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† Present address: Department of Biology, Brookhaven National Laboratory, Upton, New York.

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*STUDIES ON THE HISTOCOMPATIBILITY GENES OF THE SYRIAN HAMSTER**

BY R. E. BILLINGHAM, G. H. SAWCHUCK, AND W. K. SILVERS

THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY, PHILADELPHIA, PENNSYLVANIA

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Although Syrian hamsters (*Mesocricetus auratus*) can reject orthotopic homografts of skin just as promptly and effectively as other mammals, suggestive evidence has been obtained that the number of important histocompatibility genes segregating in the various hamster stocks so far tested may be very small.[1-3] For example, it has been shown that a high proportion of skin homografts transplanted between members of the same closed but random-bred stocks are usually accepted for a very long time, and that skin homografts may long be accepted even when transplanted between members of *different* and completely unrelated stocks. The many reported successful propagations of tumors of spontaneous or induced origin in noninbred hamsters also hint at the paucity of important histocompatibility genes in this species.[4-13]

As a general rule, solid tissue homografts that establish vascular and lymphatic connections with their hosts will be exempted from a fairly prompt immunological rejection only if *all* the important histocompatibility genes (or transplantation antigens) possessed by them are also fully represented in the hosts. This state of affairs obtains: (*a*) consistently, when grafts are made within an inbred strain (isografts) or from such a strain to its F_1 hybrid offspring, or (*b*) in a proportion of cases, when parental strain grafts are transplanted to F_2 individuals. By determining this proportion (x) experimentally, it is possible to estimate the number of histocompatibility genes present in the one parental strain but absent in the other, since x can be shown to be equal to $(3/4)^n$, where n is the number of genes concerned. Of course, it has to be assumed that the genes segregate independently, and that each determines an antigen that is *singly* sufficient to provoke a level of sensitization of the host that will lead to graft destruction during the period when the animals are maintained under observation. In mice, "weak" transplantation antigens are known that may take many weeks, or even months, to procure the ultimate breakdown of homografts.[14-16] Indeed, they may even fail to do so in some cases.

It must be emphasized that in the mouse, and in all other species where there are many histocompatibility genes, analyses of this sort are only possible or meaningful

if highly inbred or isogenic stocks are available for investigation, although in theory, at least, noninbred stocks should be suitable provided that each is uniform with respect to its histocompatibility genes.[17] The existence of the latter state of affairs in our only partially inbred hamster stocks[2] has made possible the present study, the purpose of which was to obtain an estimate of the number of histocompatibility genes involved in the rejection of skin homografts in this species.

Materials and Methods.—Small breeding nuclei of the strains of hamsters used in this investigation were obtained in 1957 from three completely independent, closed, random-bred colonies in England.[2] The designation of these stocks, their color phenotypes, and the periods for which each had been known to have been isolated when the present grafting experiments were initiated are: M.H.A., albino (4 years); L.S.H., agouti (6 years); and C.B., agouti (12 years). Since its arrival in this Institute each strain has been maintained by brother × sister matings and is currently in its seventh generation of inbreeding. All the C.B. and L.S.H. animals used in this investigation could be traced back to common F_5 or F_4 matings, whereas the M.H.A. animals were derived from three lines separated when the present inbreeding program began.

Billingham and Hildemann's[2] preliminary analyses conducted on randomly selected animals from each of the three "parental" English colonies had shown that a very high proportion of intra-strain skin homografts lived for at least 100 days, but that homografts exchanged between L.S.H. and C.B. animals were very promptly rejected, as were those transplanted from M.H.A. donors to C.B. hosts.

Operative procedures: The operative procedures employed for the preparation and transplantation of the skin grafts—in the present study disks of skin 1.3 to 1.6 cm in diameter and comprising the epidermis and full thickness of the dermis—are described in detail elsewhere.[2] In the intra-strain tests, each animal received a single graft fitted into an appropriately sized bed on the lateral thoracic wall.

