Total
		1	2	3	4	5	6	
Cross 1								
dd	(d)	12	11	11	10	17*		61
	(b)	14	15	15	16	7*		67
Prob(b)		.54	.58	.58	.62	.29		.52
bb	(d)	8	6	5	12	9*		40
	(b)	18	20	21	14	20*		93
Prob(b)		.69	.77	.81	.54	.69		.70
Cross 2								
kk	(k)	6	7	8	5*			26
	(b)	17	15	8	13*			53
Prob(b)		.74	.68	.50	.72			.67
bb	(k)	15	11	9	5*			40
	(b)	4	8	6	8*			26
Prob(b)		.21	.42	.40	.62			.39
Cross 3								
aa	**aa**	6	9	7	5	4	6	37
	bb	12	9	10	11	9	4	55
Prob(**bb**)		.67	.50	.59	.69	.69	.40	.60
bb	**aa**	13	14	8	10	8	7	60
	bb	5	4	10	7	8	5	39
Prob(**bb**)		.28	.22	.56	.41	.50	.42	.39

* Includes some data for later trials.

the higher proportion of hybrid ♀♀ used in later trials. Because interpretation is complicated by the lesser strain preference in hybrid-homozygote trials (Table III) the results were recomputed for crosses 1 and 2 with the data for hybrid ♀♀ excluded (Table V). The absence of a trend towards changing strain preference is even more evident here, except for a trend for **dd** ♂♂ of cross 1 which is not statistically significant.

Consistency of Choice. In addition to assessing the strain preference of mice of different *H-2* genotypes, we can ask whether on sequential testing each ♂ is more consistent in his choice of ♀♀ than would be expected in consequence of

TABLE V
Strain Preference on Successive Trials; Hybrid ♀♀ Excluded

♂♂	♀♀	Trial no.					Total
		1	2	3	4	5	
Cross 1							
dd	**dd**	12	5	7	4	6	34
	bb	14	12	5	3	2	36
Prob(**bb**)		.54	.71	.42	.43	.25	.51
bb	**dd**	8	2	2	5	1	18
	bb	18	7	14	7	9	55
Prob(**bb**)		.69	.78	.87	.58	.90	.75
Cross 2							
kk	**kk**	6	7	6	0		19
	bb	17	15	6	4		42
Prob(**bb**)		.74	.68	.50	1.00		.69
bb	**kk**	15	11	6	2		34
	bb	4	8	4	1		17
Prob(**bb**)		.21	.42	.40	.33		.33

genotypic strain preference alone. Any such tendency we shall call "consistency of choice." This can be determined by inspecting the mating histories of genotypically identical ♂♂ individually. If there is no consistency of choice beyond that implicit in the strain preference of a particular ♂ population, then the choices made in a sequence of trials should be independent of the first choice. But if the choices in second and subsequent trials show a higher degree of concordance with the first choice than can be accounted for by genotypic strain preference alone, then individual ♂♂ must also have a phenotypic bias towards one *H-2* type or the other.

The criterion chosen for this analysis (Tables VI and VII) is the probability of a (**b**) mating [Prob(**b**)], or a **bb** mating [Prob(**bb**)], on second and subsequent matings of individual ♂♂ that chose a (**b**) or **bb** mate in the first trial; compared with Prob(**b**) or Prob(**bb**) for genotypically identical ♂♂ that made the opposite choice on first mating. Regardless of strain preference, these probabilities should be equal if there is no consistency of choice. But often the observed proportions are very different. The most striking example is **dd** ♂♂ of cross 1 (Table VI and Fig. 2). Those individual **dd** ♂♂ that made a (**d**) choice in their first trials had only a .36 estimated probability of subsequent (**b**) matings, whereas **dd** ♂♂ that first made a (**b**) choice had a .70 probability of subsequent (**b**) matings. Or as illustrated in Fig. 2, **dd** ♂♂ whose first choice was **dd** had a .32 probability of subsequent **bb** matings, whereas **dd** ♂♂ whose first choice was **bb** had a .74 probability of subsequent **bb** matings.