Scoring of the survival times of the grafts: Primary inspection of all grafts was made on the ninth postoperative day, and subsequent inspections were carried out at two- or three-day intervals until the twentieth day, after which examinations were carried out less frequently. Appraisal of the condition and degree of viability, and assessment of the survival times of homografts that broke down at an early stage as a consequence of typical acute reactions presented no difficulty. However, many grafts healed in perfectly, regenerated good hair crops, and lived for long periods of variable duration, sometimes exceeding 150 days, in a state of complete normality before indications of a feeble, chronic reaction on the part of the host appeared. Prompt rejection of these long-term grafts was never encountered, and consequently a precise estimation of their survival endpoints was impossible. There was a progressive loss of fur, culminating in complete alopecia, increasing smoothness of the epidermis, and, finally, a scar-like appearance. This type of reaction has recently been studied in detail by Hildemann and Walford.[18] The time at which the epidermis of our bald, shiny grafts could be separated from its dermis by light scratching with the fingernail was arbitrarily taken as the survival end-point.

Plan of experiments: As necessary preliminaries to the experiments to be described, the following procedures were carried out:

1. Each of the three strains was tested for the antigenic homogeneity of its

members by pairing adult animals from *different* litters and exchanging skin grafts between them.

2. Homografts were exchanged between randomly selected individuals in the three possible strain combinations, C.B. $\rightleftharpoons$ L.S.H., C.B. $\rightleftharpoons$ M.H.A., and L.S.H. $\rightleftharpoons$ M.H.A. Median survival times of these homografts, with their confidence limits for $^{19}/_{20}$ probability, were estimated according to Litchfield's method.[19]

Then, with *each* of the two strain combinations in which homografts were promptly and consistently rejected, C.B. $\rightleftharpoons$ L.S.H. and C.B. $\rightleftharpoons$ M.H.A., three independent matings were set up. As a final check, homografts were interchanged between these intended parents to confirm their incompatibility to grafts of each other's skin. All the F_2 individuals employed for the tests to be described were derived from full-sib matings of the F_1 progeny of these individuals.

Every F_2 animal received, when it was 5–7 weeks old, a single skin homograft from a randomly selected donor of *each* of its grandparental strains, both grafts being transplanted simultaneously.

Throughout this work, the grafts were maintained under observation for 200 days—an appreciable portion of the average life-span in this species, usually stated to be about 18 months.

Although there is no evidence for the existence of any Y-linked histocompatibility gene(s) in Syrian hamsters[2, 3]—such as occurs in all mouse strains so far investigated[20] and in some isogenic strains of rat[17]—to avoid all risk of complication, male skin was never transplanted to female recipients in this work.

Results.—1. *Intra-strain grafts:* The results of the extensive series of intra-strain grafting tests (Table 1) indicated that each strain was sufficiently homozygous

TABLE 1

SUMMARY OF CONTROL SERIES OF GRAFTING TESTS

Donor strain	Recipient strain	No. grafted	No. compatible*	No. incompatible	Survival times of rejected grafts (days)	Median survival times, with confidence limits (days)
			Intra-strain Grafts			
M.H.A.	M.H.A.	19	17	2	~45, ~55	.....
C.B.	C.B.	26	25	1	14	.....
L.S.H.	L.S.H.	27	27	0	.....	.....
			Inter-strain Grafts			
C.B.	L.S.H.	29	0	29	9–16	11.2 (10.6–11.8)
L.S.H.	C.B.	27	0	27	10–23	13.5 (12.5–14.6)
C.B.	M.H.A.	16	0	16	9–11	10.6 (10.3–10.9)
M.H.A.	C.B.	16	1	15	10–17	13.0 (11.2–15.2)
L.S.H.	M.H.A.	10	6	4	11, 19, ~60, ~130	.....
M.H.A.	L.S.H.	9	2	7	12, 19, 27, 32 ~65, 2x ~130	.....

* "Compatible" grafts are those which were still in impeccable condition 200 days after transplantation.

with respect to its histocompatibility genes to justify the performance of the F_2 tests. Only one of 26 C.B. hamsters rejected its C.B. test graft; with the M.H.A. strain, 2 out of 17 rejected their intrastrain grafts, but only after intervals of about 45 and 55 days, respectively. The L.S.H. animals were completely homogeneous so far as this test could reveal.

2. *Inter-strain grafts:* Of the three strain combinations tested (see Table 1), two—C.B. $\rightleftharpoons$ L.S.H. and C.B. $\rightleftharpoons$ M.H.A. —were highly and almost consistently

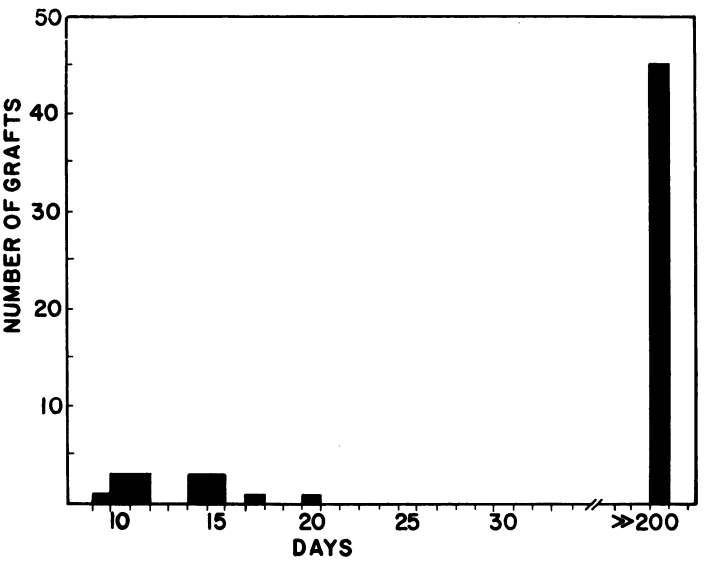

FIG. 1.—Distribution of survival times of C.B. strain grafts → (C.B. × L.S.H.) F_2 hosts.

intolerant of skin homografts interchanged between them. One out of 16 C.B. animals failed to reject its M.H.A. test graft. With the third strain combination, M.H.A. ⇌ L.S.H., which was tested on a smaller scale, a significant proportion of individuals accepted their test homografts. Accordingly, experimental analysis of the number of histocompatibility genes determining rejection of skin homografts was confined to the C.B. ⇌ L.S.H. and C.B. ⇌ M.H.A. strain combinations.

3. *Homografts from C.B. → (C.B. × L.S.H.) F_2 hybrids:* Of 60 F_2 hybrids that received technically satisfactory homografts from C.B. donors, only 15 rejected their grafts—all very promptly (within 20 days) after typical acute homograft reactions (see Fig. 1). The grafts on the remaining 45 hamsters in this series (75 per cent) were still in excellent condition when the experiment was discontinued on the 200th postoperative day. These findings constitute strong evidence that rejection of C.B. homografts by L.S.H. hosts is determined solely by a single strong histocompatibility gene (see Table 2).

4. *Homografts from L.S.H. → (C.B. × L.S.H.) F_2 hybrids:* With this donor/host combination, 32 of 59 (54 per cent) homografts survived throughout the observation period, indicating difference with respect to two histocompatibility genes. Here, there was enormous variability in the survival times of the rejected grafts:

TABLE 2

SUMMARY OF PARENTAL F_2 HYBRID GRAFTING TESTS CONDUCTED AND RESULTS

Donor/host combination	No. of grafts observed	No. of grafts surviving for longer than 200 days	Expected no. of surviving grafts at 200 days	If no. of histocompatibility genes involved is:
C.B. → (C.B. × L.S.H.) F_2	60	45 (75.0%)	45	1
L.S.H. → (C.B. × L.S.H.) F_2	59	32 (54.0%)	33	2
C.B. → (C.B. × M.H.A.) F_2	59	45 (76.0%)	45	1
M.H.A. → (C.B. × M.H.A.) F_2	58	37 (64.0%)	43.5	1 ($P = 0.05$)
			32.6	2 ($P > 0.2$)