Table VI shows analysis of consistency for all matings. In Table VII the data for all hybrid trials have been excluded. Consistency is even more evident there, although this is not reflected in the *P* value for cross 2 because the sample is smaller. There is no evidence of consistency for cross 3 (Table VI).

TABLE VI
Consistency of Choice: All Matings*

	♂♂ (No. tested‡)	♀♀ First trial	Subsequent trials		
Cross 1			(d)	(b)	Prob(b)
dd	(12)	(d)	35	20	.36
	(14)	(b)	14	33	.70
db/bd	(12)	(d)	23	38	.62
	(15)	(b)	34	43	.56
bb	(8)	(d)	13	20	.61
	(18)	(b)	19	55	.74
All	(32)	(d)	71	78	.52] A
	(47)	(b)	67	131	.66]
Significance of the difference A: $\chi^2 = 6.21$; $P < 0.02$					
Cross 2			(k)	(b)	Prob(b)
kk	(6)	(k)	8	8	.50
	(17)	(b)	12	28	.70
kb/bk	(11)	(k)	13	10	.43
	(14)	(b)	16	22	.58
bb	(15)	(k)	22	19	.46
	(4)	(b)	3	3	.50
All	(32)	(k)	43	37	.46] B
	(35)	(b)	31	53	.63]
Significance of the difference B: $\chi^2 = 4.04$; $P < 0.05$					
Cross 3			**aa**	**bb**	Prob(**bb**)
aa	(6)	**aa**	11	13	.54
	(12)	**bb**	20	30	.60
bb	(13)	**aa**	35	27	.44
	(5	**bb**	12	7	.37
All	(19)	**aa**	46	40	.47] C
	(17)	**bb**	32	37	.54]
The difference C is not significant: $\chi^2 = 0.52$					

* Schematically illustrated in Fig. 2.
‡ See trial no. 1 in Table IV.

Consistency of choice has implications that strain preference does not. Strain preference could be adequately explained on a purely genetic basis. But consistency of choice represents nonrandom variation of ♂♂ of identical genotype, and so implies that the sensory mechanism responsible for mating preference either (*a*) includes provision for memorizing the specific signals, or (*b*) can fortuitously

TABLE VII
Consistency of Choice: Hybrid ♂♂ and ♀♀ Excluded

	♂♂ (No. tested)	♀♀ First trial	Subsequent trials		
Cross 1			**dd**	**bb**	Prob(**bb**)
dd*	(12)	**dd**	17	8	.32
	(14)	**bb**	5	14	.74
bb	(8)	**dd**	5	10	.67
	(18)	**bb**	5	26	.84
All	(20)	**dd**	22	18	.45] A
	(32)	**bb**	10	40	.80]

Significance of the difference A: $\chi^2 = 10.41$; $P < 0.002$.

Cross 2			**kk**	**bb**	Prob(**bb**)
kk	(6)	**kk**	5	7	.58
	(17)	**bb**	8	18	.69
bb	(15)	**kk**	17	10	.37
	(4)	**bb**	2	3	.60
All	(21)	**kk**	22	17	.44] B
	(21)	**bb**	10	21	.68]

Significance of the difference B: $\chi^2 = 3.14$; $P < 0.07$

* Results for these ♂♂ are schematically represented in Fig. 2.

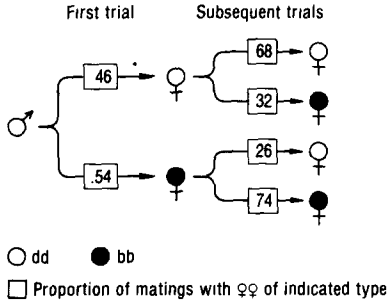

FIG. 2. Schematic representation of consistency of choice of **dd** ♂♂ for homozygous **dd** or **bb** ♀♀ in cross 1 (Table VII).

be biased one way or the other in individual ♂♂. If (*a*) is true, then in cross 1 (e.g.) **dd** ♂♂ that preferred (**d**) ♀♀ were specifically conditioned to do so, just as other genetically identical **dd** ♂♂ were specifically primed to prefer (**b**) ♀♀. But as yet we have no evidence of specific environment cues that would support the former interpretation.