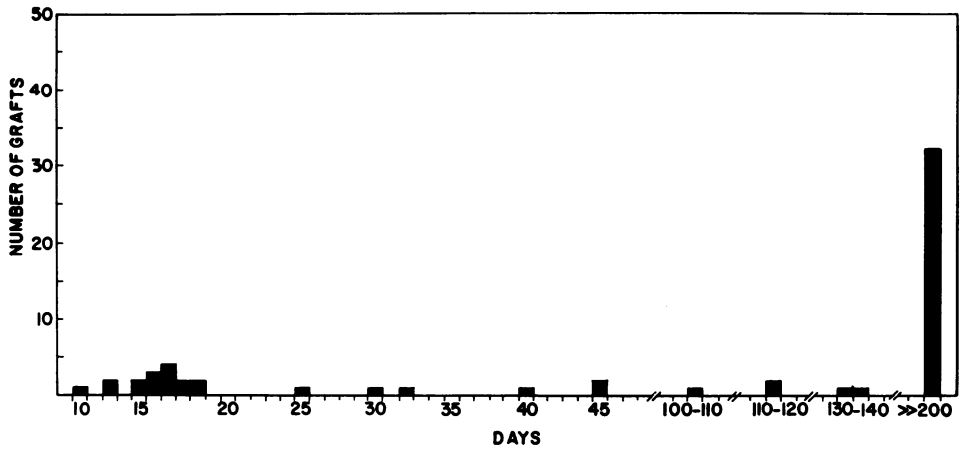

FIG. 2.—Distribution of survival times of L.S.H. strain grafts → (C.B. × L.S.H.) F_2 hosts.

they ranged from 10 to 140 days (Fig. 2). However, the prompt rejection of 16 of the grafts (i.e., within 20 days, after acute reactions) and the survival of the rest of the rejected homografts for 24 to 140 days suggest an unequal effect of the two genes. One, that is, probably determines a "strong," and the other a "weak," transplantation antigen.

5. *Homografts from C.B. → (C.B. × M.H.A.) F_2 hybrids:* In this combination, 45 of 59 grafts (76 per cent) were still in excellent condition on the 200th post-operative day. The individual survival times of 12 of the 14 rejected grafts fell within the 10–18 day range, the remaining grafts being rejected after about 25 and 115 days, respectively (Fig. 3). These data are almost exactly what would be

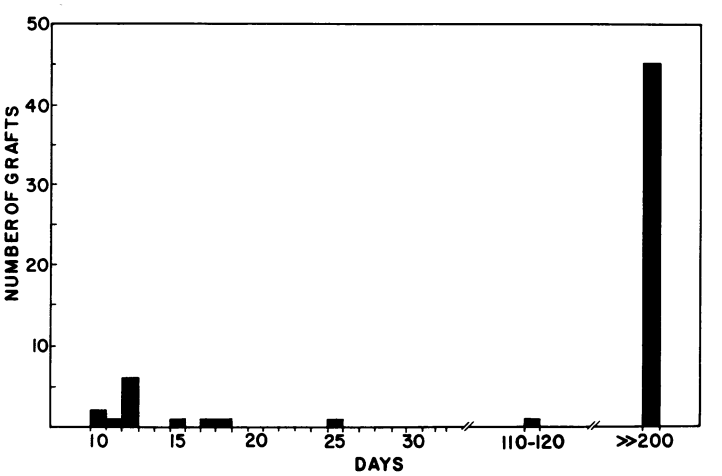

FIG. 3.—Distribution of survival times of C.B. strain grafts → (C.B. × M.H.A.) F_2 hosts.

expected if the incompatibility were determined by a single strong histocompatibility gene (Table 2).

6. *Homografts from M.H.A. → (C.B. × M.H.A.) F_2 hybrids:* Here, 37 of 58 animals (64 per cent) fully accepted their test grafts. The survival times of the

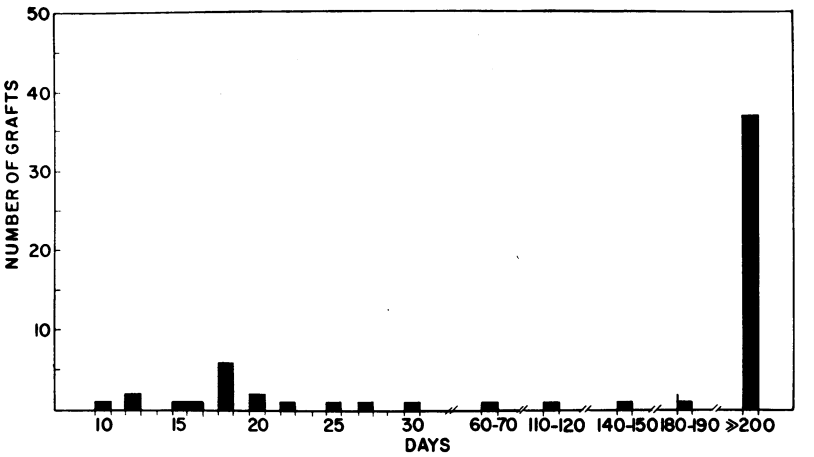

FIG. 4.—Distribution of survival times of M.H.A. strain grafts → (C.B. × M.H.A.) F_2 hosts.

21 rejected grafts covered such a wide range (Fig. 4) as to suggest that even more might have succumbed had the observation period been prolonged. It may be of some significance that the hair crops on several of the surviving grafts were conspicuously sparse on the 200th day. Of the 21 rejected grafts, 13 lived for 20 days or less.

These findings are consistent with the hypothesis that we are dealing here with only one strong factor and probably with one weak factor with incomplete penetrance (Table 2).

7. *Studies on immunologically tolerant hamsters:* By pre- or neonatal inoculation of the young of a variety of both avian and mammalian species with living tissue cells from donors of homologous origin, it is possible to make them permanently and specifically tolerant of (i.e., incapable of reacting against) "foreign" transplantation antigens present in the inoculated cells. They will then permanently accept subsequent skin homografts from the original donor strain transplanted in adult life.[21, 22]

Accordingly, fully tolerant animals *must* be incapable of reacting against the sum total of all those transplantation antigens (or histocompatibility genes) which they themselves possess and those which characterize the homologous cells toward which they have been rendered tolerant. Such animals can be useful in the elucidation of histocompatibility gene relationships of different strains, as Billingham and Brent have shown.[22]

TABLE 3

EXPERIMENTS WITH TOLERANT HAMSTERS

Strain of tolerant hosts	Strain in respect of which tolerant	No. of tolerant hosts	Survival times of grafts from strain in respect of which tolerant	Strain of second donor	Survival times* of grafts from second donors (days)
C.B.	L.S.H.	15	14 × ≫200 1 × ~157	M.H.A.	13 × ≫150 ~80, ~110
C.B.	M.H.A.	5	5 × ≫150	L.S.H.	4 × ≫120 1 × ~120

* Interval between first and second grafting operations 35–50 days.

C.B. strain hamsters, made tolerant either of L.S.H. or M.H.A. tissues by neonatal injection with bone marrow cell suspensions prepared from adult donors of these strains,[23] and bearing appropriate test skin homografts of long standing from the original donor strain, were subsequently challenged with skin homografts from the other strains (Table 3). The failure of nearly all the tolerant animals to reject skin homografts from the second donor strain during the observation period constitutes evidence that: (*a*) M.H.A. strain hamsters have no histocompatibility genes besides those present in the combined genomes of C.B. and L.S.H. hamsters; and (*b*) L.S.H. hamsters, too, have no histocompatibility genes not represented in the combined genomes of C.B. and M.H.A. animals.

Conclusions and Discussion.—The results obtained with the C.B. and L.S.H. strains indicate that the mutual incompatibility towards each other's tissues results from a difference with respect to two histocompatibility genes, only one of which determines an antigen strong enough to procure the rapid breakdown of homografts. Indeed, the C.B. → (C.B. × L.S.H.) F_2 tests revealed the existence of this strong factor only. That two loci must be recognized, however, follows from the findings with the L.S.H. → (C.B. × L.S.H.) F_2 tests. The bimodal distribution pattern of the survival times of the rejected grafts in this combination, along with the number of rejections in each group, is in complete accord with the operation of two factors, one "strong" and the other of much weaker influence. Unlike skin homografts that differ from their hosts with respect to one or more "strong" histocompatibility factors and normally have short survival times falling within a narrow time interval, the survival times of grafts that differ from their hosts only with respect to a single weak factor have been shown to vary enormously.[14, 24, 25] Hence it seems not unreasonable to refer all the breakdowns observed after 20 days to the operation of a single weak antigen. Inability to demonstrate the existence of a locus determining weak transplantation antigens with the C.B. homografts suggests that in these animals the product of the gene at this locus is too weak to have any effect, at least during the 200-day observation period.

Conclusions closely similar to those reported above may be drawn from the tests conducted with the C.B. and M.H.A. strains. Here again, grafting of (C.B. × M.H.A.) F_2 hybrids with C.B. skin gave evidence of only a single strong factor difference, whereas grafting with M.H.A. skin brought to light the effect of a second, apparently weaker, locus with incomplete penetrance distinguishing the two strains. Again, these observations are consistent with the occurrence of a histocompatibility factor in C.B. animals which is too weak to promote graft rejections.