Evidence that the Choice is Made Mainly or Entirely by the ♂ and not the ♀. The data above show that alleles of a locus in the region of *H-2* influence the mouse's choice of a mate. One partner must transmit identification signals governed by *H-2*, and the other must distinguish between different incoming

signals. Which is the active recipient? The ♂ or the ♀? The observed mating behavior suggests that the ♀♀ are passive and the ♂♂ active. But such behavior might be simulated by rejection of the ♂ by one of the ♀♀.

The histories of individual ♂♂ show that the choice of mates is not random. Strain preference and consistency of choice both indicate this. If ♀♀ were entirely passive (transmitted signals but made no choice) then their sequential mating histories should show no consistency except to the extent that where selection of one ♀ rather than the other is characteristic of the ♂ population as a whole (strain preference) the history of each ♀ will show on the average the same preponderance of matings of the preferred type. (This argument depends on the assumption that the ♀♀ were drawn at random from the population available in estrus, which was the case.) The data are analyzed in Table VIII in accordance with the postulate that the choice is made by the ♀. A slightly different method of calculation was necessary.

In terms of hypothetical selection by ♀♀, the result of a valid trial can be construed as solicitation by one ♀ or as rejection by the other. Therefore both ♀♀ in each trial were given a score: (*a*) The mated ♀ in favor of the ♂'s *H-2* type, and (*b*) the unmated ♀ in favor of the alternative *H-2* type. For example, of 89 cross 1 **dd** ♀♀ included in this analysis 49 on their first valid trial either (*a*) were presented to a **dd** ♂ and mated with him, or (*b*) were presented to a **bb** ♂ who mated with the other ♀. Either result was scored **dd** (first entry in Table VIII). In 70 subsequent valid trials these 49 ♀♀ yielded 44 scores (63%) for **dd** and 26 scores (37%) for **bb**. The 40 **dd** ♀♀ who first received **bb** scores gave virtually the same results: 23 scores (62%) for **dd** and 14 scores (38%) for **bb**.

Table VIII reveals no consistency on the part of **dd** ♀♀ in any of the crosses. We discount the data showing a trend in the reverse of consistency for **bb** ♀♀ in cross 2 because the sample is small.

Further Comment

The various ways in which genes in the major histocompatibility complex may be implicated in immunological types of recognition, notably in discrimination between "self" and "non-self," cannot be reviewed here. The *H-2*-associated mating preference we described is a form of self-identification that might be traced back to a time long before the evolution of specific adaptive immunity, as discussed elsewhere (1).

The fact that a particular ♂ may consistently prefer ♀♀ of one *H-2* type, whereas a genetically identical ♂ may consistently prefer ♀♀ of a different *H-2* type, may imply that ♂♂ can learn by experience to prefer (e.g.) **d** to **b**, or the reverse. The term "memory" has come to be used in immunological circles in reference to adaptive immunization. Analogies have been suggested between immunologic and neurologic memory [for references and discussion see Cohn (6, 7)]. The element of memory in *H-2*-associated mating preference, if memory is involved in consistency of choice, might in turn suggest a link between the two, because of several connections between immune responses and genes in the region of *H-2*. Although we as yet lack evidence regarding whether or not ♂♂ can be specifically trained to prefer one or another *H-2* type, certain negative inferences can be drawn: The mating preferences of reciprocal hybrid ♂♂ were not significantly different. Therefore the preferences of ♂♂ of hybrid genotype are not noticeably affected by exposure to contrasting *H-2* types during

TABLE VIII
Analysis of the Data for Evidence of Consistency of Choice by ♀♀

	♀♀ (No. tested)	♂♂ First trial	Subsequent trials		
Cross 1			**dd**	**bb**	Prob(bb)
dd	(49)	**dd**	44	26	.37
	(40)	**bb**	23	14	.38
bb	(34)	**dd**	19	26	.58
	(41)	**bb**	29	44	.60
Cross 2			**kk**	**bb**	Prob(bb)
kk	(5)	**kk**	3	3	.50
	(30)	**bb**	19	27	.59
bb	(26)	**kk**	29	18	.38
	(5)	**bb**	6	0	.00
Cross 3			**aa**	**bb**	Prob(bb)
aa	(19	**aa**	24	42	.64
	(23)	**bb**	38	46	.55
bb	(31)	**aa**	55	45	.45
	(15)	**bb**	26	19	.42

the period from zygosis to weaning. Nor is the first mating experience decisive, because strain preference is already evident in first trials, and does not demonstrably increase with mating experience (Tables IV and V).