Obviously, if the two histocompatibility genes which distinguish C.B. from M.H.A. strain animals are the same as those involved in the difference between C.B. and L.S.H. hamsters, then it follows that M.H.A. and L.S.H. hamsters should accept grafts interchanged between them. However, this was not found to be the case (see Table 1): 40 per cent of L.S.H. → M.H.A. homografts were rejected, as were 78 per cent of M.H.A. → L.S.H. homografts (in a trial involving a relatively small number of animals). Two graft rejections in each case were of the acute type, while the remainder were chronic in nature. From these results we can infer the existence of some heterogeneity within the M.H.A. stock, and perhaps in the L.S.H. stock as well, which evidently involves a major histocom-

patibility locus. The chronic rejections of some grafts exchanged between these strains also indicate a difference with respect to at least a single weak histocompatibility locus. Furthermore, if this is the only weak histocompatibility difference between these strains, Billingham and Hildemann's[2] work indicates that at least one antigen determined by this weak locus in L.S.H. animals must also be produced in C.B. animals, since these workers found that prior grafting of M.H.A. hamsters with C.B. skin sensitized many of them to subsequent L.S.H. grafts they might otherwise have failed to reject.

The studies on immunologically tolerant C.B. hamsters have shown very clearly that the sum total of the histocompatibility factors present in C.B. and L.S.H. animals includes all the *important* factors present in the M.H.A. strain.

Since it has been shown that the most important difference between L.S.H. and C.B. is that each possesses a single major histocompatibility factor lacking in the other, an attempt has been made to determine whether the genes concerned are alleles or not.

1. *If the factors involved are alleles*, assumed to be A and A', all F_1 hybrids will be AA', and F_2 animals should be present in a ratio of 25 per cent AA, 50 per cent AA', and 25 per cent $A'A'$.

F_2 Genotype	Expected incidence, %	Expected fate of parental grafts AA	$A'A'$
AA	25	+	0
AA'	50	+	+
$A'A'$	25	0	+

+ = acceptance for at least 20 days.
0 = early rejection after acute reaction.

So that 50 per cent of all the F_2's tested should accept test grafts from *both* parental strains, and 50 per cent should accept grafts from only *one* of the parental strains.

2. *If the factors involved are determined by independent loci*, assumed to be represented by the alleles A, a and B, b, and the additional assumption is made that only A and B express themselves, then the F_1 hybrids will be $AaBb$ and the F_2 genotypes will be present in the proportions shown below:

F_2 Genotype	Expected incidence	Expected fate of parental grafts $AAbb$	$aaBB$
A-B-	56.25	+	+
A-bb	18.75	+	0
aaB-	18.75	0	+
$aabb$	6.25	0	0

According to this hypothesis, but not to the first one, the existence of some F_2 animals that will promptly reject grafts from *both* parental strains is predicted.

The same question of allelism versus independent loci also arises for the strong factor by which C.B. differs from M.H.A. and that by which M.H.A. differs from C.B. The factors concerned should be the same as with L.S.H. and C.B., since if this were not the case, L.S.H. would differ consistently from M.H.A. by two strong factors, and vice versa, which is clearly not true. Thus, in the test for allelism versus nonallelism, summarized in Table 4, the determined compatibilities of the parental strain grafts on the two F_2's, (L.S.H. $\times$ C.B.) and (M.H.A. $\times$ C.B.), were pooled.

Comparison of the experimental results with those expected on the basis of each of the two hypotheses under consideration leads to the provisional conclusion that the strong factors concerned must be determined by independent loci rather than by alleles, unless the existence of the three animals that rejected grafts from each

TABLE 4

TEST FOR ALLELISM VERSUS INDEPENDENT LOCI WITH RESPECT TO MAJOR HISTOCOMPATIBILITY FACTORS

No. of F_2 animals tested*	No. that accepted grafts from both parental strains	No. that accepted grafts from only *one* parental strain	No. that rejected grafts from both parental strains
116	63	50	3
Expected nos. if independent loci involved:	62.25	43.5	7.25 ($0.20 > P > 0.1$)
Expected nos. if allelism involved:	58	58	0

* Pooled (L.S.H. × C.B.) and (M.H.A. × C.B.) F_2 animals—see text.

parental strain is attributed to the known nonuniformity of the parental stocks.