The stimulus is probably olfactory, although other sensory mechanisms are possible (see reference 8). The pheromone or pheromones best known in mice are excreted by the ♂, causing synchronous estrus in ♀♀ (9), pregnancy block by strange ♂♂ (10), and precocious puberty in young ♀♀ (11). The first two effects can be exerted over considerable distances (12). [These pheromone effects, and others related to ♂ aggression and identification of sex are reviewed by Whitten (13) and Bronson (8).] Possibly the putative ♀ substance specified by the major histocompatibility complex may also act at a distance, in which case receptive ♂♂ housed in quarters containing mice of several different strains may at a receptive age be primed by airborne *H-2*-associated pheromones before they are tested. The signal transmitted by the ♀ must be controlled by an *H-2*-linked gene, because genetically identical ♂♂ can distinguish between congenic ♀♀ of different *H-2* types. Similarly ♂♂ must possess a receptor gene in the *H-2* region, because congenic ♂♂ of different *H-2* types make different choices when offered the same pair of *H-2*-dissimilar ♀♀. (This could not be so if the receptor gene were on the Y chromosome, because the congenic strains we studied carry the same Y as their partner strains.) The most obvious model of mating preference therefore is that of two linked genes in the *H-2* region, one for the signal and one for the receptor. A similar model has been suggested to account

for *H-2*-associated interactions between cells cooperating in immune responses (14).

Of several uses which mating preference might serve in nature, the most easily comprehensible is maintenance of heterozygosity of genes in the vicinity of *H-2*. To cite only one obvious advantage of *H-2*-heterozygosity: This region includes *Ir* (immune response) genes with dominant alleles conferring strong responsiveness to particular antigens. Where infections are a prominent environmental hazard, hybrids would enjoy the advantage of a wider range of immune defenses. Nature is evidently prepared to pay a high price for heterozygosity in the region of *H-2*, according to current views of the *T/t* locus (15). The *t* mutants, which are prevalent in the wild and are linked to *H-2*, are lethal in the homozygous state. They would therefore decline in frequency in wild populations if it were not for their extraordinarily high and non-Mendelian rate of transmission by ♂♂. Presumably their lethality is balanced by advantages, no doubt including heterozygosity in the *H-2* region.

The *H-2*-associated mechanism of mating preference could work to the same end if choice of dissimilar *H-2* types is commoner in nature, as has proved to be the case so far in laboratory mice.

Summary

When a ♂ mouse is presented with two *H-2* congenic ♀♀ in estrus, his choice of a mate is influenced by their *H-2* types. The term "strain preference" is used to describe the general tendency of the ♂ population of one inbred strain to prefer ♀♀ of one *H-2* type rather than another. The term "consistency of choice" is used to describe the added tendency of particular ♂♂ of one inbred strain, in sequential mating trials, to prefer ♀♀ of the *H-2* type they chose in previous trials. Statistical analysis showed trends in the data that support the following conclusions: (*a*) The choice is made by the ♂, not the ♀. (*b*) The strain preference of ♂♂ may favor ♀♀ of dissimilar *H-2* type (four of six comparisons), or of similar *H-2* type (one of six comparisons). (*c*) Consistency of choice does not always correspond with strain preference. In one of six comparisons of *H-2* genotypes there was no strain preference but pronounced consistency of choice by individual ♂♂. This suggests memory, but fortuitous bias is not excluded. (*d*) Strain preference of the same ♂ population may favor ♀♀ of the same or a different *H-2* type, depending on which different *H-2* type is offered as the choice alternative to self.

These findings conform to a provisional model in which olfactory mating preference is governed by two linked genes in the region of *H-2*, one for the ♀ signal and one for the ♂ receptor. These mating preferences could in natural populations serve the purpose of increasing the representation of particular *H-2* haplotypes or of maintaining heterozygosity of genes in the region of *H-2*.

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