The apparent inconsistencies observed make it difficult to deduce the exact histocompatibility genotypes of the three strains of hamsters investigated from the combined evidence obtained. This is especially true when the results of the intra-strain tests and of those obtained from grafting parental strain skin on F_2 animals are compared with those derived from studies on tolerant animals and from the exchange of grafts between L.S.H. and M.H.A. animals. The latter results are particularly perplexing, since the fate of intra-strain grafts and the F_2 tests with the C.B. strain indicate that each of these strains is homogeneous, while, on the other hand, the fate of the grafts exchanged between them suggests that one, if not both, of these strains must be highly heterogeneous. Further studies are required to resolve this situation, which may possibly be due to the multiple origin of the M.H.A. animals. The pooling of experimental animals precludes any analysis here. Another finding to be accounted for is the apparent return to homogeneity in tests conducted upon tolerant C.B. hamsters. It seems as if the C.B. genotype adds something to the factors present in the strain in respect of which these animals are made tolerant; but this is difficult to reconcile with the fact that it adds nothing in the case of the F_2 segregants showing delayed chronic reactions.

The antigenic constitutions postulated below for our three hamster strains

	Strong factor	Weak factor
C.B.:	$\widehat{AbE}$	$\widehat{cd}$
L.S.H.:	$\widehat{aBE}$, $\widehat{aBe}$	$\widehat{Cd}$
M.H.A.:	$\widehat{aBE}$, $\widehat{aBe}$	$\widehat{cD}$

would account for the majority of the experimental findings. The bracketed symbols may represent different antigens at one locus, or different antigens at different loci. The association of *E* and *e*—factors responsible for the inferred heterogeneity within the L.S.H. and M.H.A. strains—with the strong antigens *A* and *B* has some significance, since the F_2 segregants from which C.B. grafts fail to elicit a strong reaction must carry $\widehat{AbE}$. The straightforward results obtained when the F_2 animals were grafted with C.B. skin are thus easily explicable, since such grafts would be $\widehat{AbE}\ \widehat{cd}$ and contain no foreign antigens. If the difference $E \rightarrow e$ causes little or no reaction itself but enhances the reaction when $\widehat{aBE}\ \widehat{cD}$ grafts are placed on $\widehat{aBe}\ \widehat{Cd}$ animals and $\widehat{aBE}\ \widehat{Cd}$ grafts are placed on $\widehat{aBe}\ \widehat{cD}$ animals,

a weak to strong reaction of L.S.H. to M.H.A. and vice versa is explicable in spite of the failure of intra-strain tests to reveal this heterogeneity. This scheme also accounts for reduction of the reaction in the tolerance experiments. The facts not satisfactorily explained by this hypothesis are the low penetrance of the antigens present in $\widehat{aBE}\ \widehat{cD}$ grafts on $\widehat{aBE}\ \widehat{Cd}$ animals and of the reciprocal in the tolerance experiments and in the transplants exchanged between L.S.H. and M.H.A., in comparison with the relatively high penetrance required to account for the weak reactions in the two F_2 experiments.

In the formulation of this hypothesis it has been assumed that the same heterogeneity was present in L.S.H. → L.S.H. and M.H.A. → M.H.A. as in L.S.H. ⇌ M.H.A., but was concealed by low penetrance.

The inconsistent results obtained, though difficult to appraise, are not too surprising in view of what is known about the considerable variations in the response of truly isogenic animals to weak transplantation antigens. This variation may actually be enhanced in the present instance because of the almost certain genetic heterogeneity of the subjects. Genes may be segregating that influence either the formation or expression of certain isoantigens or of the intensity of the response process itself.

Although the present study confirms earlier suspicions that the number of detectable histocompatibility genes segregating in domesticated Syrian hamsters is remarkably small, it affords no obvious clue as to the origin or biological significance of a situation which, at least in our present state of knowledge, appears to be confined to this species.

Like many other rodents, hamsters have a short gestation period, give birth to large litters, and attain sexual maturity very rapidly. Thus, from the point of view of population turnover, there has been ample opportunity for mutant histocompatibility genes to have arisen and segregated since this species was first domesticated from a single litter in 1930 and widely propagated as a laboratory mammal and pet. Hamsters are certainly not exempt from the occurrence of mutations, as evidenced by reports of at least 6 mutations involving coat and eye color.[27-29]

In addition to various hypotheses already discussed by Billingham and Hildemann,[2, 30] the following possibilities should at least be borne in mind:

(1) Hamsters may differ from other species in that their histocompatibility loci are exceedingly stable. If this is so, the original progenitor litter of all available stocks may *itself* have been almost uniformly homozygous with respect to its histocompatibility genes, and present-day wild populations may also be in this condition. It must be added that Billingham and Hildemann[2] cited evidence that the unitary origin of all domestic hamsters will not, *per se*, account for the situation we seek to explain.

(2) The paucity of histocompatibility genes in this species may be illusory, in the sense that although many different "histocompatibility" alleles may be segregating. their products may be too weak to reveal their presence in the grafting tests described. Some of the findings reported in this paper are indeed consistent with this hypothesis, and its plausibility is strengthened by observations of Hildemann and Walford,[18] that grafts which had been in residence in a state of complete nor-

mality for more than 200 days were occasionally overtaken by a delayed reaction later on. Furthermore, loci determining very weak transplantation antigens occur in mice—loci which are undetectable on some genetic backgrounds.

Finally, it must be pointed out that tissue transplantation is an unnatural procedure that just happens to reveal the existence of what are known as transplantation isoantigens (and their determinant genes). As Medawar[31] has suggested, these gene-products are constantly being released by cells in normal, intact animals and may well fulfil important physiological roles. Indeed, the variable strengths of transplantation antigens may not parallel their relative importance in their true biological context. If this is true, the postulated pleiotropic effect of these genes must clearly be recognized as an experimental artifact, and any susceptibility they may have to selective forces must originate from their unknown function(s).

Any attempt to explain the selection of these genes solely in terms of the isoantigens which they determine will be justifiable only if it can be shown that these *isoantigens per se* are in some way beneficial to a population. The apparent association of a predisposition to certain diseases with the presence of particular red cell isoantigens in man appears to present a similar problem.[32]

Summary.—Previous suspicions that Syrian hamsters, unlike other mammals, have very few detectable histocompatibility genes have been confirmed. Not more than three loci are necessary to account for rejections of skin homografts interchanged between members of three different strains, each of which behaves as if it is almost homogeneous with respect to histocompatibility genes. Only one or two of the loci detected appear to be responsible for the production of strong transplantation antigens. The biological significance of this situation is discussed.

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*CONVEX TYPE VARIETIES**,†

BY THEODORE S. MOTZKIN

DEPARTMENT OF MATHEMATICS, UNIVERSITY OF CALIFORNIA, LOS ANGELES

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1. *Introduction.*—Strictly convex hypersurfaces in affine n-space, $n > 1$, meet every straight line in at most two points, and lie on one side of every tangent hyperplane. Strictly comonotone curves meet every hyperplane in at most n points, and lie for even n on one side of every osculating hyperplane. Having thus singled out varieties of dimensions $n - 1$ and 1 with to some extent analogous properties we are led to ask whether there are similar varieties V of a dimension m between 1 and $n - 1$. We assume differentiability as needed.

We shall see that the answer to the question posed is negative for "exact minimal order", affirmative for "unilaterality" (as defined below). But while examples of strictly convex hypersurfaces (e.g., the sphere) were evident as soon as n-space was considered (for $n = 2$ and 3 coinitially with geometry), and while a special strictly comonotone curve, the norm curve, is maybe the simplest algebraic space curve,[1] the unilateral varieties other than curves and hypersurfaces perhaps escaped detection because of their non-existence for $n < 10$.

2. *Notations and Definitions.*—The desired properties of a variety of dimension m in n-space are:

M_e (*exact minimal order*): V intersects every $(n - m)$-flat (linear variety of dimension $n - m$) in at most $n - m + 1$ points.

U (*unilaterality*): for any point x on V, $V - \{x\}$ lies in an open halfspace bounded by a hyperplane H_x that is the flat of highest contact at x.

Weaker related properties also considered:

M (*minimal order*): V intersects almost every $(n - m)$-flat (i.e. all but a set of measure 0) in at most $n - m + 1$ points.

U_l (*local unilaterality*): for every x on V there exists a neighborhood N of x such that $v \cap N - \{x\}$ lies in an open halfspace bounded by H_x.

F (*flexion*): for any x on V, $V \cap H_x = \{x\}$.

F_l (*local flexion*): for any x on V there exists an N such that $V \cap N \cap H_x = \{x\}$.

Further B and S denote *boundedness* and *simplicity* (non-self-intersection) in case of varieties without a lower-dimensional boundary.

Unilaterality is a pronounced case of *outwardness*, i.e., the property of a variety consisting of the extreme points of its convex hull.